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Christine Yedinak

EDUCATION:

2009-2011 Doctorate in Nursing Practice. Oregon Health Sciences University, Portland, Oregon

1994 Master of Nursing, Family, Nurse Practitioner. Oregon Health Sciences University, Portland, Oregon

1992 **Bachelor of Science in Nursing**. Oregon Health Sciences University, Portland, Oregon

1986 **Graduate Diploma of Education (Nursing).**

1982 **Diploma in Nursing USA.** Presbyterian Hospital. Denver, Colorado

1972 **Diploma in Nursing. Australia.** Rydalmere Hospital. New South Wales, Australia.

CERTIFICATION & LISCENSURE:

1994, 1999, 2004, 2009 - Board Certification . Family Nurse Practitioner, American Nurses Credentialing Center (ANCC).

1994 Oregon State Registered Nurse Practitioner with prescriptive authority # 89006680

1982 Oregon State Registered Nurse # 89006680

1975 Colorado State Registered Nurse.

1972 Psychiatric and General Nursing Registration NSW and QLD, Australia

1991 – 2007 Advanced Certification in Life Saving (ACLS)

1990 – 2001 Pediatric Advanced Life Saving Certification (PALS)

PROFESSIONAL EXPERIENCE:

2003- Present

Oregon Health Sciences University, Portland, Oregon
Family Nurse Practitioner -OHSU Pituitary Center

- Instructor Department of Neurosurgery
- Practitioner Pituitary Disease Center- neuroendocrine practice

2001 - 2002

Oral & Maxillofacial Surgeons, PC & Eugene Surgery Center, LLC. Eugene, Oregon
Clinical Consultant / Family Nurse Practitioner

- Clinical Programs/systems development
- Development of Surgery Center
- JCAHO Accreditation
- Staff education/clinical manager development
- Clinical Specialist

1991- 2000

Oregon Health Sciences University Hospital. Portland, Oregon.
Family Nurse Practitioner/Clinical Manager/Interim Director

- Pre surgical patient assessment and optimization
- Development Ambulatory Surgery Center
- Facility design, pediatric and adult ambulatory surgery
- Operational management of Ambulatory Surgery Center, GI Unit, Pre-Admission Testing Center.
- Clinical Manager main PACU
- Staff RN, PACU

1982-1988

Nurse Educator. Cairns Base Hospital. Cairns, Queensland Australia.

- Clinical and Didactic instruction, undergraduate hospital based nursing program.
- Clinical specialties: pediatric, neonatal care, psychiatric nursing.
- Curriculum development
- Continuing education Flying Doctor Service, Community Health and Maternal & Child Health Program
- State Board Item Writer and Marking Panelist (Queensland State Nursing Registration Exam)

1975-1982
Children's Hospital. Denver, Colorado
Registered Nurse -Pediatric and Neonatal (level 3) Intensive Care

- Protocol Committee
- Co-director Hospital CPR training Program

1974.
Lutheran Hospital. Denver. Colorado
Registered Nurse Medical/Surgical Nursing

1968-1972
Rydalmere Hospital. Rydalmere, New South Wales. Australia.
Trainee Nurse

CURRENT STUDIES - INVESTIGATOR

Proof of Concept Study

Pituitary dysfunction and rate of complications after transphenoidal surgery for pituitary adenomas and other sellar masses.

Phase II, Open, Randomised, Parallel Group, Noncomparative Multicenter Study to Access the Efficacy and Safety of Repeated Subcutaneous Administration of Different Doses of BIM 23A760 in Acromegalic Patients

A randomized, double-blind study to assess the safety and efficacy of different dose levels of Pasireotide (SOM230) sc over a 6 months treatment period in patients with de novo or persistent/recurrent Cushing's disease, Novartis.

A multicenter, randomized, blinded study to assess safety and efficacy of pasireotide LAR vs.octreotide LAR in patients with active acromegaly, Novartis.

An Open Label Study of the Efficacy and Safety of CORLUX (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome, Corcept

HYPOCCS, Observational study in patients with GH deficiency, Lilly

SPEAKERS BUREAU/ ADVISORY BOARDS

2010 Ipsen/Tercia Nurses Advisory Board

2010 Ipsen/Tercica Speakers Bureau

DNP CLINICAL INQUIRY PROJECT

Domains of Life Function Scale for Patients with Pituitary Adenomas. Completed May26, 2011.

PUBLICATIONS

Dillard, T., Gultekin,S.H., Delashaw,J.B.,***Yedinak,C.G.,*** Edward A. Neuwelt,E.A & Fleseriu,M.(2011) Temozolomide for corticotroph pituitary adenomas refractory to standard therapy. *Pituitary*

DOI: 10.1007/s11102-010-0264-1

Fleseriu M., Gassner,M., ***Yedinak, C***., Chice, L., Delashaw J. B. & Loriaux, D.L.(2010). Normal hypothalamic-pituitary-adrenal axis by high-dose cosyntropin testing in patients with abnormal response to low-dose cosyntropin stimulation: a retrospective review. *Endocrine Practice. 16(1):64-70.*

Dillard T, ***Yedinak C.G***, Alumkal J, Fleseriu M. (2010). Anti-CTLA-4 antibody therapy associated autoimmune hypophysitis: serious immune related adverse events across a spectrum of cancer subtypes. *Pituitary. 13:29-38.*

Chapin,W., ***Yedinak,C.G***., Delashaw, J.B., Fleseriu, M. (2010) Cabergonline-Induced Cerebral spinal Fluid Leak in a Patient With a Large Prolactinoma and MEN1. CME review. *The Endocrinologist.*20 (4) 198-202.

Dziurzynski,K., Delashaw, Jr. J.B., Gultekin,S.H., ***Yedinak,C.*** & Fleseriu,M.(2009) Chordoid glioma-case report and review of the literature**,** *Endocrine Practice*. May-Jun;15(3):240.

Dziurzynski K, Delashaw Jr J,B.,***Yedinak,C.***,& Fleseriu M. (2009). "Idiopathic" diabetes insipidus, panhypopituitarism and severe mental status deterioration in a patient with chordoid glioma: case report and brief review of the literature. *Endocrine Practice.* 15**:**240-245.

Fleseriu,M., ***Yedinak,C.,*** Campbell,C. & Delashaw,J.B. (2008). Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions. *Journal of Neurosurgery*, 110 (2):354-358.

Fleseriu,M., Swee H., ***Yedinak, C.G***., Deveney,C., Ludlam,W. & Brett C. Sheppard,B.C.(2008). Cushing's Syndrome May be Under Appreciated in Patients Seeking Bariatric Surgery: A Plea for Screening. *Surgery for Obesity and Related Diseases.* DOI:10.1016/j.soard.2008.09.011

PRESENTATIONS

2008 *Pituitary Testing*. OHSU Pituitary Days Conference. Portland, Oregon

2007 *In search of the Pituitary* NW Regional Transcriptionist Conference.

1998 *Techniques in Post Operative Recovery*. Two day Seminar. Umpqua Valley Hospital. South Bend. Oregon.

1996 & 1997 *Anesthesia and the Surgical Patient.* Oregon Health Sciences University, School of Nursing Internship Program. Portland,Oregon.

1995-1999.*Issues in Post Anesthesia Care*. Critical Care Consortium Internship Program, Portland, Oregon.

1994-1996 *Transition to Practice in Post Anesthesia Recovery*.Oregon Health Sciences University Hospital, School of Nursing Internship Program. Portland, Oregon.

1988 *Issues in Aboriginal Health Care*. FNQ Remote Area Conference, Cairns, Australia

1981-1982 *Neonatal Resuscitation*. Perinatal Traineeship Program, Denver, Colorado

ABSTRACTS & POSTER PRESENTATIONS

Yedinak,C **(**2011) Measurement of Life Functions and Quality of Life for Patients with Pituitary Adenomas 'Rising Star' poster presentation (accepted). *Sigma Theta Tau International conference. October, Grapevine, Texas.*

Brzana,J.A.,***Yedinak,C.G.,*** Delashaw,J.B., McCartney,S., Cook,D.,& Maria Fleseriu,M.(2011). Discordant levels of GH and IGF1 in patients with acromegaly after pituitary surgery, naive to medical therapy and radiation: is the prevalence changing with newer consensus guidelines cut-offs? *Poster presentation at 12th International Pituitary Congress, Boston, MA.*

Yedinak,C. (2011) Domains of Life Functions Scale for Patients with Pituitary Adenomas. Student poster presentation *Western Institute of Nursing Conference. April. Las Vegas Nevada.*

Dillard,T., ***Yedinak,C.***, Delashaw,J.B. & Fleseriu,M.(2010). *Temozolomide for corticotroph adenomas refractory to surgery and radiation: a case of rapid tumor regression* . Poster presentation at AACE Meeting, Boston, MA

Dillard, T., Wei, K., ***Yedinak,*** C.G., & Fleseriu,M. (2010). A case of reversible valvuloptahy associated with Cabergoline therapy. *Poster session presented at AACE Meeting, Boston, MA.*

Fleseriu,M., Coppa,N., Dogan, A., Andersen,P., ***Yedinak,C.*** & Delashaw, J.B.(2010). *Short-term risk of recurrence of surgically treated, radiotherapy -naïve pituitary adenomas* . Oral poster short presentation at the 14th International Congress of Endocrinology, Kyoto, Japan.

Fleseriu,M., Dillard, T.G., ***Yedinak, C.,*** McCartney,S., Delashaw, J.B., Coppa, N,D. &Loriaux ,L,D.(2010). *Low-dose (1 microgram) Cortrosyn stimulation as a screening test for impaired hypothalamo-pituitary-adrenal axis (HPA): is it time for redefinition?.* oral poster short presentation at 14th International Congress of Endocrinology, Kyoto, Japan

Coppa, N.D., Nasseri,M., Giles,S.G., ***Yedinak, C.,*** Delashaw,J.B. & Fleseriu,M. (2010). *Cushing's Disease: Remission rate following transsphenoidal surgery in patients harboring pathologically confirmed ACTH-secreting pituitary tumors*. Poster session presented at the American Association of Neurological Surgeons, Annual Meeting, Philadelphia, PA

Fleseriu,M., ***Yedinak,C.G***, Delashaw,J.B., Cook,D.M., Ludlam.,W.H. (2007) *Normal 24 UFC in Patients with Biochemically Confirmed Cushing's Disease*. Poster presented at AACE Meeting, Seattle. WA.,

HONORS & AWARDS

1994 Honors, Sigma Theta Tau. Oregon Health Sciences, School of Nursing, Portland. Oregon

1992 Honors, Sigma Theta Tau. Oregon Health Sciences, School of Nursing, Portland. Oregon

1986 Distinction. University of Southern Queensland, Australia

PROFESSIONAL ORGANISATIONS

2011 Western Institute of Nursing

2010 The Endocrine Society –Fellow/Student Associate Member

1994, 2011 Sigma Theta Tau International

1994- Nurse Practitioners of Oregon

SPECIAL SKILLS

1982 Open Water Scuba Diving Certification

1972 Private Pilot License. Australia.

CONTINUING EDUCATION

April 13-16, 2011 *44the Annual Communicating Nursing Research conference "Transitions: Unifying Practice, Education and Research to Improve Health".* Western Institute of Nursing 18.5 CE units

March 13-18, 2011. *Mayo Clinic Endocrine Course*. Mayo School of Continuous Professional Development. 27.75 CU units (22.5 AMA PRA category 1 credits)

July 28-31, 2010. *Ashland Endocrine Conference.* Oregon Health Sciences University, School of Medicine, Continuing Medical Education. 12 CU units.

June 14-16, 2010 *12th Annual Northwest Nursing Education Institute.*Oregon. Center for Learning & Change Management, Oregon Health Sciences Univeristy. 15 CE units

October 19, 2010. *Six Weeks to Genomic Awareness.* Office of Public Health, University of Michigan. 6 CE units.

October 9-11 2009 *Medical Update Conference*. Oregon Society of Physician Assistants. 19 CE units.

July 21, 2009 *Therapeutic Advances in Somatostatin Analogs for the Management of Patients With Acromegaly or Neuroendocrine Tumors.* Medical Education Resources, Inc. 1.6 CE units

LANGUAGE FLUENCY

Basic Medical Spanish

REFERENCES

Available on Request

Portfolio Executive Summary

Chris Yedinak DNP Candidate, FNP, MN, BS, RN

This course has made explicit, micro and macro level factors in health, illness and care delivery, particularly as they apply to my practice population of patients with pituitary diseases. Using theory, literature review and research methodologies these constructs were expanded and applied to changes that promote quality outcomes for clinical issues.

From literature reviews for case studies, it became obvious that for pituitary diseases, although genetic and genomic factors were given consideration in disease etiology, differential environmental exposures, historical social factors were not reviewed. Individual belief systems, health behaviors and access to health care issues were little considered. I found no explanation for the disparity between the homogenicity of the population who present for treatment and the known socio-cultural heterogenicity within the local population and referral area. I recognize that more research in these areas is warranted.

The ethical principles and moral constructs behind care delivery became more explicit. At the micro level, I began to apply the framework of ethical principles to daily practice decisions. The moral constructs that influenced policy development in care delivery were examined. The national debate concerning health care reform was reframed as a battle between moral philosophies over universal health care. I now view policy decisions and development in reference to these principles.

Given the geographic expanse of my practice referral base, both access and care delivery may be enhanced by technology. I anticipate the use of telemedicine as a practice innovation that will 'disrupt' the traditional face to face visit modality and provides cost effective access to care for populations with geographic or social isolation. In addition to remote area use, electronic medical records, data sharing through Health Information Exchanges (HIE) and National Health Information Networks (NHIN) can reduce redundancy in testing, promote coordinated, focused quality in care and provide a means to bridge the care chasm described by the Institute of Medicine's Quality of Health Care in America Project report of 2000.

I have a deeper understanding of the economics of health care and the impact of socioeconomic factors, market forces, workplace ideologies and macro level policies on resource distribution and inequalities in health care. For my patient population these factors affect continuity of access to care, availability of treatments, covered services, out of pocket expenses, treatment (medication) accessibility and compliance. I directed the process of policy development to a legislative effort to include payment for growth hormone replacement in Medicare and third party payer formularies and contracts of covered services.

The relationship between the cost of care delivery, system and practitioner reimbursements was examined. The national spotlight on health care costs and the non-sustainable trajectory of costs for Medicare and Medicaid in an aging population has fueled efforts at decreasing health care expenditure and improving care quality and outcomes. My CIP is focused on the demonstration of the efficacious function outcomes and improved life quality.

I better understand the interaction of research, health care and change. I revisited life experiences and examined my leadership successes and failures in the light of theory and concepts such as the use of individual and organizational power and influence and the development of relationships. Multiple changes to health care are required at micro and macro levels and effective research and leadership is required in nursing to achieve the vision of the Institute of Medicine for U.S. healthcare.

Clinical Inquiry Project

Domains of Life Function Scale for Patients with Pituitary Adenomas.

Christine Yedinak

Oregon Health & Sciences University

INTRODUCTION: THE CLINICAL PROBLEM

There is a growing national demand to demonstrate quality of care, efficacious clinical outcomes and evidence based practice (Nayer, 2009; Porter, 2009). Enhanced by Center for Medicare/Medicaid Services (CMS) discussion of outcome based reimbursement and the need for fiscal restraint on what many see as the unsustainable trajectory of health care costs demand is growing to develop new methods of measurement of health care and clinical outcomes. Quality of life (QoL) has been discussed conceptually for many years but has been thrust further into clinical consciousness with this discussion.

Outcomes measurement has historically focused around biochemical parameters and disease factors causal of morbidity and mortality but was later expanded to include high risk behaviors (Hepworth, 1997). Qualitative science grew, in part, from the failure of quantitative methodologies to clearly address outcomes as defined by the patient.

Although QoL in the clinical context is agreed upon as a patient perceived outcome parameter, the definition of QoL components share less concordance. For the purpose of this project, QoL is defined as the subjective rating by the patient of their general well being in multiple domains of functioning.

The determination of specific life functions affected or disrupted by the advent of a pituitary adenoma (PA) is important in relation to appropriate treatments, referral and ultimately all outcomes and their measurement. Quality of life has been demonstrated to be impaired in some patients' PAs, particularly for those with functional (hypersecretory) adenomas and non-functional macroadenomas (tumors larger than 1 cm). Non-functional (NF) microadenomas (tumors smaller than 1 cm) are presumed to be innocent or asymptomatic, particularly if a

hormonal work-up is normal. Most often, such tumors are reported as incidental findings in a workup for some other malady.

The demonstration of clinical effect and achievement of improved QoL are not necessarily synonymous. Current treatment modalities, including replacement of hormonal deficiencies, have been shown to be inadequate to reliably restore QoL in many patients with PAs. Likewise, clinical treatment may improve functional ability in one or more aspects but may not improve QoL. Although QoL has been extensively studied in acromegaly and Cushing's disease patients and, to some degree in patients with macroadenomas, little attention has been accorded QoL changes in patients with NF microadenomas. There is little longitudinal data that reflects progressive QoL changes either in favor of improved function or decreased function.

Quality of life changes frequently persist after treatment (medical and surgical) and are reportedly worse in some cases. If biochemical hormonal balance is achieved, but QoL is not restored, this brings into question the dominant paradigm of pituitary hormonal deficiencies as causative of QoL deficits and calls for further investigation. This also questions the role of PAs themselves in QoL changes, independent of pituitary dysfunction and opens questioning of other factors inherent in QoL changes. There were no prospective studies found in a literature review designed to examine QoL for patients with NF microadenomas that confirm the absence of QoL changes. Neither were published longitudinal studies found that used the same subjects both pre and post treatments to document progressive changes in the same sample. In addition, QoL assessment in patients with PAs has focused on the measurement of patient perceptions and excluded more objective features of life functions as QoL outcome measures.

There has been an absence of a dedicated unique metric for the measurement of QoL in patients with NF pituitary tumors with and without pituitary deficiencies. Validated

questionnaires do exist for acromegaly, Cushing's disease, prolactin excess and growth hormone deficiency. Available questionnaires measure the patient's perception of a variety of life function parameters, but omit others. There is currently no single metric that makes a comprehensive evaluation of life functions and QoL applicable to all pituitary diseases inclusive of NF adenomas.

In summary, there is a need for a simple but comprehensive, standardized tool that can be used as a metric for the impact of pituitary tumors on QoL and life function changes. After validation, this instrument could be used to guide decision making with respect to choice and timing of treatments and to compare the efficacy of different treatment modalities or specific treatments over time and correlate clinical findings in pituitary diseases. Such a tool is needed to guide assessment, informed consent and treatment in both specialty care and primary care settings and to demonstrate efficacious outcomes of care.

Population Affected

The population for this study was derived from patients presenting with PAs at the Oregon Health & Science University (OHSU) Northwest Pituitary Center. Patients were referred from community and in-house endocrinologists, primary care providers, neurologists, and, laterally, from the OHSU neurosurgery department. Over 300 new patient referrals present to this center for evaluation each year. Historically, over half of these patients present with PAs that are determined to be biochemically non-functioning. Microadenomas comprise the majority of theses tumors but patients with macroadenomas with or without optic chiasm involvement can represent upward of 40% of presenting patients. The number of hypersecretory tumors seen in this clinic is similar to those reported in the literature for other centers.

At the OHSU Northwest Pituitary Center, females present more commonly than males for evaluation (2:1 and up to 5:1). Patient ages range from 16 years to 89 years. The most frequently reported reason for presentation for treatment of PA's at our center is headache. Patients are frequently referred to the center after discovery of a PA following magnetic resonance (MR) imaging for other reasons such as, a motor vehicle accident or a head injury. On presentation, all patients are evaluated for pituitary deficiencies and dysfunction and medical and/or surgical treatment is initiated as appropriate.

Epidemiology

While epidemiologic data suggests the prevalence of PA is 1:1000, evidence from recent radiographic studies estimates this prevalence to be as high as one person in every six, while evidence from autopsies indicates that up to 27% of the population could be affected with 15% being the most often quoted prevalence statistic (Daly, Burlacu, Livadariu, & Beckers, 2007;Dekkers et al., 2007; Dekkers, Pereira, & Romijn, 2008; Gorczyca & Hardy, 1988; Molitch, 2009a). Clinically nonfunctioning PAs have been estimated at 14.4% of all PAs (Daly et al., 2007; Karavitaki et al., 2007). Macroadenomas (tumors>1.0cm) are estimated to have a lower prevalence of approximately 0.2% (Dekkers et al., 2008; Nammour, Ybarra, Naheedy, Romeo, & Aron, 1997). Only an estimated 0.4% of pituitary tumors found at autopsy were macroadenomas, leading the authors to conclude that microadenomas seldom progress to macroadenomas (Dekkers et al., 2008). The lifecycle of a microadenoma is largely unknown (Melmed, 2011).

Although incidence statistics are difficult to find, the discovery of PAs is known to be increasing, most likely as a result of the increased rate of radiographic imaging for some other purpose (Molitch, 2009b;Carsote et al., 2009) resulting in the detection of tumors as an

incidental finding. However, an actual increase in incidence cannot be ruled out and genetic and genomic factors are implicated and still under review (Melmed, 2011). Statistics from a Swedish review documented a statistically significant increase in incidence of tumors in both genders (between the years 1980 and 2000) from 7.13/million inhabitants to 9.76/million (Nilsson, Gustavasson-Kadaka, Bengtsson, & Jonsson, 2000). No similar statistics have been reported in the United States.

Females are more frequently found to have microadenomas than males, with a ratio reported at some centers of at least 1.5: 1 (Barzaghi, Losa, Giovanelli, & Mortini, 2007; Brazier et al., 1992). A study in Finland found an incidence of 2.2 per 100,000 in males and 5.9 per 100,000 in females. Microadenomas are reportedly more common at ages less than 65 years while macroadenomas show a peak incidence in people between 60 and 70 years. Based on a review of statistics from patients presenting to the OHSU Northwest Pituitary Center between 2007-2010, the relative incidence of macroadenomas to microadenomas at this center is approximately 2:1. Gender distribution for patients presenting with macroadenomas during this time period was approximately equal with an average age at presentation of 51 years. Gender distribution for microadenomas was OHSU Northwest Pituitary Center OHSU Northwest Pituitary Center overwhelmingly female, with a ratio of female:male of 5:1 (measured over one 12 month period 2009) with an average age at presentation of 35 years.

Background

Pituitary tumors represent the third most common brain tumor (Forsyth & Posner, 1993) with headache the most common presentation in many clinical settings. Reportedly the most common human ailment experienced by upwards of 70% of the population (Jordan & Expert Panel on Neurologic Imaging, 2007). headache frequently leads to diagnostic imaging.

Neurologic imaging guidelines moderately to strongly recommend computed tomography (CT) or Magnetic Resonance (MR) imaging for a variety of headaches including, new onset and in patients over the age of 60 years (Jordan & Expert Panel on Neurologic Imaging, 2007). Head injury guidelines also call for CT based on similar criteria (Jordan & Expert Panel on Neurologic Imaging, 2007). Many pituitary tumors are discovered incidentally in this manner.

Quality of life decrements are clearly documented in the literature for hypersecretory pituitary adenomas, macroadenomas, and those with documented pituitary deficiencies. The AcroQoL was developed as a specific tool for use in acromegaly, and several studies have demonstrated marked decrease in QoL dimensions in both controlled and uncontrolled disease (T'Sjoen, Bex, Maiter, Velkeniers, & Abs, 2007; van der Klaauw et al., 2008). The same effect has been demonstrated in Cushing's disease and in macroadenomas (Kauppinen-Makelin et al., 2006; Matta et al., 2008; Miller, Doll, David, & Wass, 2008; Wassenaar et al., 2010; Webb, 2006; Webb, Badia, Surinach, & Spanish AcroQoL Study Group, 2006; Webb & Badia, 2007) and prolactinomas (Dekkers et al., 2006; Keil et al., 2009; Page, Hammersley, Burke, & Wass, 1997; Webb et al., 2008). There are no studies that target NF microadenomas to assess QoL changes or that have followed QoL and documented changes in the same PAs patients over time.

The evaluation of QoL has been reported using a variety of disparate assessment tools from patient diaries and interviews to multiple validated population based health assessment questionnaires. Studies in patients with pituitary adenomas (PPAs)have used the Hospital Anxiety and Depression Scale (HADS), Multi-dimensional Fatigue Inventory (MFI-20), Nottingham Health Profile (NPH), the European Organization for research and treatment of cancer (EORTC QLQ 30) Brain Tumor Specific Module (BN-20) questionnaire, and many the Short Form Health Survey (SF-36), the Rand-36 (Barzaghi et al., 2007), the Arthritis Impact

Measurement scales 2 (AIMS2) for acromegaly specific QoL assessment, personality assessment using the QoL scale Brief WHOQoL-B (VanderZee, Sanderman, & Heyink, 1996; VanderZee, Sanderman, Heyink, & de Haes, 1996)(Kars, van der Klaauw, Onstein, Pereira, & Romijn, 2007; Peace et al., 1997; Sobrinho, 2007). These compare QoL in either pre or post treatment pituitary adenoma patients with a control population mostly of European origin. Many pituitary disease researchers have used various combinations of these surveys (Dekkers et al., 2006; Johnson, Woodburn, & Vance, 2003; Brazier et al., 1992; Dekkers et al., 2006; Liu, Li, Ren, & Liu, 2010; Webb et al., 2008). The use of this variety of combinations of instruments has made valid comparisons between studies and conclusions regarding QoL in pituitary disease difficult .

The use of multiple assessment tools also reflects the lack of definitional agreement of health related QoL (Sievers et al., 2009; VanderZee, Sanderman, & Heyink, 1996; VanderZee, Sanderman, Heyink et al., 1996) and inhibits the development of a standardized tool. Difficulty in applying a specific tool across diseases, ages, genders, and macro and micro cultures further complicates the QoL tool standardization effort. In a comparison of the NHP and SF-36, researchers concluded that although the SF-36 was generally favored by more patients, stronger symptoms experienced in elderly patients were more favorably assessed by the NHP (Kan & Cusimano, 2006). Vanderzee and colleagues (1996) and Jagsch and Pils (2006) compared the NHP and the Rand-36 and found the latter to be more reliable in patients with chronic diseases whereas Jagsch et al (2006) emphasized the need for tools that were more specific to the population under scrutiny.

Attempts have been made to validate the utility of non disease specific tools and develop total QoL scores for use in pituitary diseases (VanderZee, Sanderman, & Heyink, 1996; VanderZee, Sanderman, Heyink et al., 1996). These efforts are continuing but have been shown

to have limitation for use in PPAs. No agreement has emerged as to the meaning of a total score. Kan et al (2005) in recognition of the lack of agreement, standardization and definition of health related quality of life with respect to PPAs, developed and attempted to validate their own questionnaire. Although the tool developed by Kan et al represents an attempt at a pituitary disease specific QoL, it has significant limitations for generalization.

Multiple factors inherent in the treatment process can affect QoL. The principle reasons for the removal of a NF adenoma is optic chiasm compression causing visual field deficits, intractable headache and tumor growth. There is evidence that removal of microadenomas provides headache reliable and sustained relief or improvement in up to 56% of cases post surgically (Fleseriu, Yedinak, Campbell, & Delashaw 2008). Growth is estimated to occur in 10% of NF microadenomas and 20% of NF macroadenomas necessitating surgical intervention (Kan & Cusimano, 2006). Although minimized in the hands of a skilled surgeon, the risks (such as cerebrospinal fluid (CSF) leak and diabetes insipidus (DI)) associated with pituitary tumor resection are not insignificant and can impact QoL. Risks are reported to increase with age (Kilty, McLaughlin, Bojanowski, & Lavigne, 2010). To be most applicable, disease specific measurement tools need to flexible enough to account for such variables over time.

In summary, pituitary tumors can incur significant morbidity and affect QoL. Life functions may be affected by multiple factors specific to PPAs, including the type of tumor, size, activity, location, treatment, and patient age at diagnosis. These factors can all have ramifications for multiple domains of life function and affect subjective and object health and QoL. Multiple tools have been developed to measure QoL but there is currently no comprehensive metric that is specific to pituitary dysfunction. Additionally, no effort has been directed to clarifying the

absence of QoL changes in non-functioning pituitary microadenomas. Standardization allows for comparability of data across locations and can provide direction in treatment.

Organizational/Local Knowledge of the Clinical Problem

Although there has been growing agreement in the literature regarding the value of measurement of outcomes such as QoL, the analysis of the concept is still considered 'soft science' and does not generate the same response as 'hard science' or biochemical, cellular or physiologically based interventions and investigations (Frost & Sloan, 2002). Although some more recent studies have concluded benefit in QoL analysis, the full value of this information in practical or economic terms is yet to be clearly demonstrated.

The current tool used for intake assessment of new patient referrals to the Pituitary Center at OHSU is acknowledged as symptom based and lacking in specificity and sensitivity for that purpose. It does not attempt to address QoL factors and weakly attempts to examine temporal changes. It is time consuming for both staff and patients to complete; the questions are vague and redundant; it is often misinterpreted, incomplete, or not completed by the patient. There is no language version other than English and no embedded cultural sensitivity. Treatment is focused on biochemical parameters and referrals are reactive to symptoms. The proposed clinical inquiry project is designed to address these gaps in clinical practice at the OHSU Northwest Pituitary Center and to provide a foundation for future clinical outcomes research in this arena.

Importance to Advanced Practice Nursing

The field of QoL evaluation and measurement of treatment outcomes is fast becoming a driving force in both nursing and medicine. The concept of measuring patient functional deficits and promoting adaptive outcomes is embedded in nursing care (Cowen & Moorhead, 2011). This

project proposes to address a disease specific issue and more fully approach concept development of quality of life within the context of pituitary diseases. Additionally, it is hoped that this project will add further dimension and discussion to the care of pituitary patients; to inform clinical practice, outcomes knowledge, and be acceptable for evaluation of patients in specialty neuroendocrine practices or for treatment follow up in a variety of advanced practice nursing settings.

Desired Outcomes

The goal of this project is the adaptation of currently available QoL metrics to the measurement of changes in life functions in patient with pituitary adenomas/diseases. It is hoped that this project will further elucidate functional changes associated with the presence of a pituitary tumor and shed further light on the meaning of pituitary adenomas/disease to the daily function and QoL of these patients.

Purpose Statement

This study was a practice improvement project aimed to improve the measurement of outcomes in patients with pituitary adenomas. This included: analysis of the concepts associated with QoL within the context of pituitary disease; the identification and categorization of attributes or characteristics associated with functional changes impacting QoL in patients who present with PAs at OHSU. The second purpose was the development of an instrument, the Domains of life Function Scale for Patients with Pituitary Adenomas of Life (DOLFS) that measures attributes characteristic life functions described in domains with the aim of developing an overall and component QoL score. Once developed, the instrument was piloted to evaluate internal validity and reliability and item performance. Lastly, the output was to be evaluated to

tentatively validate these attributes in this context and the need for a generic tool to differentiate levels of function or dysfunction in the population of patients with Pas; both NF and HF.

Clinical Inquiry Questions

This project addressed two questions: What life functions reflect decreased or altered QoL for patients with pituitary adenomas; and secondly, is QoL altered for patients with all types of PAs?

Synthesis of Evidence

Introduction

Clinical effect is defined as the change that is the result of treatment (in Agnes, Webster's New World Dictionary, 2001). Treatment is defined in terms of empiricism and the medical model driven by physiologic and biochemical changes. Often described as patient–reported outcomes (Jagsch & Pils, 2006), QoL is defined almost entirely in perceptual terms and has no one clear description. Consequently, the dimensions of QoL have likewise been elusive, and multiple tools and instruments have been developed in an attempt to measure the concept. Each tool is developed based on various domains of life function that, most often, have been qualitatively derived and categorized from negative health related experiences of a patient population under investigation. However, it could be argued that more objective factors beyond perception are similarly responsible for influencing QoL. In addition, both symptoms and the clinical treatment received by the patient can impact various domains of life function, such as employability or work attendance and qualitatively alter life experiences and satisfaction.

With regard to pituitary tumors and diseases, surgical and hormonal treatments may have efficacious outcomes with respect to tumor removal and rebalance and replacement of pituitary dysfunction, but this is not always synonymous with improved or restored QoL. A number of generic health related QoL tools have been applied to the evaluation of QoL in this context.

Recent efforts in pituitary diseases have become more minutely focused on specific pituitary diseases and dysfunction. These efforts recognize disease differences and the need for an instrument to more effectively identify QoL changes that can be addressed in the clinical setting. However, no single instrument has emerged as a clinical tool for this purpose in PA's.

Measurement instruments used for QoL have largely been derived from clinical effect studies, morbidity statistics and indices such as incidence and prevalence, disability, symptom or functional indices and patient satisfaction (Hunt & McEwen, 1980). The perspective of all indices has been based on a deviation from a reference or 'normal'. The definition of 'normal' has been more challenging, but is imperative for use as a comparator or control to the population under investigation. 'Normal' QoL is relevant to age, gender, culture, and community. The ultimate goal of measurement is the management of contextual services needed for the treatment of the affected population (Hunt & McEwen, 1980).

Critical synthesis of relevant literature

State of the science

The Short Form-36 (SF-36), developed by the RAND corporation as a measure of outcomes, has been used extensively in research in QoL studies in pituitary adenomas (Dekkers et al., 2006; Johnson, Woodburn, & Vance, 2003; Kan & Cusimano, 2006; Sonino et al., 2007; van der Klaauw et al., 2008; Webb et al., 2008). Numerous other instruments have been used for the evaluation of patients with chronic disease and patients with PA's. These include: the Hospital Anxiety and Depression Scale (HADS)(Dekkers et al., 2006; van der Klaauw et al., 2008); the Nottingham Health Profile (NHP)(Dekkers et al., 2006; van der Klaauw et al., 2008); the Multi-dimensional Fatigue Inventory (MFI-20) (Dekkers et al., 2006; van der Klaauw et al., 2008); the Specific Signs and Symptoms Score (SSS)(T'Sjoen, Bex, Maiter, Velkeniers, & Abs, 2007); the

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30) and the specific Brain Cancer module (BN-20)(Budrukkar et al., 2009); The General Well Being Schedule (GWBS) (Page, Hammersley, Burke, & Wass, 1997); Fact-g/Fact-Br(Kan & Cusimano, 2006); Karnofsky Performance Scale(Kan & Cusimano, 2006); Visual Related QoL Questionnaire (Okamoto, Okamoto, Hiraoka, Yamada, & Oshika, 2008)(and RAND corporation); and the Medical Outcomes Study (MOS a forerunner of SF-36) (Sonino et al., 2007). Up to four instruments have been used in a single study. Although combining instruments may aid in the validation of the use of the tool(s) or to achieve the purpose of the study, there has been no attempt at standardization of tools used for more general application or the development of reference values in the scope of pituitary disorders. Lack of standardization makes efforts at comparison of study results and sometimes clinical application of findings difficult if not impossible.

Johnson, Woodburn and Vance (2003) evaluated QoL of 168 patients with pituitary adenomas pretreatment using the SF-36. This study was inclusive of de novo patients and those treated at other facilities with active disease. Patients with microadenomas were excluded from this analysis. All patients were noted to have statistically significant physical and mental QoL impairment when compared to instrument standards in a 'normal'/control population.

Canadian researchers Kan and Cusimano (2005) solicited volunteers from the Pituitary Tumor Support Network of Canada (PTSN) to derive issues relevant to QoL in patients with pituitary tumors. The only inclusion criterion was the existence of a PA. There were no exclusion criteria or controls for other disease variables. Items for inclusion in a questionnaire were selected by a panel consisting of two family caregivers, two registered nurses, and a neurosurgeon experienced in the management of patients with PAs. After a literature review,

items were reduced and re-reviewed for validity by 20 additional patients from the same sample. The authors acknowledged the clinical need for a tool to guide treatment, reduce the burden of symptoms and life stressors for QoL to improve. However, factors such as tumor secretory activity or pituitary deficiency, treatment modalities, age, and gender were not considered in the development of this generic pituitary adenoma tool. The tool's lack of sensitivity also limits its clinical utility.

In recognition of a need for pituitary disease specific tools, two instruments, the Cushing's SF-36 (Webb et al., 2008) and the AcroQol (T'Sjoen et al., 2007; Webb, Badia, Surinach, & Spanish AcroQol Study Group, 2006; Webb & Badia, 2007) were developed. This allowed more sensitive discrimination of factors affected by disease and to some degree treatment but there is no evidence that this has been used to guide treatment. Multiple studies have been undertaken examining changes in Cushing's disease (CD). In a small single site study, personality was demonstrated to be unaffected by CD but increased psychological distress, including anxiety (p=0.046), depression (p=0.013) and 'psychotic symptoms' (not described) (p=0.006) was reported that led to a generalized decrease in QoL (p=0.02) (Sonino, Bonnini, Fallo, Boscaro, & Fava, 2006). Several healthy subject, controlled, and multisite studies have confirmed a general decrease in perception of well being and QoL in newly diagnosed CD that was worse in currently hypercortisolemic patients than in those in long term remission (van Aken et al., 2005)(p=< 0.001). Scores for anxiety and depression were less than for healthy controls and improved, but not normalized, in remission (Webb et al., 2008). It is important to note that the domains of the CD QoL tool were developed from group interviews with 10 patients focusing on dysfunction. In this manner many areas of improved or 'normal' function were possibly either excluded or de-emphasized and the generalizability of the tool for use in a variety of populations is questionable.

Tools developed for the purpose of assessing QoL with acromegaly share the same developmental and conceptual basis as the CD QoL tool (Webb et al., 2002; Webb et al., 2008). Several studies have utilized this tool to analyze functioning in long term cure of acromegaly and have demonstrated persistent decreased QoL (Biermasz et al., 2004; T'Sjoen et al., 2007; Bex et al., 2007; Wassenaar et al., 2010; Webb, 2006; Webb & Badia, 2007). Comparisons with age and gender matched controls confirmed this finding (Biermasz et al., 2004). The SF-36, the NHP, the FMI-20 and HADS were all used to confirm statistical significance of this effect and demonstrate tool validity in the assessment of specific areas of functioning. The specifics of dysfunction are not clearly delineated.

Using a Belgian acromegaly registry (AcroBel), 58% of 291 patients with active and controlled disease were found to have preserved pituitary function apart from GH secretion (T'Sjoen et al., 2007). No statistically significant correlation was found between biochemical markers of disease activity and AcroQoL scores however, a negative correlation was found between the median scores on the Signs and Symptoms Scale (SSS) and the median of the AcroQol total scores for those studied (r=-0.478; p=<0.001). In a 6-month follow up of a double-blind placebo-controlled randomized, cross over study in a treatment protocol for acromegaly, QoL improved significantly with treatment and was more sensitive to change than biochemical measurement of IGF-1. These results suggest some measurable value in QoL studies with respect to outcome improvement. The development of standardized tools that establish reference values using this information, can only aid in this effort.

Other factors are variably excluded from recognition in many QoL tools. The SF-36 excludes the evaluation of sexual function and personality factors are generally excluded. The contribution of pituitary dysfunction to changes in personality has been considered a valid factor in the

perception of QoL in patients with PAs (Santos et al., 2009; Sievers et al., 2009). Sievers and colleagues (2009) investigated 70 patients with acromegaly and 58 with NFPA using age and gender matched healthy controls, the Eysenck personality Questionnaire and the tri-dimensional personality questionnaire. The individual's level of desire to be socially acceptable was evaluated. No casual relationship was discovered that indicated personality changed either as a result of NFA or acromegaly, but common features of personality emerged in acromegaly. Harm avoidance, neuroticism, a higher state of anticipatory worry, pessimism, fatigability, impulsiveness, deceased novelty seeking and asthenia were found to be statistically more prevalent. Personality factors were not affected by adenoma type, surgery or radiation. The clinical importance of this is yet to be elucidated. Patients with PA's may experience multiple dysfunctions that associate with decreased QoL. The more factors identified using broad based assessment tools the more targeted clinical responses can be to address these issues.

Treatment effects, such as surgical resection (transsphenoidal and transcranial) for NFPA on QoL have been variably reported. Anterior pituitary function was shown not to improve significantly post operatively in two large studies, with the majority of pre operative patients having similar degrees of hypopituitarism pre and post operatively (Nomikos, Ladar, Fahlbusch, & Buchfelder, 2004; Wichers-Rother, Hoven, Kristof, Bliesener, & Stoffel-Wagner, 2004). A smaller study compared QoL for 48 post operative PPAs and 42 age and gender matched post mastoid surgery subjects. Scores on the SF-36 and the Global Well Being Scale (GWBS) were found to be similar in both groups despite anterior pituitary deficiencies in some post operative PPA's (Page et al., 1997). Page et al, (1997) reported that only those patients (18) who had received radiotherapy had lower scores for mental health (depression and decreased control of emotions (p <0.05)). This is in contrast to findings reported by Decker et al (2006) demonstrating

lower QoL in PPAs after transsphenoidal surgery when compared to 'normal' controls. Other studies also linked hypopituitarism negatively to QoL (van der Klaauw et al., 2008). This difference may be accounted for in the assessment instruments, differences in patient ages at time of assessment, the impact of surgery and time elapsed since surgical resection or other unidentified factors. Standardization of QoL assessment tools may help to clarify these issues.

Complications of surgical treatments have not been assessed in the context of QoL. The incidence of cerebrospinal fluid (CSF) leak associated with the creation of a defect in the dura through the thin diaphragma sellae in the pituitary and consequent CSF leak has been reported as high as 19.2% despite surgical advances to minimize this risk (Carsote et al., 2009; Mavrakis & Tritos, 2004; Molitch, 2009a). Of these patients 8% require one or more surgical revisions including lumbar drains, shunts and or more extensive procedures to repair the CSF leak. Transnasal/ transsphenoidal resection of pituitary tumors has been shown to incur extracranial complications such as septal deviations and intranasal changes in 29.6% of the operated cases (Gonzalez-Tortosa & Poza-Poza, 2010; Han, He, Mao, & Wang, 2008; Sciarretta et al., 2010) and visual changes (Rabadan, Hernandez, & Ruggeri, 2009) all of which is likely to impact QoL and are not assessed at all in currently available, standardized instruments.

Other post-operative complications include DI estimated in one study to be as high as 23% with reports of a higher incidence with microadenomas (Molitch, 2009b). Postoperative hypopituitarism, meningitis estimated at 5.5%, pneumocephalus 2.4%, visual deterioration 1.5%, hematoma 0.8% and 30-day mortality rate of 0.8% (Barzaghi et al., 2007) are small but added risks to QoL.

In acknowledgment of the impact of age and gender differences in the validation of results, two further studies used age, gender matched controls from the patient's direct social

environment (Dekkers, Pereira, & Romijn, 2008; van der Klaauw et al., 2008). One study is noted to have derived comparators from the literature when geographical controls were not available. Patients with controlled, hypersecretory tumors were included in one large study (403 patients) (van der Klaauw et al., 2008) while another smaller study (99 patients) was limited to nonfunctioning macroadenomas with only the latter considering pituitary dysfunction as a variable. Both studies were conducted post treatment in a Western European population and concluded that long term QoL deficit persisted despite treatment and hormonal replacement. Only one comparable study was found in the literature to verify the same experience in the U.S. population (Johnson, Woodburn & Vance, 2003).

Morbidity and mortality risks for patients with PA's increase with advancing age. Researchers at Johns Hopkins Department of Neurosurgery, using a random sample of 8,400 patients with a mean age of 70 years from non-federal hospitals in 37 states, reported a mortality of 3.8% with odds increasing by 30% after the age of 80 years (Kilty, McLaughlin, Bojanowski, & Lavigne, 2010) . One study of 370 (29.8%) microadenomas and 870 (70.2%) macroadenomas reported a higher morbidity with age over 65 years (6.6% vs 3.1%; p= 0.05) and large tumor size (15% vs 3%; p= 0.0002) (Kalinin et al., 2009; Takeda et al., 2010). Given that the incidence of macroadenomas is highest in this age group, the concomitant morbidity risk further challenges QoL and function.

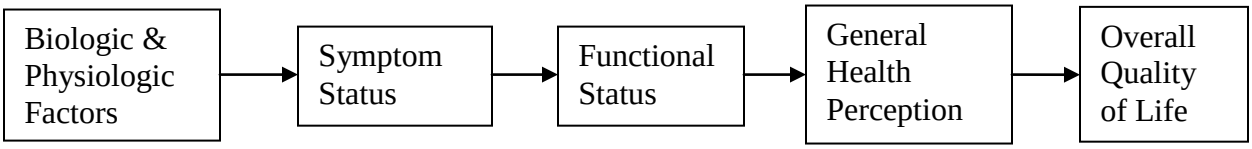
Conceptual Framework

The concept of outcomes in health care has traditionally focused on biological and physiologic factors whereas QoL measures extend outcomes analysis to conceptual functions of life and how these respond to disease and treatment. For the purpose of this project Wilson and Cleary's (in Fairclough, 2010) conceptual model of progressive levels of outcomes was adapted

as a foundational model for the development of the concept of QoL in pituitary diseases (see figure 1). Under this model biologic and physiologic factors lead to symptom development that drives functional status, general health perception and overall quality of life. This model is unidirectional. This project theorizes that perception of QoL is a dynamic, progressive and developmental process in which interactions between variables over time can change and be influenced by this interaction throughout the life cycle (see figure 2).

Figure 1

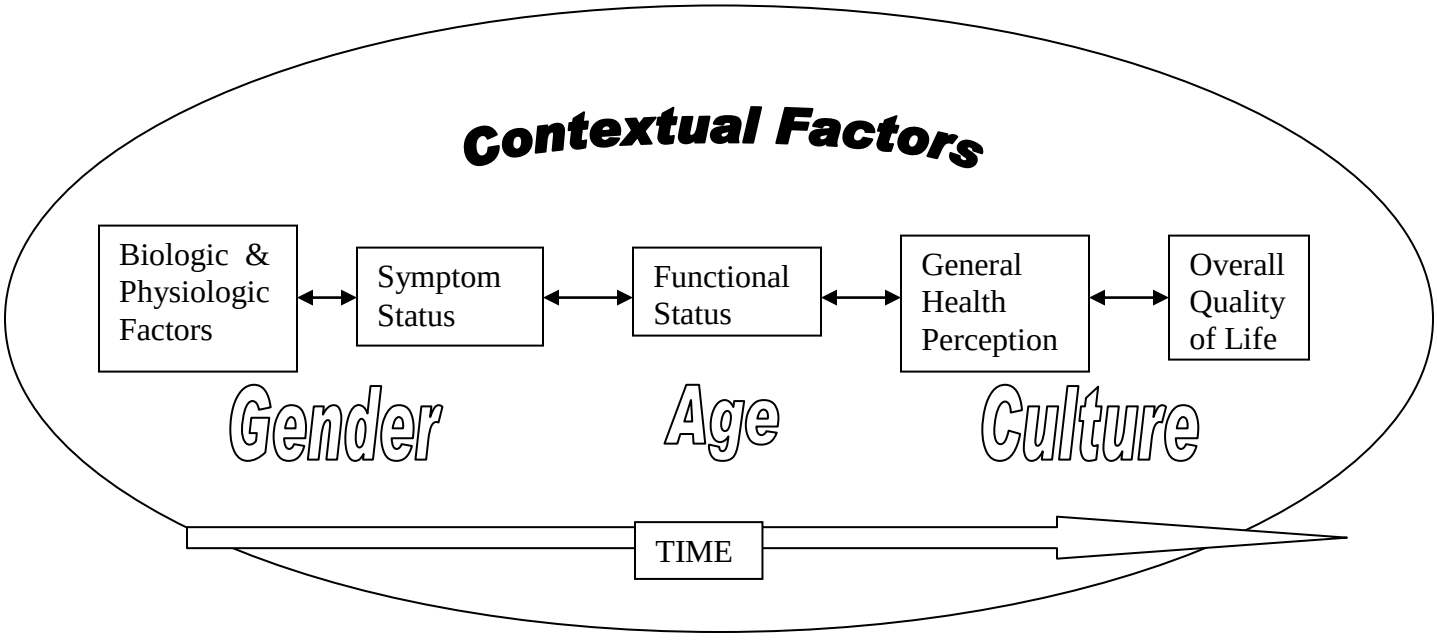
Progressive Levels of Outcome



(Wilson & Cleary, 1995 in Fairclough, 2010)

Figure 2

Expanded Concept of Progressive Level of Outcome



Gaps

The definition of the dimensions of life functions is currently incomplete. QoL studies allow for identification of dimensions affected by disease but not always contemplated as health problems in treatment (Santos et al., 2009). However, neither objective nor perceptual components of QoL alone are adequate as outcome measures for use in treatment monitoring and direction. Numerous variables associated with pituitary disease and dysfunction that have the potential to affect QoL, are not assessed in currently used QoL instruments. Macro factors such as age, gender, culture and personality traits have been shown to affect QoL at the very least in respect to adherence to treatment and patient- provider contact (Sievers et al., 2009). Vision, which is not accounted for in most generic QoL measures is a significant factor in patients with macroadenomas (Okamoto et al., 2008). Micro factors, such as post treatment daytime somnolence, are known to promote dysfunction (van der Klaauw, Dekkers, Pereira, van Kralingen, & Romijn, 2007). Many of these factors described in social functioning such as support and sexuality are variably accounted for in standardized tools.

Most tools have some form of quantification of a particular experience or perception of a function or its characteristic. The underlying assumption is that all patients/respondents weight the importance to their lives of the particular function, equally. Most tools do not evaluate the veracity of this assumption. The development of a tool, with broader and more inclusive functional dimensions, one that has the flexibility to assess change over time and allows the patient to identify their level of tolerance or discomfort with the dysfunction is called for.

In addition, the use of multiple tools for a single assessment is cumbersome and impractical for clinical purposes and challenging for research purposes. A complexity of tools

has been used in the assessment of QoL in an attempt to validate findings against a standard however; there is no single tool that is currently developed to provide a pituitary disease specific standard. Disease specific tools have been shown to improve utility for clinical practice and research and therapeutic outcomes (Santos et al., 2009). However, these tools are more specific and useful post diagnosis and treatment, and a broader standardized tool is required for initial clinical evaluation.

Critique

The determination of baseline QoL has not been undertaken in patients with all types of PAs nor has a comparison with age and gender matched community cohorts been performed in the U.S. A determination of whether QoL is indeed altered, when compared to an unaffected control group, would help to establish a U.S standard that could highlight QoL changes that are more likely to occur as a result of pituitary disease. Currently, no studies have been designed that address changes with respect to microadenomas or confirm that patients with microadenomas without pituitary dysfunction have the same QoL as age, gender matched community peers. No attempt has been made to determine if pituitary tumors in themselves cause some baseline disruption of QoL and, if so, what areas of function are affected. There were no longitudinal studies found in the literature that assessed pre treatment and post treatment QoL or followed changes in QoL over time.

Validated tools are currently available for the purpose of simply quantifying the presence or absence of a QoL deficit. When a single point in time measurement is indicated, existing tools may be adequate. For the purpose of ongoing treatment and evaluation for patients with PA, it is proposed that a more detailed, focused and sensitive tool is required to measure outcomes to achieve quality care in this population.

Other Sources of Evidence: Guidelines

There are no clinical guidelines in the literature that relate to QoL for patients with PAs. Likewise, current guidelines for the assessment and treatment of pituitary dysfunction do not consider QoL issues. Other guidelines that relate to growth hormone (GH) deficiency and evaluation and treatment of CD, prolactinomas and acromegaly are not directly useful for the purpose of this project.

Summary

Quality of life assessment has been shown to be a more sensitive indicator of outcomes than biochemical indicators. The development of a reliable tool with disease related validity in the assessment of the impact and meaning of disease and treatment in patients with PAs is called for. Perceptual and objective dimension of functions can provide direction for both clinical treatment and research to ultimately reduce the burden of dysfunction in pituitary diseases.

METHODS

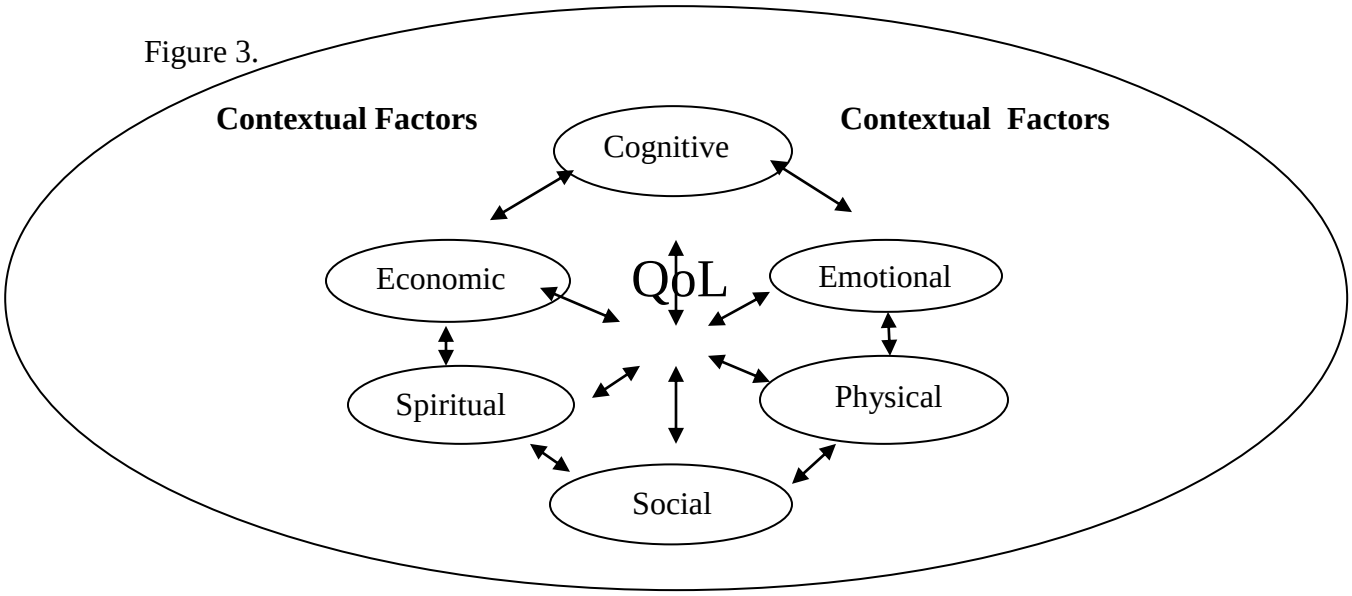
Clinical Inquiry Design

This project was a prospective, mixed methods study that aimed to survey adult PA patients' regarding their perceptions of life function changes. A subsequent Domains of Life Function Scale (DOLFS) for Patients with Pituitary Adenomas instrument was developed, in 3 phases: item generation, item selection and tool piloting.

Based on the expanded model of Progressive Levels of Outcome previously described the definition of functionality includes biological, physiologic and symptom related factors. However, the literature describes numerous life functions that contribute to QoL that assert their own measure of affect on the individual overall health perception and ultimate life quality. For the purpose of this project, life functions were described and defined by domains. Using the

National Library of Medicine PubMed (PubMed) and Ovid MEDLINE databases that include international literature, six domains were identified as pertinent to this QoL project: Cognitive, Emotional, Physical, Social, Economic and Spiritual (see figure 3).

Figure 3.



project, these definitions were framed within the general confines of the individual's context.

The existing literature was queried in order to define the domain constructs by the attributes most likely to be empirical indicators of that domain in the context of pituitary disease. Items were selected from existing QoL questionnaires that, when adapted, most closely contributed to the understanding of the meaning of the attribute to the domain functioning for the respondent.

Based on research with respect to pituitary diseases and the writer's clinical experience, attributes or characteristics of each domain were outlined that defined the concepts associated with each function. The Cognitive Domain was defined by the ability to learn, concentrate, avoid distraction, mental agility, event memory and recall, and verbal recall. The Emotional Domain was defined as inclusive of anxiety, physiologic and emotional factors in body image, depression, locus of control, motivation, somatization, emotional stability and self esteem. Personality factors of extroversion, introversion and impulsivity and treatment expectations were

also included as more directly interacting with other emotional attributes. The Physical Domain was defined by levels of energy and fatigue, independence in activities of daily living, mobility, sleep quality and disturbances and sensory symptoms known to be related to pituitary diseases. The Social Domain was defined by the attributes of social activity participation, intimacy and sexual functions, role participation, social support. The Economic Domain was defined by the level of economic stress experienced by cost of care associated with the disease, the affect on the individual's ability to generate an income and their ability to continue in creative, production and satisfying endeavors. The Spiritual Domain was defined by the individual perception of the impact of the disease on their faith, the participation in religious events.

Numerous factors were considered in tool construction as recommended by De Vellis (2003). Items for each domain were selected to avoid repetition, to discriminate degrees of dysfunction and be sensitive to changes in known symptoms or indicators of specific pituitary diseases or dysfunction. Consideration was given to the age and disabilities of the population to be served. The tool syntax was crafted to avoid ambiguity, be applicable to a broad cultural base, avoid assumptions about the population and be understandable to all educational levels. A large pool of items was generated in order to improve selection of items that improve the internal consistency and reliability of the instrument. It is recognized that a large number of items may forfeit accuracy of the latter responses as the result of responder fatigue.

The preliminary survey tool was piloted with new patients as they presented for clinic evaluation. Qualitative evaluation questions regarding utility of the tool, missing data, confusing script or other limitations of the tool or its presentation were included at the conclusion of the instrument. Some life functions or attributes important to an individual patient may be missing from the pilot instrument. Allowing the patient to recommend attributes they consider as missing

from the tool, provides the opportunity for either tool expansion or the individualization of the tool to track changes specific for that individual.

Although standardization and generalization of this tool is desirable, it is not feasible in the time available for this project. Validity and reliability can only be achieved with more extensive use of the instrument over time. If a composite score is appropriate and achievable as part of this standardization, consideration also needs to be given to weighting each domain for relevance to clinical application and importance to individual patients as patient centered outcomes.

Setting

Patients were surveyed during clinic visits two days a week in the context of the OHSU Northwest Pituitary Center. Informed consent was obtained and the patient was given the questionnaire and instructions. They were asked to complete the survey in the privacy of the exam room prior to and between provider evaluations. In the context of an initial evaluation, each patient undergoes three independent provider assessments. During this time the patient is in a fixed location for 1.5-2.5 hours providing ample time without interruption. Two Licensed Practical Nurses (LPN's) who act as clinic support staff were involved in preparing questionnaires for distribution to patients at the time they presented to clinic. All questionnaires were to be completed at the time of the visit.

A principle driving force is the need for redesign of the current intake assessment form for both new and returning patients. This tool falls short in appreciating treatment specific effects, has no temporal relationship and is symptom based. No attempt is made to quantify deficiencies.

Clinic staff were responsible for transcribing data into the electronic medical record (EMR). This may require interpretation of the patient's meaning as the result ambiguities in this form and data entry introducing compounding the impact of transcription errors. Returning patients, familiar with the current form, will require instruction and information to adapt to a new instrument.

The patient population referred to the OHSU Northwest Pituitary Center was primarily Caucasian. However, the referral area includes sizable Hispanic, Russian, and Vietnamese populations. It was impractical to translate the pilot tool into these languages, which limited cultural variability of the sample and excluded these populations from participation unless fluent in verbal and written English. Funding was not available to purchase language/interpretation resources, which are typically scarce.

Implementation is minimally constrained by the need for staff in-service training for tool administration particularly if direct input into the computer cannot be achieved. Incorporation into the EMR requires retooling of the templates to accommodate this transcription.

All providers in this subspecialty are in accord with the need for retooling and involved in instrument development. Time limitations in the clinical environment dictate the rate of implementation.

No impact was anticipated on current clinic routines, and the time required for patients to complete the tool was designed so as not to inhibit clinic scheduling or flow of usual activities. The same process as currently used was employed for the distribution of the tools to patients on presentation to the clinic. There are currently no policies or other procedures that are appreciated that provided other restraining forces.

Sample

The patient sample was a convenience sample of patients presenting to the OHSU Northwest Pituitary Center for evaluation and treatment of a PA. The primary inclusion criteria required MR imaging that confirmed a pituitary lesion or biochemical evidence of pituitary hormonal hypersecretion. Patients were required to be able to read and write English in order to complete the questionnaire. Patients were recruited by personal contact. Participation required a signed informed consent.

Exclusion criteria included patients with diagnosed concomitant, uncontrolled systemic diseases or disorders other than those possible with pituitary disease (e.g. diabetes mellitus, non-rheumatoid arthritis). These included but were not limited to: immune system disorders, cancers (including adrenal cancer and carcinoid tumors), psychiatric disorders, cardiovascular disease or injury, other neurological dysfunction, history of extremity amputation, recent operative procedure for reasons other than pituitary resection; major life stressor (including death in close family member, job change, major illness or injury, divorce or dissolution of an intimate relationship) within the preceding six months.

The sample size was limited by patient availability during the time provided for data collection. A minimum of five patients for each of the following pituitary diagnoses were to be included: Non-functional microadenoma without hormonal deficit, non-functioning microadenoma with one or more hormonal deficit, non-functioning macroadenoma without pituitary deficit or visual field deficit, non-functioning macroadenoma with one or more pituitary deficit without visual field deficit, macroadenoma with optic chiasm involvement and without hormonal deficit, prolactinoma, adrenocorticotropic hormone (ACTH) excess or CD, and GH excess or acromegaly. A total of 40 patients were to be solicited for this survey.

An average of two to three patients per week usually presented for evaluation of PAs at the OHSU Northwest Pituitary Center. Of these approximately 80% have non-functioning adenomas and the remainder a variety of hypersecretory tumors with prolactinomas representing approximately 70%. Patients with microadenomas and macroadenomas (with and without pituitary and visual deficiencies) were anticipated to be the most numerous participants to be recruited. Patients with hypersecretory tumors such as GH (Acromegaly) and ACTH (Cushing's disease) had historically presented at approximately one every 2 to 3 weeks. Although difficult to predict, based on the historical data, these numbers were anticipated to remain consistent during the course of data collection for this project. The referral base for OHSU Pituitary Center is primarily from northern California to Alaska, Nebraska, Nevada, Idaho, and Montana. However, patients have been referred from all U.S. states, improving the probability and variability of participant recruitment.

Description of Intervention

The DOLFS was designed as a self administered tool that would require little or no staff involvement in its completion. No other language versions were provided at piloting. Multiple language translations will be attempted with future iterations of the tool. This project represents a modification to an existing practice and an improvement in data collection for patients presenting for consultation.

Measures

A total of 205 questions were generated and numbered on the final questionnaire for ease of data recording and analysis. The document is comprised of eight single sided letter size pages and response discriminators were reprinted beside each descriptor to decrease reader fatigue. The final page of the tool includes a qualitative component to allow the patient the opportunity of

feedback for the purpose of enhancing the tool. They are asked to add a description of functional alterations or symptoms they have experienced that are not already included. The participant is also asked to provide feedback regarding issues with the tool itself, such as clarity, content, format and ease of use (see appendix 2).

Items were written as previously described that reflected empirical indicators of each of six domains of functioning. Disease specific physiologic indicators and symptoms were embedded in appropriate domains. Items were written to quantify the level of discomfort experienced by the patient with respect to each indicator. For each attribute a minimum three items were written to better determine the most effective item to reflect the attribute after statistical analysis. A legend of individual questions or items according to their relationship to the attribute and the domain was prepared (see appendix 3). Items were then grouped by common antecedent direction: "I am bothered by", " I have difficulty with", and statements prefaced by 'I' and 'My' that most closely corresponded to the individual's daily experience.

Using a Likert type scale, patients were asked to quantify their level of function or experience for each item on a 6 point scale. Response categories ranged from 1(for the purpose of statistical analysis) -not applicable, 2-'not at all'- the indicator was present but the responder was not bothered by it, 3- a little (bothered), 4-somewhat (bothered), 5-'quite a bit (bothered), 6-very much (bothered). These categories allow for the potential of developing a summative score for each attribute, each domain and ultimately a total QoL score. Questions 1 and 2 pertained to the responders overall perception of their current versus desired level of health. This may be useful as a correlate to total domain scores. The second general question attempts to quantify the rate of progression of the discomfort/dysfunction.

Although a total score for each domain can be generated as well as an instrument total score it is considered beyond the scope of this project. The ultimate value of these scores will primarily be apparent on post treatment evaluations as a specific comparator for each patient's progress or to identify areas of deficit or need for further treatment. It is hoped that this can also be further utilized as a means to correlate post treatment experience and outcomes for each pituitary disease process.

Data Collection Procedures

Participants were recruited on their initial presentation to the clinic for evaluation. Patients were offered the opportunity to participate by personal contact prior to initial evaluation. All consenting patients were given the self administered instrument and basic instruction as to how to complete the document and requested to provide feedback they felt appropriate but in particular about the questionnaires content, length and format. Participants were also asked to include a start and stop time so that the average time for completion of the questionnaire could be calculated. The instrument was to be completed in the exam room either before provider visits or between provider visits. Completed questionnaires were left with a medical assistant at the completion of the visit.

For the purposes of this project, demographic data and diagnosis (when known) was solicited and added to the document for later data entry and analysis by the author. The patient was identified by a unique identifier only. Diagnosis, size of tumor, pituitary deficiencies was added as this information became known. Each patient was provided with an envelope in which to seal a completed form before delivery to a medical assistant. Data was entered into a secure, password protected, depository.

Analytic Methods

Statistical analysis was done using PASW Statistics program version 18 (SPSS, 2009). Items level analysis was performed both by assessing response variability and discrimination and item difficulty using percentage of responders who endorsed and those who did not endorse items. Items that did not demonstrate variability and/or were extremely kurtosed were discarded.

Internal consistency and reliability of the tool was assessed using a coefficient or Cronbach's alpha after the elimination of items that did not meet item level criteria. Correlation coefficients were calculated between item and each domain score using independent means *t* test to determine level of significance and calculation of size effect when comparing responses from subjects with NF and HF adenomas. A Pearson's correlation was performed to determine any correlation between age, tumor size, tumor function, concomitant disease, gender or responses to overall questions regarding perceptions of health status.

Costs, including fixed room and facility charges and staffing costs were assumed in patient visit costs and covered by university clinical services. Statistical support was provided internally by the OHSU School of Nursing. Support was gratefully provided by the OHSU Department of Neurological Surgery.

Protection of Human Subjects/Ethics

This project was approved by the OHSU Internal Review Board (IRB). Written informed consent was obtained from all patients prior to the collection of information (see Appendix 1). No transmission of data was required. Patient identifiers beyond patient number were not included on the instrument collected. All paper survey documents are held in a secured office. All data was entered into a password protected repository.

Plan for Dissemination to Key Stakeholders

An abstract and manuscript of this project and findings is being prepared for submission for publication in one of several journals of endocrinology including, Clinical Endocrinology and Metabolism, or Pituitary. A poster entitled "The Measurement of Quality of Life in Patients with Pituitary Adenomas" was presented at the Western Institute of Nursing Conference in April 2011. A second abstract, "Measurement of Life Functions and Quality of Life for Patients with Pituitary Adenomas", was accepted for a poster presentation at the Sigma Theta Tau International conference in Texas scheduled for October 2011. A presentation will be prepared for Endocrinology Grand Rounds and/or an abstract submitted for presentation at the OHSU Endocrinology Conference in August of 2012.

Project Timeline

The project proposal was submitted to the IRB by late November 2010 and approved in December 2010. Data collection began in January of 2011 and continued until April 2011.

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Appendix 1 Evidence Table

Authors/Design	PURPOSE	SUBJECTS	INTERVENTIONS	OUTCOME MEASURES	RESULTS	CONCLUSIONS	COMMENTS
Barzaghi et al 2007 Complications transsphenoidal surgery in pt with PA: experience at a single center Retrospective analysis	Report	420 All PA's with few PRL	None	Mortality morbitidy	Medical complications Incr >65yrs 4.9%vs 1.4% (*P*=0.009) & large adenomas 5.6 vs 1.6% (p = 0.0002		Descriptive- one site Consistent with other readings
Budrukkar et al 2009 Prospective assessment of QOL in adult pts with primary barin tumors in routine neurooncology practice. prospective	Evaluate various factors on QOL in pt with brain tumors	250 adults neoplasms over one yr 159 completed (66%) themselves	Data collection usine EORTC0 QLQ-30	Five function scales: Physical role Emotional Cognitive Social Three symptom scales. Fatigue, nausea, vomiting and pain 6 single item scales, Dyspnea, insomnia appetite loss, constipation, diarrhea, financial effects	84 pt required assistance to fill out form-neurological def(42%) and 74& of these with motor weakness. illiteracy (37%) 87% presented with HA, Memory loss (36%. Seizures 31%, Gail abnormal 22% Behavior probl (16%) focal seizures (9%)		Analysis SPSS version 14 Consider cultural changes Malignancy not nec comparable to PA. tumor position impt to fx Scale EORTCO poss for Domain and item use
Dekkers et al 2006 QOL is decreased after <u>treatment</u> for NFPmacro Case controlled	Determine if treatment makes a diff in QOL	128 consective NFMA All post op TSS- Only 116 participated	Hospital Anxiety and Depression Scale, Mulitdimensional Fatigue Index, Nottingham Health Profile	QOL scores for each tool per patient compared to reference ranges for tool derived from gen population	HADS- NS MFI-20 Sig Gen fatig(0.01) Physical fatig Reduced activity Reduced	Mostly not disease specific QOL changes Stat sig QOL decreases in MFI-20	No same group comparison ?. Not all matched to local culture – European with multiple cultural influences– controls only age matched by group not individuals- assumed healthy but no information given. No information about

Prospective Non random		Controls- 125 age adjusted references from literature or make identified age and gender	SF-36 Questionnaires mailed Pit fx		motivation Mental fatigue (all <0.05) NHP Pain NS SF-36 Physical function Pain and health change NS	NPH SF-36	No control for post op complications 41% with VF deficts (unknow if both pre and post op) not included in stat analysis as independent variable GH def assumed based on other axis dysf
Kan et al 2006 Validation of QOL quest for Pt with PA Prospective Non randomized	Develop and validate self administered questionnaire to measure QOL in PA	84 in focus group 20 pt in item validation and selection group 44 pt in pilot group for new instrument	Focus groups Tool development and Tool pilot	106 item questionnaire, validated 30 most important items chosen by 20 patients 17 items selected by HC professionals. New instrument RAND-36 FACT-G/Fact-Br Karnofsky Performance Scale (KPS) Pearson's correlation coefficients Student's t test for two sets of scores obtained one month apart	47 of 55 (85.5%) Questionnairs completed Test/Retest on 24 reliabilty 0.88 Concurrent validity- 47 responses 0.75 Pearson's correlation coefficient. (20 pt) Extreme groups did not compare well to RAND	Authors concluded valid and reliable questionnaire for pt centered outcomes measure – For clinical trials and disease progression. Correspond favorably with reference questionnaires	Scale includes disease specific symptoms, general , emotional health and social /family wellbeing and relationships, satisfaction with provider and treatment. No objective measures of function Lengthy (54 questions) not suitable for clinic setting . Authors reported 11 min to complete. No pt requested help Tested against population norms Over one third of responses were labeled as 'extreme' Only 24 patient did test- retest reliability. No control group to compare responses done one mth apart. Focus musculoskeletal for PT not specific disease. Concept of change/decr QoL in aging. Tool does not include Gonadal/Sexual fx Changes in social support or role

							changes as a result of the tumor Not disease specific No local control group. Does not discrimation between micro and macroadenoma for NFPA No post tx comparison. Culture not considered No age and gender comparisons No pre op or pre treatment comparisons done No non functioning microadenomas included Did include age and gender matched control subjects from the social environment of the patient Cumbersome. Questions redundant for clinical use No specifics re TX not sued in stat analysis only surgically 'cured acromeg and cushing pt included compared w paragangliomas XRT and hypopit but no spec def considered.
Jagsch et al 2006 Which instrument is more suitable to assess health-related QOL- NHP or SF-36 Prospective Non-random	Patient reported outcome measures (subjective HR-QoL) multiple instruments to determine most appropriate in outcome	Two groups 1. Elderly- 46 (mean age 68y) 2. Young- (mean 36) Acted as control group	Both groups completed both forms & assessed each instrument on Visual Analogue Scale for suitability for use in research	VAS of pt assessment of utility of tool for application in scientific study	Young group acted as control ? Had difficulty with negative questions and limited reponses Y/N No statist gender diff	Instrument should be chosen for specific situation and user	

	studies in gerontology						
Johnson et Al 2003 Quality of life in Patients with a pituitary adenoma	To assess perception of the impact of a PA prior to tx	168 patient with PA hypersecretion and/or PA 42 Cushings Dz 39 Prolactinoma 36 acromagaly 51 NF PA	SF-36 version2 Use of a validated instrument	8 health scores Physical fx Role –physical Bodily pain General health Vitality, Social fx Role emotional Mental fx Normal population score of 50 Scores for each type of tumor compared	PA- all impaired. Cushings' *P*< 0.05 Acromgely Sig decrease Physical Fx Role physical Gen health Vitality *P*< 0.05		Recommend using instrument pre and post treatment routinely
Vander Klaauw et al 2008 Disease- specific impairments in qulaity of life during long-term follow up of patient with different pituitary adenomas Prospective Post treatment	Evaluate QoL based on age and gender adjusted (Z socres) in pt with PA	Convenience sample: Total 403 patients Acromegaly-118 Cushings's 58 Prolactinoma 118 NF macro A - 99 Control pop 440 Pt in f.up for 13 +/- 8 yrs Pituitary deficiency defined By std	Hospital Anxiety and Depression Scale (HADS) Multidimensional Fatigue Inventory (MFI)-20 Nottingham Health Profile (NHP) SF-36 Mailed to home	Determined z scores for questionnaires measured After tx for PA Each PA compared with controls for each of subsections of each instrument. Absolute QoL scores compared all pt and controls by indep *t* test, Anova and Tukey's pot hoc	All with impaired QoL compared to controls all *P*= 0.001 Is sig dx specific Diff between type of PA *P*=0.003 No diff in z scores for subscales with except of physical ability *p* =0.002 – Acro>NFMA, PRL.	All impaired No diff in acro – all tx & CD with anxiety PRL- size no diff Age & gender neg predictor of physical fx Males -better3/7 subscales XRT no influence Hypo pit neg infl Length of .up neg influence Need to inform pt to avoid inapprop expectations.	

Page et al 1996 An account o QOL of patients after treatment for non-functioning pituitary tumors. Prospective Case controlled Post treatment Convenience	Determine effect of Anterior pit def and XRT on QOL in pt with NFPA	Convenience sampling 48 pt NOPA No GH replacement Control group 42 pt after mastoid surgery Criteria: PA by histology Sellar enlargement Tumor >1.0cm PRL<8,000 PRL <5% of cells histol No other excess stanining No biochem excess other than PRL. Only TSS surgery included	Use of SF-36 & General Well Being Schedule (GWBS)	Difference between scores on each QoL tool for controls vs pt with PA Non parametric stats	No difference was determined Between scores for QOL IGF-1 was significantly lower in Pit Pt than controls *P* <0.0001 with 69% PA pts with IGF-1 below age match range compared wth 14 *p* <0.002 XRT lower mental health scores Depression and emotional control *p* <0.05	GH therapy not warranted in all cases. (Note this was not purpose of this study) May be an effect of XRT on QOL needs further investigation	Similar age range but not matched gender and age. Not std set of ant Pit fx evaluated for all pats- selective check on hormones PRL excess was no exclusion criteria Only macroadenomas assessed Results contrary to other studies finding lower Qol- ? artifact, insensitivity of tools for use in PA. subject selection? Control group, are changes related to surgery, other factors such as personality etc
Santos et al 2009 QoL in pt with PA	Highlight recent findinds in QoL in defferent types of PA and hypopituitaryism	Multiple sudies	Acromegaly Study-Neggers - 20pt receiving somatostatin analogue- double-blind, placebo-controlled, randomized, cross-over study:	none	Acromegaly QOL sign improve with pegvis.no change in IGF-1-CLINICAL IMPROVEMEN - MORE SENSITIVE	Qol studies allow for identification Of dimensios that are affected by the disease but not always contemplated as health problems in treatment.	Leaves question – are there parameters that do improve for specific individuals or collectively after treatment- need pre and post tx analysis of same pop- ust be sensitive instrument Are muscle skel better than pre tx or not cured pt with acro/

			pegvisomant or placebo x16week Qol improved sign Matta- physical and psycho scores better in cured than active Miller- musc/skel SF-36& AimS2 worse than gen pub Personality traits associated CUSH- SF-36 Needs more study PROLACTINOMA Qol inversely correlated with PRL level Vander KLaauw- Neg corr with Hypopit VISION – decreased QoL		than IGF-1 P.S. used AcroQol	Disease focused QoL tools Imporved utility for clinical practice and research and therapeutic outcomes.	Evaluation of personality traits affected Qol, treatment adherence and patient –doctor contact.
Sievers et al 2009 Personality in pt with PA is characterized by increased anxiety-related traits: comparison of 70 acromegalic pt with patients with NFPA and age and gender –matched controls. Cross sectional prospective	To determine if pt with acromegaly had an altered personality compared withpateints with NFPA and healthy controls.	70 acromegaly 58 NFPA 140 mentally age and gender matched	Eysenck personality Questionnaire-Tridimentional personality questionnaire	Personality type with subscales; Extraversion; Psychoticism. Neruoticism (Eysenck) TPQ- Level of desire to be socially acceptable Correlation between sub- scales	Acromegaly with increased: Neurotic EPQ-N $P<0.001$ Harm avoidant TPQ-HA $p<0.001$. Reduced novelty seeking ($p<0.001$) High social conformity EPQ-DS $p<0.001$. Compared with both controls and NFPA. Also higher in NFPA than in controls	Acromeglic pt more harm avoidant, neurotic, high social conformity NFPA and acromeg with increased Anticipatory worries and pessimism Higher fear of uncertainty, fatiguability and asthenia. Diff with acromegaly	Not 1:1 matched age and gender. Unknown if from same social environment. No causal relationship between acromeg and person alterations need more prospective studies. ? are personality alterations result of acromegaly i.e. PA or GH excess, changes in neurotransmission associated with pit axis changes. No difference noted in personality changes associated with tumor size. Need to assess personality changes with respect to other tumors. Given unknown origin of tumors difficulty to determine changes as caused by

					Acromegaly Worse novelty seeking and impulsive for age and general, adenoma tyupe surgery radiation and deficiency & All Clinical variables. (*p* =0.032. Improvement noted in treated pt with acromeg ness adjusted	No diff between micro and macr with and without pit deficiencies	tumor.
T'Sjoen Et al 2007 Health-related QoL in acromegalic subjects: data from AcroBel, the Belgian Registry on acromegaly Crossectional design Based on	Assess impairment in QoL in atient with controlled and uncontrolled acromegaly	291 pt with acro 237 Macro 42 micro 11 unknown 1 carcinoid 202 GH ex only 69 co-GH/PRL 15 alpha sub or TSH 169 pit fx OK 120- 1 or more def 42% arthropathy 39% HTN 27% CTS 23% DM 21% goiter 116	Specific signs and symptoms score (SSS) & AcroQoL questionnaire f.up 10 years	Assessment of perception of QoL using Specific signs and symptoms score (SSS) & AcroQoL questionnaire	IGF-1 z score correlated with the age at diagnosis (r=0.190, *p*=0.001) Glycemic control neg correlated SSS subsores no diff except soft tissue swelling scored higher in active Dz. Joint pain worse in older patients otherwise no diff Females increased headache & fatigue scores. Excess perspiration	No sig relation between AcroQol scores and biochem marker of disease and GH. No difference in QoL score between patient with active and inactive disease Cosmetic and orthopeaedic deformities independent of GH levels)(possible reason for worse Qol scores)	Use to select treatment options based on scores Notes" pt's perspective well-being is an important outocome". Need to identify what is most important factor in patient Qol. –Have patient rate own cometic and orthopedic changes

		(40%)surgery 18 (16%) XRT 71(24%) both 185(64%) med tx 134(46%) Somato 39(13%) DA 12(4%) both			assoc with increased body weight Neg correlation between median SSS and AcroQol scores in the whole study pop		
Webb et al 2008 Evaluation of health –related QoL in patients with cushing's syndrome with a new questionnaire Observational, international, cross-sectional	Evaluate the effects of chronic exposure to hypercortisolism on QoL	125 pts (Spain, France, Germany, Netherlands, Italy) 107 pituitary dependent CD 18 adrenal dependent CS	2-mth f.up Clinical and hormonal data SF-36 Cushings QoL score	Feasibility of clinic use Relaiblity, Validity of 'questionnaire Correlation between Cushings QoL scores and pt self perceived general health status and dimensions of SF;-36 Impact of XRT	Correlation sig between CushingQol scores and SF-36 (Pearson's correlation coefficient >0.597) Current hypercortisolism scored worse Linear regression-female gender predictors of worse QoL	Disease specific CushQoL, is feasible (4 mins to compl) Reliable and valid. Sensitivity to change and test-retest reliability needs longitudinal studies.	Most pt with cushing's female.

APPENDIX 2

Oregon Health & Science University Consent and Authorization Form eIRB#: **6979** Protocol Approval Date: 12-22-2010	MED. REC. NO. _____ NAME_____ BIRTHDATE _____

OREGON HEALTH & SCIENCE UNIVERSITY
Consent and Authorization Form

TITLE: Domains of Life Function Scale for Patients with Pituitary Adenomas

PRINCIPAL INVESTIGATOR:	Gary Laustsen PhD APRN-CNP	(541) 9623132
CO-INVESTIGATORS:	Chris Yedinak MN FNP	(503) 494-6576
	Michael Leo PhD	(503) 494-1137

PURPOSE:

You have been invited to be in this research project because you have been diagnosed with a pituitary adenoma or pituitary disease. Pituitary adenomas are tumors in the pituitary gland that may cause several medical disorders. A person's pituitary gland may make too much or not enough of a specific hormone, and a tumor may affect your eye sight or cause symptoms that change your ability to function in life and hence your quality of life.

The primary purpose of this study is to understand the changes that occur in the lives of people with pituitary adenomas. We are seeking to understand how this affects your life and the amount of change you have experienced in what you do, or would like to do every day. It is also hoped that we will better understand if these changes occur for patients with all types of pituitary adenomas and if there are differences between specific types of pituitary tumors.

You will be asked to complete a questionnaire to tell us the specific symptoms and changes you have experienced as a result of these symptoms. You will also be asked how much these changes have impacted your life.

Approximately 40 men and women with pituitary adenomas and pituitary dysfunction will participate in this study. All participants will be OHSU patients.

PROCEDURES:

Your participation in this study will limited to one event. You will be asked to complete a questionnaire before the conclusion of your visit today. The questionnaire includes questions about your symptoms and the extent to which these are affecting what you do every day. You will be asked to place your completed

questionnaire in the envelope provided, seal it, and leave it with the medical assistant as you check out.

If you agree to participate in this study, we will review the laboratory information collected during your work up, your MRI and your diagnosis. We will collect and analyze your perceptions of your symptoms and how they are affecting what you do in your life and the medical data and information that led to your diagnosis. This will include the size of your tumor (obtained from your MRI), and your pituitary hormone levels (obtained from the results of your blood work). This information will be stored in a protected database for use, by the researchers named above, in future research to compare changes you may experience during your treatment.

RISKS, DISCOMFORTS and BENEFITS:

This is an observational study and the reason for this study is to observe the effects of the pituitary adenoma or disease on your quality of life. There should be no physical risks or discomforts to you as a direct result of taking part in this study.

You will not benefit from participating in this study. However, by serving as a subject, you may help us learn how to help patients with pituitary adenomas and disease in the future.

CONFIDENTIALITY AND PRIVACY OF YOUR PROTECTED HEALTH INFORMATION:

We will not use your name or your identity for publication or publicity purposes.

All of your information will be kept in a password-protected database maintained by the co-investigator.
The use and sharing of your protected health information will only be for the purposes described in this consent.

Any information transferred electronically will be coded to protect your confidentiality.

The persons who are authorized to use and/or disclose your health information are all of the investigators who are listed on page one of this Research Consent Form and the OHSU Institutional Review Board. The Office for Human Research Protections is authorized to receive this information as required for its research oversight activities.

COSTS:

There will be no cost to you for participating in this study. You or your insurance company will be billed for the regular clinic visit during which this information will be collected.

PARTICIPATION:

You do not have to join this or any research study. Your participation in this study is voluntary. If you refuse to join, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If you have any questions regarding this study now or in the future, contact the principal investigator of this study, Gary Laustsen PhD APRN-CNP, (541) 9623132 or co investigator Christine Yedinak MN FNP, (503) 494-6576. If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

We will give you a copy of this signed and dated form.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

_____
Name of Subject

_____ _____
Signature of Subject Date of Signature (Month/Day/Year)

_____ _____
Printed Name of Person Obtaining Consent Date of Signature (Month/Day/Year)

_____ Date :
Signature of Person Obtaining Consent

Appendix 3 Legend- Description of Domain Characteristics

DOMAIN	Characteristic	Question #	Question	
COGNITIVE	ability to learn	76	I have difficulty learning new information or new things.	**CA**
		78	I have trouble learning a new skill despite repeating it several times	CA
	concentration& distractibility	79	I have difficulty concentrating to finish what I am doing	CC
		123	My brain has trouble keeping track of things	CC
		149	I am easily distracted	CC
	mental agility	142	I feel I make mistakes easily	CM
		Not incl	my head feels foggy	CM
		Not Incl	I am slow to think about things	CM
		Not Incl	I need help in daily/monthly financial matters	CM
	memory and recall	81	I have trouble remembering information from medical appointments	CM R
	Verbal recall	82	I have had trouble recalling names of things.	CV
		83	I have trouble finding the right word when talking	CV
		84	I have had trouble keeping track of what is being said in a conversation	CV
EMOTIONAL	anxiety	130	I have feelings of panic	EA
		147	I feel Like something awful will happen	EA
		161	I Worry	EA
		169	I Feel Overwhelmed	EA
		190	I feel Tense or wound up	EA
		195	I feel Vulnerable	EA
	body image	3	an absence of facial hair	EBI
		4	needing to shave my facial hair	EBI
		5	Facial flushing or redness	EBI
		6	Puffy eye lids	EBI
		7	acne	EBI
		8	Thinning hair/bald patches/hair loss	EBI
		9	A loss of part of my eyebrow hair	EBI
		10	Gaps between my teeth	EBI
		11	My jaw size	EBI
		12	My lips swelling	EBI
		13	My nose getting wider	EBI
		14	Deep furrows in my brow	EBI

		15	Protruding/growing brows	EBI
		16	A hoarse voice	EBI
		17	A thick tongue that changes my speech	EBI
		18	Snoring when I fall asleep	EBI
		19	A barrel shaped chest	EBI
		20	Fine facial wrinkles	EBI
		21	A hump on the back of my neck	EBI
		22	A larger than usual breast size	EBI
		23	A smaller than usual breast size	EBI
		24	breast/nipple discharge	EBI
		25	General weight loss	EBI
		26	Midsection weight gain	EBI
		27	an increase in ring and/or shoe size	EBI
		28	bruising	EBI
		29	thin/fragile skin	EBI
		30	coarse skin	EBI
		31	oily skin	EBI
		32	dry skin	EBI
		33	skin tags	EBI
		34	dark brown/black velvety skin patches under arms and/or in skin folds	EBI
		35	easy sweating/ body odor	EBI
		36	slow wound healing	EBI
		37	stretch marks on abdomen or other body parts colored dark pink or purple	EBI
		38	large areas of skin that have turned dark	EBI
		39	yellowing of my skin	EBI
		40	skin Rash	EBI
		41	dry parchment like skin	EBI
		42	brittle fingernails	EBI
		43	the way my body looks	EBI
		194	I avoid social activities because of my appearance	EBI
		132	I think people avoid me because of my appearance	EBI
	depression	120	Guilty	ED
		126	I don’t particularly like the person I am	ED
		140	Worthless	ED
		143	Restlessness and agitated	ED
		151	easily Annoyed	ED

		172	Irritable	ED
		175	Angry	ED
		192	hopeless about my future	ED
		198	Suicidal	ED
		199	Like crying	ED
	locus of control	121	my illness was meant to be	EL
		128	regularly Dr. visits will help me avoid getting sick	EL
		135	I am responsible for my on health	EL
		170	My health is in the hands of my health care team	EL
		174	it will take luck for me to recover from being illness	EL
		189	I have faith I will get better	EL
		205	I can help myself recover from being ill	EL
		111	I feel out of control	EL
	motivation	122	Others seem to get more done in a day than me	EM
		160	I lack motivation to do things.	EM
		186	I lack energy to do my household chores	EM
		164	motivated if my work is acknowledged/	EM
		156	I like seeing what I have accomplished myself	EM
		162	I feel like getting things done around the house	EM
	extroversion	108	I like to let people know my opinion and where I stand on issues	EPE
		113	I find it easy to talk with anyone	EPE
		141	I like being around a large number of people	EPE
		201	I prefer talking with others about my illness	EPE
	introversion	193	I like time to think things through well before acting	EPI
		114	I find it hard to talk wo people I don't know	EPI
		124	I like to keep the way I feel about things to myself	EPI
	somatization	103	I read medical books or the internet	EPS
		154	I worry about something bad happening to my health	EPS
		159	I spend time researching my health problems	EPS

		148	I am worried about symptoms I read on the internet	
	impulsivity	105	I get agitated if things don't happen quickly	EPU
		107	Planning usually doesn't help things be more sucessful	EPU
		144	I make decisions quickly	EPU
	emotional stability	89	I have rapid changes in mood	ES
		110	I am Optimistic about my future	ES
		155	I take most things in stride	ES
	self esteem	196	I feel Good about myself	ESE
		202	I get upset if I am criticized	ESE
		204	I am confident in my decisions	ESE
	treatment expectations	127	I expect I will never be healthy	ET
		133	I think my recovery will take some time	ET
		145	I anticipate a full recovery	ET
PHYSICAL DOMAIN	Energy & Fatigue	109	I lack energy to do social activities with friends	PE/F
		136	my fatigued interferes with my work life	PF
		157	I am fatigued during the day	PF
		177	my fatigue disrupts my family life	PF
		118	my exercise is limited by my fatigue	PF
	independence in activities of daily living	112	I need help with transportation	PI
		119	I can take care of myself	PI
		150	I need help to do laundry	PI
		173	I need help to do my shopping	PI
		178	I need help to do cooking	PI
		88	I have difficulty carrying a bag of groceries	PI
	mobility	90	general weakness	PM
		91	walking up one flight of stairs	PM
		92	standing from a sitting position without using my hands to help	PM
		93	bending, kneeling or stooping	PM
		94	Loose joints (they move in unusual directions)	PM
		95	Swelling in my feet and ankles	PM

		96	walking a mile	PM
		97	being able to exercise because of weakness	PM
	sensory symptoms	44	Headaches	PS
		45	Blind spots in my vision	PS
		46	Dizziness with standing	PS
		47	Dry mouth	PS
		48	Ringing in my ears	PS
		49	difficulty breathing	PS
		50	Nasal congestion or drainage	PS
		51	Increasing roundness of my face	PS
		52	A bad/salty taste in my mouth	PS
		53	Thirst that is difficult to quench	PS
		54	Loss of sense of smell and/or taste	PS
		55	Numbness or tingling on my scalp	PS
		56	A faster than usual heart rate	PS
		57	A slower than usual heart rate	PS
		58	Abdominal pain/discomfort	PS
		59	nausea	PS
		60	vomiting	PS
		61	constipation	PS
		62	diarrhea	PS
		63	poor appetite	PS
		64	hunger	PS
		65	flatulence /gas	PS
		66	Muscle pain	PS
		67	Joint pain	PS
		68	have abnormal sensations such as prickling, burning, tingling	PS
		69	Wrist pain	PS
		70	muscle cramping	PS
		71	cold skin	PS
		72	hot flashes/night sweats	PS
		73	Pain when I try to exercise	PS
		74	urinating frequently during the day (every 1-2 hours)	PS
	sleep	104	I wake early morning & can't go back to sleep	PSL
		117	I wake up tired	PSL
		153	urinating frequently at night (every 1- 2 hours)	PS

				L
		163	I fall asleep when I sit quietly/read	PS L
		180	I sleep much of the day	PS L
		182	I fall asleep at stop lights while driving	PS L
SOCIAL DOMAIN	social activity participation	125	I get together with friends	SA
		134	I prefer to stay home than to go out with my friends	SA
		176	I enjoy activities like I did before my illnessenjoy social activities	SA
		188	I prefer watching sports rather than participating in sports.	SA
		129	I prefer to stay home than to an event with people	SA
	intimacy and sexual function	75	I have an irregular menstrual cycle (period)	SI
		116	my sexual interest is decreased	SI
		131	I have a morning erection	SI
		137	I have decreased vaginal moisture	SI
		139	I have had an increase In my sexual interest.	SI
		152	My partner and I have had trouble getting pregnant	SI
		168	I have had a decline in my sexual interest	SI
		183	I have a morning erections	SI
		184	My testicles have shrunk	SI
		197	my sexual interest is increased	SI
		115	I feel my body is not attractive to my partner	SI
		158	I feel my body is not attractive	SI
	role participation (home, work and/or school)	101	I have trouble finishing projects at home or at work	SR
		102	I have trouble doing things at work in a reasonable time.	SR
		138	My illness has caused my to let people down	SR
		165	I like to get started on new projects at work	SR
		171	I am happy with what I am able to achieve each day	
	social support	179	I have someone I trust that I can confide in.	SS
		185	I have friends who try ot help me	SS

		200	I have family members who try to help me	SS
		167	I talk with my friends about my health issues	SS
		191	my spouse/partner is supportive	SS
		167	I talk with my friends about my health issues	SS
ECONOMIC	Assessment of the economic burden of disease.	85	I have trouble finding the money to buy my medications	Ec B
	ECONOMIC	181	I feel stressed because of my medical bills	Ec B
		86	I have difficulty finding the money to pay for my insurance	Ec B
	Ability to generate an income to support their needs	146	I'm limited in the kind of work I can do because of my illness	EcI
	ECONOMIC	187	My job performance is affected by my illness	EcI
		203	I am worried about earning enough to pay my bills since my ilness	EcI
	individual ‘s ability to participate in satisfying productive or creative endeavors	156	I like seeing what I have accomplished myself	Ecc
		166	I feel productive	Ecc
		87	I have difficulty coming up with new ideas	Ecc
SPIRITUAL DOMAIN		98	I have difficulty participating in my regular religious activities	SP
		99	I have had difficulty attending important religious events	SP
		100	staying in contact with people of my faith	SP
		106	my faith has changed because of my illness	SP

APPENDIX 4
DOMAINS OF LIFE FUNCTIONS LIFE SCALE FOR PATIENTS with PITUITARY ADENOMAS (DOLFS)
Please circle the response to the right that correspond most closely with your daily experience.

		1	2	3	4	5
1.	How healthy do you feel today compared with your desired state of health?	Much worse	A little worse	Same	Better	Much better
2.	How do you feel today compared with 12 months ago?	Much worse	A little worse	Same	Better	Much better

I am bothered by:		1	2	3	4	5	6
3.	an absence of facial hair (males only)	N/A	Not at all	a little	somewhat	quite a bit	very much
4.	needing to shave my facial hair (females only)	N/A	Not at all	a little	somewhat	quite a bit	very much
5.	Facial flushing or redness	N/A	Not at all	a little	somewhat	quite a bit	very much
6.	Puffy eye lids	N/A	Not at all	a little	somewhat	quite a bit	very much
7.	acne	N/A	Not at all	a little	somewhat	quite a bit	very much
8.	Thinning hair/bald patches/hair loss	N/A	Not at all	a little	somewhat	quite a bit	very much
9.	A Loss of part of my eyebrow hair	N/A	Not at all	a little	somewhat	quite a bit	very much
10.	Gaps between my teeth	N/A	Not at all	a little	somewhat	quite a bit	very much
11.	My jaw size	N/A	Not at all	a little	somewhat	quite a bit	very much
12.	My lips swelling	N/A	Not at all	a little	somewhat	quite a bit	very much
13.	My nose getting wider	N/A	Not at all	a little	somewhat	quite a bit	very much
14.	Deep furrows in my brow	N/A	Not at all	a little	somewhat	quite a bit	very much
15.	Protruding/growing brows	N/A	Not at all	a little	somewhat	quite a bit	very much
16.	A hoarse voice	N/A	Not at all	a little	somewhat	quite a bit	very much
17.	A thick tongue that changes my speech	N/A	Not at all	a little	somewhat	quite a bit	very much
18.	Snoring when I fall asleep	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
19. a barrel like shape to my chest	N/A	Not at all	a little	somewhat	quite a bit	very much
20. Fine facial wrinkles	N/A	Not at all	a little	somewhat	quite a bit	very much
21. A hump on the back of my neck	N/A	Not at all	a little	somewhat	quite a bit	very much
22. A larger than usual breast size	N/A	Not at all	a little	somewhat	quite a bit	very much
23. A smaller than usual breast size	N/A	Not at all	a little	somewhat	quite a bit	very much
24. breast/nipple discharge	N/A	Not at all	a little	somewhat	quite a bit	very much
25. General weight loss	N/A	Not at all	a little	somewhat	quite a bit	very much
26. Midsection weight gain	N/A	Not at all	a little	somewhat	quite a bit	very much
27. an increase in ring and/or shoe size	N/A	Not at all	a little	somewhat	quite a bit	very much
28. bruising	N/A	Not at all	a little	somewhat	quite a bit	very much
29. thin/fragile skin	N/A	Not at all	a little	somewhat	quite a bit	very much
30. coarse skin	N/A	Not at all	a little	somewhat	quite a bit	very much
31. oily skin	N/A	Not at all	a little	somewhat	quite a bit	very much
32. dry skin	N/A	Not at all	a little	somewhat	quite a bit	very much
33. skin tags	N/A	Not at all	a little	somewhat	quite a bit	very much
34. dark brown/ skin patches under arms, in skin folds	N/A	Not at all	a little	somewhat	quite a bit	very much
35. easy sweating/ body odor	N/A	Not at all	a little	somewhat	quite a bit	very much
36. slow wound healing	N/A	Not at all	a little	somewhat	quite a bit	very much
37. dark pink stretch marks on abdomen/other body parts	N/A	Not at all	a little	somewhat	quite a bit	very much
38. large areas of skin that have turned dark	N/A	Not at all	a little	somewhat	quite a bit	very much
39. yellowing of my skin	N/A	Not at all	a little	somewhat	quite a bit	very much
40. skin Rash	N/A	Not at all	a little	somewhat	quite a bit	very much
41. dry parchment like skin	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
42. brittle fingernails	N/A	Not at all	a little	somewhat	quite a bit	very much
43. the way my body looks	N/A	Not at all	a little	somewhat	quite a bit	very much
44. Headaches	N/A	Not at all	a little	somewhat	quite a bit	very much
45. Blind spots in my vision	N/A	Not at all	a little	somewhat	quite a bit	very much
46. Dizziness with standing	N/A	Not at all	a little	somewhat	quite a bit	very much
47. Dry mouth	N/A	Not at all	a little	somewhat	quite a bit	very much
48. Ringing in my ears	N/A	Not at all	a little	somewhat	quite a bit	very much
49. difficulty breathing	N/A	Not at all	a little	somewhat	quite a bit	very much
50. Nasal congestion or drainage	N/A	Not at all	a little	somewhat	quite a bit	very much
51. Increasing roundness of my face	N/A	Not at all	a little	somewhat	quite a bit	very much
52. A bad/salty taste in my mouth	N/A	Not at all	a little	somewhat	quite a bit	very much
53. Thirst that is difficult to quench	N/A	Not at all	a little	somewhat	quite a bit	very much
54. Loss of sense of smell and/or taste	N/A	Not at all	a little	somewhat	quite a bit	very much
55. Numbness or tingling on my scalp	N/A	Not at all	a little	somewhat	quite a bit	very much
56. A faster than usual heart rate	N/A	Not at all	a little	somewhat	quite a bit	very much
57. A slower than usual heart rate	N/A	Not at all	a little	somewhat	quite a bit	very much
58. Abdominal pain/discomfort	N/A	Not at all	a little	somewhat	quite a bit	very much
59. nausea	N/A	Not at all	a little	somewhat	quite a bit	very much
60. vomiting	N/A	Not at all	a little	somewhat	quite a bit	very much
61. constipation	N/A	Not at all	a little	somewhat	quite a bit	very much
62. diarrhea	N/A	Not at all	a little	somewhat	quite a bit	very much
63. poor appetite	N/A	Not at all	a little	somewhat	quite a bit	very much
64. hunger	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
65. flatulence /gas	N/A	Not at all	a little	somewhat	quite a bit	very much
66. Muscle pain	N/A	Not at all	a little	somewhat	quite a bit	very much
67. Joint pain	N/A	Not at all	a little	somewhat	quite a bit	very much
68. skin sensations such as prickling, burning, tingling	N/A	Not at all	a little	somewhat	quite a bit	very much
69. Wrist pain	N/A	Not at all	a little	somewhat	quite a bit	very much
70. muscle cramping	N/A	Not at all	a little	somewhat	quite a bit	very much
71. cold skin	N/A	Not at all	a little	somewhat	quite a bit	very much
72. hot flashes/night sweats	N/A	Not at all	a little	somewhat	quite a bit	very much
73. Pain when I try to exercise	N/A	Not at all	a little	somewhat	quite a bit	very much
74. frequent urination during the day (every 1-2 hours)	N/A	Not at all	a little	somewhat	quite a bit	very much
75. an irregular menstrual cycle (period) (female only)	N/A	Not at all	a little	somewhat	quite a bit	very much

I have difficulty with:						
76. learning new information or new things.	N/A	Not at all	a little	somewhat	quite a bit	very much
77. recounting facts about something that is new to me.	N/A	Not at all	a little	somewhat	quite a bit	very much
78. learning a new skill despite repeating it several times	N/A	Not at all	a little	somewhat	quite a bit	very much
79. concentrating to finish what I am doing	N/A	Not at all	a little	somewhat	quite a bit	very much
80. calculating numbers in my head	N/A	Not at all	a little	somewhat	quite a bit	very much
81. remembering information from medical appointments	N/A	Not at all	a little	somewhat	quite a bit	very much
82. recalling names of things.	N/A	Not at all	a little	somewhat	quite a bit	very much
83. finding the right word when talking	N/A	Not at all	a little	somewhat	quite a bit	very much
84. keeping track of what is being said in a conversation	N/A	Not at all	a little	somewhat	quite a bit	very much
85. finding the money to buy my medications	N/A	Not at all	a little	somewhat	quite a bit	very much

I have difficulty with:

86.	finding the money to pay for my insurance	N/A	Not at all	a little	somewhat	quite a bit	very much
87.	coming up with new ideas	N/A	Not at all	a little	somewhat	quite a bit	very much
88.	carrying a bag of groceries	N/A	Not at all	a little	somewhat	quite a bit	very much
89.	rapid changes in mood	N/A	Not at all	a little	somewhat	quite a bit	very much
90.	general weakness	N/A	Not at all	a little	somewhat	quite a bit	very much
91.	walking up one flight of stairs	N/A	Not at all	a little	somewhat	quite a bit	very much
92.	standing from a sitting position	N/A	Not at all	a little	somewhat	quite a bit	very much
93.	bending, kneeling or stooping	N/A	Not at all	a little	somewhat	quite a bit	very much
94.	Loose joints (they move in unusual directions)	N/A	Not at all	a little	somewhat	quite a bit	very much
95.	Swelling in my feet and ankles	N/A	Not at all	a little	somewhat	quite a bit	very much
96.	walking a mile	N/A	Not at all	a little	somewhat	quite a bit	very much
97.	being able to exercise because of weakness	N/A	Not at all	a little	somewhat	quite a bit	very much
98.	participating in my regular religious activities	N/A	Not at all	a little	somewhat	quite a bit	very much
99.	attending important religious events	N/A	Not at all	a little	somewhat	quite a bit	very much
100	staying in contact with people of my faith	N/A	Not at all	a little	somewhat	quite a bit	very much
101	finishing projects at home or at work	N/A	Not at all	a little	somewhat	quite a bit	very much
102	doing things at work/school in a reasonable time.	N/A	Not at all	a little	somewhat	quite a bit	very much

Please circle the response that corresponds most closely with your daily experience.

103	I prefer reading about my illness in books or on the internet	N/A	Not at all	a little	somewhat	quite a bit	very much
104	I wake early in the morning & can't go back to sleep	N/A	Not at all	a little	somewhat	quite a bit	very much
105	I get agitated if things don't happen quickly	N/A	Not at all	a little	somewhat	quite a bit	very much
106	My faith has changed because of my illness	N/A	Not at all	a little	somewhat	quite a bit	very much

107	Planning my activities isn't successful for me	N/A	Not at all	a little	somewhat	quite a bit	very much
108	I like to let people know my opinion about issues	N/A	Not at all	a little	somewhat	quite a bit	very much
109	I lack energy for social activities with friends	N/A	Not at all	a little	somewhat	quite a bit	very much
110	I am optimistic about my future	N/A	Not at all	a little	somewhat	quite a bit	very much
111	I feel out of control	N/A	Not at all	a little	somewhat	quite a bit	very much
112	I need help with transportation	N/A	Not at all	a little	somewhat	quite a bit	very much
113	I find it easy to talk with anyone	N/A	Not at all	a little	somewhat	quite a bit	very much
114	I find it hard to talk to people I don't know	N/A	Not at all	a little	somewhat	quite a bit	very much
115	I feel my body is not attractive to my partner	N/A	Not at all	a little	somewhat	quite a bit	very much
116	My sexual interest has declined	N/A	Not at all	a little	somewhat	quite a bit	very much
117	I wake up tired	N/A	Not at all	a little	somewhat	quite a bit	very much
118	My exercise is limited by fatigue	N/A	Not at all	a little	somewhat	quite a bit	very much
119	I can take care of myself	N/A	Not at all	a little	somewhat	quite a bit	very much
120	I feel Guilty	N/A	Not at all	a little	somewhat	quite a bit	very much
121	I feel my illness was meant to be	N/A	Not at all	a little	somewhat	quite a bit	very much
122	Others seem to get more done in a day than me	N/A	Not at all	a little	somewhat	quite a bit	very much
123	My brain has trouble keeping track of things	N/A	Not at all	a little	somewhat	quite a bit	very much
124	I like to keep the way I feel about things to myself	N/A	Not at all	a little	somewhat	quite a bit	very much
125	I get together with friends	N/A	Not at all	a little	somewhat	quite a bit	very much
126	I feel I don’t particularly like the person I am	N/A	Not at all	a little	somewhat	quite a bit	very much
127	I expect I will never be healthy	N/A	Not at all	a little	somewhat	quite a bit	very much
128	I feel regular Dr. visits will help me avoid getting sick	N/A	Not at all	a little	somewhat	quite a bit	very much
129	I prefer to stay home rather than go to an event with people	N/A	Not at all	a little	somewhat	quite a bit	very much
130	I feel panicked	N/A	Not at all	a little	somewhat	quite a bit	very much

131	I have a morning erection (Male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
132	I think people avoid me because of my appearance	N/A	Not at all	a little	somewhat	quite a bit	very much
133	I think my recovery will take some time	N/A	Not at all	a little	somewhat	quite a bit	very much
134	I prefer to stay home rather than go out with my friends	N/A	Not at all	a little	somewhat	quite a bit	very much
135	I feel responsible for my own health	N/A	Not at all	a little	somewhat	quite a bit	very much
136	My fatigue interferes with my work life	N/A	Not at all	a little	somewhat	quite a bit	very much
137	I am decreased vaginal moisture (female only)	N/A	Not at all	a little	somewhat	quite a bit	very much
138	My illness has caused me to let people down	N/A	Not at all	a little	somewhat	quite a bit	very much
139	I have had an increase in my sexual interest	N/A	Not at all	a little	somewhat	quite a bit	very much
140	I feel Worthless	N/A	Not at all	a little	somewhat	quite a bit	very much
141	I like being around a large number of people	N/A	Not at all	a little	somewhat	quite a bit	very much
142	I feel I make mistakes easily	N/A	Not at all	a little	somewhat	quite a bit	very much
143	I feel Restlessness and agitated	N/A	Not at all	a little	somewhat	quite a bit	very much
144	I make decisions quickly	N/A	Not at all	a little	somewhat	quite a bit	very much
145	I anticipate a full recovery	N/A	Not at all	a little	somewhat	quite a bit	very much
146	I am limited in the kind of work I can do (by my illness)	N/A	Not at all	a little	somewhat	quite a bit	very much
147	I feel like something awful will happen	N/A	Not at all	a little	somewhat	quite a bit	very much
148	I am worried about symptoms I read on the internet	N/A	Not at all	a little	somewhat	quite a bit	very much
149	I am easily distracted	N/A	Not at all	a little	somewhat	quite a bit	very much
150	I need help to do laundry	N/A	Not at all	a little	somewhat	quite a bit	very much
151	I feel easily Annoyed	N/A	Not at all	a little	somewhat	quite a bit	very much
152	My partner and I have had trouble getting pregnant	N/A	Not at all	a little	somewhat	quite a bit	very much
153	I have frequent urination at night (every 1- 2 hours)	N/A	Not at all	a little	somewhat	quite a bit	very much
154	I worry about something bad happening to my health	N/A	Not at all	a little	somewhat	quite a bit	very much

155	I take most things in stride	N/A	Not at all	a little	somewhat	quite a bit	very much
156	I like seeing what I have accomplished myself	N/A	Not at all	a little	somewhat	quite a bit	very much
157	I am fatigued during the day	N/A	Not at all	a little	somewhat	quite a bit	very much
158	I feel my body is not attractive	N/A	Not at all	a little	somewhat	quite a bit	very much
159	I spend time researching my health problems	N/A	Not at all	a little	somewhat	quite a bit	very much
160	I lack motivation to do things.	N/A	Not at all	a little	somewhat	quite a bit	very much
161	I feel worried	N/A	Not at all	a little	somewhat	quite a bit	very much
162	I feel like getting things done around the house	N/A	Not at all	a little	somewhat	quite a bit	very much
163	I fall asleep when I sit quietly/read	N/A	Not at all	a little	somewhat	quite a bit	very much
164	I am motivated if my work is acknowledged	N/A	Not at all	a little	somewhat	quite a bit	very much
165	I like to get started on new projects at work	N/A	Not at all	a little	somewhat	quite a bit	very much
166	I feel productive	N/A	Not at all	a little	somewhat	quite a bit	very much
167	I talk with my friends about my health issues	N/A	Not at all	a little	somewhat	quite a bit	very much
168	I have had a decline in my sexual interest	N/A	Not at all	a little	somewhat	quite a bit	very much
169	I feel overwhelmed	N/A	Not at all	a little	somewhat	quite a bit	very much
170	I feel my health is in the hands of my health care team	N/A	Not at all	a little	somewhat	quite a bit	very much
171	I am happy with what I am able to achieve each day	N/A	Not at all	a little	somewhat	quite a bit	very much
172	I feel Irritable	N/A	Not at all	a little	somewhat	quite a bit	very much
173	I need help to do my shopping	N/A	Not at all	a little	somewhat	quite a bit	very much
174	I feel it will take luck for me to recover from any illness	N/A	Not at all	a little	somewhat	quite a bit	very much
175	I feel Angry	N/A	Not at all	a little	somewhat	quite a bit	very much
176	I enjoy social activities	N/A	Not at all	a little	somewhat	quite a bit	very much
177	My fatigue disrupts my family life	N/A	Not at all	a little	somewhat	quite a bit	very much
178	I need help to be able to cook	N/A	Not at all	a little	somewhat	quite a bit	very much

179	I have someone I trust that I can confide in.	N/A	Not at all	a little	somewhat	quite a bit	very much
180	I sleep much of the day	N/A	Not at all	a little	somewhat	quite a bit	very much
181	I feel stressed because of my medical bills	N/A	Not at all	a little	somewhat	quite a bit	very much
182	I fall asleep at stop lights while driving	N/A	Not at all	a little	somewhat	quite a bit	very much
183	I have a morning erection (Male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
184	My testicles have shrunk in size (male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
185	I have friends who try to help me	N/A	Not at all	a little	somewhat	quite a bit	very much
186	I lack energy to do my household chores	N/A	Not at all	a little	somewhat	quite a bit	very much
187	My job/school performance has declined	N/A	Not at all	a little	somewhat	quite a bit	very much
188	I prefer watching sports rather than participating in sports.	N/A	Not at all	a little	somewhat	quite a bit	very much
189	I have faith I will get better	N/A	Not at all	a little	somewhat	quite a bit	very much
190	I feel tense or wound up	N/A	Not at all	a little	somewhat	quite a bit	very much
191	my spouse/partner is supportive	N/A	Not at all	a little	somewhat	quite a bit	very much
192	I feel hopeless about my future	N/A	Not at all	a little	somewhat	quite a bit	very much
193	I like time to think things through before acting	N/A	Not at all	a little	somewhat	quite a bit	very much
194	I avoid social activities because of my appearance	N/A	Not at all	a little	somewhat	quite a bit	very much
195	I feel vulnerable	N/A	Not at all	a little	somewhat	quite a bit	very much
196	I feel good about myself	N/A	Not at all	a little	somewhat	quite a bit	very much
197	My sexual interest has improved	N/A	Not at all	a little	somewhat	quite a bit	very much
198	I feel Suicidal	N/A	Not at all	a little	somewhat	quite a bit	very much
199	I feel Like crying	N/A	Not at all	a little	somewhat	quite a bit	very much
200	I have family members who try to help me	N/A	Not at all	a little	somewhat	quite a bit	very much
201	I prefer talking with others with my illness	N/A	Not at all	a little	somewhat	quite a bit	very much
202	I get upset if I am criticized	N/A	Not at all	a little	somewhat	quite a bit	very much

203	I am worried about earning enough to pay my bills	N/A	Not at all	a little	somewhat	quite a bit	very much
204	I am confident in my decisions	N/A	Not at all	a little	somewhat	quite a bit	very much
205	I feel I can help myself recover from being ill	N/A	Not at all	a little	somewhat	quite a bit	very much

Please add symptoms and changes you have experienced that are not included in this questionnaire

Please indicate confusing or unclear questions or instructions.

Is there anything else that is not included in this questionnaire that affects your life that you would like share?

THANK-YOU for completing this survey.

Patient Characteristics

Appendix 5

ID	Age	Gender	# pit Def	Tumor Size	Pit Surg	Med Hx	Dx
1	44	m	0	M	Y	1	NF
2	30	f	0	m	N	0	NF
3	31	m	1	m	N	0	Prolactin
4	26	m	1	m	N	0	Prolactin
6	19	f	0	m	N	0	Prolactin
7	44	f	0	m	N	1	NF
9	29	f	1	m	N	0	Prolactin
10	41	f	0	M	Y	0	Co-sec
11	26	f	0	m	N	0	NF
12	45	f	0	M	Y	1	GH
13	41	f	0	m	N	0	Prolactin
14	32	m	2	m	N	0	NF
15	49	m	2	M	Y	0	Prolactin
16	62	f	1	M	Y	1	GH
17	28	f	2	M	Y	0	GH
18	66	m	1	m	Y	1	NF
19	49	f	0	M	Y	1	NF
20	31	f	1	m	N	1	Prolactin
21	19	m	1	m	N	0	NF
22	65	m	2	M	Y	1	Gon
23	67	m	2	M	N	1	Prolactin
24	42	m	0	M	Y	0	NF
25	46	f	0	M	Y	0	other
26	67	f	1	M	Y	1	Co-sec
28	34	m	1	m	Y	0	other
29	58	m	0	m	Y	1	NF
30	62	m	1	M	Y	1	GH
31	70	f	0	m	N	1	NF
32	46	f	0	M	Y	0	NF

NF=Non Functioning/secreting tumors by pathology or biochemistry. Other= Hypersecreting tumors: GH=growth hormone, Prolactin, Gonadotroph.
Co-sec= tumors secreting more than one hormone by pathology
MH=Medical History: 0=None 1=Concomitant controlled disease

Appendix 6 Deleted Items.

Question #	Discrimination: Mean % present	Distribution Standard Deviation from mean	Kurtosis
9	.1379		
12	.000		
13	.1377		
14	.1379		
23	.0690		
25	. 0690		
38	.0345		
39	.0345		
57	.000		
60	.1724		
94	.1286		
133	.8621		
135	1.000		
156	.9286		
164	.9310		
193	1.000		
204	1.000		
205	.9655		
TOTAL 18			
Retained items for population sampling /selection bias/assessment timing			
10	.1379		
11	.1724		
15	.0690		
16	.1724		
17	.1379		
22	.2414		
24	.1379		
30	.1379		
34	.1034		
36	.2414		
40	.2414		
41	.1724		
42	.2857		
45	.2414		
52	.2414		
54	.1724		
55	.1724		
62	.2414		
63	.2069		
69	.2414		
85	.2759		
88	.2069		

110	.8966
112	.2069
124	.9310
125	.9310
129	.8276
132	.1724
139	.2143
144	.8966
145	.8276
150	.1379
153	.2500
155	.9310
165	.8276
166	.8621
169	.8276
171	.8966
173	.1379
176	.8929
182	.0690
184	.1034
189	.9655
192	.2414
194	.2414
196	.8929
197	.1379
198	.1034
200	.9655
202	.8276
TOTAL 50	

To be Revised:

108	.8966
124	.9310
152	.0.345
95	.2759
96	.2759
98	.1724
99	.1724
100	.1724
TOTAL 8	

Appendix 7 **Correlations**

		age	sex	Size_M	surg_M	Function	MH	qu5s1	qu5s3
age	Pearson Correlation	1	.119	.454*	.472**	.027	.733**	.211	-.548
	Sig. (2-tailed)		.539	.013	.010	.889	.000	.311	.101
	N	29	29	29	29	29	29	25	10
sex	Pearson Correlation	.119	1	-.038	.115	-.194	.024	.116	.[a]
	Sig. (2-tailed)	.539		.844	.551	.313	.901	.580	.000
	N	29	29	29	29	29	29	25	10
Size_M/m	Pearson Correlation	.454*	-.038	1	.732**	.169	.239	.116	-.520
	Sig. (2-tailed)	.013	.844		.000	.381	.211	.580	.123
	N	29	29	29	29	29	29	25	10
surg_Y/N	Pearson Correlation	.472**	.115	.732**	1	-.087	.255	.000	-.520
	Sig. (2-tailed)	.010	.551	.000		.652	.182	1.000	.123
	N	29	29	29	29	29	29	25	10
Function	Pearson Correlation	.027	-.194	.169	-.087	1	.087	.462*	.120
	Sig. (2-tailed)	.889	.313	.381	.652		.652	.020	.741
	N	29	29	29	29	29	29	25	10
Medical History	Pearson Correlation	.733**	.024	.239	.255	.087	1	.116	-.392
	Sig. (2-tailed)	.000	.901	.211	.182	.652		.580	.262
	N	29	29	29	29	29	29	25	10
qu5s1	Pearson Correlation	.211	.116	.116	.000	.462*	.116	1	-.056
	Sig. (2-tailed)	.311	.580	.580	1.000	.020	.580		.886
	N	25	25	25	25	25	25	25	9
qu5s3	Pearson Correlation	-.548	.[a]	-.520	-.520	.120	-.392	-.056	1
	Sig. (2-tailed)	.101	.000	.123	.123	.741	.262	.886	
	N	10	10	10	10	10	10	9	10

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

a. Cannot be computed because at least one of the variables is constant.

Appendix 8 **Domain & Attribute Statistics**

	function		N	Mean	Std. Deviation	Std. Error Mean
COGNITIVE DOMAIN	dimension1	.00	16	33.1875	12.02341	3.00585
		1.00	9	27.3333	4.44410	1.48137
Cog Concentration	dimension1	.00	17	10.1765	3.45028	.83682
		1.00	10	9.0000	1.41421	.44721
Cog Memory Recall	dimension1	.00	16	3.1250	1.45488	.36372
		1.00	11	2.4545	.68755	.20730
Cog Verbal recall	dimension1	.00	16	10.5000	4.03320	1.00830
		1.00	12	8.0833	2.64432	.76335
EMOTIONAL DOMAIN	dimension	.00	14	269.5000	33.43133	8.93490
		1.00	9	233.2222	14.22830	4.74277
Emot Anxiety	dimension	.00	17	21.8824	6.34313	1.53843
		1.00	12	17.5000	4.79583	1.38444
Emot Body Image	dimension1	.00	14	92.8571	17.37751	4.64434
		1.00	10	80.0000	5.79272	1.83182
Emot Depression	dimension1	.00	17	30.8235	3.76223	.91248
		1.00	12	29.8333	2.44330	.70532
Emot Motivation	dimension1	.00	17	23.9412	3.34422	.81109
		1.00	11	22.5455	2.01810	.60848
Emot Somatization	dimension1	.00	17	13.3529	3.95192	.95848
		1.00	12	10.9167	2.35327	.67933
Emot Stability	dimension1	.00	17	11.4706	1.50489	.36499
		1.00	12	12.3333	1.72328	.49747
Emot Self Esteem	dimension1	.00	17	12.1765	2.32474	.56383
		1.00	11	12.8182	1.88776	.56918
PHYSICAL DOMAIN	dimension	.00	13	156.9231	40.01554	11.09831
		1.00	10	128.6000	16.97842	5.36905
Phy Energy/ Fatigue	dimension1	.00	17	16.9412	6.67524	1.61898
		1.00	12	17.0833	5.93079	1.71207
Phy Independence	dimension1	.00	17	18.4118	5.38585	1.30626
		1.00	12	15.7500	1.54479	.44594
Phy Mobility	dimension1	.00	17	19.3529	8.03851	1.94963

		1.00	12	17.1667	4.66775	1.34746
Phy Sensory	dimension1	.00	14	75.5000	21.70342	5.80048
		1.00	10	63.0000	7.34847	2.32379
Phy Sleep	dimension1	.00	15	20.0000	3.13961	.81064
		1.00	12	16.2500	2.49089	.71906
SOCIAL DOMAIN	dimensio1	.00	13	106.7692	13.63301	3.78112
		1.00	8	108.7500	10.18051	3.59936
Soc Activity	dimension1	.00	16	18.0000	3.16228	.79057
		1.00	12	18.6667	2.05971	.59459
Soc Role Paraticipation	dimension1	.00	17	12.5882	2.62342	.63627
		1.00	12	11.6667	1.55700	.44947
Soc Support	dimension1	.00	17	27.2353	5.64058	1.36804
		1.00	12	26.6667	4.07505	1.17637
Soc intimacy/sexual interest/function	dimension1	.00	14	23.2857	4.21405	1.12625
		1.00	8	24.1250	4.42194	1.56339
ECONOMIC DOMAIN	dimension	.00	17	29.2941	6.84438	1.66001
		1.00	11	27.2727	3.43776	1.03652
Econ Economic stress	dimension1	.00	17	8.8235	3.59227	.87125
		1.00	12	7.2500	1.60255	.46262
Econ Ability to Generate Income	dimension1	.00	17	9.5882	3.57174	.86628
		1.00	12	7.5000	1.62369	.46872
Econ Ability to be productive/creative	dimension1	.00	17	10.8824	2.20461	.53470
		1.00	11	12.2727	2.10195	.63376
SPIRITUAL DOMAIN	dimension1	.00	17	9.0588	3.94447	.95667
		1.00	12	5.9167	2.02073	.58333
PERSONALITY FACTORS						
EXTROVERSION	dimension1	.00	17	14.2353	3.09292	.75014
		1.00	12	13.2500	2.05050	.59193
INTROVERSION	dimension1	.00	17	11.5882	2.93809	.71259
		1.00	12	11.6667	1.72328	.49747
IMPULSIVITY	dimension1	.00	17	10.1765	2.37790	.57673
		1.00	12	9.5833	1.78164	.51432
TREATMENT EXPECTATIONS	dimension	.00	17	10.2353	2.56246	.62149
		1.00	12	10.9167	1.83196	.52884
LOCUS OF CONTROL	dimension	.00	17	5.5882	1.32565	.32152
		1.00	12	5.8333	1.02986	.29729

APPENDIX 9

Detail of Qualitative Responses.

1. "I'm not sure if I am supposed to answer questions specifically with regards to how symptoms of pituitary adenoma make impact my life, or just answer the questions in general … for example, my job and feeling fatigue I contribute to some of the way I answered the questions, but I do not think they are necessarily related to my pituitary adenoma symptoms.
2. " brain injury and tumor appears to have made permanent changes to my life. ie. seizures, migraines, crying"
3. "I don't want to do all my activities (hunting, hiking, camping) because I am so tired. I feel horrible about my appearance and don't want to go out in public.
4. The questionnaire is missing -depression, migraine
5. The questionnaire is missing -Difficulty breathing
6. The questionnaire is missing-Missing- the effects of work life on energy throughout the day
7. The questionnaire is missing- I Fall asleep quickly but wake up one hour later and can be awake for up to 4 hours
8. The questionnaire is missing- PTSD, I am a displaced home maker with $1000 month spousal support for one more year.
9. Planning things isn't successful? Unclear
10. Lots about work but college is major part of my life and has been affected by this.
11. Difficulty falling asleep/blood pressure increasing
12. In the "I am bothered by section, n/a and "not at all" can often be used interchangeably. I mainly checked " not at all" but could just as easily picked N/A
    -include- frustration with doctors dismissing symptoms because pituitary disease is rare.

13. Your might want to screen out confounding variables (frequent urination due to BPH, global health rating influenced by other medical conditions etc.) This now reads as if your patient population has no other medical conditions that have contributed to their experiences.
14. "I am unable to experience joy and happiness".
    The questionnaire is missing -Anxiety, unable to sleep without pills, unable to live without anti-anxiety pills.
    Feel depressed, have had vulvadynia for 9 mths which limits activities with friends. Obsessive hand washing and being germophobic afraid of getting sick. Have lost 20lbs since December without trying. Feel I'm aging quickly.

Clinical Inquiry Project Report

Domains of Life Function Scale for Patients with Pituitary Adenomas.

Christine Yedinak

Oregon Health & Sciences University

CLINICAL INQUIRY REPORT

Results

Sample

Twenty-nine (13 [45%] male and 16 [55%] female) patients met the inclusion criteria and were enrolled during the period of data collection. Subject ages ranged from 19 - 70 years (median 44 years) with 7 of 16 (43%) females aged 41-49 years and 8 of 13 (64%) males over 42 years of age. Subject tumors were assessed as: microadenomas (52%) and macroadenomas (48%). Of these, 48.2 % (14) hypersecreted one or more hormones and were considered hypersecretory/functional tumors (HF), while 44.8% (13) were considered non-functional (NF). Two pituitary tumors (6.8%) were classified as 'other' and determined to be hypophysitis and chondrosarcoma by pathology but were treated as NF (non-secretory) tumors for the purposes of this project. On biochemical evaluation, 14 subjects (48.3%) had no pituitary deficiencies, 10 subjects (34.5%) had one deficiency and 5 (17.2%) presented with two deficiencies. Fewer than half the participants had a significant medical history (6 NF and 7 HF), and all disorders were stable and without change in medication for at least 6 months. Three subjects had a remote history of cancer and three with diabetes mellitus. One patient with recurrent tumor had a remote history of Cushing's disease CD with evidence of current disease. The majority of participants (55.5%) underwent subsequent surgery. Of the16 surgical subjects, 13 (81%) had macroadenomas and 3 (18%) had microadenomas (see tables 1 & Appendix 4).

Table 1. Patient demographics (n=29)

		Frequency (n)	Percent
Gender	Female	16	55.2
	Male	13	44.8
Medical History	No medical history	16	55.2
	1-3 stable diagnoses	13	44.8

Diagnosis	Non-functional (NF)	13	44.8
	Prolactinoma (Prl)	7	24.1
	Growth Hormone (GH)	4	13.8
	Co-secretion	2	6.9
	Other	3	10.3
Deficiencies	None	14	48.3
	1 hormonal deficiencies	10	34.5
	2 hormonal deficiencies	5	17.2
Tumor size	Microadenoma (<1.0cm)	15	51.7
	Macroadenoma (>1.0cm)	14	48.3
Surgery	None	13	44.8
	Yes	16	55.2

Findings

Of the 205 items in the questionnaire, 1.56% had missing or incomplete data. Instrument items were evaluated for response distribution, variance, item difficulty, and discrimination. Items were removed that demonstrated extreme kurtosis and a standard deviation of less than 0.5. This was cross-referenced with the mean difficulty of each item. Items with a mean percentage response of < .3 and > .8 were reviewed for removal. A total of 18 items were removed and 8 items retained but require syntactical revision (see appendix 5). Fifty items require further sampling.

		Size	Question1	Question2	Function
Size	Pearson Correlation	1	.116	.166	-.316
	Sig. (2-tailed)		.580	.439	.095
	N	29	25	24	29
Question1	Pearson Correlation	.116	1	.723**	-.361
	Sig. (2-tailed)	.580		.000	.076
	N	25	25	24	25
Question2	Pearson Correlation	.166	.723**	1	-.319
	Sig. (2-tailed)	.439	.000		.129
	N	24	24	24	24
Function	Pearson Correlation	-.316	-.361	-.319	1
	Sig. (2-tailed)	.095	.076	.129	
	N	29	25	24	29

Ninety percent of participants endorsed 11 items as experienced to some degree and over 80% endorsed the presence 31 items. Three items yielded 100% endorsement. All participants felt responsible for their own health, felt they were confident in their decisions and that they usually needed time to think things through before acting. High response rates were distributed across domains and after testing with a larger sample are likely to be discarded (see appendix 3).

Table 2. Correlations

Using Pearson's correlation, a positive correlation was found between size of tumor, increasing age (r=.454, p=0.05) and subsequent surgical resection (r=.472, p=0.01). Likewise, increasing age correlated positively with presence of concomitant illness (r=.733, p=0.01). There was no correlation between age and the subject's overall perception of their desired or current state of health. Gender did not correlate with size of tumor, surgical resection, concomitant disease or overall health ratings. Overall health ratings of desired health positively correlated with perception of health status over the previous 12 months (N25 r=.723,p=0.01). The mean of these responses indicated that the subjects rated their overall health at a little worse than desired (mean=2.0 with worse health over the previous 12 months (mean= 2.3on a

progressively improving scale of 1-5). No correlation was found between size of tumor or tumor function and perception of health status (see table 2 & appendix 4). After exclusion of items not meeting criteria for adequate variance and discrimination, scale reliability analysis revealed a Cronbach's alpha for internal consistency of .968 using 184 items.

Domain responses were analyzed (after the exclusion of invalid items) with respect to two questions: What life functions reflect decreased or altered QoL for patients with pituitary adenomas; and secondly, is QoL altered for patients with all types of PA's? The mean scores were evaluated for each domain characteristic and for each functional domain. Types of pituitary adenomas were limited by the size of the project sample and data collection time to two groups, non-functional and hyperfunctional (NF and HF, respectively). An independent *t* test was performed to evaluate the difference between the mean scores for domains and for domain attributes to demonstrate perception of greater or lesser dysfunction between groups (NF and HF). Independent *t* tests were run for each. When only the presence or absence of the characteristic/attribute was considered, significant differences ($p>.05$) were found between groups in the Emotional Domain ($t_{(21)}=2.42, p=.024$) and Physical Domain. Scores for those who endorsed the presence or absence of the characteristic indicated a significant difference between groups (NF and HF). Only scores for depression reached significance ($t_{(27)}=2.998$, $p=.06$) while body image scores approached significance ($t_{(22)}=1.80$, $p=.085$). Severity domain scores were congruent with percentage of respondent endorsement evaluation in the Emotional Domain ($t_{(21)} = 3.06$, $p=.006$) and Physical Domain ($t_{(21)}=2.089$, $p=.049$). The Spiritual Domain was also significantly different between groups ($t_{(27)}=2.56$, $p=0.18$). Independent *t* tests of domain characteristics based on severity or the amount of disturbance perceived by the subject, revealed significant differences between groups with respect to body image ($t_{(22)}=2.240$, $p= .036$), anxiety

($t_{(27)}$=2.02, p=0.54), sleep disturbance ($t_{(25)}$=3.37, p=.002). Somatization ($t_{27)}$ =1.91, p=0.68), verbal recall ($t_{(26)}$=1.80, p=.083) and physical sensory symptoms ($t_{(22)}$=1.74, p=.096) approached, but did not reach, significance.

Mean scores indicating higher levels of dysfunction were found for subjects with NF adenomas in the Cognitive Domain (with respect to concentration, memory recall, and verbal recall), Emotional Domain (anxiety, body image, depression, motivation, and somatization), Physical Domain (energy/fatigue, deficits in independence, poorer mobility, more sensory disturbances and poorer sleep), Economic Domain and Spiritual Domain. Social Domain characteristics were reported as similar for both groups, including levels of social activity, role participation, social support and intimacy/sexual interest and function. Economic concerns and employment limitations associated with this illness were slightly higher for subjects with NF adenomas. Personality scores, (extroversion, introversion and impulsivity), treatment expectations and locus of control were similar between groups (see appendix 4).

From the qualitative component of the questionnaire, a total of 14 comments were contributed by 12 subjects. Suggestions regarding items not already included in the questionnaire, included: differentiating migraine from headache, more specific questions regarding sleep (I Fall asleep quickly but wake up one hour later) and one subject recommended the inclusion of school with 'work' environment. One subject reported her work life had the most effect on her energy level. One subject was confused regarding the selection of 'N/A' versus 'not at all' and one patient did not understand the wording of item 123, "My brain has trouble keeping track of things". There were no repeated patterns or themes in the responses (see appendix 5).

Macro and or Micro Financial Considerations

This instrument will require further development, long term data collection and analysis. Although the tool is easy to administer, the data entry and analysis is cumbersome in a clinical environment. Ongoing development will focus on utilizing a computerized format through a platform such as RedCap (http://project-redcap.org) to allow data entry directly by the patient. A grant will be necessary to support the time of the administrator, the development of the computer format and psychometric statistical analysis.

Situational Analysis

The tool was easy to administer and was completed by subjects in an average of 20 minutes. A few male subjects solicited the help of spouses to read the questions aloud to complete the questionnaire. There was no evidence that questions were interpreted by the spouse. However, this could represent a threat to the integrity of the methodology if the spouse were also to select responses. Although all subjects were provided opportunities to discuss concerns or confusions during tool completion, no issues were forthcoming. Although all subjects were provided the same instructions for the document completion, confusion was evident in the use of the discriminators "N/A" and "Not at all". Participants were asked to leave their completed questionnaire with a medical assistant as they were discharged from their clinic visit. Only one qualified subject failed to do so. Subjects completed the questionnaire in between visits by providers. This distraction may have contributed to missing data.

The timing of the introduction of the tool to the subject during their visit was important to achieve participation. If the subject was given the tool near the end of their visit, the tool was generally completed in greater haste raising the question of accuracy and error. Several options can be considered. Using an online tool enables the questionnaire to be completed from the patient's home prior to each visit. Questionnaires could also be administered by trained

reception personnel allowing completion in the waiting room before the clinic visit. Both options improve clinic flow, achieve less disruption to room turnover, provide less disruption for other waiting patients and improve missing item rates that may have resulted from distractions and disruption during tool completion.

Outcomes

Changes in the process of care as a result of this project are anticipated in the long term. It is anticipated that the identification and clarity of functional deficits afforded by this tool will help to shape future clinical and nursing research for this population. Current tools are used simply to confirm or deny the presence of functional and quality of life deficits. There is little discussion or research effort focused in the direction of minimization or treating these deficits.

DISCUSSION

Interpretation

The demographics of the sample in this study are similar to those found in the literature. More females presented and were enrolled than males with a diagnosis of microadenomas. Male participants presented at an older age and more commonly with a macroadenoma. Headache was the chief complaint of all participants, and those subjects with macroadenomas were more likely to proceed to surgical resection to preserve the integrity of the optic chiasm, although no patient presented with visual field disturbances. Less than half the sample population had concomitant medical diseases and all had been stable over the preceding 6 months. Likewise, fewer than half the sampled patients were found to have pituitary deficits that may have contributed to their perceptions of poor functional status.

In response to the clinical inquiry questions: “What life functions reflect decreased or altered QoL for patients with pituitary adenomas; and secondly, is QoL altered for patients with

all types of PAs? ”, preliminary answers are proposed from this data that require larger samples and reference to a standard or control group to provide unequivocal answers. However, from the overall response to perceptions of desired and current health status, subjects with NF adenomas perceived they had poorer health, worse over the last 12 months, than did those with functional adenomas. This group was represented by twice as many subjects with microadenomas as macroadenomas (N=10). Subjects with NF adenomas also reported higher perception of cognitive, emotional, physical and economic dysfunction but were no more depressed and were as able to participate in social activities as their cohorts with functional adenomas despite a perception of greater difficulties with mobility and less independence in performing activities of daily living. There was also no difference in their sense of control, personality factors, and expectations with respect to treatment or perceived social support. They did report higher levels of somatization, anxiety, physical changes in body image, and perception of sensory symptoms. This is highly suggestive that NF microadenomas are not asymptomatic.

As measured by Cronbach’s alpha the tool demonstrated good internal consistency and hence generalizability with regards to patients with PAs. However, the predictive power of this data is limited by the small sample size. Some items require syntactical revision to remove references to marital status, sexual orientation and to include alternatives to work environments for students, retirees and those on disability.

Context

It is recognized that as a referral practice, some selection bias is inherent in the population of patients who present for further evaluation of a pituitary adenoma. Some tumors are incidental findings as the result of imaging for head trauma, but many are the consequence of a workup for symptoms such as headache (Molitch, 2009b;Carsote et al 2009). Therefore, many

referrals are the direct result of a known dysfunction that skews the data in the direction of significance. Likewise, the life cycle of a NF microadenoma is not clearly elucidated. Many such tumors are found at autopsy making correlation with QoL factors impossible (Daly, Burlacu, Livadariu, & Beckers, 2007;Dekkers et al., 2007; Dekkers, Pereira, & Romijn, 2008; Gorczyca & Hardy, 1988; Molitch, 2009a).

Although item responses relating to the Spiritual domain showed normal distribution, variance and minimal kurtosis (N= 10 & N = 12, respectively) 34.5 % of this study sample selected the response 'not applicable'. This raises the question of sampling bias that threatens generalizability. Issues of access to health care may contribute to this sampling bias. More literature review is needed to evaluate the key concepts in this domain in order to revise items. Likewise, the inclusion of populations at other sites and the translation of this tool into the most common local languages may be useful in future data collection to minimize this bias.

Limitations

Other sampling limitations are evident. Of the 50 items that were reviewed and retained in a probationary status, further sampling is necessary for item analysis. The majority of these items had low percentage response rates, likely resulting from the lack of pertinence to the types of pituitary tumors experience in this sample or for evaluation during the treatment trajectory. For example, no patients presented or met inclusion criteria with CD, and inadequate numbers of patients with other functional tumors presented in order to fully evaluate the reliability of these items. Additionally, the sample was limited in demographic variability; a broader sample is required to enhance generalizability. Items that demonstrated low (<.3) or high (>.8) mean response rates that were retained will be further tested for validity over time or for revision to more fully reflect the target domain characteristic.

Larger studies including patients that have not presented for treatment of symptoms and/or comparison with a standardized reference group would help to quantify this bias in order to calculate tumor effect. A registry for all pituitary tumors is not established in the U.S. However, this is the standard for some European countries making broader, although culturally specific, evaluation of QoL/functional changes possible in a population with NF pituitary adenomas who have not presented for treatment. Also to be considered in this equation, in the U.S where universal health care is not the standard, access to care can prevent symptomatic patients from obtaining evaluation and treatment. In countries with such health care systems, this barrier is removed. Although impractical, comparison to an age and sex matched standardized reference group that is culturally appropriate to the U.S, inclusive of people from different regional, socio-economic, educational backgrounds with negative brain imaging would provide the least error in effect size. However, age, sex and matched controls from the subjects environment may provide the closest approximation to a standard (given the prevalence of pituitary adenomas in the population there remains the likelihood that, statistically, up to one third of controls may have an undiagnosed tumor).

Conclusions

The ultimate goal of measurement is the management of contextual services needed for the treatment of the affected population (Hunt & McEwen, 1980). To do this a valid and reliable tool is paramount. The goal of this project was the piloting of a tool that was designed to be culturally appropriate, allowed for the strength of the symptom or dysfunction to be determined by the patient, and to provide enough flexibility for the measurement of changes over time and over the life cycle. The tool demonstrated internal consistency but requires further testing with a broader population to demonstrate content validity and reliability.

It remains to be seen if this instrument can rise to the challenge. However, in the pilot review, it has demonstrated sensitivity in discriminating between patients with NF and HF PAs. Results of this survey indicate that patients who present for assessment of NF microadenomas at OHSU, experience greater dysfunction in more characteristics and functional domains than patients with macroadenomas. The may be the result of sampling error and further study is required before conclusions can be drawn.

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OHSU

Domains of life Function Scale for Patients with Pituitary Adenomas

Presented by: Chris Yedinak DNP candidate, FNP-BC, MN,RN

Date: May 26, 2011

Program Goals:

- Define role in specialty practice
- Define intervention parameters
- Develop evidence based practice for symptom management
- Apply transitional research /methods clinical practice

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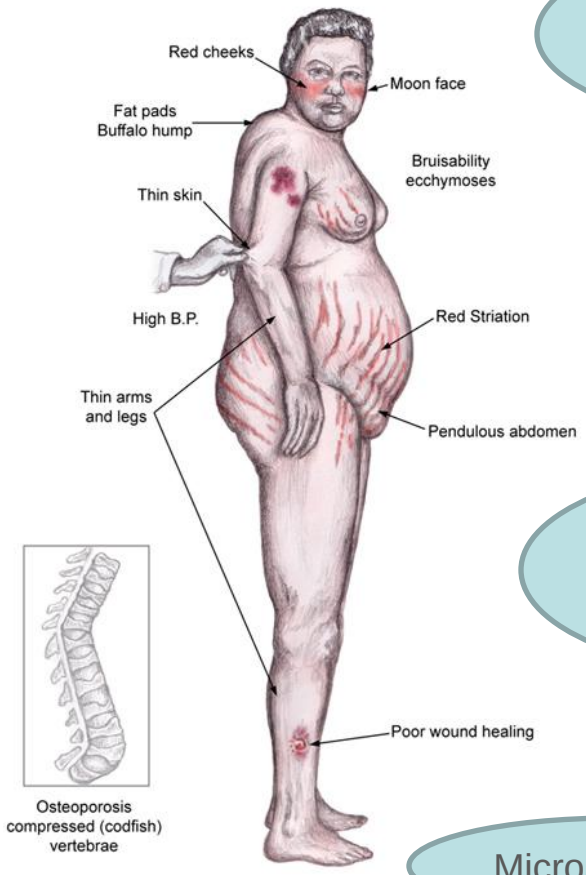
Population:

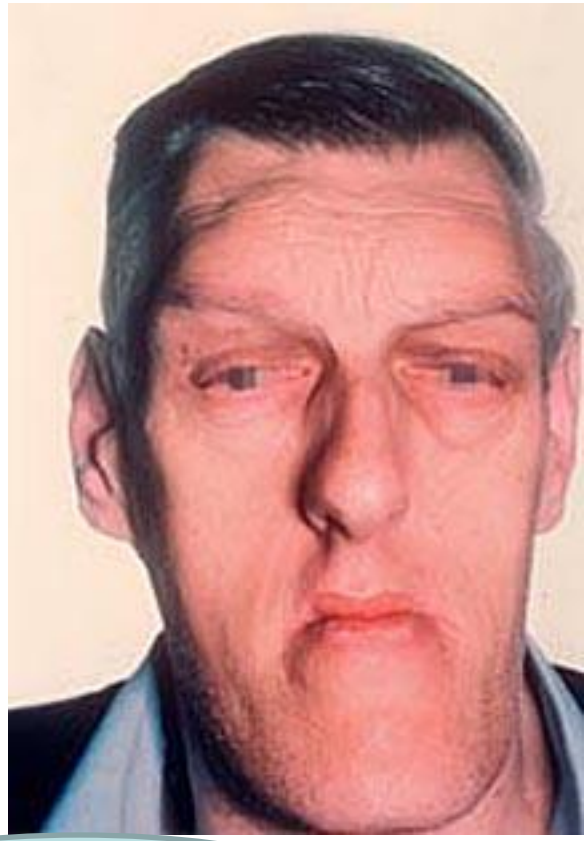


Prolactinoma

TSH

Gonadotroph

Microadenoma



Macroadenoma

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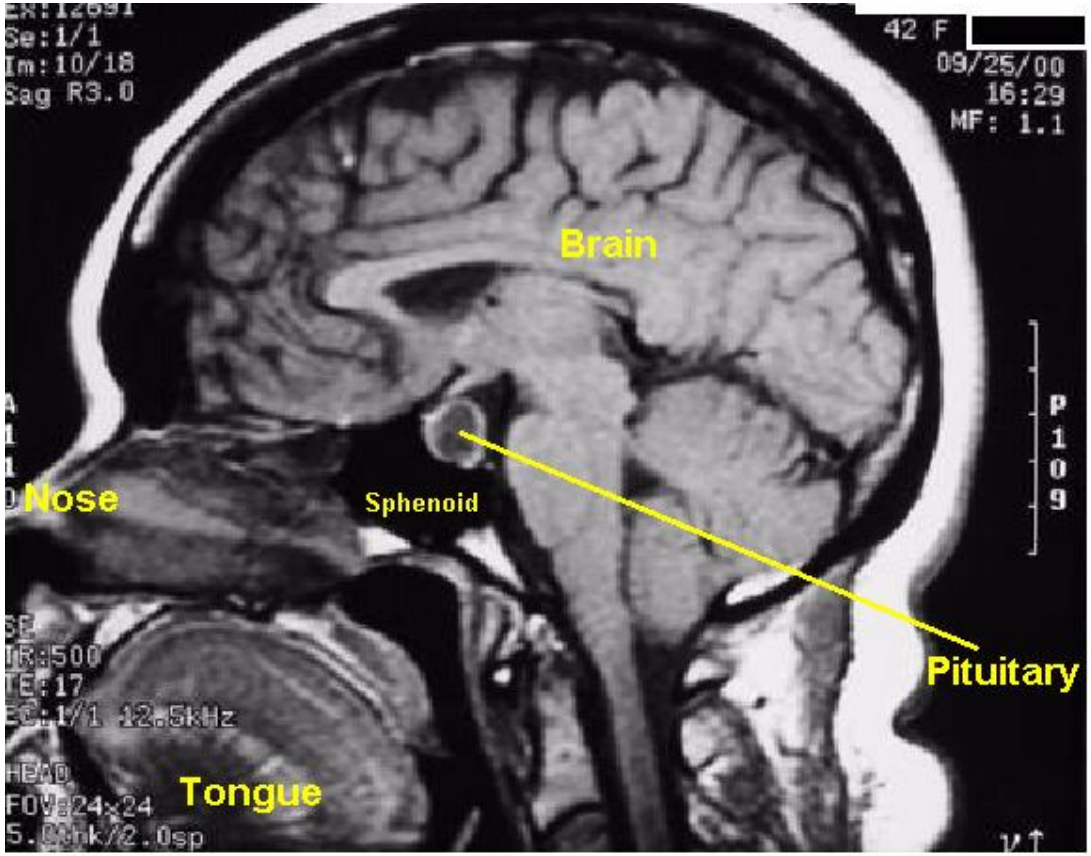
Pituitary gland:



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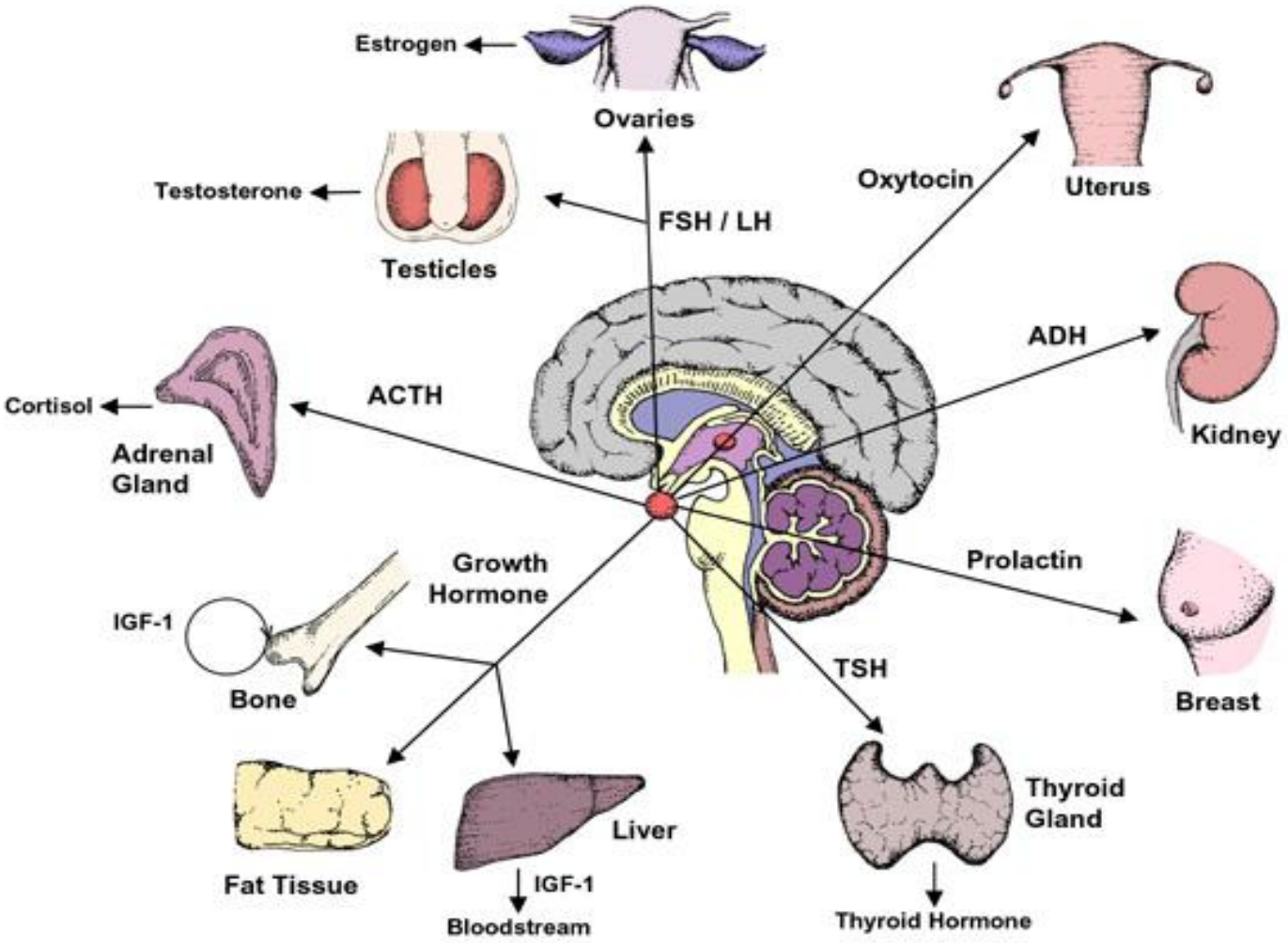
Master Gland



Clinical Problem

- Reduce health care costs – using outcomes to target dysfunction and direct clinical care
- Reimbursement based on outcomes- **performance-based reimbursement schemes**
- Evidence based medicine
- Move from physiologic & biochemical outcomes to functional, patient centered outcomes.
- Morbidity greater than mortality in pituitary diseases.
- Need to understand the impact of pituitary diseases on Quality of Life (QoL).
- Human costs- burden of dysfunction & morbidity

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Prevalence :

- Studies of autopsy reports indicate PAs as incidental finding in 10% to 27% of subjects . Imaging studies 1:6 scans
- Estimated population prevalence of 1:1000

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Incidence:

- Age range locally, 16 years to 89 years
- Median age at presentation (US) 50 years
- Incidence increases with age -Highest 65-74 years
- Gender distribution varies according to type of adenoma.
- The incidence of pituitary dysfunction is unknown

Population Affected

- Patients presenting at the OHSU Pituitary Center
- National referral base- Chiefly NW

- Over 250 new referrals annually

- Female/male ratio 2:1- 5:1

- USA (2009)reported female/male 2.3: 2.1

*The Central Brain Tumor Registry of the United States (2009)

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Background:

- No standard definition of QoL- contextual
- No definition of QoL in pituitary disease
- The use of multiple tools
- No standardized metric- disease specific content in PA

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Evidence:

- Johnson, Woodburn & Vance (2003) 186 subjects No microadenomas
- Kilty et.al., (2010)
- van der Klaauw et.al., (2008) **Number of hormonal deficits**
- Sievers, C., et. al., (2009). personality
- Santos, A. et.al.,(2009). **Treatments for hormonal excess**

  QoI more sensitive than biochemistry in treatment
- Dekkers, O.M. et.al., (2006) **Surgical intervention**
- Page,R.C. et. al., (1997) **Radiotherapy**

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Gaps:

- Omissions- vision, sleep, sexual fx, temporal measures, spiritual
- Microadenomas excluded
- No weighting of importance to patient
- Only one US based study.
- End point evaluations

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Purpose:

- practice improvement project
- develop an measurement instrument generic to PA
- identify life functions pertinent to patients with pituitary dz
- To categorize functions into domains that are specific to each type of PA.
- Use this instrument in the measurement of baseline QoL and as a treatment outcome measure.
- To identify contextual services needed to improve QoL and future research

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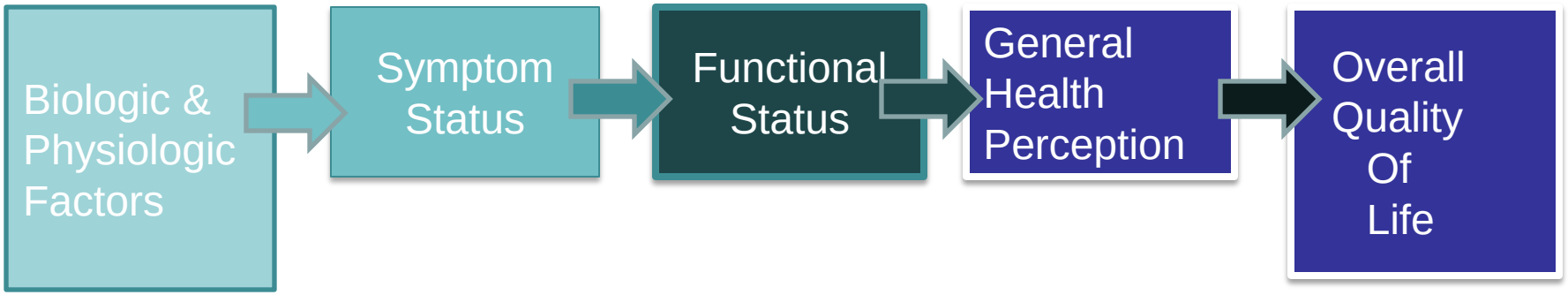
Conceptual Framework

Wilson & Cleary Conceptual Model of Relationship Among Health Outcomes (1995)*



In Fairclough ,D.L., (2010) Design and Analysis of Quality of Life Studies in Clinical trials (2nd Ed) .Boca Raton: CRC press

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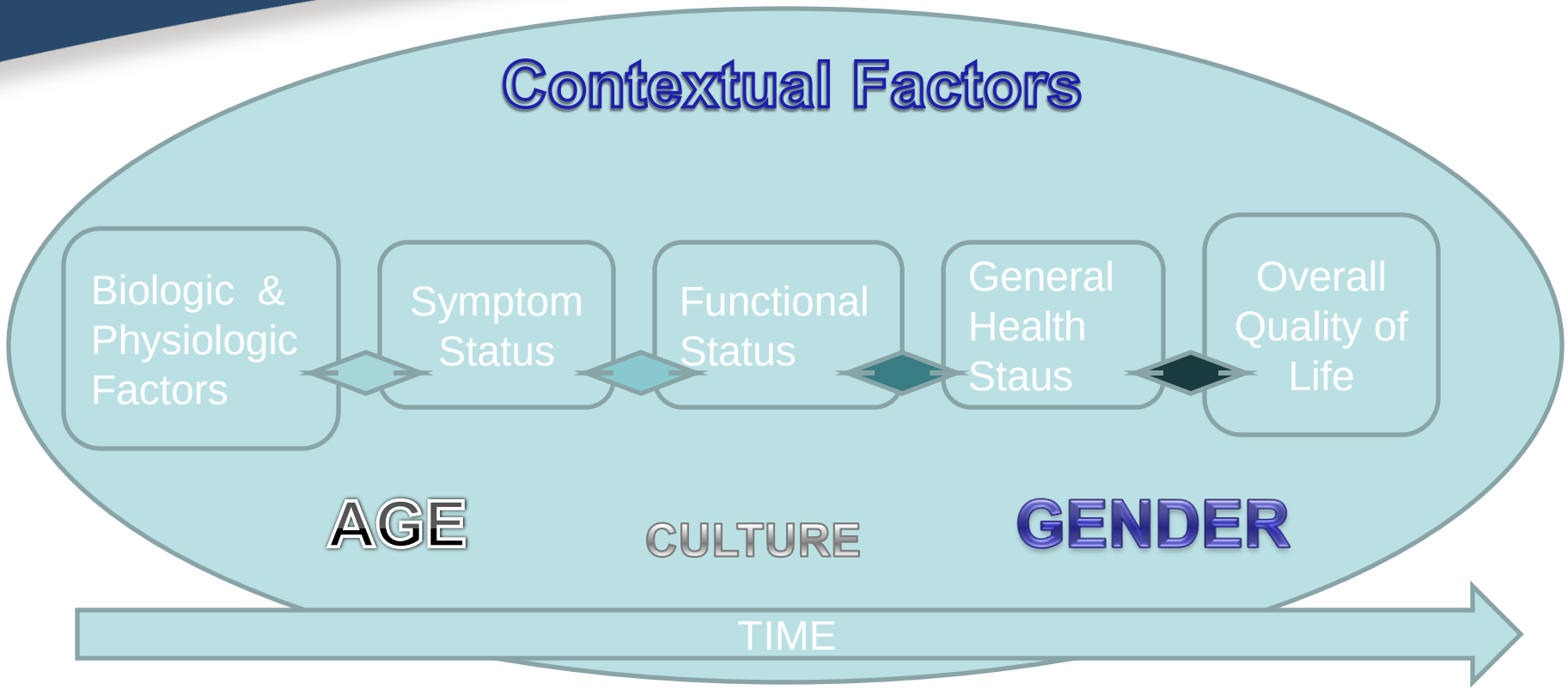
Adapted Conceptual Framework



Adapted from: Wilson & Cleary Conceptual Model of Relationship Among Health Outcomes (1995)*

In Fairclough ,D.L., (2010) Design and Analysis of Quality of Life Studies in Clinical trials (2nd Ed) .Boca Raton: CRC press

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Definition: Quality of Life

The subjective rating by the patient of their general well being in multiple domains of functioning.

Methods & Design:

- A prospective, mixed methods study
- Quantitative- 6 domains of function described by empirical indicators/Attributes
- A qualitative component . Solicits feedback from patients surveyed to be used to further content development.
- Survey instrument- The Domains of Life Functions scale (DOLFs)- developed and piloted.

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Instrument Development: Domains

- Review of literature
- Review of commonly used QoL metrics
- DOLFS Domains of Life Function Scale for Patients with Pituitary Adenomas

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Validated Tools - Reviewed and adapted

- Beck Depression Inventory
- Hospital Anxiety & Depression Scale (HADS)
- AcroQoL
- TRIM- AGHD
- Cushing's QoL
- The International Classification of Functioning, - Disability and Health (ICF)
- Visual Functioning Questionnaire-25 (VFQ-25)
- The Quality of Well-Being Scale (QWB, V1.04)
- Eysenck Personality Inventory
- FACIT-Sp 12 (spiritual)

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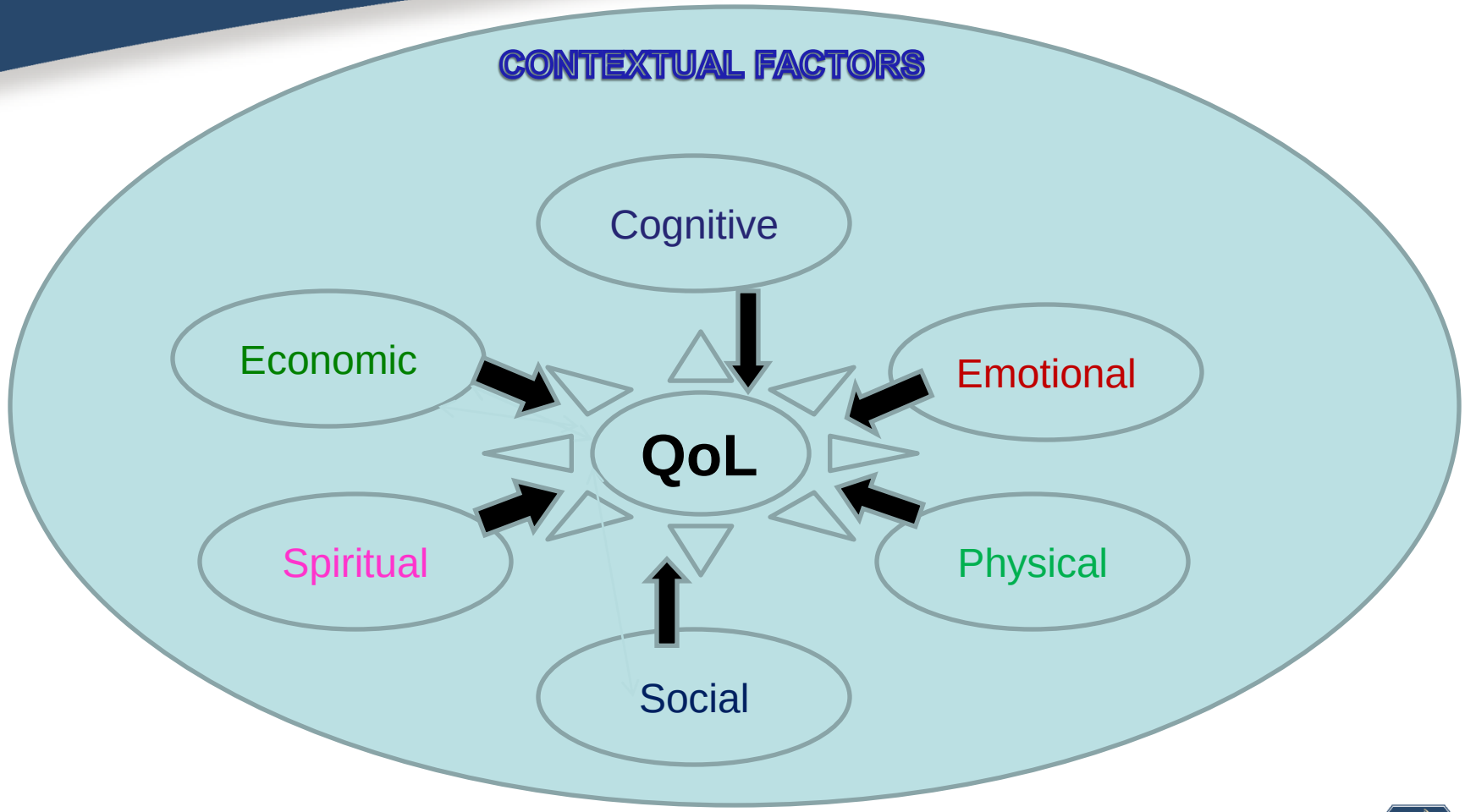
Clinical Questions:

- What is the effect of each pituitary disease on specific life functions
- Is QoL affected for patients with all types of PA’
- Does the DOLFs have internal consistency and reliability

Conceptualization : Quality of Life



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Operationalized: Cognitive

Cognitive:

- Ability to Learn
- Concentration and distractibility
- Mental agility
- Memory and factual recall
- Verbal recall

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Domain Operationalized: Emotional

- Anxiety
- Body image
- Depression
- Motivation
- Emotional stability
- Self esteem
- somatization

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Domain Operationalized:

Physical Domain:

- Energy/Fatigue
- Independence in activities of daily living
- Mobility
- Sensory symptoms

Social Domain

- Social activity participation
- Intimacy and sexual interest & activity
- Role participation
- Social support

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Attribute Operationalized:

Economic Domain:

- Economic stress- medical
- Ability to generate income
- Individuals ability to engage in productive and satisfying activities

Spiritual Domain

- Participation in regular religious activities
- Attending religious activities
- Changes in social relationships
- Changes in fundamental beliefs

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Attributes Operationalized :

Personality:

- Extroversion
- Introversion
- Impulsivity

Treatment Expectations:

- Anticipate being healthy
- Don’t anticipate being healthy
- Anticipate a slow recovery

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Attribute Operationalized: Locus of Control

- Effect of illness on sense of control
- Internal locus vs external locus with respect to health
- Definition of external source- medical providers vs deity or other force

Description of Intervention: Domains of Life Functions Scale for Patients with Pituitary Adenomas (DOLF)

	DOMAINS OF LIFE FUNCTION SCALE FOR PATIENTS with PITUITARY ADENOMAS (DOLFS) Please CIRCLE the response to the right that corresponds most closely with your daily experience .						
1.	How healthy do you feel today compared with your desired state of health?		Much Worse	A little worse	same	Better	Much better
2	How do you feel today compared with 12 months ago ?		Much Worse	A little worse	Same	Better	Much better
3	I am bothered by :	1	2	3	4	5	6
4	an absence of facial hair (males only)	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
5	**needing to shave my facial hair (females only)**	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
6	Facial flushing	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
7	Puffy eye lids	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
..	**IHAVE DIFFICULTY WITH :**						
76	Learning new information	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
77	Recounting facts about something that is new to me	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
103	I prefer reading about my illness on the internet	N/A	Not at all	A little	Somewhat	Quite a bit	Very much
104	I wake early in the morning and cant return to sleep	N/A	Not at all	A little	Somewhat	Quite a bit	Very much

Sample:

- Convenience sample-new referrals
- IRB approved for 40 subjects
- Min 5 subjects in each disease category for both micro and macroadenomas
- Enrolled 29
- No patients enrolled with Cushing's disease
- 2 groups- NF & HF (micro- macro)

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Inclusion/Exclusion criteria:

- Pre treatment
- Pituitary tumor/adenoma present
- English literacy

- Unstable concomitant disease or new treatments within the last 6 months
- Major life event within the last 6 months

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ANALYSIS: Content Analysis

- Item analysis- distribution and variance Highly kurtosed items removed
  - Low standard deviation (< .5) removed
  - Total of 18 questions on first analysis
- Item difficulty-% attribute present vs% not present
  - Items removed/evaluated with a mean of <.3 and >.8

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Tool internal consistency and reliability:

Cronbach's alpha = .968

based on 184 items

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Characteristics of Subjects

N= 29		Frequency	Percent
Gender	Male	16	55.2
	female	13	44.8
Medical History	No	16	55.2
	Yes	13	44.8
Diagnosis	NF	13	44.8
	HF	7	24.1
Pituitary deficiencies	Yes	4	13.8
	No	2	6.9
Tumor size	microadenoma	3	10.3
	macroadenoma	14	48.3
surgery	yes	10	34.5
	no	5	17.2

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Tumor characteristics

Tumor	Microadenoma (<1cm)	Macroadenoma (>1cm)
Non- functioning (NF)	8	4
Prolactinoma	6	2
Growth hormone (acromegaly)	0	4
Co-secreting (Prl/GH)	0	2
Gonadotroph	0	1
Cushing's/ACTH	0	0
Other	2	

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Correlations: Pearsons

N=29	Age	Gender	Size_M	Surg	Function	MH	Overall	12 m
Age	-	-	.454*	.472**		.733**		
Gender	-	-	-	-	-	-	-	-
Size M/m	.454*	-	-	.732**	-	-	-	-
Surgery	.472**	-	.732**	-	-	-	-	-
Function	-	-	-	-	-	-	.462*	-
MH	.733**	-	-	-	-	-	-	-
Overall	-	-	-	-	.462*	-	-	-
12 months	-	-	-	-	-	-	.723**	-

*Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).

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Findings by Domain: Severity scores Independent *t* Test

DOMAIN	Significant difference between NF & HF (<.05 sig)
Cognitive	-
Emotional	$t_{(21)}$=3.06,p=.025
Physical	$t_{(21)}$=2.09,p=.049
Social	-
Economic	-
Spiritual	$t_{(27)}$=3.026,p=.006

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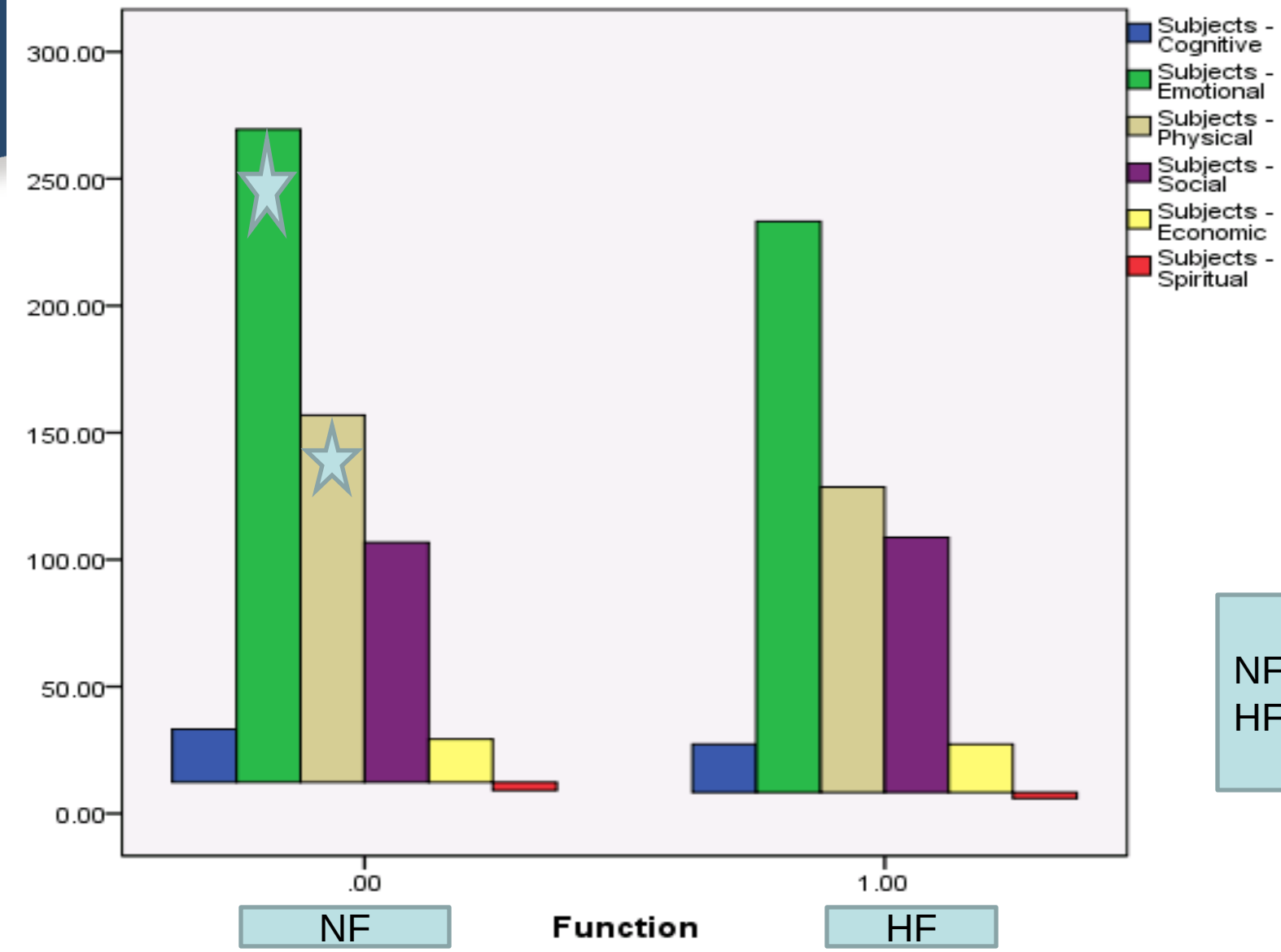
Findings by Domain



NF=14.9
HF=11.39

Attribute analysis : Independent *t* test
significant difference between NF and HF (P< .05)

Non-Functional (NF)		Hyperfunctional (HF)
Body image	$t_{(22)}$=2.24,p=.036	
Anxiety	$t_{(27)}$=2.02,p=.054	
Sleep disturbance	$t_{(25)}$=3.37,p=.002	
Somatization	$t_{(27)}$=1.91,p=.068	
Verbal recall	$t_{(26)}$=1.80,p=.083	
sensory symptoms	$t_{(23)}$=1.74,p=.096	

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Non-functional:

- Higher dysfunction
  - Concentration & memory recall
  - Anxiety,
  - Body image
  - Depression
  - Motivation
  - Somatization
  - Energy/fatigue
  - Poorer mobility
  - More sensory symptoms

No difference

-Social activity

- Role participation

-Social support

-Intimacy / sexual function

- Economic concerns

- Personality scores

-treatment expectations

-Locus of control

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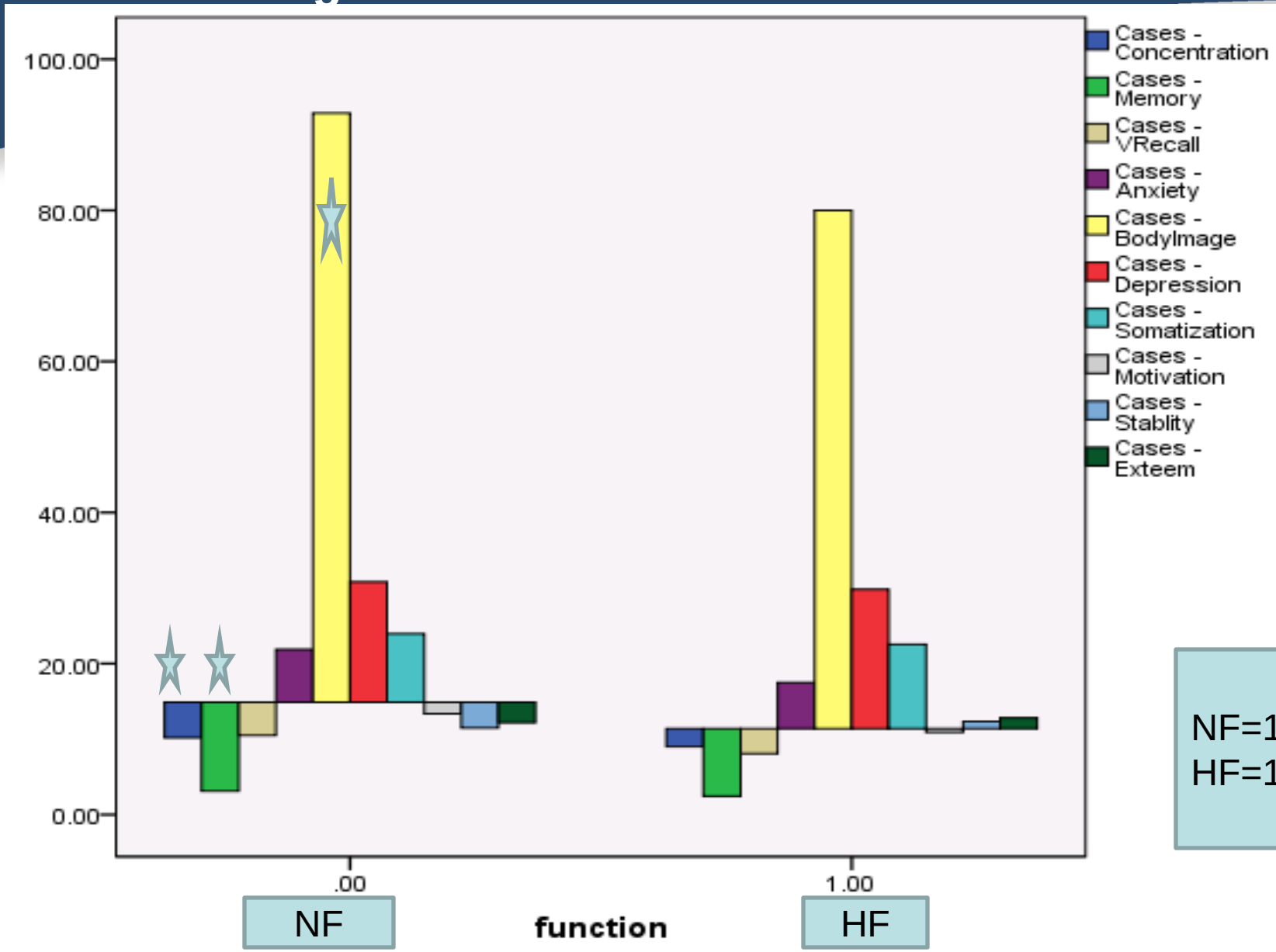
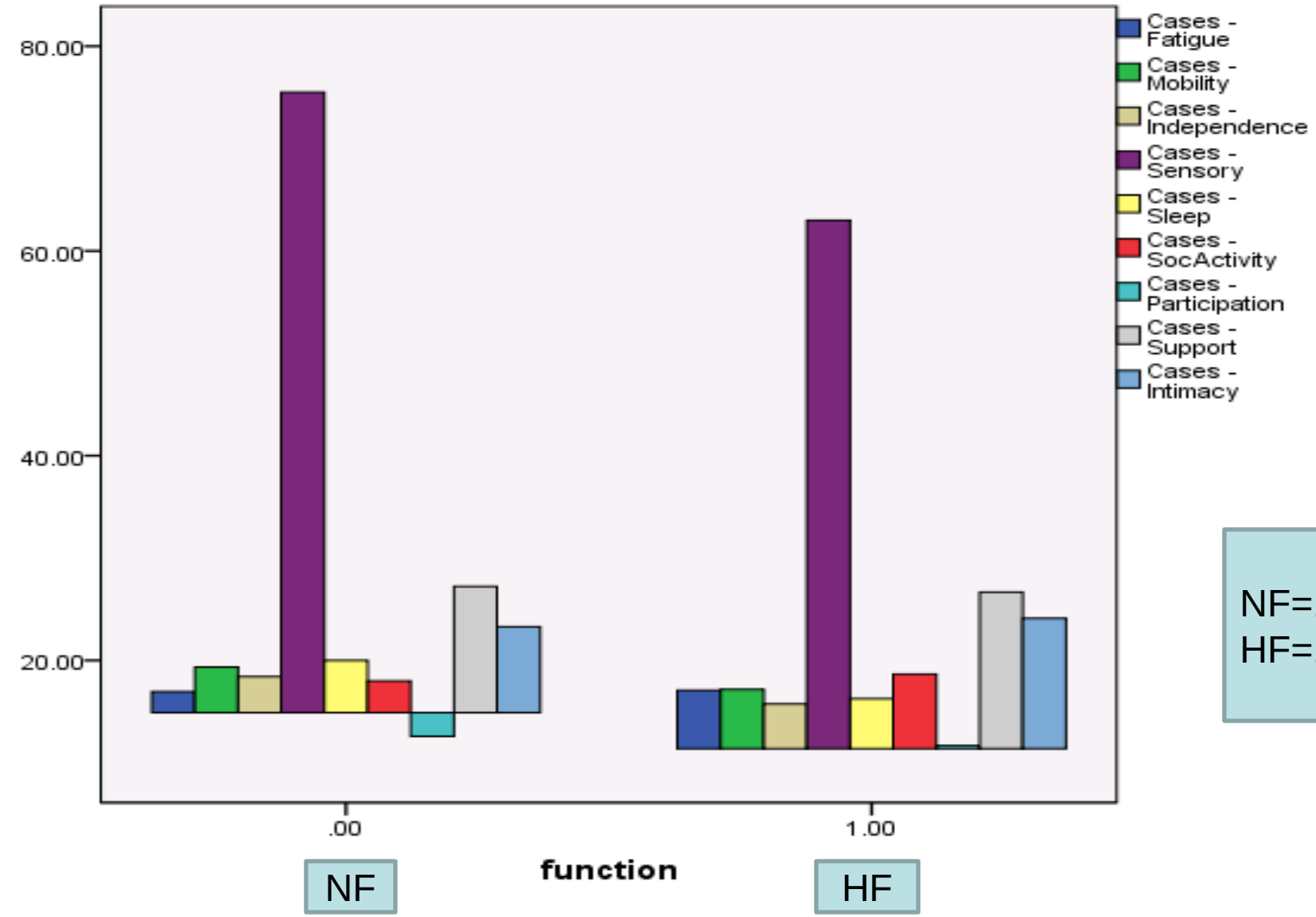
Findings by Attribute:

Cognitive & Emotional characteristics



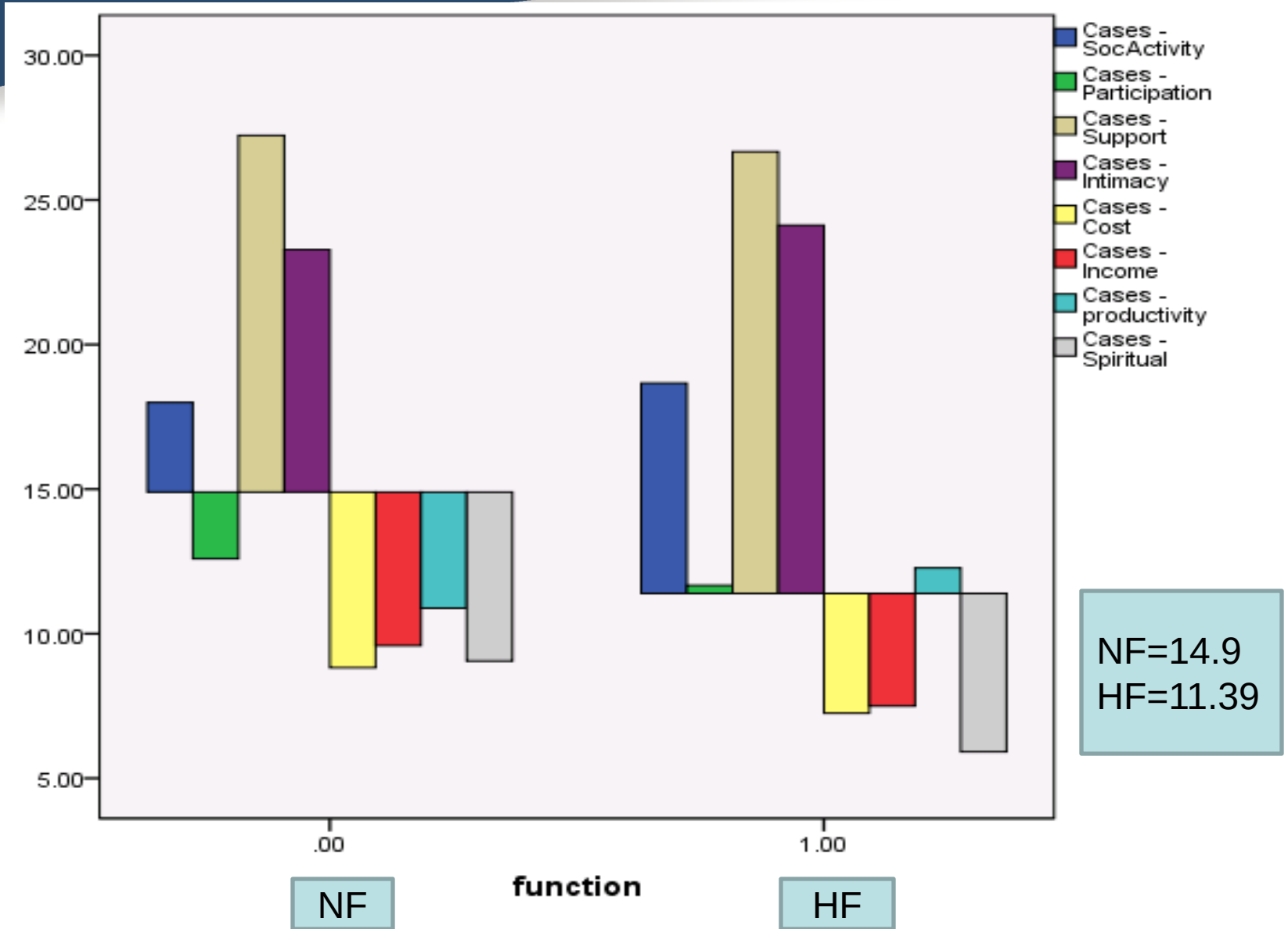
NF=14.9
HF=11.39

Findings by Attribute:
Physical & Social characteristics



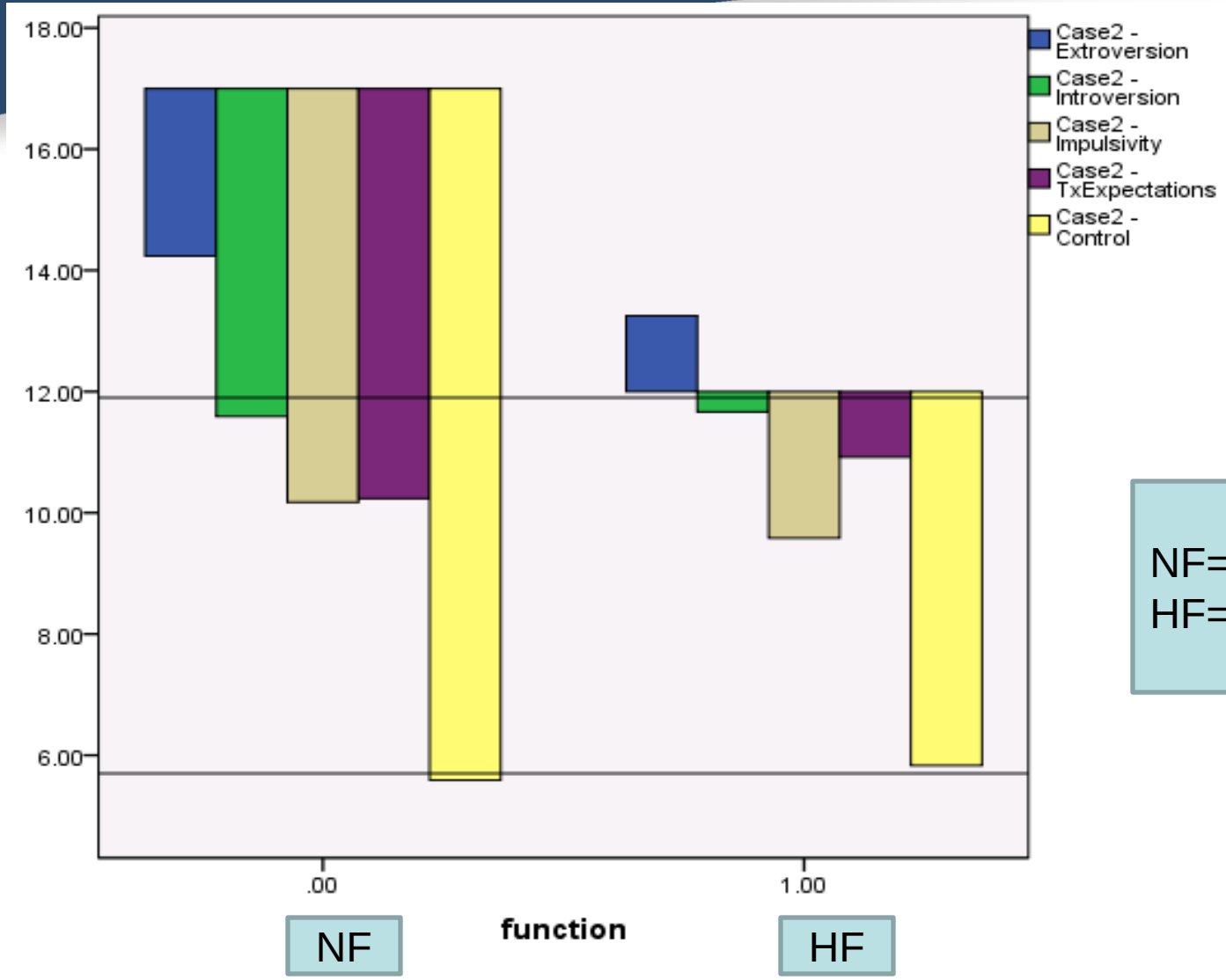
NF=14.9
HF=11.39

Findings by Attribute:
Social, Economic & Spiritual Characteristics



NF=14.9
HF=11.39

Findings by Attribute:
Personality, Treatment Expectations & Locus of Control



NF

HF

NF=17
HF=12

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Conclusion

- Patients with NF micro & macroadenomas experience decreased QoL – predominance of micro in sample
- DOLFS demonstrates internal consistency reliability
- Needs further testing

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Considerations: Challenges

- Number of subjects
- Impact of convenience sampling -skews data
- Not all types of functional adenomas were represented.
- Minimal numbers in groups by diagnosis.
- Responder fatigue- minimal qualitative data
- Difference between N/A and “Not at all”- not perceived by all respondents.

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Strengths:

- Self administered
- Completion time less than 20 minutes
- Minimal missing data despite interruptions
- Tool required little introduction
- Recruitment only limited by inclusion criteria.
- Amenable to an electronic format

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Future:

- Increase sample
- Analysis to include more subjects in each diagnostic category
- Electronic format
- Funding?!

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Program Accomplishments

- 1.Practice
  - State of the science in pituitary diseases
  - Identify gaps in knowledge in symptoms management
  - Collaborated with associated specialties

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Program Accomplishments

- 2. Influencing Health Outcomes

  - DOLFS- identification of baseline indicators of dysfunction on which to base further research.

  - Poster Presentations:

    a. Western Institute of Nursing conference

    b. Sigma Theta Tau International (STTI) 2011 Biennial Convention

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3. Policy & Systems

- Western Institute of Nursing
- Endocrine society
- Sigma Theta Tau International

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- Gary Laustsen, PhD, FNP-BC, RN
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Epilogue:

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Clinical Inquiry Project: Appendix

Domains of Life Function Scale for Patients with Pituitary Adenomas.

Christine Yedinak

Oregon Health & Sciences University

Appendix 1 Evidence Table

Authors/Design	PURPOSE	SUBJECTS	INTERVENTIONS	OUTCOME MEASURES	RESULTS	CONCLUSIONS	COMMENTS
Barzaghi et al 2007 Complications transsphenoidal surgery in pt with PA: experience at a single center Retrospective analysis	Report	420 All PA's with few PRL	None	Mortality morbitidy	Medical complications Incr >65yrs 4.9%vs 1.4% (*P*=0.009) & large adenomas 5.6 vs 1.6% (p = 0.0002		Descriptive- one site Consistent with other readings
Budrukkar et al 2009 Prospective assessment of QOL in adult pts with primary barin tumors in routine neurooncology practice. prospective	Evaluate various factors on QOL in pt with brain tumors	250 adults neoplasms over one yr 159 completed (66%) themselves	Data collection usine EORTC0 QLQ-30	Five function scales: Physical role Emotional Cognitive Social Three symptom scales. Fatigue, nausea, vomiting and pain 6 single item scales, Dyspnea, insomnia appetite loss, constipation, diarrhea, financial effects	84 pt required assistance to fill out form-neurological def(42%) and 74& of these with motor weakness. illiteracy (37%) 87% presented with HA, Memory loss (36%. Seizures 31%, Gail abnormal 22% Behavior probl (16%) focal seizures (9%)		Analysis SPSS version 14 Consider cultural changes Malignancy not nec comparable to PA. tumor position impt to fx Scale EORTCO poss for Domain and item use
Dekkers et al 2006 QOL is decreased after <u>treatment</u> for NFPmacro Case controlled	Determine if treatment makes a diff in QOL	128 consective NFMA All post op TSS- Only 116 participated	Hospital Anxiety and Depression Scale, Mulitdimensional Fatigue Index, Nottingham Health Profile	QOL scores for each tool per patient compared to reference ranges for tool derived from gen population	HADS- NS MFI-20 Sig Gen fatig(0.01) Physical fatig Reduced activity Reduced	Mostly not disease specific QOL changes Stat sig QOL decreases in MFI-20	No same group comparison ?. Not all matched to local culture – European with multiple cultural influences– controls only age matched by group not individuals- assumed healthy but no information given. No information about

Prospective Non random		Controls- 125 age adjusted references from literature or make identified age and gender	SF-36 Questionnaires mailed Pit fx		motivation Mental fatigue (all <0.05) NHP Pain NS SF-36 Physical function Pain and health change NS	NPH SF-36	No control for post op complications 41% with VF deficts (unknow if both pre and post op) not included in stat analysis as independent variable GH def assumed based on other axis dysf
Kan et al 2006 Validation of QOL quest for Pt with PA Prospective Non randomized	Develop and validate self administered questionnaire to measure QOL in PA	84 in focus group 20 pt in item validation and selection group 44 pt in pilot group for new instrument	Focus groups Tool development and Tool pilot	106 item questionnaire, validated 30 most important items chosen by 20 patients 17 items selected by HC professionals. New instrument RAND-36 FACT-G/Fact-Br Karnofsky Performance Scale (KPS) Pearson's correlation coefficients Student's t test for two sets of scores obtained one month apart	47 of 55 (85.5%) Questionnairs completed Test/Retest on 24 reliabilty 0.88 Concurrent validity- 47 responses 0.75 Pearson's correlation coefficient. (20 pt) Extreme groups did not compare well to RAND	Authors concluded valid and reliable questionnaire for pt centered outcomes measure – For clinical trials and disease progression. Correspond favorably with reference questionnaires	Scale includes disease specific symptoms, general , emotional health and social /family wellbeing and relationships, satisfaction with provider and treatment. No objective measures of function Lengthy (54 questions) not suitable for clinic setting . Authors reported 11 min to complete. No pt requested help Tested against population norms Over one third of responses were labeled as 'extreme' Only 24 patient did test- retest reliability. No control group to compare responses done one mth apart. Focus musculoskeletal for PT not specific disease. Concept of change/decr QoL in aging. Tool does not include Gonadal/Sexual fx Changes in social support or role

							changes as a result of the tumor Not disease specific No local control group. Does not discrimation between micro and macroadenoma for NFPA No post tx comparison. Culture not considered No age and gender comparisons No pre op or pre treatment comparisons done No non functioning microadenomas included Did include age and gender matched control subjects from the social environment of the patient Cumbersome. Questions redundant for clinical use No specifics re TX not sued in stat analysis only surgically 'cured acromeg and cushing pt included compared w paragangliomas XRT and hypopit but no spec def considered.
Jagsch et al 2006 Which instrument is more suitable to assess health-related QOL- NHP or SF-36 Prospective Non-random	Patient reported outcome measures (subjective HR-QoL) multiple instruments to determine most appropriate in outcome	Two groups 1. Elderly- 46 (mean age 68y) 2. Young- (mean 36) Acted as control group	Both groups completed both forms & assessed each instrument on Visual Analogue Scale for suitability for use in research	VAS of pt assessment of utility of tool for application in scientific study	Young group acted as control ? Had difficulty with negative questions and limited reponses Y/N No statist gender diff	Instrument should be chosen for specific situation and user	

	studies in gerontology						
Johnson et Al 2003 Quality of life in Patients with a pituitary adenoma	To assess perception of the impact of a PA prior to tx	168 patient with PA hypersecretion and/or PA 42 Cushings Dz 39 Prolactinoma 36 acromagaly 51 NF PA	SF-36 version2 Use of a validated instrument	8 health scores Physical fx Role –physical Bodily pain General health Vitality, Social fx Role emotional Mental fx Normal population score of 50 Scores for each type of tumor compared	PA- all impaired. Cushings' *P*< 0.05 Acromgely Sig decrease Physical Fx Role physical Gen health Vitality *P*< 0.05		Recommend using instrument pre and post treatment routinely
Vander Klaauw et al 2008 Disease- specific impairments in qulaity of life during long-term follow up of patient with different pituitary adenomas Prospective Post treatment	Evaluate QoL based on age and gender adjusted (Z socres) in pt with PA	Convenience sample: Total 403 patients Acromegaly-118 Cushings's 58 Prolactinoma 118 NF macro A - 99 Control pop 440 Pt in f.up for 13 +/- 8 yrs Pituitary deficiency defined By std	Hospital Anxiety and Depression Scale (HADS) Multidimensional Fatigue Inventory (MFI)-20 Nottingham Health Profile (NHP) SF-36 Mailed to home	Determined z scores for questionnaires measured After tx for PA Each PA compared with controls for each of subsections of each instrument. Absolute QoL scores compared all pt and controls by indep *t* test, Anova and Tukey's pot hoc	All with impaired QoL compared to controls all *P*= 0.001 Is sig dx specific Diff between type of PA *P*=0.003 No diff in z scores for subscales with except of physical ability *p* =0.002 – Acro>NFMA, PRL.	All impaired No diff in acro – all tx & CD with anxiety PRL- size no diff Age & gender neg predictor of physical fx Males -better3/7 subscales XRT no influence Hypo pit neg infl Length of .up neg influence Need to inform pt to avoid inapprop expectations.	

Page et al 1996 An account o QOL of patients after treatment for non-functioning pituitary tumors. Prospective Case controlled Post treatment Convenience	Determine effect of Anterior pit def and XRT on QOL in pt with NFPA	Convenience sampling 48 pt NOPA No GH replacement Control group 42 pt after mastoid surgery Criteria: PA by histology Sellar enlargement Tumor >1.0cm PRL<8,000 PRL <5% of cells histol No other excess stanining No biochem excess other than PRL. Only TSS surgery included	Use of SF-36 & General Well Being Schedule (GWBS)	Difference between scores on each QoL tool for controls vs pt with PA Non parametric stats	No difference was determined Between scores for QOL IGF-1 was significantly lower in Pit Pt than controls *P* <0.0001 with 69% PA pts with IGF-1 below age match range compared wth 14 *p* <0.002 XRT lower mental health scores Depression and emotional control *p* <0.05	GH therapy not warranted in all cases. (Note this was not purpose of this study) May be an effect of XRT on QOL needs further investigation	Similar age range but not matched gender and age. Not std set of ant Pit fx evaluated for all pats- selective check on hormones PRL excess was no exclusion criteria Only macroadenomas assessed Results contrary to other studies finding lower Qol- ? artifact, insensitivity of tools for use in PA. subject selection? Control group, are changes related to surgery, other factors such as personality etc
Santos et al 2009 QoL in pt with PA	Highlight recent findinds in QoL in defferent types of PA and hypopituitaryism	Multiple sudies	Acromegaly Study-Neggers - 20pt receiving somatostatin analogue- double-blind, placebo-controlled, randomized, cross-over study:	none	Acromegaly QOL sign improve with pegvis.no change in IGF-1-CLINICAL IMPROVEMEN - MORE SENSITIVE	Qol studies allow for identification Of dimensios that are affected by the disease but not always contemplated as health problems in treatment.	Leaves question – are there parameters that do improve for specific individuals or collectively after treatment- need pre and post tx analysis of same pop- ust be sensitive instrument Are muscle skel better than pre tx or not cured pt with acro/

			pegvisomant or placebo x16week Qol improved sign Matta- physical and psycho scores better in cured than active Miller- musc/skel SF-36& AimS2 worse than gen pub Personality traits associated CUSH- SF-36 Needs more study PROLACTINOMA Qol inversely correlated with PRL level Vander KLaauw- Neg corr with Hypopit VISION – decreased QoL		than IGF-1 P.S. used AcroQol	Disease focused QoL tools Imporved utility for clinical practice and research and therapeutic outcomes.	Evaluation of personality traits affected Qol, treatment adherence and patient –doctor contact.
Sievers et al 2009 Personality in pt with PA is characterized by increased anxiety-related traits: comparison of 70 acromegalic pt with patients with NFPA and age and gender –matched controls. Cross sectional prospective	To determine if pt with acromegaly had an altered personality compared withpateints with NFPA and healthy controls.	70 acromegaly 58 NFPA 140 mentally age and gender matched	Eysenck personality Questionnaire-Tridimentional personality questionnaire	Personality type with subscales; Extraversion; Psychoticism. Neruoticism (Eysenck) TPQ- Level of desire to be socially acceptable Correlation between sub- scales	Acromegaly with increased: Neurotic EPQ-N $P<0.001$ Harm avoidant TPQ-HA $p<0.001$. Reduced novelty seeking ($p<0.001$) High social conformity EPQ-DS $p<0.001$. Compared with both controls and NFPA. Also higher in NFPA than in controls	Acromeglic pt more harm avoidant, neurotic, high social conformity NFPA and acromeg with increased Anticipatory worries and pessimism Higher fear of uncertainty, fatiguability and asthenia. Diff with acromegaly	Not 1:1 matched age and gender. Unknown if from same social environment. No causal relationship between acromeg and person alterations need more prospective studies. ? are personality alterations result of acromegaly i.e. PA or GH excess, changes in neurotransmission associated with pit axis changes. No difference noted in personality changes associated with tumor size. Need to assess personality changes with respect to other tumors. Given unknown origin of tumors difficulty to determine changes as caused by

					Acromegaly Worse novelty seeking and impulsive for age and general, adenoma tyupe surgery radiation and deficiency & All Clinical variables. (*p* =0.032. Improvement noted in treated pt with acromeg ness adjusted	No diff between micro and macr with and without pit deficiencies	tumor.
T'Sjoen Et al 2007 Health-related QoL in acromegalic subjects: data from AcroBel, the Belgian Registry on acromegaly Crossectional design Based on	Assess impairment in QoL in atient with controlled and uncontrolled acromegaly	291 pt with acro 237 Macro 42 micro 11 unknown 1 carcinoid 202 GH ex only 69 co-GH/PRL 15 alpha sub or TSH 169 pit fx OK 120- 1 or more def 42% arthropathy 39% HTN 27% CTS 23% DM 21% goiter 116	Specific signs and symptoms score (SSS) & AcroQoL questionnaire f.up 10 years	Assessment of perception of QoL using Specific signs and symptoms score (SSS) & AcroQoL questionnaire	IGF-1 z score correlated with the age at diagnosis (r=0.190, *p*=0.001) Glycemic control neg correlated SSS subsores no diff except soft tissue swelling scored higher in active Dz. Joint pain worse in older patients otherwise no diff Females increased headache & fatigue scores. Excess perspiration	No sig relation between AcroQol scores and biochem marker of disease and GH. No difference in QoL score between patient with active and inactive disease Cosmetic and orthopeaedic deformities independent of GH levels)(possible reason for worse Qol scores)	Use to select treatment options based on scores Notes" pt's perspective well-being is an important outocome". Need to identify what is most important factor in patient Qol. –Have patient rate own cometic and orthopedic changes

		(40%)surgery 18 (16%) XRT 71(24%) both 185(64%) med tx 134(46%) Somato 39(13%) DA 12(4%) both			assoc with increased body weight Neg correlation between median SSS and AcroQol scores in the whole study pop		
Webb et al 2008 Evaluation of health –related QoL in patients with cushing's syndrome with a new questionnaire Observational, international, cross-sectional	Evaluate the effects of chronic exposure to hypercortisolism on QoL	125 pts (Spain, France, Germany, Netherlands, Italy) 107 pituitary dependent CD 18 adrenal dependent CS	2-mth f.up Clinical and hormonal data SF-36 Cushings QoL score	Feasibility of clinic use Relaiblity, Validity of 'questionnaire Correlation between Cushings QoL scores and pt self perceived general health status and dimensions of SF;-36 Impact of XRT	Correlation sig between CushingQol scores and SF-36 (Pearson's correlation coefficient >0.597) Current hypercortisolism scored worse Linear regression-female gender predictors of worse QoL	Disease specific CushQoL, is feasible (4 mins to compl) Reliable and valid. Sensitivity to change and test-retest reliability needs longitudinal studies.	Most pt with cushing's female.

APPENDIX 2

Oregon Health & Science University Consent and Authorization Form eIRB#: **6979** Protocol Approval Date: 12-22-2010	MED. REC. NO. _____ NAME_____ BIRTHDATE _____

OREGON HEALTH & SCIENCE UNIVERSITY
Consent and Authorization Form

TITLE: Domains of Life Function Scale for Patients with Pituitary Adenomas

PRINCIPAL INVESTIGATOR:	Gary Laustsen PhD APRN-CNP	(541) 9623132
CO-INVESTIGATORS:	Chris Yedinak MN FNP	(503) 494-6576
	Michael Leo PhD	(503) 494-1137

PURPOSE:

You have been invited to be in this research project because you have been diagnosed with a pituitary adenoma or pituitary disease. Pituitary adenomas are tumors in the pituitary gland that may cause several medical disorders. A person's pituitary gland may make too much or not enough of a specific hormone, and a tumor may affect your eye sight or cause symptoms that change your ability to function in life and hence your quality of life.

The primary purpose of this study is to understand the changes that occur in the lives of people with pituitary adenomas. We are seeking to understand how this affects your life and the amount of change you have experienced in what you do, or would like to do every day. It is also hoped that we will better understand if these changes occur for patients with all types of pituitary adenomas and if there are differences between specific types of pituitary tumors.

You will be asked to complete a questionnaire to tell us the specific symptoms and changes you have experienced as a result of these symptoms. You will also be asked how much these changes have impacted your life.

Approximately 40 men and women with pituitary adenomas and pituitary dysfunction will participate in this study. All participants will be OHSU patients.

PROCEDURES:

Your participation in this study will limited to one event. You will be asked to complete a questionnaire before the conclusion of your visit today. The questionnaire includes questions about your symptoms and the extent to which these are affecting what you do every day. You will be asked to place your completed

questionnaire in the envelope provided, seal it, and leave it with the medical assistant as you check out.

If you agree to participate in this study, we will review the laboratory information collected during your work up, your MRI and your diagnosis. We will collect and analyze your perceptions of your symptoms and how they are affecting what you do in your life and the medical data and information that led to your diagnosis. This will include the size of your tumor (obtained from your MRI), and your pituitary hormone levels (obtained from the results of your blood work). This information will be stored in a protected database for use, by the researchers named above, in future research to compare changes you may experience during your treatment.

RISKS, DISCOMFORTS and BENEFITS:

This is an observational study and the reason for this study is to observe the effects of the pituitary adenoma or disease on your quality of life. There should be no physical risks or discomforts to you as a direct result of taking part in this study.

You will not benefit from participating in this study. However, by serving as a subject, you may help us learn how to help patients with pituitary adenomas and disease in the future.

CONFIDENTIALITY AND PRIVACY OF YOUR PROTECTED HEALTH INFORMATION:

We will not use your name or your identity for publication or publicity purposes.

All of your information will be kept in a password-protected database maintained by the co-investigator.
The use and sharing of your protected health information will only be for the purposes described in this consent.

Any information transferred electronically will be coded to protect your confidentiality.

The persons who are authorized to use and/or disclose your health information are all of the investigators who are listed on page one of this Research Consent Form and the OHSU Institutional Review Board. The Office for Human Research Protections is authorized to receive this information as required for its research oversight activities.

COSTS:

There will be no cost to you for participating in this study. You or your insurance company will be billed for the regular clinic visit during which this information will be collected.

PARTICIPATION:

You do not have to join this or any research study. Your participation in this study is voluntary. If you refuse to join, there will be no penalty or loss of any benefits to which you are otherwise entitled.

If you have any questions regarding this study now or in the future, contact the principal investigator of this study, Gary Laustsen PhD APRN-CNP, (541) 9623132 or co investigator Christine Yedinak MN FNP, (503) 494-6576. If you have any questions regarding your rights as a research subject, you may contact the OHSU Research Integrity Office at (503) 494-7887.

We will give you a copy of this signed and dated form.

SIGNATURES:

Your signature below indicates that you have read this entire form and that you agree to be in this study.

_____
Name of Subject

_____ _____
Signature of Subject Date of Signature (Month/Day/Year)

_____ _____
Printed Name of Person Obtaining Consent Date of Signature (Month/Day/Year)

_____ Date :
Signature of Person Obtaining Consent

Appendix 3 Legend- Description of Domain Characteristics

DOMAIN	Characteristic	Question #	Question	
COGNITIVE	ability to learn	76	I have difficulty learning new information or new things.	**CA**
		78	I have trouble learning a new skill despite repeating it several times	CA
	concentration& distractibility	79	I have difficulty concentrating to finish what I am doing	CC
		123	My brain has trouble keeping track of things	CC
		149	I am easily distracted	CC
	mental agility	142	I feel I make mistakes easily	CM
		Not incl	my head feels foggy	CM
		Not Incl	I am slow to think about things	CM
		Not Incl	I need help in daily/monthly financial matters	CM
	memory and recall	81	I have trouble remembering information from medical appointments	CM R
	Verbal recall	82	I have had trouble recalling names of things.	CV
		83	I have trouble finding the right word when talking	CV
		84	I have had trouble keeping track of what is being said in a conversation	CV
EMOTIONAL	anxiety	130	I have feelings of panic	EA
		147	I feel Like something awful will happen	EA
		161	I Worry	EA
		169	I Feel Overwhelmed	EA
		190	I feel Tense or wound up	EA
		195	I feel Vulnerable	EA
	body image	3	an absence of facial hair	EBI
		4	needing to shave my facial hair	EBI
		5	Facial flushing or redness	EBI
		6	Puffy eye lids	EBI
		7	acne	EBI
		8	Thinning hair/bald patches/hair loss	EBI
		9	A loss of part of my eyebrow hair	EBI
		10	Gaps between my teeth	EBI
		11	My jaw size	EBI
		12	My lips swelling	EBI
		13	My nose getting wider	EBI
		14	Deep furrows in my brow	EBI

		15	Protruding/growing brows	EBI
		16	A hoarse voice	EBI
		17	A thick tongue that changes my speech	EBI
		18	Snoring when I fall asleep	EBI
		19	A barrel shaped chest	EBI
		20	Fine facial wrinkles	EBI
		21	A hump on the back of my neck	EBI
		22	A larger than usual breast size	EBI
		23	A smaller than usual breast size	EBI
		24	breast/nipple discharge	EBI
		25	General weight loss	EBI
		26	Midsection weight gain	EBI
		27	an increase in ring and/or shoe size	EBI
		28	bruising	EBI
		29	thin/fragile skin	EBI
		30	coarse skin	EBI
		31	oily skin	EBI
		32	dry skin	EBI
		33	skin tags	EBI
		34	dark brown/black velvety skin patches under arms and/or in skin folds	EBI
		35	easy sweating/ body odor	EBI
		36	slow wound healing	EBI
		37	stretch marks on abdomen or other body parts colored dark pink or purple	EBI
		38	large areas of skin that have turned dark	EBI
		39	yellowing of my skin	EBI
		40	skin Rash	EBI
		41	dry parchment like skin	EBI
		42	brittle fingernails	EBI
		43	the way my body looks	EBI
		194	I avoid social activities because of my appearance	EBI
		132	I think people avoid me because of my appearance	EBI
	depression	120	Guilty	ED
		126	I don’t particularly like the person I am	ED
		140	Worthless	ED
		143	Restlessness and agitated	ED
		151	easily Annoyed	ED

		172	Irritable	ED
		175	Angry	ED
		192	hopeless about my future	ED
		198	Suicidal	ED
		199	Like crying	ED
	locus of control	121	my illness was meant to be	EL
		128	regularly Dr. visits will help me avoid getting sick	EL
		135	I am responsible for my on health	EL
		170	My health is in the hands of my health care team	EL
		174	it will take luck for me to recover from being illness	EL
		189	I have faith I will get better	EL
		205	I can help myself recover from being ill	EL
		111	I feel out of control	EL
	motivation	122	Others seem to get more done in a day than me	EM
		160	I lack motivation to do things.	EM
		186	I lack energy to do my household chores	EM
		164	motivated if my work is acknowledged/	EM
		156	I like seeing what I have accomplished myself	EM
		162	I feel like getting things done around the house	EM
	extroversion	108	I like to let people know my opinion and where I stand on issues	EPE
		113	I find it easy to talk with anyone	EPE
		141	I like being around a large number of people	EPE
		201	I prefer talking with others about my illness	EPE
	introversion	193	I like time to think things through well before acting	EPI
		114	I find it hard to talk wo people I don't know	EPI
		124	I like to keep the way I feel about things to myself	EPI
	somatization	103	I read medical books or the internet	EPS
		154	I worry about something bad happening to my health	EPS
		159	I spend time researching my health problems	EPS

		148	I am worried about symptoms I read on the internet	
	impulsivity	105	I get agitated if things don't happen quickly	EPU
		107	Planning usually doesn't help things be more sucessful	EPU
		144	I make decisions quickly	EPU
	emotional stability	89	I have rapid changes in mood	ES
		110	I am Optimistic about my future	ES
		155	I take most things in stride	ES
	self esteem	196	I feel Good about myself	ESE
		202	I get upset if I am criticized	ESE
		204	I am confident in my decisions	ESE
	treatment expectations	127	I expect I will never be healthy	ET
		133	I think my recovery will take some time	ET
		145	I anticipate a full recovery	ET
PHYSICAL DOMAIN	Energy & Fatigue	109	I lack energy to do social activities with friends	PE/F
		136	my fatigued interferes with my work life	PF
		157	I am fatigued during the day	PF
		177	my fatigue disrupts my family life	PF
		118	my exercise is limited by my fatigue	PF
	independence in activities of daily living	112	I need help with transportation	PI
		119	I can take care of myself	PI
		150	I need help to do laundry	PI
		173	I need help to do my shopping	PI
		178	I need help to do cooking	PI
		88	I have difficulty carrying a bag of groceries	PI
	mobility	90	general weakness	PM
		91	walking up one flight of stairs	PM
		92	standing from a sitting position without using my hands to help	PM
		93	bending, kneeling or stooping	PM
		94	Loose joints (they move in unusual directions)	PM
		95	Swelling in my feet and ankles	PM

		96	walking a mile	PM
		97	being able to exercise because of weakness	PM
	sensory symptoms	44	Headaches	PS
		45	Blind spots in my vision	PS
		46	Dizziness with standing	PS
		47	Dry mouth	PS
		48	Ringing in my ears	PS
		49	difficulty breathing	PS
		50	Nasal congestion or drainage	PS
		51	Increasing roundness of my face	PS
		52	A bad/salty taste in my mouth	PS
		53	Thirst that is difficult to quench	PS
		54	Loss of sense of smell and/or taste	PS
		55	Numbness or tingling on my scalp	PS
		56	A faster than usual heart rate	PS
		57	A slower than usual heart rate	PS
		58	Abdominal pain/discomfort	PS
		59	nausea	PS
		60	vomiting	PS
		61	constipation	PS
		62	diarrhea	PS
		63	poor appetite	PS
		64	hunger	PS
		65	flatulence /gas	PS
		66	Muscle pain	PS
		67	Joint pain	PS
		68	have abnormal sensations such as prickling, burning, tingling	PS
		69	Wrist pain	PS
		70	muscle cramping	PS
		71	cold skin	PS
		72	hot flashes/night sweats	PS
		73	Pain when I try to exercise	PS
		74	urinating frequently during the day (every 1-2 hours)	PS
	sleep	104	I wake early morning & can't go back to sleep	PSL
		117	I wake up tired	PSL
		153	urinating frequently at night (every 1- 2 hours)	PS

				L
		163	I fall asleep when I sit quietly/read	PSL
		180	I sleep much of the day	PSL
		182	I fall asleep at stop lights while driving	PSL
SOCIAL DOMAIN	social activity participation	125	I get together with friends	SA
		134	I prefer to stay home than to go out with my friends	SA
		176	I enjoy activities like I did before my illnessenjoy social activities	SA
		188	I prefer watching sports rather than participating in sports.	SA
		129	I prefer to stay home than to an event with people	SA
	intimacy and sexual function	75	I have an irregular menstrual cycle (period)	SI
		116	my sexual interest is decreased	SI
		131	I have a morning erection	SI
		137	I have decreased vaginal moisture	SI
		139	I have had an increase In my sexual interest.	SI
		152	My partner and I have had trouble getting pregnant	SI
		168	I have had a decline in my sexual interest	SI
		183	I have a morning erections	SI
		184	My testicles have shrunk	SI
		197	my sexual interest is increased	SI
		115	I feel my body is not attractive to my partner	SI
		158	I feel my body is not attractive	SI
	role participation (home, work and/or school)	101	I have trouble finishing projects at home or at work	SR
		102	I have trouble doing things at work in a reasonable time.	SR
		138	My illness has caused my to let people down	SR
		165	I like to get started on new projects at work	SR
		171	I am happy with what I am able to achieve each day	
	social support	179	I have someone I trust that I can confide in.	SS
		185	I have friends who try ot help me	SS

		200	I have family members who try to help me	SS
		167	I talk with my friends about my health issues	SS
		191	my spouse/partner is supportive	SS
		167	I talk with my friends about my health issues	SS
ECONOMIC	Assessment of the economic burden of disease.	85	I have trouble finding the money to buy my medications	Ec B
	ECONOMIC	181	I feel stressed because of my medical bills	Ec B
		86	I have difficulty finding the money to pay for my insurance	Ec B
	Ability to generate an income to support their needs	146	I'm limited in the kind of work I can do because of my illness	EcI
	ECONOMIC	187	My job performance is affected by my illness	EcI
		203	I am worried about earning enough to pay my bills since my ilness	EcI
	individual ‘s ability to participate in satisfying productive or creative endeavors	156	I like seeing what I have accomplished myself	Ecc
		166	I feel productive	Ecc
		87	I have difficulty coming up with new ideas	Ecc
SPIRITUAL DOMAIN		98	I have difficulty participating in my regular religious activities	SP
		99	I have had difficulty attending important religious events	SP
		100	staying in contact with people of my faith	SP
		106	my faith has changed because of my illness	SP

APPENDIX 4
DOMAINS OF LIFE FUNCTIONS LIFE SCALE FOR PATIENTS with PITUITARY ADENOMAS (DOLFS)
Please circle the response to the right that correspond most closely with your daily experience.

		1	2	3	4	5
1.	How healthy do you feel today compared with your desired state of health?	Much worse	A little worse	Same	Better	Much better
2.	How do you feel today compared with 12 months ago?	Much worse	A little worse	Same	Better	Much better

I am bothered by:		1	2	3	4	5	6
3.	an absence of facial hair (males only)	N/A	Not at all	a little	somewhat	quite a bit	very much
4.	needing to shave my facial hair (females only)	N/A	Not at all	a little	somewhat	quite a bit	very much
5.	Facial flushing or redness	N/A	Not at all	a little	somewhat	quite a bit	very much
6.	Puffy eye lids	N/A	Not at all	a little	somewhat	quite a bit	very much
7.	acne	N/A	Not at all	a little	somewhat	quite a bit	very much
8.	Thinning hair/bald patches/hair loss	N/A	Not at all	a little	somewhat	quite a bit	very much
9.	A Loss of part of my eyebrow hair	N/A	Not at all	a little	somewhat	quite a bit	very much
10.	Gaps between my teeth	N/A	Not at all	a little	somewhat	quite a bit	very much
11.	My jaw size	N/A	Not at all	a little	somewhat	quite a bit	very much
12.	My lips swelling	N/A	Not at all	a little	somewhat	quite a bit	very much
13.	My nose getting wider	N/A	Not at all	a little	somewhat	quite a bit	very much
14.	Deep furrows in my brow	N/A	Not at all	a little	somewhat	quite a bit	very much
15.	Protruding/growing brows	N/A	Not at all	a little	somewhat	quite a bit	very much
16.	A hoarse voice	N/A	Not at all	a little	somewhat	quite a bit	very much
17.	A thick tongue that changes my speech	N/A	Not at all	a little	somewhat	quite a bit	very much
18.	Snoring when I fall asleep	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
19. a barrel like shape to my chest	N/A	Not at all	a little	somewhat	quite a bit	very much
20. Fine facial wrinkles	N/A	Not at all	a little	somewhat	quite a bit	very much
21. A hump on the back of my neck	N/A	Not at all	a little	somewhat	quite a bit	very much
22. A larger than usual breast size	N/A	Not at all	a little	somewhat	quite a bit	very much
23. A smaller than usual breast size	N/A	Not at all	a little	somewhat	quite a bit	very much
24. breast/nipple discharge	N/A	Not at all	a little	somewhat	quite a bit	very much
25. General weight loss	N/A	Not at all	a little	somewhat	quite a bit	very much
26. Midsection weight gain	N/A	Not at all	a little	somewhat	quite a bit	very much
27. an increase in ring and/or shoe size	N/A	Not at all	a little	somewhat	quite a bit	very much
28. bruising	N/A	Not at all	a little	somewhat	quite a bit	very much
29. thin/fragile skin	N/A	Not at all	a little	somewhat	quite a bit	very much
30. coarse skin	N/A	Not at all	a little	somewhat	quite a bit	very much
31. oily skin	N/A	Not at all	a little	somewhat	quite a bit	very much
32. dry skin	N/A	Not at all	a little	somewhat	quite a bit	very much
33. skin tags	N/A	Not at all	a little	somewhat	quite a bit	very much
34. dark brown/ skin patches under arms, in skin folds	N/A	Not at all	a little	somewhat	quite a bit	very much
35. easy sweating/ body odor	N/A	Not at all	a little	somewhat	quite a bit	very much
36. slow wound healing	N/A	Not at all	a little	somewhat	quite a bit	very much
37. dark pink stretch marks on abdomen/other body parts	N/A	Not at all	a little	somewhat	quite a bit	very much
38. large areas of skin that have turned dark	N/A	Not at all	a little	somewhat	quite a bit	very much
39. yellowing of my skin	N/A	Not at all	a little	somewhat	quite a bit	very much
40. skin Rash	N/A	Not at all	a little	somewhat	quite a bit	very much
41. dry parchment like skin	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
42. brittle fingernails	N/A	Not at all	a little	somewhat	quite a bit	very much
43. the way my body looks	N/A	Not at all	a little	somewhat	quite a bit	very much
44. Headaches	N/A	Not at all	a little	somewhat	quite a bit	very much
45. Blind spots in my vision	N/A	Not at all	a little	somewhat	quite a bit	very much
46. Dizziness with standing	N/A	Not at all	a little	somewhat	quite a bit	very much
47. Dry mouth	N/A	Not at all	a little	somewhat	quite a bit	very much
48. Ringing in my ears	N/A	Not at all	a little	somewhat	quite a bit	very much
49. difficulty breathing	N/A	Not at all	a little	somewhat	quite a bit	very much
50. Nasal congestion or drainage	N/A	Not at all	a little	somewhat	quite a bit	very much
51. Increasing roundness of my face	N/A	Not at all	a little	somewhat	quite a bit	very much
52. A bad/salty taste in my mouth	N/A	Not at all	a little	somewhat	quite a bit	very much
53. Thirst that is difficult to quench	N/A	Not at all	a little	somewhat	quite a bit	very much
54. Loss of sense of smell and/or taste	N/A	Not at all	a little	somewhat	quite a bit	very much
55. Numbness or tingling on my scalp	N/A	Not at all	a little	somewhat	quite a bit	very much
56. A faster than usual heart rate	N/A	Not at all	a little	somewhat	quite a bit	very much
57. A slower than usual heart rate	N/A	Not at all	a little	somewhat	quite a bit	very much
58. Abdominal pain/discomfort	N/A	Not at all	a little	somewhat	quite a bit	very much
59. nausea	N/A	Not at all	a little	somewhat	quite a bit	very much
60. vomiting	N/A	Not at all	a little	somewhat	quite a bit	very much
61. constipation	N/A	Not at all	a little	somewhat	quite a bit	very much
62. diarrhea	N/A	Not at all	a little	somewhat	quite a bit	very much
63. poor appetite	N/A	Not at all	a little	somewhat	quite a bit	very much
64. hunger	N/A	Not at all	a little	somewhat	quite a bit	very much

I am bothered by:	1	2	3	4	5	6
65. flatulence /gas	N/A	Not at all	a little	somewhat	quite a bit	very much
66. Muscle pain	N/A	Not at all	a little	somewhat	quite a bit	very much
67. Joint pain	N/A	Not at all	a little	somewhat	quite a bit	very much
68. skin sensations such as prickling, burning, tingling	N/A	Not at all	a little	somewhat	quite a bit	very much
69. Wrist pain	N/A	Not at all	a little	somewhat	quite a bit	very much
70. muscle cramping	N/A	Not at all	a little	somewhat	quite a bit	very much
71. cold skin	N/A	Not at all	a little	somewhat	quite a bit	very much
72. hot flashes/night sweats	N/A	Not at all	a little	somewhat	quite a bit	very much
73. Pain when I try to exercise	N/A	Not at all	a little	somewhat	quite a bit	very much
74. frequent urination during the day (every 1-2 hours)	N/A	Not at all	a little	somewhat	quite a bit	very much
75. an irregular menstrual cycle (period) (female only)	N/A	Not at all	a little	somewhat	quite a bit	very much

I have difficulty with:						
76. learning new information or new things.	N/A	Not at all	a little	somewhat	quite a bit	very much
77. recounting facts about something that is new to me.	N/A	Not at all	a little	somewhat	quite a bit	very much
78. learning a new skill despite repeating it several times	N/A	Not at all	a little	somewhat	quite a bit	very much
79. concentrating to finish what I am doing	N/A	Not at all	a little	somewhat	quite a bit	very much
80. calculating numbers in my head	N/A	Not at all	a little	somewhat	quite a bit	very much
81. remembering information from medical appointments	N/A	Not at all	a little	somewhat	quite a bit	very much
82. recalling names of things.	N/A	Not at all	a little	somewhat	quite a bit	very much
83. finding the right word when talking	N/A	Not at all	a little	somewhat	quite a bit	very much
84. keeping track of what is being said in a conversation	N/A	Not at all	a little	somewhat	quite a bit	very much
85. finding the money to buy my medications	N/A	Not at all	a little	somewhat	quite a bit	very much

I have difficulty with:

86.	finding the money to pay for my insurance	N/A	Not at all	a little	somewhat	quite a bit	very much
87.	coming up with new ideas	N/A	Not at all	a little	somewhat	quite a bit	very much
88.	carrying a bag of groceries	N/A	Not at all	a little	somewhat	quite a bit	very much
89.	rapid changes in mood	N/A	Not at all	a little	somewhat	quite a bit	very much
90.	general weakness	N/A	Not at all	a little	somewhat	quite a bit	very much
91.	walking up one flight of stairs	N/A	Not at all	a little	somewhat	quite a bit	very much
92.	standing from a sitting position	N/A	Not at all	a little	somewhat	quite a bit	very much
93.	bending, kneeling or stooping	N/A	Not at all	a little	somewhat	quite a bit	very much
94.	Loose joints (they move in unusual directions)	N/A	Not at all	a little	somewhat	quite a bit	very much
95.	Swelling in my feet and ankles	N/A	Not at all	a little	somewhat	quite a bit	very much
96.	walking a mile	N/A	Not at all	a little	somewhat	quite a bit	very much
97.	being able to exercise because of weakness	N/A	Not at all	a little	somewhat	quite a bit	very much
98.	participating in my regular religious activities	N/A	Not at all	a little	somewhat	quite a bit	very much
99.	attending important religious events	N/A	Not at all	a little	somewhat	quite a bit	very much
100	staying in contact with people of my faith	N/A	Not at all	a little	somewhat	quite a bit	very much
101	finishing projects at home or at work	N/A	Not at all	a little	somewhat	quite a bit	very much
102	doing things at work/school in a reasonable time.	N/A	Not at all	a little	somewhat	quite a bit	very much

Please circle the response that corresponds most closely with your daily experience.

103	I prefer reading about my illness in books or on the internet	N/A	Not at all	a little	somewhat	quite a bit	very much
104	I wake early in the morning & can't go back to sleep	N/A	Not at all	a little	somewhat	quite a bit	very much
105	I get agitated if things don't happen quickly	N/A	Not at all	a little	somewhat	quite a bit	very much
106	My faith has changed because of my illness	N/A	Not at all	a little	somewhat	quite a bit	very much

107	Planning my activities isn't successful for me	N/A	Not at all	a little	somewhat	quite a bit	very much
108	I like to let people know my opinion about issues	N/A	Not at all	a little	somewhat	quite a bit	very much
109	I lack energy for social activities with friends	N/A	Not at all	a little	somewhat	quite a bit	very much
110	I am optimistic about my future	N/A	Not at all	a little	somewhat	quite a bit	very much
111	I feel out of control	N/A	Not at all	a little	somewhat	quite a bit	very much
112	I need help with transportation	N/A	Not at all	a little	somewhat	quite a bit	very much
113	I find it easy to talk with anyone	N/A	Not at all	a little	somewhat	quite a bit	very much
114	I find it hard to talk to people I don't know	N/A	Not at all	a little	somewhat	quite a bit	very much
115	I feel my body is not attractive to my partner	N/A	Not at all	a little	somewhat	quite a bit	very much
116	My sexual interest has declined	N/A	Not at all	a little	somewhat	quite a bit	very much
117	I wake up tired	N/A	Not at all	a little	somewhat	quite a bit	very much
118	My exercise is limited by fatigue	N/A	Not at all	a little	somewhat	quite a bit	very much
119	I can take care of myself	N/A	Not at all	a little	somewhat	quite a bit	very much
120	I feel Guilty	N/A	Not at all	a little	somewhat	quite a bit	very much
121	I feel my illness was meant to be	N/A	Not at all	a little	somewhat	quite a bit	very much
122	Others seem to get more done in a day than me	N/A	Not at all	a little	somewhat	quite a bit	very much
123	My brain has trouble keeping track of things	N/A	Not at all	a little	somewhat	quite a bit	very much
124	I like to keep the way I feel about things to myself	N/A	Not at all	a little	somewhat	quite a bit	very much
125	I get together with friends	N/A	Not at all	a little	somewhat	quite a bit	very much
126	I feel I don’t particularly like the person I am	N/A	Not at all	a little	somewhat	quite a bit	very much
127	I expect I will never be healthy	N/A	Not at all	a little	somewhat	quite a bit	very much
128	I feel regular Dr. visits will help me avoid getting sick	N/A	Not at all	a little	somewhat	quite a bit	very much
129	I prefer to stay home rather than go to an event with people	N/A	Not at all	a little	somewhat	quite a bit	very much
130	I feel panicked	N/A	Not at all	a little	somewhat	quite a bit	very much

131	I have a morning erection (Male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
132	I think people avoid me because of my appearance	N/A	Not at all	a little	somewhat	quite a bit	very much
133	I think my recovery will take some time	N/A	Not at all	a little	somewhat	quite a bit	very much
134	I prefer to stay home rather than go out with my friends	N/A	Not at all	a little	somewhat	quite a bit	very much
135	I feel responsible for my own health	N/A	Not at all	a little	somewhat	quite a bit	very much
136	My fatigue interferes with my work life	N/A	Not at all	a little	somewhat	quite a bit	very much
137	I am decreased vaginal moisture (female only)	N/A	Not at all	a little	somewhat	quite a bit	very much
138	My illness has caused me to let people down	N/A	Not at all	a little	somewhat	quite a bit	very much
139	I have had an increase in my sexual interest	N/A	Not at all	a little	somewhat	quite a bit	very much
140	I feel Worthless	N/A	Not at all	a little	somewhat	quite a bit	very much
141	I like being around a large number of people	N/A	Not at all	a little	somewhat	quite a bit	very much
142	I feel I make mistakes easily	N/A	Not at all	a little	somewhat	quite a bit	very much
143	I feel Restlessness and agitated	N/A	Not at all	a little	somewhat	quite a bit	very much
144	I make decisions quickly	N/A	Not at all	a little	somewhat	quite a bit	very much
145	I anticipate a full recovery	N/A	Not at all	a little	somewhat	quite a bit	very much
146	I am limited in the kind of work I can do (by my illness)	N/A	Not at all	a little	somewhat	quite a bit	very much
147	I feel like something awful will happen	N/A	Not at all	a little	somewhat	quite a bit	very much
148	I am worried about symptoms I read on the internet	N/A	Not at all	a little	somewhat	quite a bit	very much
149	I am easily distracted	N/A	Not at all	a little	somewhat	quite a bit	very much
150	I need help to do laundry	N/A	Not at all	a little	somewhat	quite a bit	very much
151	I feel easily Annoyed	N/A	Not at all	a little	somewhat	quite a bit	very much
152	My partner and I have had trouble getting pregnant	N/A	Not at all	a little	somewhat	quite a bit	very much
153	I have frequent urination at night (every 1- 2 hours)	N/A	Not at all	a little	somewhat	quite a bit	very much
154	I worry about something bad happening to my health	N/A	Not at all	a little	somewhat	quite a bit	very much

155	I take most things in stride	N/A	Not at all	a little	somewhat	quite a bit	very much
156	I like seeing what I have accomplished myself	N/A	Not at all	a little	somewhat	quite a bit	very much
157	I am fatigued during the day	N/A	Not at all	a little	somewhat	quite a bit	very much
158	I feel my body is not attractive	N/A	Not at all	a little	somewhat	quite a bit	very much
159	I spend time researching my health problems	N/A	Not at all	a little	somewhat	quite a bit	very much
160	I lack motivation to do things.	N/A	Not at all	a little	somewhat	quite a bit	very much
161	I feel worried	N/A	Not at all	a little	somewhat	quite a bit	very much
162	I feel like getting things done around the house	N/A	Not at all	a little	somewhat	quite a bit	very much
163	I fall asleep when I sit quietly/read	N/A	Not at all	a little	somewhat	quite a bit	very much
164	I am motivated if my work is acknowledged	N/A	Not at all	a little	somewhat	quite a bit	very much
165	I like to get started on new projects at work	N/A	Not at all	a little	somewhat	quite a bit	very much
166	I feel productive	N/A	Not at all	a little	somewhat	quite a bit	very much
167	I talk with my friends about my health issues	N/A	Not at all	a little	somewhat	quite a bit	very much
168	I have had a decline in my sexual interest	N/A	Not at all	a little	somewhat	quite a bit	very much
169	I feel overwhelmed	N/A	Not at all	a little	somewhat	quite a bit	very much
170	I feel my health is in the hands of my health care team	N/A	Not at all	a little	somewhat	quite a bit	very much
171	I am happy with what I am able to achieve each day	N/A	Not at all	a little	somewhat	quite a bit	very much
172	I feel Irritable	N/A	Not at all	a little	somewhat	quite a bit	very much
173	I need help to do my shopping	N/A	Not at all	a little	somewhat	quite a bit	very much
174	I feel it will take luck for me to recover from any illness	N/A	Not at all	a little	somewhat	quite a bit	very much
175	I feel Angry	N/A	Not at all	a little	somewhat	quite a bit	very much
176	I enjoy social activities	N/A	Not at all	a little	somewhat	quite a bit	very much
177	My fatigue disrupts my family life	N/A	Not at all	a little	somewhat	quite a bit	very much
178	I need help to be able to cook	N/A	Not at all	a little	somewhat	quite a bit	very much

179	I have someone I trust that I can confide in.	N/A	Not at all	a little	somewhat	quite a bit	very much
180	I sleep much of the day	N/A	Not at all	a little	somewhat	quite a bit	very much
181	I feel stressed because of my medical bills	N/A	Not at all	a little	somewhat	quite a bit	very much
182	I fall asleep at stop lights while driving	N/A	Not at all	a little	somewhat	quite a bit	very much
183	I have a morning erection (Male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
184	My testicles have shrunk in size (male only)	N/A	Not at all	a little	somewhat	quite a bit	very much
185	I have friends who try to help me	N/A	Not at all	a little	somewhat	quite a bit	very much
186	I lack energy to do my household chores	N/A	Not at all	a little	somewhat	quite a bit	very much
187	My job/school performance has declined	N/A	Not at all	a little	somewhat	quite a bit	very much
188	I prefer watching sports rather than participating in sports.	N/A	Not at all	a little	somewhat	quite a bit	very much
189	I have faith I will get better	N/A	Not at all	a little	somewhat	quite a bit	very much
190	I feel tense or wound up	N/A	Not at all	a little	somewhat	quite a bit	very much
191	my spouse/partner is supportive	N/A	Not at all	a little	somewhat	quite a bit	very much
192	I feel hopeless about my future	N/A	Not at all	a little	somewhat	quite a bit	very much
193	I like time to think things through before acting	N/A	Not at all	a little	somewhat	quite a bit	very much
194	I avoid social activities because of my appearance	N/A	Not at all	a little	somewhat	quite a bit	very much
195	I feel vulnerable	N/A	Not at all	a little	somewhat	quite a bit	very much
196	I feel good about myself	N/A	Not at all	a little	somewhat	quite a bit	very much
197	My sexual interest has improved	N/A	Not at all	a little	somewhat	quite a bit	very much
198	I feel Suicidal	N/A	Not at all	a little	somewhat	quite a bit	very much
199	I feel Like crying	N/A	Not at all	a little	somewhat	quite a bit	very much
200	I have family members who try to help me	N/A	Not at all	a little	somewhat	quite a bit	very much
201	I prefer talking with others with my illness	N/A	Not at all	a little	somewhat	quite a bit	very much
202	I get upset if I am criticized	N/A	Not at all	a little	somewhat	quite a bit	very much

203	I am worried about earning enough to pay my bills	N/A	Not at all	a little	somewhat	quite a bit	very much
204	I am confident in my decisions	N/A	Not at all	a little	somewhat	quite a bit	very much
205	I feel I can help myself recover from being ill	N/A	Not at all	a little	somewhat	quite a bit	very much

Please add symptoms and changes you have experienced that are not included in this questionnaire

Please indicate confusing or unclear questions or instructions.

Is there anything else that is not included in this questionnaire that affects your life that you would like share?

THANK-YOU for completing this survey.

Patient Characteristics

Appendix 5

ID	Age	Gender	# pit Def	Tumor Size	Pit Surg	Med Hx	Dx
1	44	m	0	M	Y	1	NF
2	30	f	0	m	N	0	NF
3	31	m	1	m	N	0	Prolactin
4	26	m	1	m	N	0	Prolactin
6	19	f	0	m	N	0	Prolactin
7	44	f	0	m	N	1	NF
9	29	f	1	m	N	0	Prolactin
10	41	f	0	M	Y	0	Co-sec
11	26	f	0	m	N	0	NF
12	45	f	0	M	Y	1	GH
13	41	f	0	m	N	0	Prolactin
14	32	m	2	m	N	0	NF
15	49	m	2	M	Y	0	Prolactin
16	62	f	1	M	Y	1	GH
17	28	f	2	M	Y	0	GH
18	66	m	1	m	Y	1	NF
19	49	f	0	M	Y	1	NF
20	31	f	1	m	N	1	Prolactin
21	19	m	1	m	N	0	NF
22	65	m	2	M	Y	1	Gon
23	67	m	2	M	N	1	Prolactin
24	42	m	0	M	Y	0	NF
25	46	f	0	M	Y	0	other
26	67	f	1	M	Y	1	Co-sec
28	34	m	1	m	Y	0	other
29	58	m	0	m	Y	1	NF
30	62	m	1	M	Y	1	GH
31	70	f	0	m	N	1	NF
32	46	f	0	M	Y	0	NF

NF=Non Functioning/secreting tumors by pathology or biochemistry. Other= Hypersecreting tumors: GH=growth hormone, Prolactin, Gonadotroph.
Co-sec= tumors secreting more than one hormone by pathology
MH=Medical History: 0=None 1=Concomitant controlled disease

Appendix 6 Deleted Items.

Question #	Discrimination: Mean % present	Distribution Standard Deviation from mean	Kurtosis
9	.1379		
12	.000		
13	.1377		
14	.1379		
23	.0690		
25	. 0690		
38	.0345		
39	.0345		
57	.000		
60	.1724		
94	.1286		
133	.8621		
135	1.000		
156	.9286		
164	.9310		
193	1.000		
204	1.000		
205	.9655		
TOTAL 18			
Retained items for population sampling /selection bias/assessment timing			
10	.1379		
11	.1724		
15	.0690		
16	.1724		
17	.1379		
22	.2414		
24	.1379		
30	.1379		
34	.1034		
36	.2414		
40	.2414		
41	.1724		
42	.2857		
45	.2414		
52	.2414		
54	.1724		
55	.1724		
62	.2414		
63	.2069		
69	.2414		
85	.2759		
88	.2069		

110	.8966
112	.2069
124	.9310
125	.9310
129	.8276
132	.1724
139	.2143
144	.8966
145	.8276
150	.1379
153	.2500
155	.9310
165	.8276
166	.8621
169	.8276
171	.8966
173	.1379
176	.8929
182	.0690
184	.1034
189	.9655
192	.2414
194	.2414
196	.8929
197	.1379
198	.1034
200	.9655
202	.8276
TOTAL 50	

To be Revised:

108	.8966
124	.9310
152	.0.345
95	.2759
96	.2759
98	.1724
99	.1724
100	.1724
TOTAL 8	

Appendix 7 **Correlations**

		age	sex	Size_M	surg_M	Function	MH	qu5s1	qu5s3
age	Pearson Correlation	1	.119	.454*	.472**	.027	.733**	.211	-.548
	Sig. (2-tailed)		.539	.013	.010	.889	.000	.311	.101
	N	29	29	29	29	29	29	25	10
sex	Pearson Correlation	.119	1	-.038	.115	-.194	.024	.116	.[a]
	Sig. (2-tailed)	.539		.844	.551	.313	.901	.580	.000
	N	29	29	29	29	29	29	25	10
Size_M/m	Pearson Correlation	.454*	-.038	1	.732**	.169	.239	.116	-.520
	Sig. (2-tailed)	.013	.844		.000	.381	.211	.580	.123
	N	29	29	29	29	29	29	25	10
surg_Y/N	Pearson Correlation	.472**	.115	.732**	1	-.087	.255	.000	-.520
	Sig. (2-tailed)	.010	.551	.000		.652	.182	1.000	.123
	N	29	29	29	29	29	29	25	10
Function	Pearson Correlation	.027	-.194	.169	-.087	1	.087	.462*	.120
	Sig. (2-tailed)	.889	.313	.381	.652		.652	.020	.741
	N	29	29	29	29	29	29	25	10
Medical History	Pearson Correlation	.733**	.024	.239	.255	.087	1	.116	-.392
	Sig. (2-tailed)	.000	.901	.211	.182	.652		.580	.262
	N	29	29	29	29	29	29	25	10
qu5s1	Pearson Correlation	.211	.116	.116	.000	.462*	.116	1	-.056
	Sig. (2-tailed)	.311	.580	.580	1.000	.020	.580		.886
	N	25	25	25	25	25	25	25	9
qu5s3	Pearson Correlation	-.548	.[a]	-.520	-.520	.120	-.392	-.056	1
	Sig. (2-tailed)	.101	.000	.123	.123	.741	.262	.886	
	N	10	10	10	10	10	10	9	10

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

a. Cannot be computed because at least one of the variables is constant.

Appendix 8 **Domain & Attribute Statistics**

	function		N	Mean	Std. Deviation	Std. Error Mean
COGNITIVE DOMAIN	dimension1	.00	16	33.1875	12.02341	3.00585
		1.00	9	27.3333	4.44410	1.48137
Cog Concentration	dimension1	.00	17	10.1765	3.45028	.83682
		1.00	10	9.0000	1.41421	.44721
Cog Memory Recall	dimension1	.00	16	3.1250	1.45488	.36372
		1.00	11	2.4545	.68755	.20730
Cog Verbal recall	dimension1	.00	16	10.5000	4.03320	1.00830
		1.00	12	8.0833	2.64432	.76335
EMOTIONAL DOMAIN	dimension	.00	14	269.5000	33.43133	8.93490
		1.00	9	233.2222	14.22830	4.74277
Emot Anxiety	dimension	.00	17	21.8824	6.34313	1.53843
		1.00	12	17.5000	4.79583	1.38444
Emot Body Image	dimension1	.00	14	92.8571	17.37751	4.64434
		1.00	10	80.0000	5.79272	1.83182
Emot Depression	dimension1	.00	17	30.8235	3.76223	.91248
		1.00	12	29.8333	2.44330	.70532
Emot Motivation	dimension1	.00	17	23.9412	3.34422	.81109
		1.00	11	22.5455	2.01810	.60848
Emot Somatization	dimension1	.00	17	13.3529	3.95192	.95848
		1.00	12	10.9167	2.35327	.67933
Emot Stability	dimension1	.00	17	11.4706	1.50489	.36499
		1.00	12	12.3333	1.72328	.49747
Emot Self Esteem	dimension1	.00	17	12.1765	2.32474	.56383
		1.00	11	12.8182	1.88776	.56918
PHYSICAL DOMAIN	dimension	.00	13	156.9231	40.01554	11.09831
		1.00	10	128.6000	16.97842	5.36905
Phy Energy/ Fatigue	dimension1	.00	17	16.9412	6.67524	1.61898
		1.00	12	17.0833	5.93079	1.71207
Phy Independence	dimension1	.00	17	18.4118	5.38585	1.30626
		1.00	12	15.7500	1.54479	.44594
Phy Mobility	dimension1	.00	17	19.3529	8.03851	1.94963

		1.00	12	17.1667	4.66775	1.34746
Phy Sensory	dimension1	.00	14	75.5000	21.70342	5.80048
		1.00	10	63.0000	7.34847	2.32379
Phy Sleep	dimension1	.00	15	20.0000	3.13961	.81064
		1.00	12	16.2500	2.49089	.71906
SOCIAL DOMAIN	dimensio1	.00	13	106.7692	13.63301	3.78112
		1.00	8	108.7500	10.18051	3.59936
Soc Activity	dimension1	.00	16	18.0000	3.16228	.79057
		1.00	12	18.6667	2.05971	.59459
Soc Role Paraticipation	dimension1	.00	17	12.5882	2.62342	.63627
		1.00	12	11.6667	1.55700	.44947
Soc Support	dimension1	.00	17	27.2353	5.64058	1.36804
		1.00	12	26.6667	4.07505	1.17637
Soc intimacy/sexual interest/function	dimension1	.00	14	23.2857	4.21405	1.12625
		1.00	8	24.1250	4.42194	1.56339
ECONOMIC DOMAIN	dimension	.00	17	29.2941	6.84438	1.66001
		1.00	11	27.2727	3.43776	1.03652
Econ Economic stress	dimension1	.00	17	8.8235	3.59227	.87125
		1.00	12	7.2500	1.60255	.46262
Econ Ability to Generate Income	dimension1	.00	17	9.5882	3.57174	.86628
		1.00	12	7.5000	1.62369	.46872
Econ Ability to be productive/creative	dimension1	.00	17	10.8824	2.20461	.53470
		1.00	11	12.2727	2.10195	.63376
SPIRITUAL DOMAIN	dimension1	.00	17	9.0588	3.94447	.95667
		1.00	12	5.9167	2.02073	.58333
PERSONALITY FACTORS						
EXTROVERSION	dimension1	.00	17	14.2353	3.09292	.75014
		1.00	12	13.2500	2.05050	.59193
INTROVERSION	dimension1	.00	17	11.5882	2.93809	.71259
		1.00	12	11.6667	1.72328	.49747
IMPULSIVITY	dimension1	.00	17	10.1765	2.37790	.57673
		1.00	12	9.5833	1.78164	.51432
TREATMENT EXPECTATIONS	dimension	.00	17	10.2353	2.56246	.62149
		1.00	12	10.9167	1.83196	.52884
LOCUS OF CONTROL	dimension	.00	17	5.5882	1.32565	.32152
		1.00	12	5.8333	1.02986	.29729

APPENDIX 9

Detail of Qualitative Responses.

1. "I'm not sure if I am supposed to answer questions specifically with regards to how symptoms of pituitary adenoma make impact my life, or just answer the questions in general … for example, my job and feeling fatigue I contribute to some of the way I answered the questions, but I do not think they are necessarily related to my pituitary adenoma symptoms.
2. " brain injury and tumor appears to have made permanent changes to my life. ie. seizures, migraines, crying"
3. "I don't want to do all my activities (hunting, hiking, camping) because I am so tired. I feel horrible about my appearance and don't want to go out in public.
4. The questionnaire is missing -depression, migraine
5. The questionnaire is missing -Difficulty breathing
6. The questionnaire is missing-Missing- the effects of work life on energy throughout the day
7. The questionnaire is missing- I Fall asleep quickly but wake up one hour later and can be awake for up to 4 hours
8. The questionnaire is missing- PTSD, I am a displaced home maker with $1000 month spousal support for one more year.
9. Planning things isn't successful? Unclear
10. Lots about work but college is major part of my life and has been affected by this.
11. Difficulty falling asleep/blood pressure increasing
12. In the "I am bothered by section, n/a and "not at all" can often be used interchangeably. I mainly checked " not at all" but could just as easily picked N/A
    -include- frustration with doctors dismissing symptoms because pituitary disease is rare.

13. Your might want to screen out confounding variables (frequent urination due to BPH, global health rating influenced by other medical conditions etc.) This now reads as if your patient population has no other medical conditions that have contributed to their experiences.
14. "I am unable to experience joy and happiness".
    The questionnaire is missing -Anxiety, unable to sleep without pills, unable to live without anti-anxiety pills.
    Feel depressed, have had vulvadynia for 9 mths which limits activities with friends. Obsessive hand washing and being germophobic afraid of getting sick. Have lost 20lbs since December without trying. Feel I'm aging quickly.

Executive Summary

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Doctor of Nursing Practice Candidate

Domains of life Function Scale for Patients with Pituitary Adenomas

Objective: The development and piloting of a scale for the measurement of perceptions of functional status and quality of life (QoL) in patients with pituitary adenomas (PPAs). Two inquiry questions were posed: What life functions reflect decreased or altered QoL for patients with pituitary adenomas; and secondly, is QoL altered for patients with all types of PA's?

Methods: The Domains of Life Functions Scale (DOLF) for Patients with Pituitary Adenomas was developed and piloted. Based on a concept analysis of QoL indicators and an outcome model, six pertinent domains of life function were identified: cognitive, emotional, physical, social, economic and spiritual. Defining attributes were operationalized and 205 items were written with reference to existing tools. Twenty nine de novo subjects with known PA's, 13 hyperfunctioning (HF) and 16 non-functioning (NF) were enrolled. All phases of data collection were performed by the author. Successes and difficulties: There were few challenges in the administration of this study. Inclusion criteria restricted enrollment but all qualified patients agreed to participate. One subject failed to complete the tool and was excluded. The length of the tool failed to represent a barrier to completion. The 205 item tool was completed in an average of 20 minutes. However, very little qualitative data was collected regarding the questions or format responder fatigue needs to be considered. Further testing is indicated to confirm content and construct validity. A face to face exit interview may be needed to obtain some of this data.

Findings: Enrolled subjects (16 female, 13 male) were divided into two groups (NF,HF) for analysis. There was no significant difference between groups in the number of pituitary deficiencies, tumor size or medical history. A correlation was found between tumor size and increasing age rated to desired health considered worse over the last 12 months. No correlation was found between NF and HF groups and overall health rating. The DOLF demonstrated adequate internal consistency. Domain and attribute responses revealed significantly greater physical and emotional dysfunction in the NF group. Attribute scores were significant in NF group for depression, body image, anxiety and sleep disturbance.

Outcome: Pituitary adenomas exert a significant effect on QoL, regardless of size and function. Further assessment of dysfunction is warranted for patients with NFPA's. Although further validity and reliability testing is required, the DOLF is a useful tool for QoL assessment in PPAs and allows the APN/care provider to more specifically target dysfunctions, monitor outcomes over time in response to current treatments and investigate options for resistant dysfunction.

Studies Strengths: The time required to complete the DOLF scale was no greater than the currently used intake form and is likely to be more useful for further assessment, treatment and research.

Health Policy, Medicare and Growth Hormone

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Introduction

Patient with pituitary dysfunction or damage are frequently diagnosed with growth hormone deficiency (GHD). The prevalence of GHD has been estimated at 80% of patients with one of six pituitary hormonal deficiencies and 90% of those with two or more deficiencies (Toogood, Beardwell, & Shalet, 1994). The cost of replacement for an average dose of replacement can range from $500-1000 a month with out of packet expenses dependent on insurance coverage or exclusions. Health Insurance coverage varies by policy with some completely excluding coverage for all adult GHD replacement therapy and some covering all but contractual co-pay. Most commercial insurers cover the cost of testing for GHD. Medicare patient without Part D coverage or those with high co-pays incur significant out of pocket expenses for growth hormone replacement and some patients switching from commercial coverage find that growth hormone is excluded or the cost is prohibitive. Likewise, the cost of testing for GHD is not covered by Medicare often excluding patients on Medicare from evaluation and subsequent treatment.

Context

Health care expenditure consumes progressively more of both tax revenues and share of the GDP. Currently at 16 percent of GDP it is projected to consume 50 percent of GDP by 2082 at the current rate of growth (Congressional Budget Office & Congress of the United States., 2008). Spending for Medicare, Medicaid and Social Security is projected to become unsustainable after an increase of a further 4 percent. In 2008, Medicare enrollees numbered 44,831,390 (Center for Disease Control and Prevention, 2009). Enrollment is anticipated to

accelerate in 2010 when members of the "baby boom" population start to become eligible and is projected to peak at around 79 million in 2030 (Kaiser Family Foundation 2004).

The Debt Reduction Act 2005 (Sen Gregg, 2006) enacted wide sweeping legislation to reduce government spending. Many provisions applied to medical care. Under this act, the Medicare Payment Advisory Commission (MedPAC) was required to report to Congress on mechanisms that could be used to replace the sustainable growth rate system. Payments were reduced to support premiums for Medicare Advantage Oranizations (part C: Sec. 5301) and changes were made to cost sharing, decreasing benefits and increasing costs to recipients. Restrictions were placed on drug prescriptions and dispensing for medicaid. Part A payments and reimbursement to hospitals were revised and based on performance. Emphasis was placed on the investigation and elimination of waste and fraud and the reimbursement to physicians for outpatient services for Medicare and Medicaid was revised .

The current political debate about health care reform centers on costs to stakeholders. The current administration aims for sweeping reforms focused on access and equity (Antiel, Curlin, James, & Tilburt, 2009; Iglehart, 2009).(Center for Disease Control and Prevention, 2009). Opposition to proposed reforms comes from the commercial insurers, medical devices and pharmaceutical industries and some labor union and business groups (Center for Disease Control and Prevention, 2009)(Ca health care reform 2009). Health insurers complain that penalties for not buying insurance are too low, suppliers of durable medical equipment that proposed industry fees are too high, pharmaceutical companies object to decreased subsidies for Medicare drugs and labor unions to taxes proposed on Cadillac health care plans. Business groups fear staffing effects the loss of the employer based insurance system (Center for Disease Control and Prevention, 2009). Support comes from the AMA and Medical Group Management

Association who seek a fix to low rates of Medicare reimbursement (Center for Disease Control and Prevention, 2009). Current grass roots support is currently running at 43 percent.

Medicare is currently partly financed from payroll taxes. However, the workforce is projected to shrink significantly over the next 30 years as baby boomers retire. The impact of 35 percent of the workforce leaving high need labor forces such as agriculture, teaching, medical care and sales is the cornerstone of much angst among budget analysts and is likely to have a significant impact on funding for Medicare and other services (Center for Disease Control and Prevention, 2009). Teaching, health care and the agricultural work force are expected to suffer significant shortages. (USDA 2004, US Bureau of Statistics 2008, UDA 2004, 2006)

In 2005 it was estimated that for 67% of those older than 65, more than half their income was from Social Security (80% of African-Americans , 76% of Hispanics, 75% of unmarried women) (AARP 2005, SSA 2005). Although the cost of Medicare part A & B cover hospital and outpatient services, there are a number of services excluded and co-pays and deductibles apply (CMS 2009). Medigap insurance (Part C) can be purchased to help cover some of these fees and Part D can be purchased to cover some of the cost of drugs. The cost of health care insurance for a Medicare recipient (for minimum coverage and excluding co-pays, deductibles), at the lowest rate is 10.7% of social security income. With the addition of out of pocket expenses for drugs, co-pays and deductibles, Medicare recipients can spend on average up to 40% of their annual income on health care and insurance (Jorgensen, Pedersen, & Thuesen, 1989).

Attitudes towards aging influence are culturally defined and as such influence policy development. The expectation of illness and disability (Johnson, Bengtson, Coleman, & Kirkwood, 2005) are a part of aging is being remodeled in western societies and US to be

replaced by a more active, wellness oriented model. Groups such as AARP, the National Association of Area Agencies on Aging, Grey Panthers (2008) and the burgeoning population of retiring " baby boomers" are redefining aging and providing a vocal, growing, political platform for issues in aging. The AARP (2009) alone boasts a membership of over 35 million representing a powerful lobby with a central mission to address issues related to aging. However, there remains a significant population with an impoverished lifestyle that leads to impoverished quality and quantity of service (Johnson et al., 2005).

Growth hormone (GH) has been characterized in the popular press as an anti-aging drug to restore the youthful figure and vigor of the aging. The media have contributed to the reputation of growth hormone in the sensationalizing of its abuse by Athletes for the purpose of performance enhancement. Vance (1990) emphasized that claims of improvement in athletic performance in healthy individuals given GH are unproven and popular press claims of youth restoring properties of GH are without substantiation.

Legitimate use of this drug was originally for supplementation in children with short stature or growth delays and its advantage for the use of treatment in growth hormone deficient (GHD) adults has only recently received appreciable attention.

The Problem

Medicare patients, particularly those over the age of 65, are largely denied the opportunity of testing for and the benefits of treatment of growth hormone deficiency based on the exclusion of testing as a covered Medicare service.

Evidence

Growth Hormone deficiency is the result of dysfunction or damage to the hypothalamus or the pituitary gland as a result of pituitary adenomas, pituitary surgery, pituitary radiation

therapy, chemotherapy, pituitary apoplexy, head trauma, infiltrative disease, internal carotid artery aneurysm(Schneider et al., 2006; Sullivan, 2005; Toogood et al., 1994; Vance, 1990; Vance, 1994). GHD is the most common deficiency after pituitary surgery (Schneider et al., 2006). Declines in growth hormone levels have also been shown to be age related and are measured by a decline in Insulin Growth Factor complex (Corpas, Harman, & Blackman, 1993; Iranmanesh, Lizarralde, & Veldhuis, 1991; Toogood, O'Neill, & Shalet, 1996). Deficiency can result in increased cardiovascular and bone fracture risks, increase in adiposity related diseases, decreased mobility and decreased quality of life (Vance, 1990). Consensus guidelines (Consensus guidelines for the diagnosis and treatment of adults with growth hormone deficiency: Summary statement of the growth hormone research society workshop on adult growth hormone deficiency.1998) also report improvement in Muscle strength and exercise performance, sense of well-being and other psychological benefits.

Multiple studies have documented deficiency associated reduction in bone mineral density ((Degerblad, Elgindy, Hall, Sjoberg, & Thoren, 1992; Johansson, Burman, Westermark, & Ljunghall, 1992; Rosen, Hansson, Granhed, Szucs, & Bengtsson, 1993; Salomon, Cuneo, Hesp, & Sonksen, 1989). Exogenous replacement has been shown to improve bone density over time (Johannsson, Rosen, Bosaeus, Sjostrom, & Bengtsson, 1996; Lucidi et al., 1998). In a placebo controlled, double blinded, randomized study (Fernholm et al., 2000) examined the effects of GH replacement as measured by IGF-1 on 31 patients aged 60-79 years who were pan-hypopituitary and found beneficial effects on body composition with decreased adiposity, increased lean body mass and an increase in bone metabolism markers indicating active bone remodeling.

The combined annual costs of all osteoporotic fractures in the elderly have been estimated to be $20 billion in the USA (Sambrook, 2006). The prevelence of hip fractures in 2005 was 328 per 100,000 in 2005 with a treatment cost estimated at $13,470 per fracture. In contrast the average cost of Recombinant Growth Hormone replacement is estimated at $4-6,000 annually (Lilly 2009). Even if one fracture in 100,000 were prevented, in the population over 65 over the next 20 years, the savings would be in the order of $45.6 billion.

It is known that adiposity in GH deficiency is concentrated abdominally which increases cardiovascular risk (Jorgensen et al., 1989; Salomon et al., 1989). Many studies demonstrate improvement in adiposity, high triglycerides and liposity (Fernholm et al., 2000; Rudman et al., 1990; Vahl, Klausen, Christiansen, & Jorgensen, 1999) with GH replacement. Rudman et al (Rudman et al., 1990) also demonstrated a 5% increase in muscle volume after 6 months of replacement therapy that was associated with increased exercise capacity, isometric strength and increase in basal metabolic rate. A Brazilian study by Cenci et al (Cenci et al., 2008) prospectively evaluated insulin sensitivity, visceral adiposity, lipid profile, and carotid artery wall thickness over 5 years of GH replacement in GHD patients and noted reduction in all parameters.

Atherosclerotic heart disease alone in the US in 2007 cost the economy and estimated $151.6 billion in direct and indirect costs (health care services, medications and lost productivity) (Center for Disease Control and Prevention, 2009). By 2009 this figure was estimated to be $304.6 billion. Every year about 785,000 Americans have a first heart attack while another 470,000 who have already had one or more heart attacks have another attack (Center for Disease Control and Prevention, 2009). The cost of one revascularization procedure in 2004 was $ 28558 for percutaneous coronary artery stenting and $60853 per coronary artery

by pass surgery (Nagle & Smith, 2004). Preventing the need for one percent of these procedures by treatment with GH could gross an estimated savings of between $ 225 and 470 million a year. Estimated cost of growth hormone for the same population is approximately $47 million.

Eight to 20 percent of older adults in the community and up to 37 percent in primary care settings suffer from depressive symptoms. Treatment is successful, with response rates between 60 and 80 percent (US HHS 1999). The annual economic cost of depression in US is reported as over $100,000 billion (Ford & Ford, 2009). At a minimum, treatment with a common prescriptive medication at current medication costs is the estimated at $456 billion over the next 20 years or 22.8 billion a year. If 1% of this population is successfully treated and symptoms are reduced with growth hormone the anticipated savings are estimated at $ 2.8 billion annually.

The social implications in terms of maintaining individual independence and productivity are difficult to estimate. However, given the aging workforce in critical areas such as agriculture, education and health, improvements provided by replacement of growth hormone can only have a positive effect in maintaining these work forces.

The diagnosis of GHD requires some expense in testing. The cost of the test is usually covered by commercial insurers but excluded by Medicare. To be covered by insurance carriers, drug therapies such as GH, must meet criteria for "medical necessity". If considered experimental or if evidence is determined to be inconclusive or lack evidence of efficacy, coverage is usually denied. Isolated GH deficiency is most often denied in our clinic population and increasingly patients have been denied coverage for GHD associated with pan-hypopituitarism or complete failure of the pituitary to secrete hormones.

Although Medicare carriers deny claims for testing for GHD, most part D carriers will cover (with variable co-payments up to 75%) specific GH replacements. Patients over the age of

65 on Medicare at time of diagnosis are most often excluded from seeking a diagnosis at a time when they may benefit the most from GH replacement. Those patients diagnosed and treated before the age of 65 who, once they become Medicare eligible, and are either refused coverage or begin to incur significant out of pocket expense. This may mean discontinuation of a beneficial treatment or the patient may be forced to select which ailments they will continue to treat.

For providers, Medpac (2009) reports the average Medicare margin after reimbursement was –5.9 percent in 2007 which was projected to fall to –6.9 percent in 2009. Drugs used for testing for GHD are not covered for reimbursement by local carriers for Medicare. This provides a significant disincentive to providers for the testing of patients covered by Medicare and further establishes a selection and treatment bias and inequity.

There is significant disagreement as to the extent of the anticipated increase in Medicare expenditure over the next 20 years. The Social Security Medical Board of Trustees report Medicare's annual costs were 3.2 percent of Gross Domestic Product (GDP) in 2008 and are projected to reach 11.4 percent of GDP in 2083 (Social Security Administration, Master Beneficiary Record, 2009) with anticipated exhaustion of Medicare Hospital Insurance Trust (financing Part B and part D insurance) by 2017. Given the projected number of retirees and current level of expenditure, financing via payroll taxes and general funds is projected to fail to keep up with expenditures.

Using experts in the field and literature reviews of evidence based practice, the Rand Corporation (Goldman et al 2004) identified 33 key potential health care breakthroughs that have likelihood of being implemented in the next 10-20 years and the impact of these on cost and health of the elderly. They examined advances in biomedical, molecular, cellular and tissue

and genetic engineering, biomicroelectromechanical systems and microfluidics, microsurgical, minimally invasive and robotic surgical techniques, imaging technologies and bioinformatics in both clinical and research applications. From this they developed a model to quantify the effects on illness prevention, early disease detection and treatment (Goldman et al, 2004). The resultant Future Elderly Model allow for an objective evaluation of the relationship between disability/disease status, time sensitive costs of treatment, as well as trends in disability/disease. The authors described FEM as a "microsimulation model that tracks elderly, Medicare-eligible individuals over time to project their health conditions, their functional status, and ultimately their Medicare and total health care expenditures. Model developers elected not consider policy changes in Medicare over time. The projected increase in rate of increase in expenditure using the FEM was 55% lower over the next 20 years (until 2030) than that predicted by the Social Security and Medicare Trustees.

Alternatives

No change in current practices and policies or maintain stratification of coverage and access based on insurance, age, ability to pay or socioeconomic status.

Reduce the number of Medicare Advantage and Part D plans offered or combine plans into several choices based. Purchase options to provide additional choice for patients who wish to add further coverage for specific additional coverage that reflect personal choices in health care.

Expansion of defined benefits plans to provide each beneficiary a standardize coverage inclusive of preventative care, health promotion, basic and catastrophic coverage.

Control the cost of drugs along with standardization of co-pays and deductibles in Medicare plans.

Increase the age of Medicare eligibility to age 67 and allowing retirees to buy into Medicare between ages 62 and 66.

Provide direct employer support and subsidies for Individual Health Savings Accounts and continuation of employer benefits for a period beyond retirement.

Projected Outcomes

Without any changes in current policy, only those patients who have the means to pay for the cost of evaluation plus the out of pocket expenses of replacement drug will continue to benefit from treatment. Individuals with GHD will have higher risks of cardiovascular and cerebrovascular disease, increase risk of falls and fractures and decreased life satisfaction associated with psychological issues. Inequitable risk is incurred by those over the age of 65 and low income disadvantaged populations such as women, African Americans and Hispanics.

Reducing the number of Medicare Advantage (MA) and combining these with Part D plans offering decreasing choices would help simplify the complexity and confusion now confronting Medicare beneficiaries. With fewer choices and more participants per plan purchasing power is increased and costs to participants decreased. It is recognized that federal oversight of this process may be necessary to achieve this goal.

Defined benefit plans with standardized benefits provide equitable access to care for participants and some distribution of risk between plans. The cost of catastrophic and high cost drugs and services are unlikely to be covered.

Drug cost controls may be achieved through preferred pricing for drugs supplied to Medicare Part D participants with authority to the Secretary of Health and Human Services to negotiate directly with pharmaceutical manufacturers for lower prescription drug prices in Medicare Part D. Precedent for this practice is already established with other federal programs,

such as the Veterans Administration who use their bulk purchasing power to obtain lower drug prices than are currently available under Medicare Part D (NAAAA 2009). It is assumed that the collective negotiation power of 43- 79 million Medicare beneficiaries would achieve lower drug prices, driving significant savings to Medicare which should be passed on to beneficiaries in the form of lower or no out of pocket expenses.

Gradually increasing the Medicare eligibility age to 67 but allowing early retirees between ages 62 and 66 to buy into the program helps address three pressing public issues. It reduces Medicare costs; improves insurance coverage among older adults younger than 65, and increase labor supply at older ages by strengthening work incentives at older ages (Johnson et al., 2005)

Direct employer support and subsidies for those employers who continue offering benefits to retirees for a stipulated period after retirement, particularly for large corporations, could extend Medicare program solvency. The addition of a subsidy provided to individuals who establish Individual Health savings Accounts during a working lifetime, particularly those who are likely to turn 65 between 2020 and 2030 may further improve solvency. IHSA's have been criticized for catering to higher income bracket employees who are typically a healthier population (Shearer, 2004) Subsidization to provide encouragement for this practice may offset upfront cost and still provide access to health services and/or treatments.

Evaluation

No action neither contributes to the health needs of this population nor reduces the costs associated with increased risk of disease or dysfunction. As population numbers increase the prevalence of GHD and associated costs are likely to increase. Resource expenditure is

negatively impacted and objectives of equity and accessibility are not achieved. Overall weighting of this alterative is negative.

Reducing the number of plans helps distribute health risk further by increasing the number of participants per plan thus reducing plan expenditures (Musich, Hook, Barnett, & Edington, 2003). This saving can be passed to participants reducing costs of health insurance and improving the member's access to care and ability to purchase an expanded range of coverage more specific to their needs. To fully achieve these ends government oversight is needed to limit the rates charged by profit motivated insurers. Resource expenditure at a federal level is not likely to change under this scenario but individual expenditure should be improved. This may fall short of providing both access and adequate drug coverage for higher cost drugs but this coverage may be plan dependent.

This option has relevance to the stated problem with respect to improving access to evaluation but represents limited movement toward the goal. Resource expenditures are likely to be improved but the problem of treatment and access to drug remains limited.

Defined benefits also offer cost advantages to members by decreasing contributions. Benefits are usually limited and benefit definition that includes a requirement to offer preventative care services health promotion and the standardized level of coverage would need government oversight to establish. If inclusive of screening for early identification and treatment of disease and dysfunction this would include screening for GHD with an end purpose of minimizing concomitant risks. Standardization of plans and benefits should decrease sales and marketing costs and activities for commercial insurers but monitoring and enforcement activities would most likely need to continue. The costs of more expensive drug therapies are less likely

to be covered under a defined benefit plan and as such would not provide broad support for beneficiaries at all socioeconomic levels.

A review of health promotion and disease management programs in 2003 demonstrated a significant return on investment. Benefit-to-cost ratios, ranged from $1.49 to $4.91 (median of $3.14). Models from business demonstrate the efficacy of prevention programs: Motorola's wellness program saved the company $3.93 for every $1 invested; Northeast Utilities reduced claims by 1,400,000 over 2 years; Johnson and Johnson's Health and Wellness with average annual health care savings of $ 224.66 per employee and Caterpillar's Healthy Balance Program projected to same $700 million by 2015. Direct health care costs of obesity are estimated at between 4.3 – 9.1 percent of percent of total health care expenditures with 50 % of these costs borne by Medicare and Medicaid. Research suggests that those over the age of 65 have much larger annual Medicare expenditures than non-obese people.

This option has relevance in terms of access to treatment for the target population, is an improvement over the current condition but results may be limited by the increased out of pocket expenses anticipated for drug therapy. Overall health impact with respect to preventative care is anticipated to reflect a significant health improvement but may be more limited with respect to GHD.

Controlling drug costs through direct negotiation and contract pricing provides the opportunity for reducing supply costs for recipients and Medicare. As long as cost to the patient is controlled, access is improved. However, this does not address the issue of testing.

This option is relevant, indicates progress toward solving the problem at hand has efficacy with respect to access to drug and impacts the availability of GH for treatment with subsequent impact on concomitant risks.

Increasing Medicare eligibility age to 67 would leave many older, low income African Americans, Hispanics, and poor adults without coverage unless a buy-in option were heavily subsidized. Additionally, cost savings have been estimated as modest because most of the Medicare beneficiaries dropped from the program would be relatively healthy and therefore low-cost. .

Increasing the age of retirement is only relevant to the problem of GHD and replacement if insurance coverage is extended through this period that provides coverage for evaluation and treatment. The issue of transition coverage remains unchanged. No real progress is achieved toward solving the problem at hand under this alternative. This option is efficient in its use of resources but not specifically or effectively addressed to GHD. Anticipated impact on the desired outcome is therefore minimal.

Direct subsidies to employers who continue benefits to retired workers and subsidies for workers who establish IHSA's is relevant to diagnosis and treatment of GHD but does not address transition from employer plans to Medicare at the conclusion of the defined period. Progress toward the goal is achieved with improvement in access but this is limited and longer coverage for replacement GH under employer plans. In terms of Medicare resources this is sparing but differential plans will continue to offer variable levels of access and drug coverage. Therefore, this has limited effect and is more likely to impact higher socioeconomic beneficiaries.

Decision

The efficacy of GH replacement for individuals with clear GHD after pituitary dysfunction has increasing support from studies demonstrating a higher risk of cardiac disease, fractures and decreased quality of life. Current Medicare policy excluded coverage for the cost

of testing for evaluation of GHD for all beneficiaries. Coverage for the cost of treatment varies significantly based on the purchasing power of the individual participant. This confers greater risk and the possibility of increased cost to Medicare for the treatment of diseases that may have been preventable. This also ignores the issues of life quality.

Of the policy options discussed, the federal regulation of Medicare Advantage plans to provide for preventative care screening for all diseases or disorders that can offer an efficacious treatment alternative provides for the need for testing coverage for GHD.

With respect to treatment, allowing bulk purchasing and price negotiations challenges drug manufactures to reduce cost and compete for contracts to supply cost effectiveness to both Medicare Part D program and beneficiaries. Low income subsidies may still need to be applied for some participants.

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Case Study

Aggressive Pituitary Adenoma

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Purpose

The purpose of this case study is to describe the case of a patient with an aggressively growing pituitary adenomas that failed to respond to conventional treatments and required novel therapy to arrest the disease progress.

Background

Pituitary adenomas (PAs) represent about 10-15% percent of all brain tumors (Daly, Burlacu, Livadariu, & Beckers, 2007; Lim, Shahinian, Maya, Yong, & Heaney, 2006). The Central Brain Tumor Registry of the United States (2009) reports prevalence rates in the USA for males as 2.1 and females 2.3/100,000 person years with a median age at diagnosis of 50 years. The incidence increases with age, the highest between 65 years and 74 years (CBTRUS 2009). About 10% of the normal adult population have been found to have pituitary abnormalities on MRI scans Hall, Luciano, Doppman, Patronas, & Oldfield, 1994) and up to 27% of people are found to have pituitary adenomas on autopsy(Daly et al., 2007). Of these, approximately 25 % are found to have excess pituitary hormonal secretion. After surgical resection and histological examination 1.1- 6% of these tumors are discovered to have 'silent' hormonal excess (Karavitaki, Ansorge, & Wass, 2007).

Silent adenomas are described as PA's where the patient demonstrates no stigmata of disease or any biochemical evidence of hormonal excess on standard testing prior to tumor excision. One study reported that more than half of the biochemically and clinically non functioning pituitary adenomas (NFPA) were immunopositive for various hormones (Rishi et al., 2010) by pathology. The researchers observed that silent adrenocorticotrophic hormone (ACTH) producing tumors were the second most common in this category, displaying (ACTH)

immunoreactivity in 17-22% of these tumors (Karavitaki et al., 2007). Patients display no clinical signs of Cushing's disease as they do with active ACTH producing tumors. Additionally, standard testing for Cushing's disease, such as 24 hour urine free cortisol, midnight salivary cortisol levels, dexamethasone suppression and CRH stimulation testing, are all negative for hypercortisolemia or cortisol excess(Ambrosi et al., 1992; Lopez, Kleinschmidt-Demasters Bk, Sze, Woodmansee, & Lillehei, 2004; Pawlikowski, Kunert-Radek, & Radek, 2008; Sahli, Christ, Seiler, Kappeler, & Vajtai, 2006; Webb et al., 2003).

The majority of patients with Silent Corticotroph adenomas (SCAs) present with visual field deficits or blindness in one or both eyes and are found to have macroadenomas (tumors >1cm), often with suprasellar extension and optic chiasm compression, on magnetic resonance imaging (MRI) (Karavitaki et al., 2007; Lopez et al., 2004; Pawlikowski et al., 2008). There is conflicting evidence as to the gender distribution in SCA's incidence. Some report the incidence as higher in females (70.4%) (Webb et al., 2003) and others report a male/female ratio of 69.9 males to 30.5 females (Scheithauer et al., 2007).

Numerous studies and case reports have described a higher incidence of tumor recurrence for patients with silent pituitary adenomas and those identified as 'atypical adenomas' on pathology (Cho et al., 2010; Sahli et al., 2006; Webb et al., 2003; Zada et al., 2010). Zada and colleagues (2010) found that 15% of resected pituitary adenomas were classified as 'atypical adenomas by WHO classification and these tended to be more aggressive and invasive macroadenomas. Several studies demonstrated recurrence rates for SCAs to be twice as high as for Cushing's disease adenomas, or between 32 -37% of NFPA showing immunostaining for

ACTH (Bradley, Wass, & Turner, 2003; Pawlikowski et al., 2008). Although not supporting a difference in recurrence rates between SCAs and non-SCAs, Cho and colleagues (2010) found, in their population, that younger patients had a higher frequency of multiple and late recurrences and more aggressive tumor behavior. Tumor recurrence is estimated to occur at a mean of 5.8 -6 years at a rate of 0.06 percent or 6 patients in 100 (Ebersold, Quast, Laws, Scheithauer, & Randall, 1986; Bradley et al., 2003; Ebersold et al., 1986). However in several studies and in 2 patients with SCAs at OHSU Pituitary center, recurrence has been as soon as 4-6 months post resection.

It is important to differentiate aggressive pituitary tumor growth from pituitary carcinoma. By the 2004 WHO definition, pituitary carcinoma is tumor tissue that is not contiguous with the pituitary tissues or is found also in extracranial sites. This disorder is rare and accounts for only about 0.1% of all pituitary tumors. In contrast, aggressive pituitary adenomas show abnormally fast growth but are confined to the sellar and surrounding regions and remain attached to the pituitary (Lim et al., 2006). These tumors tend to express higher rates of markers of cell proliferation on pathology such as Ki-67 and p53 (Gurlek, Karavitaki, Ansorge, & Wass, 2007; Pawlikowski et al., 2008).

Patients with tumors that demonstrate aggressive growth experience significant morbidity including cranial nerve damage, particularly occulomotor, cranial nerve palsies, visual field deficits and blindness (Benveniste et al., 2005; Zhao et al., 2010). They incur the need for repeated surgical resection and radiation treatment in an effort to control growth. Mortality is low estimated at approximately 0.2%, but increased with older age at resection, macroadenomas, male gender and associated radiotherapy (Chang et al., 2008; Schaller, 2003). Death is related to tumor erosion into the internal carotid arteries and hemorrhage, pulmonary embolism and

meningitis. Rapidly growing, invasive tumors have been shown to have worse outcomes (Schaller, 2003).

Attempts to identify predictors of recurrence continue. Pre-operative tumor invasiveness, cavernous sinus extension, or dural invasion, tumor subtypes have not been shown to be predictive (Karavitaki et al., 2007). Markers of increased mitotic activity such as KI-67/MIB-1 in excess of 3% and excessive p53 immunoreativity in tumor cells have been found in 'atypical' variants and SCA's and are now considered as indicative of more aggressive and invasive macroadenomas. Zada et al. (2010) reports that the degree of ACTH immunoreactivity and Ki-67 index do not seem to be associated with increased risk of recurrence. However, elevation of this index has been shown to be a risk factor for recurrence (Karavitaki et al., 2007). Several authors reported cases of patients with recurrent SCAs that converted to active ACTH and consequent Cushing's disease (Ambrosi et al., 1992; Baldeweg, Pollock, Powell, & Ahlquist, 2005; Salgado et al., 2006).

Investigations have focused on genetic anomalies involved in the transcription, synthesis, processing and expression of prohormones of ACTH, such as the defective expression of PC1/3, which may be the key to understanding why biologically inactive, unprocessed variants of ACTH are secreted in SCAs (Tateno et al., 2007). This theory was supported by Tani and colleagues (2010), who found that the CDKN2A gene expression was four times greater in Cushing's disease than in SCAs. Likewise, Wang et al. (2010) demonstrated that HMGA1 expression was significantly higher in invasive adenomas or macroadenomas than in non-invasive adenomas or microadenomas (invasive versus non-invasive, $P < 0.05$; macroadenoma

versus microadenoma, $P < 0.05$). In addition, HMGA1 showed the highest level in the most aggressive pituitary adenomas. Thodou and colleagues (Thodou, Argyrakos, & Kontogeorgos, 2007) studied Galectin-3 (Gal-3) which belongs to the family of carbohydrate-binding proteins with high affinity for galactoside. This is involved in many biological processes, including cell growth and differentiation, cell adhesion, tumor progression, apoptosis and metastasis. Gal-3 is highly expressed in functioning corticotroph adenomas of the pituitary gland, while silent adenomas exhibit very focal to no expression of Gal-3. These researchers propose that these observations can be used in the pathological diagnosis to separate functioning from silent corticotroph adenomas.

Treatment

Surgery is both the first and second line treatment for any marcroadenoma, particularly those with optic chiasm involvement or those with subsequent growth. This is frequently followed by radiation treatments and may be with combined with suppressive chemotherapy (Buchfelder, 2009). Chemotherapeutic options for pituitary cancers, prolactinomas and growth hormone secreting tumors have been available for some time, but the suppressive therapy for SCAs and NFPA has not (Marek, 2010).

The risks associated with surgical resection are not insignificant {{480 Chang,E.F. 2008; 425 Schaller,B). Each surgical resection incurs a greater risk that both anterior and posterior pituitary damage can be incurred, with subsequent adrenal insufficiency, hypothyroidism, hypogonadism and infertility, growth hormone deficiency, diabetes Insipidus coagulopathies (Ballian et al., 2010; Manetti et al., 2010; Messer et al., 2010). Optic chiasm damage is possible but rare, as is hemorrhage from damage to the internal carotid arteries that feed the pituitary or

apoplexy (hemorrhage within the tumor itself) (Messer et al., 2010). Infections such as sinus infection and meningitis can occur, as can CSF leaks that may require repeated surgical interventions including a tracheostomy to decrease intracranial pressure.

Adjunctive Radiation therapy is also not innocent of sequelae. It is generally appreciated that pituitary function will depreciate over time post radiation therapy. The risk of developing new onset anterior pituitary deficits was found to be 16% and 45% at 2 and 5 years, respectively with more preservation of function with less radiation exposure (Leenstra et al., 2010). Treatment with pituitary hormone suppressive medication at the time of gamma knife radiation, a prior craniotomy, and larger adenoma volume at the time of radiosurgery, were all found to be significantly related to loss of pituitary function (Sheehan, Rainey, Nguyen, Grimsdale, & Han, 2010). Greenman (Greenman et al., 2003) reviewed outcomes for 122 patients post radiotherapy. Five of 14 patients (35%) of patients had tumor re-growth, whereas, 52% (41/78) of patient with residual tumors and no radiation had re-growth. The presence of cavernous sinus invasion before surgery (P = 0.02, odds ratio 2.72; confidence interval 1.1-6.43) and the extent of suprasellar extension in the postoperative residual tumor were strong predictors of tumor enlargement. Radiation necrosis and optic chiasm damage and anopsia have both been recorded in OHSU patients. Aggressive SCAs are frequently treated with all these modalities but can continue to show persistent growth, as demonstrated by the case under discussion.

Apart from a means of early identification of these tumors, there is much interest in finding an effective suppressive chemotherapeutic agent. Recently, Temozolomide (Temodar) has shown promise in the treatment of these tumors. Temozolomide is a cytotoxic drug that methylates DNA at guanine 0-6 position and thereby exerts an antitumoral effect. First used as an agent in the treatment of gliomas, it has been successfully utilized as salvage treatment for

persistent and aggressive prolactinomas that have not responded to conventional suppressive dopamine agonist therapies (Byrne, Karapetis, & Vrodos, 2009; Neff et al., 2007). In the treatment of pituitary cancers several groups of researchers found tumor shrinkage at all tumor sites, pain resolution and functional improvement using this drug (Fadul et al., 2006; Hagen, Schroeder, Hansen, Hagen, & Andersen, 2009; Kovacs et al., 2007; Kovacs et al., 2008; Lim et al., 2006; Syro, Ortiz, Scheithauer, Lloyd, Lau, Gonzalez, Uribe, Cusimano, Kovacs, & Horvath, 2010). Fadul and colleagues (2008) reported a case of a patient able to hold a full time job 12 months after discontinuing Temozolomide.

O-6 Methylguanine DNA methyltransferase (MGMT) is a DNA repair enzyme that removes the alkyl group from the O-6 position of DNA . The higher the level of MGMT or the more methylation of the MGMT gene, the more there is resistance to the effects of Temozolomide and the less effective it is in treatment (Kovacs et al., 2007; Kovacs et al., 2008; Syro, Ortiz, Scheithauer, Lloyd, Lau, Gonzalez, Uribe, Cusimano, Kovacs, & Horvath et al., 2010). It is proposed that MGMT immunostaining of resected tumors may predict responsiveness of pituitary adenomas (PAs) to treatment with this drug. In a study of 60 patients with PAs, 9 of 15 (60%) of patients with invasive non-cancerous adenomas demonstrated low MGMT immunoexpression (Lau et al., 2010). In a 2010 study, Syro (2010) reported the use of Temozolomide in 19 patients, 13 with pituitary adenomas and 6 with pituitary carcinomas. Ten of the 13 adenomas responded favorably to Temozolomide treatment, but two patients whose tumor expressed high levels of Methylguanine DNA methyltransferase (MGMT) did not respond to treatment. The patient in this case study represents the first published case of a patient with SCA responsive to Temozolamide therapy.

Key word search

Search 1: pituitary adenoma, aggressive tumors, growth, treatment, clinical,

Search 2: ACTH, silent ACTH, Temozolomide

Case Study

Mr. G is a 56-year-old Male who presented initially in 1996 to a center in San Francisco with symptoms of florid Cushing's syndrome. MRI indicated a 3 cm pituitary macroadenoma. By patient report elevated cortisol levels were initially found in urine, saliva and with dexamethasone suppression testing. After cavernous sinus sampling was positive for a pituitary source of ACTH, he was diagnosed with Cushing's disease. He was treated initially with transsphenoidal surgery (TSS) and pathology confirmed a Corticotroph Adenoma (CA). He demonstrated persistent cortisol excess post surgically and proceeded to radiation therapy with 5 weeks of conventional radiotherapy. Remission of Cushing's syndrome was achieved. No tumor markers were available for this primary resection but given the size of the tumor, a macroadenoma, the literature supports a high probability of recurrence although the majority of data refers to tumors that are SCAs then convert to Cushing's disease. (Ambrosi et al., 1992; Baldeweg et al., 2005; Salgado et al., 2006). This case is unusual for the size of the patients' tumor at initial presentation. Patients with Macroadenomas presenting with symptoms and biochemistry consistent with florid Cushing's disease are rare. The majority of cases of Cushing's disease present with microadenomas or no adenoma is seen on MRI (Ballian et al., 2010; Kho, Nieman, &

Gelato, 2002). In retrospect, a review of the literature also suggests that male gender and relatively young age at first presentation increases the risk of tumor recurrence.

In 2007 (11 years after his first surgery and radiation treatment and at the latter end of the range for recurrence predicted in the literature), Mr G. developed symptoms of a recurrence of Cushing's disease, with midsection weight gain, fatigue and moon facies, sexual dysfunction, headaches and visual field deficits. Imaging revealed a 2.3 x 2.5 x 2.0 cm pituitary tumor with optic chiasm compression. He had an elevated serum ACTH 116 pg/mL (<46pg/ml) and positive overnight dexamethasone suppression test with a cortisol level after 1.0 mg of dexamethasone of > 2 ng/dl (normal level of <1ng/dl). In August 2007, at an outside facility, he underwent a second, translabial transsphenoidal resection of his recurrent pituitary adenoma that was giving him recurrent Cushing's disease. Post operatively he had restoration of eucortisolemia initially, then developed adrenal insufficiency (lack of stimulation of cortisol level to achieve >18ng/dl with synthetic ACTH administration). Post operative in October 2007 imaging again showed a persistent tumor, size unchanged, with optic chiasm involvement.

Mr. G presented to OHSU for ongoing care and reassessment in late November of 2007 with right eye proptosis. Formal testing indicated decreased "right-sided ocular motility, increased intraocular pressure bilaterally, and superior bitemporal hemianopsia". He complained of headaches, daytime fatigue, mood lability with anxiety and depression, difficulty with concentration and short term memory plus symptoms of hypogonadism, blurry vision, morning nausea and weakness, centripetal weight gain, nocturia, increased thirst, hunger and reflux. His past medical history was otherwise positive for hypertension, nephrolithiasis, dyslipidemia and GERD. He had no known drug allergies, and medications included: Omeprazole, HC (20mg in

AM), Fenofibrate, Amlodipine, LT4 (50 mcg /day), Percocet PRN, testosterone 200 mg IM q 2 weeks. He was not treated with other steroids.

His family history included prostate CA in his father and lupus. He had no history of illicit drug use, drank 2-3 beers a week and smoked 1.5 packs of cigarettes a day for 25 years. He had quit smoking after his last surgery. He was married and monogamous for 30 years and was employed as an electrician in a small business in a rural community. His wife was also employed outside the home, and, in addition, ran a small home business selling preserves. They both had health insurance coverage through their employers. Mr. G had two healthy independent children age 25 years and 23 years and a 76 year old mother living who was also independent and living next door. He and his wife were actively involved in their local church. He had no specific hobbies but enjoyed football. He did not exercise regularly and had not done so for a number of years.

On physical exam his vital signs were: blood pressure 155/88, heart rate 77, height 5'11'', weight 202lbs, BMI 28.2. Pertinent positive findings included: mild facial rounding, visual field with bitemporal visual field restriction on confrontation, mild dorsocervical and supraclavicular fat, several violaceous striae on abdomen, central obesity, scattered ecchymoses, thinning of skin, +1 pretibial edema, psoriatic lesions on LE. Pertinent negative findings included: no nasal drainage, EOMI, normal thyroid size and texture, no acanthosis.

A work up for evidence of recurrent Cushing's disease and hypercortisolemia was negative, although ACTH remained elevated. Mr. G's biochemistry showed that he had acute renal failure with hypokalemia, adrenal insufficiency or hypocortisolism (defined as cortisol less than 18ng.dl 30 minutes after ACTH stimulation testing). Thyroid function was normal and testosterone was

adequately replaced at trough level. His prolactin level was normal. FSH, LH was appropriately low. His IGF-1 was low, which might indicate low growth hormone levels but given the aggressive nature of this tumor, evidence of growth hormone deficiency was not pursued. Replacement of a potential growth factor under these circumstances is not recommended.

Laboratory results:

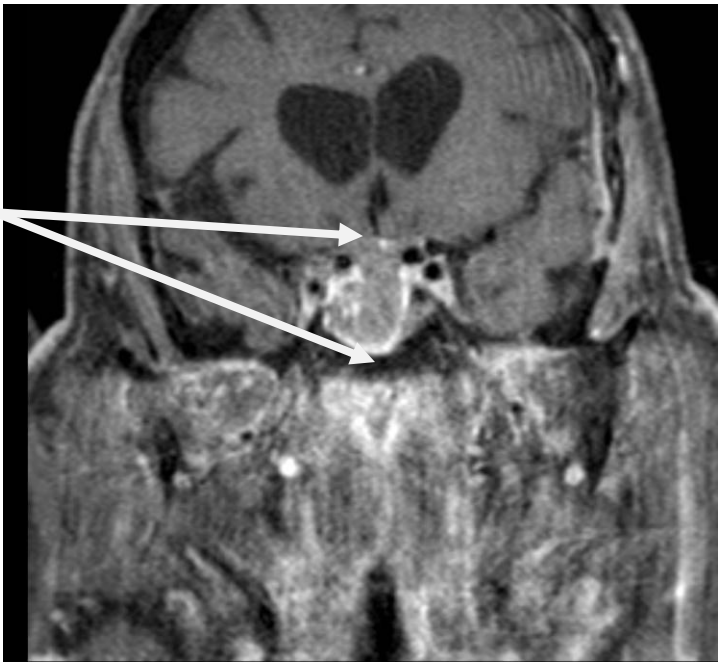
Component *Latest Ref Rng*	**12/7/2007**	**12/7/2007**	**12/7/2007**
GLUCOSE, PLASMA *60 - 99 mg/dL*	**76**		
BUN *6 - 20 mg/dL*	**27 (H)**		
CREATININE *0.7 - 1.3 mg/dL*	**1.6 (H)**		
SODIUM *136 - 145 mmol/L*	**140**		
POTASSIUM *3.5 - 5.1 mmol/L*	**3.4 (L)**		
CHLORIDE *98 - 107 mmol/L*	**106**		
CO2 *23 - 29 mmol/L*	**27**		
CALCIUM *8.5 - 10.5 mg/dL*	**9.0**		
CORTISOL, TOTAL SERUM *** time dependent *ug/dl***	**10.4**		**16.8**
TIME *Hrs:mins*	**00:00**	**00:00**	**00:30**
ACTH, PLASMA **<46 *pg/mL***	**144 (H)**		
TESTOSTERONE **175-750 *ng/dl***	**201**		
TSH, SERUM **0.34-5.6 *uIU/ml***	**0.50**		

PROLACTIN, SERUM 3-13 *ng/ml*	**8**		
FSH, SERUM <19 *mIU/mL*	**< 1**		
LUTEINIZING HORMONE, SERUM <11 *mIU/mL*	**< 1**		
IGF-1, SERUM 82-225 *ng/mL*	**81 (L)**		
FREE T4, SERUM 0.6-1.2 *ng/dL*	**0.8**		

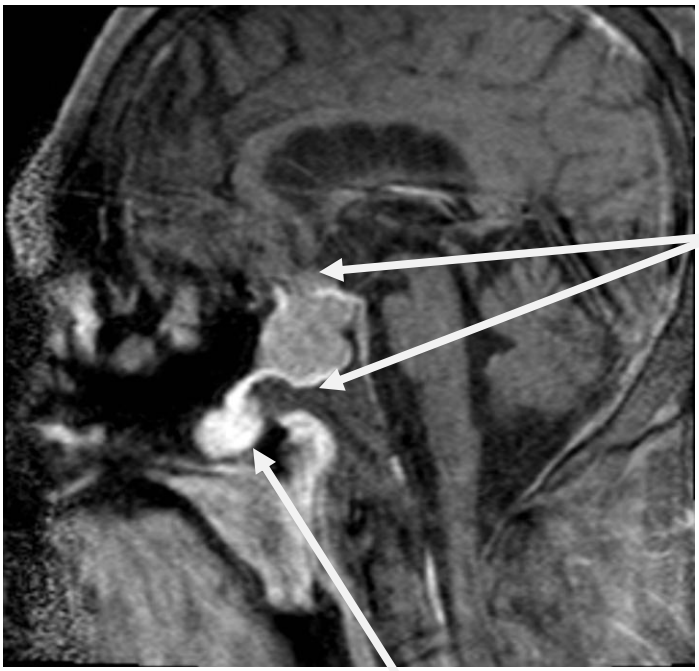
Mr. G underwent a Transnasal transsphenoidal resection to debulk tumor from the optic chiasm in December 2007 at OHSU. Pathology indicated corticotroph (ACTH) producing adenoma. At a follow-up visit in April 2008, the patient reported no headaches and no change in visual deficits. MRI report indicated:

> "Sellar and suprasellar mass appears to have different morphology compared to the prior study, but overall similar size or perhaps slightly increased size [compared to pre-op]. The lesion does displace the chiasm superiorly, and appears to invade the right cavernous sinus."

At that time the increase in size was thought to be a measurement and post operative artifact and the patient was returned for repeat MRI October 2008. He was noted to have a worsening visual filed exam by confrontation, worsening symptoms of headache and polyuria. MRI indicated the tumor had doubled in size to 4.2 x 2.5 x 4.0cm. Mr. G. subsequently underwent a craniotomy for tumor debulking November 2008 to preserve his vision. Pathology indicated an ACTH producing tumor but no other markers were evaluated.



T1-Coronal view



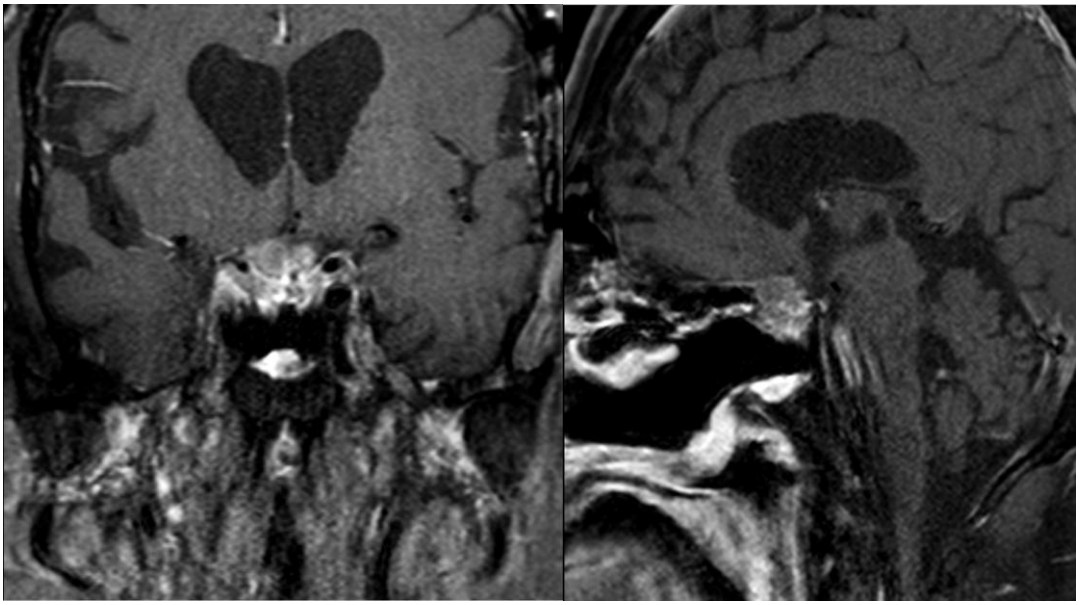
T1- Sagittal view
Sinus fat packing

.

His post operative course was complicated by diabetes Insipidus (DI), confusion and agitation. The DI resolved within one month, as did the agitation, but confusion persisted. He was discharged to a skilled nursing facility (SNF) for one month. However, for his safety he required constant companionship after discharge. Home care was provided alternately by his wife and his mother. A follow up MRI February 2009 indicated tumor re-growth of 2.1 x 2.4 x 2.4cm, and by June 2009 this had again doubled in size and a new nodule was noted. He had no biochemistry or stigmata of Cushing's disease. He proceeded to a second craniotomy for tumor debulking in July 2009. This patient's course was consistent with the literature regarding aggressive SCA tumors, but the rate of recurrence demonstrated at 6 months was more aggressive that most other reports. The tumor pathology was consistent with an "atypical" Corticotroph Adenoma, known to be particularly aggressive tumor subtype. Ki67 staining index

was requested and reported as 5-6%. This is consistent with literature indicating an aggressive tumor with a high risk of recurrence. This patient did not meet WHO criteria for a diagnosis of adrenal carcinoma, which predicts a 4 year life expectancy (Lim et al., 2006; Losa et al., 2010). Several published case reports indicated successful use of Temozolomide in aggressive pituitary adenomas, although none of these reports were associated with SCA's or corticotroph adenomas. In response, a tumor sample was sent to a reference lab for evaluation of MGMT levels. No methylation of O6-methylguanine methyltransferase (MGMT) promoter was identified by methylation-specific polymerase chain reaction (PCR) testing.

Mr. G was referred to the Neuro-Oncology clinic for monthly treatments with Temozolomide (Temodar) chemotherapy in August 2009. He was given 3 monthly treatment with this drug as recommended in the literature. He tolerated the drug with minimal side effects. Reported side effects have included alopecia, fatigue, nausea, vomiting, anorexia, headache, constipation, convulsions and thrombocytopenia. He had persistent fatigued with periodic episodes of confusion, but headaches had improved at follow up in Nov 2009. His vision demonstrated bitemporal visual field restriction of approximately 50%. MRI of Nov 2009 revealed a 60% decrease in post operative tumor size, now 1.6x1.3x1.5cm, with no optic chiasm involvement. Reimaging of March 2010 showed no growth or change in size of residual tumor. His ACTH level at this visit was normalized at 46 pg/ml (<46pg/ml).



10 weeks post treatment with Temodar

Mr. G required one further surgical intervention in Aug 2010 for the placement of a lumbar peritoneal shunt when he acutely developed progressive headaches with ataxia, radiographic evidence of infarction of his ventricles and obstructive communicating hydrocephalus. This is not a complication that has been reported in the literature for SC, nor post treatment with Temozolomide, so causative factors are unclear.

In the interim after presentation, the patient was forced to take a medical retirement, and, after retaining a lawyer, was granted disability in early 2010 after 2 years of appeals. The patient's wife and mother have shared the burden of care with assistance from visiting nurses and respite by friends. The patients' quality of life has declined dramatically. Although no formal cognitive testing has been undertaken, from family reports, he is now unable to concentrate on complex tasks, cannot read and has difficulty with written language. He has maintained his basic

self care and is attempting to reestablish a role in family life. Although his condition is currently stable, his long term outcome and prospects for survival are unknown.

Summary

Mr. G. a 55 year old male presented 11 years after initial surgery and radiotherapy with recurrent / persistent Cushing's disease. On initial presentation, his tumor was reportedly a macroadenoma of 3cm. He had failed two transsphenoidal surgeries prior to presentation at OHSU. Although he presented with stigmata of Cushing's disease and elevated ACTH levels, no other biochemistry to support persistent or recurrent Cushing's disease was found. This suggested an inactive or silent form of ACTH or SCA.

He underwent a third Transnasal transsphenoidal resection at OHSU for optic chiasm compression and tumor debulking. Tumor pathology confirmed a corticotroph adenoma. However, within 4 months there was suspicion of tumor re-growth and in 10 months the tumor had doubled its preoperative size. He had persistently elevated ACTH levels and underwent two subsequent craniotomies for tumor debulking and persistent optic chiasm involvement. Indices of tumor aggression were found on pathology and DNA testing was performed on samples obtained at the second craniotomy. A low level of MGMT was found, suggesting the possibility that this tumor would respond to treatment with Temozolomide. After 3 months of treatment, the residual tumor was reduced by 60% and was stable 3 months after discontinuation of treatment. ACTH levels had normalized at 6 months after initiation of treatment.

Although the patient has had to undergo a further surgery for obstructive hydrocephalus, he has reported the resolution of symptoms, although his quality of life has not yet returned to preoperative levels. It is unclear at this time if this patients' life expectancy will be normalized

or if he will have any significant improvement in his quality of life or functionality over time. It is known that his vision is unlikely to return to a preoperative level.

Conclusion

Corticotroph macroadenomas are by far a minority in the population of pituitary adenomas, but they have been found to have a higher risk for becoming recurrent or subsequently aggressive in growth and resistance to conventional surgical and radiotherapies. Not classified as carcinomas because of a lack of remote metastasis, these patients, never-the-less, exhibit worse survival rates than those with non aggressive macroadenomas.

The ability to predict those tumors that are more likely to fall into this category is dependent on tumor immunostaining and the determination of markers of increased mitotic activity. This may help to alter the course of treatment for those patients with a higher index of Ki-67 and p53. Inclusion of these indexes are currently not a standard of practice in pathology laboratories. These may need to be requested if there is a high level of suspicion based on patient criteria such as, a macroadenoma on initial presentation, young age at presentation, male gender, tumor recurrence in less than 5-6 years particularly after radiotherapy and silent hormonal secretion.

Although more long term studies are required to demonstrate the efficacy of Temozolomide, it appears promising for early treatment of those patients whose tumor demonstrates high indexes of mitotic activity and low levels of MGMT. Early treatment may avoid further visual deficit, repeated surgical resections and quality of life compromise for identified patients. The optimal number of treatments and long term effects of treatment are yet to be determined before this treatment can becomes a standard of practice. Current use of

Temozolomide in this context is limited to a salvage treatment for those patients who have failed conventional therapies. It remains to be seen if length of survival can also be improved.

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Case Study- Fall Residency

ACROMEGALY

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Purpose

The purpose of this paper is to discuss the case of a patient with a delayed diagnosis of a pituitary tumor and acromegaly. Early indicators for recognition and evaluation of acromegaly in primary care are discussed along with endocrine evaluation and options for treatment.

Background

The prevalence and incidence of acromegaly has been estimated from a composite of multiple countries as 53.2 cases per million population with an incidence of 3.06 new cases per million population per year (van der Lely, Beckers, Daly, Lamberts, & Clemmons, 2007). Some sources suggest this statistic is considerably underestimated. Both familial and sporadic genetic and epigenetic factors appear to be involved in tumorigenesis. Less than 5% of pituitary adenomas are estimated to be inherited (Melmed, 2009).

First described in medical literature by Andrea Verga in 1864 and Pierre Marie in 1886, depictions in reliefs of the Egyptian Pharaoh Akhenaten (who reigned with Queen Nefertiti) and the biblical story of David and Goliath along with other art and literature, confirm the presence of acromegaly and giantism for thousands of years(de Herder, 2009; Melmed, 2009; van der Lely et al., 2007). Caused by an excess production of growth hormone by a tumor in the anterior pituitary, the sequelae have likely become more apparent with increasing longevity of the general population.

Growth Hormone (GH) secreting cells comprise an estimated 50% of cells in the normal anterior pituitary. Genetic control of GH products is encoded by 5 separate genes on the long arm of chromosome 17 ((Melmed, 2009). Synthesis and release of GH is controlled by the

hypothalamus in response to Growth Hormone Releasing Hormone and a complexity of peripheral factors involving Ghrelin and Insulin Growth Factor-1 (IGF-1) and inhibited by Somatostatin. Five receptor subtypes have been identified for somatostatin on GH cells. Primarily produced in and released from the hypothalamus with some peripheral tissue release from the CNS, GI tract and pancreas, Somatostatin sets the basal tone of GH release (Chanson, Salenave, Kamenicky, Cazabat, & Young, 2009; Melmed, 2009). Secretion of GH is pulsatile and circadian. Small pulses of hormone release occur by day or during wake time with higher spikes at night or during REM sleep and associated with other, yet unknown, factors (Sassin et al., 1969; Surya, Symons, Rothman, & Barkan, 2006).

GH regulates somatic cell growth both directly and through the actions of Insulin Growth Factor 1 (IGF-1). GH and IGF-1 receptors are expressed on a wide range of somatic cells, including liver, fat and muscle. Produced largely by the liver in a linear logarithmic fashion under the influence of GH, IGF-1 mediates skeletal growth, carbohydrate, lipid and mineral metabolism. Cell proliferation (particularly chondrocyte), is directly mediated by IGF-1. GH appears to have an anabolic effect on muscle and act directly on epiphyseal cells to induce bone growth(Melmed, 2009).

Significance of the Problem

Patients with acromegaly and GH excess suffer from multiple morbidities, lower quality of life and a mortality rate estimated at 2-4 times that of the general population. The average life span is on average 10 years shorter for individuals with acrogmegaly. The disease is most often diagnosed in middle-aged adults, with an average age 40 years. Men and women are equally affected (Chanson & Salenave, 2008).

Mortality is largely attributed to cardiovascular disease (47%), cancer (26.4%) and respiratory disease (8.3%) (Clemente Gallego, Gomez Bueno, & Lucas Morante, 2009; Colao, 2009; Melmed, 2009; van der Lely et al., 2007; Vance, 2008). The presence of hypertension and diabetes, early age of onset, the size of the pituitary tumor and the duration from the time of disease onset to diagnosis predict both the likelihood of mortality and increased morbidity. The average time from onset to diagnosis is estimated at around 10 years (Chanson et al., 2009; Melmed, 2009). Treatment that normalizes growth hormone levels has been demonstrated to improve life expectancy to that of the general population (Chanson et al., 2009; Clemente Gallego et al., 2009; Colao, 2009; Melmed, 2009; van der Lely et al., 2007). The later the diagnosis, the greater the morbidity and the more likely the burden of residual symptoms will cause persistent changes in quality of life.

Literature review strategy and search terms: using Pub-med search using key words: Acromegly, pituitary adenoma, diagnosis, treatment**,** IGF-1,

(Colao, 2009)Definition of key concepts

Physical changes in acromegaly are slow and insidious. In a study of over 600 subjects, the most frequent clinical symptoms that may help direct early diagnosis for the alert practitioner were described as facial changes, hyperhidrosis (abnormally increased perspiration), headaches, paresthesia ("pins and needles" tingling sensation), sexual dysfunction, arthalgias (Melmed, 2009). Worsening joint pain which may be as one of the earliest presentations pointing to the possibility of acromegaly (Barkan, 2007; Colao et al., 2005). Snoring, wrist pain, excess skin tag formation, thickening and oily skin, ring size changes and increasing shoe size, facial changes with increased size of lips, skin thickening, deep furrows across the forehead and broadening of the nose occur as soft and connective tissue changes progress(van der Lely et al.,

2007)(Chanson & Salenave, 2008; Melmed, 2009; van der Lely et al., 2007). Review of old photographs, a drivers license or photo identification in the patients medical records may be a valuable tool to assess progressive changes.

With time, voice character begins to change and deepen with progressive swelling of pharyngeal tissue. Macroglossia can make speech more challenging. Snoring worsens and often leads to the diagnosis of sleep apnea. Males may complain of gynecomastia. The patient may present with recurrent sinus infections. It is not uncommon for these patients to present with a history of multiple surgical procedures for connective and soft tissue disorders and cosmetic procedures. Wrist pain is often followed by a diagnosis and surgery for carpel tunnel syndrome, palatoplasty for reduction of snoring and treatment of sleep apnea, cosmetic surgeries for lip reduction and gynecomastia and La forte procedures for prognathism and malocclusion. A history of multiple muscle and joint injuries and arthroscopic procedures, particularly of the shoulders, knees and hips associated with joint laxity warrants further investigation. Soft tissue changes also occur to multiple organs including heart, lungs, kidneys, liver and pancreas (Chanson et al., 2009; Clemente Gallego et al., 2009; Melmed, 2009).

The diagnosis is often made late and recognized in characteristic bony and soft tissue facial features and dysmorphic extremities and kyphosis when the individual presents to a new provider (Chanson & Salenave, 2008). Radiographic evidence of hypertrophy of the frontal sinuses and the cranium become progressively more apparent over time. The patient may develop hypertension, goiter, progressive joint dysfunction, and, later, peripheral visual field changes and deficits with tumor growth and optic chiasm involvement (Melmed, 2009). Reports of peripheral visual field changes and deficits necessitates and immediate referral to an ophthalmologist for visual field exam, pituitary protocol MRI and referral to a neurosurgeon

skilled in the resection of pituitary tumors. The patient may require urgent surgical decompression to preserve vision.

Hypertension may become apparent, both because of the advent of obstructive (less often central) sleep apnea and because of vascular volume increases from sodium re-absorption at the distal renal tubules. Cardiovascular disease results from the influence of GH and IGF-1 on increased heart rate and systolic output, biventricular hypertrophy and decreased myocardial contractility. Fibrotic changes can lead to valvular disease with the risk increasing with length of exposure to excess GH(Chanson et al., 2009; Melmed, 2009). Sixty percent of acromegaly associated deaths are estimated to be related to cardiac disease.(Colao, 2009).

IGF-1 normally performs a protective metabolic function, however, under the influence of excess levels of GH, triglycerides are hydrolyzed to free fatty acids and glycerol, promoting insulin resistance, and the development of hyperglycemia and diabetes(Chanson & Salenave, 2008; Melmed, 2009).(Pawlikowski, Pisarek, Kunert-Radek, & Radek, 2008) In a large 5 year prospective study, Schneider and colleagues (Schneider et al., 2010)reported that high IGF-1 (above the 90^{th} age-sex percentile), with or without acromegaly, was predictive of the development of diabetes.

A coupling of excess GH and changed dynamics of pulsatile PTH excretion in several studies has been suggested as a mechanism in increase urine calcium, and, along with disturbances in calcium and phosphorous metabolism, may account for the increased incidence of renal calculi in patients with acromegaly (Heilberg, Czepielewski, Ajzen, Ramos, & Schor, 1991; Mazziotti et al., 2006). An increased PTH pulsatile action also has an associated decrease in mineral bone density in these patients (White et al., 2006).

Initial biochemical assessment is as simple as obtaining a serum IGF-1 level. An IGF-1 level that is elevated for age and gender should be further evaluated. A random GH level, with an undetectable value, excludes acromegaly, but is generally not a reliable indicator of disease because of its pulsatile nature (Cordero & Barkan, 2008). Referral to an endocrinologist preferably with a sub-specialization in pituitary diseases is warranted if the IGF-1 is elevated.

An MRI using a pituitary protocol may be useful in revealing the presence of a pituitary adenoma. The increasing sophistication of imaging modalities and the incidental finding of a pituitary tumor on MRI for patients scanned after a head injury or during a workup for headache may provide increasing opportunities for the earlier diagnosis of this disease. However, vigilance by the primary care provider (and often by dentists) with attention to early signs and symptoms can lead to a diagnosis and treatment averting the cascade of catastrophic somatic and quality of life changes.

A full endocrine work-up for acromegaly includes an oral glucose tolerance test. Historically, the suppression of GH levels below 1ug/L in response to a glucose load and with a normal IGF1 makes the diagnosis of acromegaly less likely (Chanson et al., 2009; Cordero & Barkan, 2008; Melmed, 2009). However, recent data suggests that a nadir below 0.3ug/L is required to exclude the diagnosis (Chanson et al., 2009; Melmed, 2009). An oral glucose tolerance test will secondarily assess for glucose intolerance and Diabetes Mellitus. Full pituitary function evaluation is pertinent with evaluation of prolactin levels (can be co-secreted in excess GH secretion), thyroid function and gonadal function in particular. The thyroid should be evaluated for nodularity and PTH and Ca with suspicion of parathyroid disease. An echocardiogram, colonoscopy, sleep study and bone density evaluations are likewise recommended (Chanson et al., 2009; Cordero & Barkan, 2008).

Surgical, medical and radiotherapy options have been shown to be effective in the treatment of acromegaly. First line treatment has been the surgical, transsphenoidal removal of the pituitary tumor (Chanson & Salenave, 2008; Chanson & Salenave, 2008; Melmed, 2009) and has shown to be effective in retrospective reviews to achieve biochemical 'cure' in 52-57% of cases (Beauregard, Truong, Hardy, & Serri, 2003; Nomikos, Buchfelder, & Fahlbusch, 2005). Medical treatments with somatostatin analogue therapies, dopamine agonists and growth hormone receptor antagonists or a combination of these agents have been used to normalize IGF-1 and shrink pituitary tumors.

Native somatostatins are short acting and act directly to inhibit tumor GH production. There are 5 different somatostatin receptor subtypes 1-5 with subtypes 2 and 5 more specific to inhibit GH production. Somatostatin analogues (ligands) have been developed that target one or both of these receptors and are used as first choice medical treatment in persistent, post surgical acromegaly. Ocreotide binds preferentially to subtype 2 receptors and is available in short acting doses (8hour), requiring three injections daily or long acting LAR preparations requiring injection every 28 days. Long-acting release (LAR) formulation of Lanreotide that targets receptor subtype 5 is also administered intramuscularly every 28 days.(Chanson et al., 2009; Colao & Lombardi, 2010; Melmed, 2009). Tumor shrinkage of up to 25% has been demonstrated when using these medications.(Colao & Lombardi, 2010; Luque-Ramirez et al., 2010). In high risk surgical cases, firstline treatment with somatostatins to block excess GH production and shrink tumor has been shown to be effective (Colao et al., 2006; Colao et al., 2006). Clinical trials are ongoing for a new somatostatin analogue, Paseriotide, that targets subtypes 1,2,3 and 5 with a superior affinity for subtype 5(Petersenn et al., 2010).

Dopamine agonists, bromocriptine and cabergoline, have been used to reduce tumor GH levels and tumor size but have been shown in some cases to be less effective when used alone to antagonize IGF-1 production (Chanson et al., 2009; Moyes, Metcalfe, & Drake, 2008). Clinical trials are ongoing for combination somatostatin and dopamine agonist therapies.

The Growth Hormone Receptor (GHR) antagonist Pegvisomant (Somovert), acts to block the action of GH at the target tissue binding sites, blocking IGF-1 generation. GH levels may increase under these circumstances and although IGF-1 is normalized, tumor growth has been reported in a few cases (Chanson et al., 2009). Regular monitoring with MRI is advised for patients using GHR antagonists. Combination therapies of somatostain receptor ligands and GHR antagonists are employed when somatostatin ligands alone result in inadequate IGF-1 control.

Side effects of medical treatment can include nausea and diarrhea for several days after each shot, headaches, changes in glucose metabolism and asymptomatic gallstone formation (Attanasio et al., 2008; Melmed et al., 2005). These often resolve after several months of treatment or with treatment withdrawal. Liver functions need to be monitored for increased transaminases at the beginning of therapy with Pegvisomant. There have been are reports of hepatitis(Katznelson, 2010)(Katznelson, 2008; Lima et al., 2010).

Radiotherapy (RT) has been shown to improve remission rates over 15-20 years with reports of up to 77% of patients achieving a GH level below 2.5ng/ml 20 years after conventional RT (Platta, Mackay, & Welsh, 2010). Tumor growth has been reported as 100% controlled after a mean of 5.2 years (Schalin-Jantti et al., 2010)Adjunctive medical therapies are indicated in the interim to control GH/IGF-1 levels until therapeutic advantage can be achieved from RT. Varying degrees of anterior pituitary dysfunction requiring replacement hormonal

therapy (ACTH/cortisol, thyroid and gonadal dysfunction) can result from radiotherapy. Radionecrosis and optic neuropathy are now rare but possible complications of RT (Chanson et al., 2009).

Treatment has been shown to improve hypertension cardiac function and cardiomyopathy (Clemente Gallego et al., 2009). Headache control is usually improved along with fluid retention, sleep apnea and exercise tolerance (Katznelson, 2010). Reversal of soft tissue changes is achieved, but bone growth changes persist. Quality of life can remain compromised with the advent of osteoarthritic changes and kyphosis associated with higher or longer term GH exposure (Wassenaar et al., 2010). The earlier acromegaly is diagnosis, the greater the likelihood of influencing the long term outcome.

Case presentation

History of Present Illness: JF is a 31-year-old right-handed gentleman who was referred to the Pituitary Center from neurology after an evaluation for poorly controlled petite mal seizure activity, originally diagnosed at age 12. He had failed several medications and gained 145 pounds in the 12 months prior to presentation. During a sleep study EEG 3-4 years before presentation he was diagnosed with sleep apnea and given CPAP.

JF denied a history of head trauma or CNS infection. He did have nuchal cord x 2 at birth without known sequelae. He denied any significant change over time in his facial features and indicated his appearance and height were similar to other family members. He denied any increase in the size of his hands or feet or any coarsening of his facial features. He has had no complaints of carpal tunnel syndrome, no history of blood in his stool. He did have multiple sinus infections and was being treated with antibiotics at the time of presentation. His blood

pressure had been slightly elevated for several years but he had not sought treatment. He had no history of symptoms of hyperglycemia or diabetes. He had been married for 6 years but he and his wife had been unsuccessful in their attempts to conceive. He reported his libido and sexual function as poor.

He did feel his face had become "more puffy" but he had no gaps between his teeth. His dentist had noted a malocclusion and he subsequently underwent a surgical La Forte resection. He reported a history of migraine headaches for several years, but these spontaneously resolved. His skin had become somewhat oily over the last ten years, and he complained of generalized skin tags (many removed by his dermatologist). He was concerned about the velvety dark patches developing under his arms. He had developed acid reflux that he self treated. He noted worsening constipation, brittle fingernails and dry skin over the last few years.

Over the past two to three years he had been plagued by increasing fatigue, making it difficult for him to maintain his work schedule and disrupting his participation in social activities. For a number of years he had been complaining of severe joint aches, some memory deficits, increased anxiety, and emotional lability. He was finding it more difficult to participate in his routine gym activities and felt he was becoming progressively weaker. He attributed a recent frequency of muscle strains to his declining physical condition.

By his late teens JF became self conscious of his large lip size since late adolescence and underwent a cosmetic surgical lip reduction. He developed gynecomastia that was followed by an elective breast reduction surgery. He reported a recent episode of renal calculi and a strong family history of kidney stones. His last MRI prior to presentation in clinic was at age 19 years of age he had changed neurologists. No pituitary adenoma was evident or reported at that time.

JF ‘s seizure activity was eventually controlled using both Lamictal and Zonegran. He used Zantac to control his acid reflux and was treated with Augmentin and Prednisone for chronic sinus infections. He took ibuprofen for chronic back and joint pain but did not find this improved either his comfort level or mobility a great deal. He took both Magnesium and Miralax to relieve his constipation. He had no history of allergies to prescribe medication but did have seasonal allergies that he credited for his sinus infections.

His family history is significant for a distant paternal cousin with grand mal seizures, a paternal grandfather with rheumatoid arthritis, and a strong family history of multiple family members with arthritis. His mother has a history of melanoma and a sister is treated for depression. He was unaware of any family history of pancreatic tumors, parathyroid disease, pituitary tumors and thyroid disease. Interestingly, he did have a family history of kidney stones.

JF is employed as a surgical technician at a local hospital and been continuously employed in that role, maintaining a regular work schedule. He is married, with a supportive wife who is employed as a physician’s assistant. Hiking and biking were his chief recreational activities. However, he was finding these progressively too strenuous. His wife reported he had been withdrawing from all social and recreational activities. She felt he was becoming more distant and his moods more labile. He denied current or historical use of alcohol, tobacco, or illicit drugs. He reported no specific religious or spiritual affiliation and was motivated to follow through with treatment.

His physical exam was remarkable for his height of 6 feet 8 inches, weight 298 lbs and BMI of 32.7. He was normotensive at 132/70. HEENT exam was remarkable for frontal bossing, coarse facial features, a broad nose, enlarged lips, tongue and jaw. His visual fields

were normal to confrontation, cranial nerves were grossly intact and there was no facial asymmetry or ptosis. He had velvety axillary pigmentation bilaterally. His chest was somewhat barrel shaped with pronounced kyphosis. Cardiac exam was normal without evidence of a murmur. A musculoskeletal exam revealed enlarged hands and feet but joints were without significant laxity. He had scattered skin tags and coarse, dry textured skin.

MR imaging revealed a 2.5 x 2.6 x 2.3cm hypo-intense/hypo-enhancing lesion within the sella. There was erosion of the dorsum and tuberculum sella reported along with upward optic chiasm displacement (See figure 1). Laboratory testing revealed a normal glucose, IGF-1 elevated at 1510 (115-307 ng/mL), thyroid function was low with a free T4 of 0.5 (0.6-1.6ng/dl) and TSH of 0.80 uIU/ml (0.34-5.60 uIU/ml). Rheumatoid factor was negative, sedimentation rate was normal as was ANA. Prolactin level was slightly elevated at 29ng.ml (3-13ng/ml) and likely related to pressure on the pituitary stalk in preference to a co- hypersecretion of prolactin. His testosterone level was now normal at 210ng/dl (175-781ng/dl) with an inappropriately low FSH of 7 (<19 mIU/mL) and LH of 4 (<11mIU/mL) (See table 1).

Cortisol level after stimulation with cortrosyn (to evaluate the HPA axis function), indicated some mildly blunted function with a baseline level of 5.9ug/dl and a level of 15.2 ug/dl after stimulation. The cut off for normal cortisol values 30 minutes after stimulation with 1ug cortrosyn is an expected 18ug/dl.

An oral glucose tolerance test was done to evaluate growth hormone suppression. Normal growth hormone excretion will suppress to less that 0.4ng/ml and results from JF's testing indicated significant growth hormone excess with a nadir level of 20.9ng/ml and a baseline level of 31.0 ng/ml. Glucose metabolism was normal with no evidence of diabetes mellitus.

Owing to his history of familial kidney stones, it was necessary to rule out primary hyperparathyroidism associated with pituitary adenomas and the possibility of Multiple Endocrine Neoplasias 1 (MEN1). Both calcium and parathyroid hormone (PTH) were normal. In his case, his kidney stones could be related to his antiepileptic medications. JF was referred to neuro-ophthalmology for a visual field exam, to cardiology for an echocardiogram and gastroenterology for a colonoscopy. All tests were negative.

JF proceeded to resection of his pituitary macroadenoma in May 2008. The tissue pathology confirmed a diagnosis of a growth hormone producing pituitary adenoma. No other hormonal hypersecretion was noted and no markers of tumor aggression were found on further examination.

It was recommended that JF discuss his diagnosis and the possibility of a familial inherited pattern of disease. It was evident by family photos supplied by the patient during his evaluation that one male sibling may also be affected with this disease. Although the diagnosis was clear by both biochemical evaluation and surgically obtained histology, the patient's brother refused to accept the possibility that he may be affected and denied evaluation. Resources were provided to JF for sharing with his brother and we discussed the concept of readiness.

Post operative testing indicated normal levels of growth hormone but IGF-1 remained elevated. The implications of this remain unclear. As JF and his wife were anxious to proceed with plans for pregnancy, but were unsuccessful at 6 months post operatively. They were referred to the fertility clinic for work up with recommendations to proceed as soon as possible given concerns that JF would need further medical treatment if his surgical remission failed.

Conclusion

JF had an early history suggestive of acromegaly. Being above average height suggests an onset prior to closure of his epiphyseal plates. He was unaware of any hand and feet growth which most likely occurred in his later teenage years. He developed migraine headaches, enlargement of lips, malocclusion and gynecomastia and underwent cosmetic surgical procedures without a provider assessing his history in its entirety. Nephrolithiasis, joint pains, emotional changes, hypertension, hypogonadism, sleep apnea, recurrent sinusitis as later signs complete the picture of an acromegalic. Old photographs may have been helpful in an early diagnosis for JF. An IGF-1 before any of the cosmetic/reconstructive surgeries JF experienced could have avoided years of irreversible pain and irreparable somatic damage.

Although the possibility of familial acromegaly was raised with the patient's sibling, he (the sibling) remained resistant to evaluation. It was recommended that he discuss this further with his local provider who additionally provided care for this sibling. This raised a number of ethical concerns with respect to JF's brother's right to privacy versus our responsibility to inform this person of the risk or significant life function changes and higher risks of mortality. After much discussion among providers and with JF, it was decided that although it was our obligation in terms of beneficence and non maleficence to provide the information regarding his potential for disease, it was ultimately the brother's choice to proceed with evaluation and treatment.

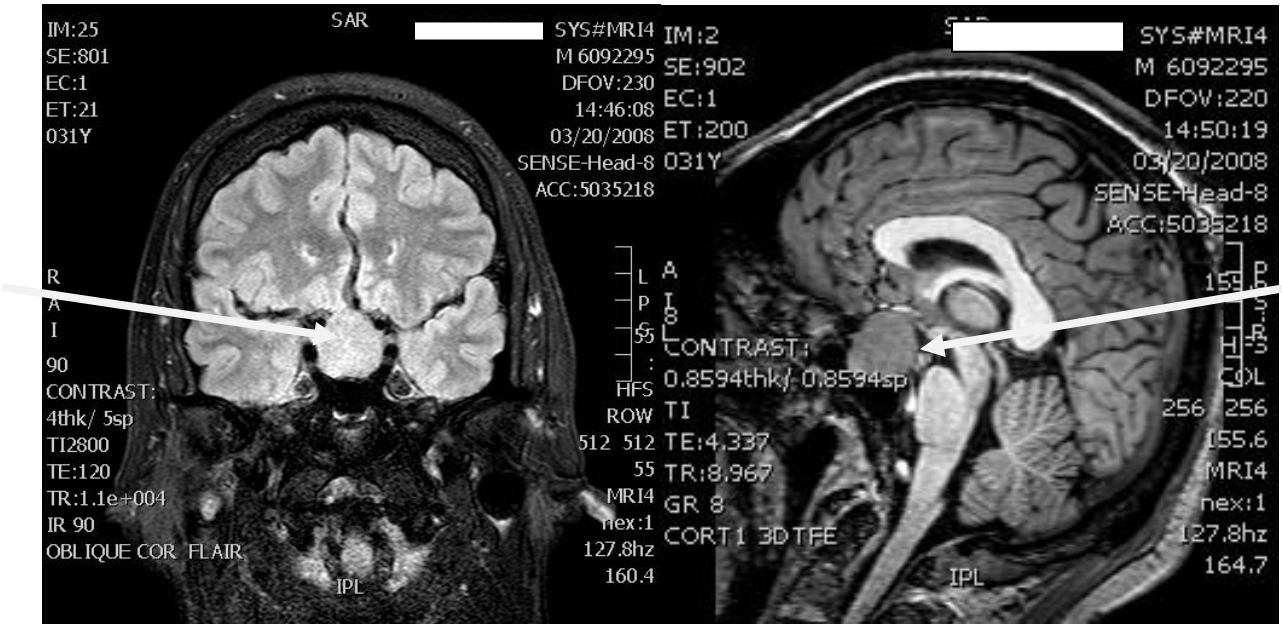
At the time of writing, this couple is undergoing invitro fertilization. Although JF's sperm count and motility were norm, they remained unable to conceive. The etiology of their infertility is unknown.

Table 1.

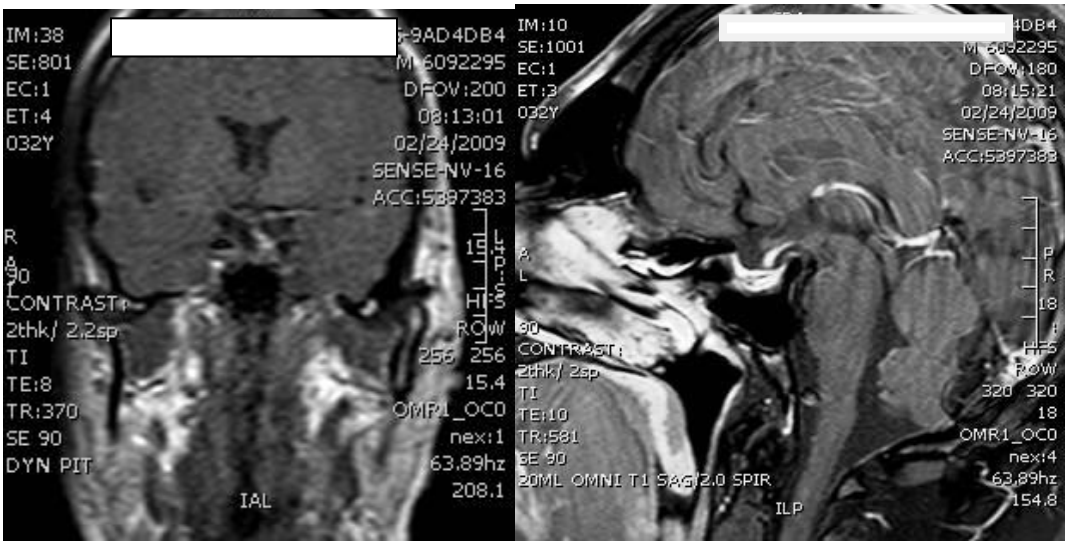
Ca (8.5-10.5 mg/dL)	9.8
PTH (15.0-75.0 pg/mL)	10.0
Free T4 (0.6- 1.6ng/dl	0.5
TSH (0.34-5.60 uIU/ml)	0.80
Prolactin (3-13ng/ml)	29
Testosterone (175-781ng/dl)	210
FSH of (<19 mIU/mL)	7
LH (<11mIU/mL).	4
IGF-1 (115-307 ng/mL)	1510

Figure 1

A **B**



C **D**



A. T2 Coronal view pre operative macroadenoma
B. T1 sagittal view pre operative macroadenoma
C. T1 coronal view post operative transsphenoidal resection
D. T1 sagittal view post operative transsphenoidal resection

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Treatment of a Patient with a Complicated Case of Cushing's Disease.

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Purpose: To describe the treatment of a patient with a complicated case of Cushing's disease.

Literature review strategy and search terms: Pituitary, Cushing's disease, treatment, recurrence, adrenalectomy, radiation treatment, Nelson's syndrome, pregnancy.

Background

Cushing's disease (CD) is a disease characterized by over production of the glucocorticoid, cortisol under the influence of abnormally elevated adrenocorticotrophic hormone (ACTH) (Melmed, 2002). Cushing's syndrome is differentiated from CD by its dependence on hormonal excess centrally from the pituitary gland (Bertagna, Guignat, Groussin, & Bertherat, 2009; Melmed, 2002).

While 90% of the pituitary tumors responsible for CD are microadenomas (tumors less than 1mm), the 10% that represent macroadenomas are typically more aggressive and more challenging to cure (Bertagna et al., 2009). However, cure of CD is a temporally relevant term and is increasingly being discussed more in terms of disease remission.

CD is considered a rare disorder with an estimated prevalence of 2-3 per million and a female / male ratio of between 3:1 and 10:1(Clayton, 2010; Melmed, 2002; Steffensen, Bak, Rubeck, & Jorgensen, 2010b). Distribution of age at diagnosis ranges from 25-45 years for adults. The distribution for children is different, and usually over 9 years of age with no gender differences in incidence (Melmed, 2002). Adult incidence is estimated to be in the range of 0.1 to 1 new cases per 100,000 per year, although many believe that the incidence is under recognized (Arnardottir & Sigurjonsdottir, 2010). However, even after treatment, there is evidence that the risk of recurrence does not remit for upward of 20 years (Steffensen, Bak, Rubeck, & Jorgensen, 2010a).

Significance of the Problem

CD is a serious chronic disease leading to a 2-3 fold increase in mortality (Clayton, 2010; Clayton, Raskauskiene, Reulen, & Jones, 2010; Steffensen, Bak, Rubeck, & Jorgensen, 2010a). This is largely, but not exclusively, from cardiovascular events. Prothrombic states, atherosclerosis and hyperlipidemia, hypertension and uncontrolled diabetes with associated complications and infections contribute to these events (Clayton, 2010; De Leo et al., 2010; Yaneva, Vandeva, Zacharieva, Daly, & Beckers, 2010b). Hypercoagulability in CD has also been associated with genetic polymorphisms in the promoter gene for factor VIII and von Willebrand factor (VWF) in some patients. However, impaired fibrinolytic capacity and an increase in clotting factors are also present in CD. Although normalization of mortality risk is generally achieved with disease remission, patients with persistent poorly controlled, long term diabetes or hypertension and those with recurrent disease incurred significantly higher mortality rates (Clayton et al., 2010; Clayton, 2010). This emphasizes the need for early identification and treatment.

ACTH and consequent cortisol production, follow a circadian pattern with peak plasma levels of ACTH occurring between 2-4 am (Krieger, Allen, Rizzo, & Krieger, 1971; Melmed, 2002). Levels gradually fall during the morning and, under normal stress levels, reach their lowest levels around midnight. Acute stress causes a reactive rise in ACTH, interrupting the normal cycle (Melmed, 2002). In 1932 Harvey Cushing proposed that the clinical manifestations of what is now known as CD were the result of hypersecretion from basophil adenomas in the pituitary gland (Melmed, 2002). It is now known that these manifestations are the results of chronic overstimulation and secretion of cortisol, from up-regulation of the adrenal gland cortisol production under the influence of excess, non-circadian ACTH production (Melmed, 2002).

Multiple genetic mutations have been described in CD, including changes in: hormonal expression, growth factors and their receptors, cell-cycle regulators and various genes related to hormonal

gene transcription, synthesis, and secretion. CD can be an inherited condition in the form of Multiple Endocrine Neoplasia type 1 (MEN1) and Familial Isolated Pituitary Adenomas (FIPA). These account for approximately 5% of pituitary adenomas (Yaneva, Vandeva, Zacharieva, Daly, & Beckers, 2010a). The synthesis of ACTH is regulated by POMC gene transcription and stimulated primarily by hypothalamic corticotrophin-releasing hormone (CRH) (Melmed, 2002).

Similarities are apparent between the metabolic syndrome and mild CD resulting in a diagnostic challenge and necessitating more accurate diagnostic testing, particularly in the earliest stages of disease (Alexandraki & Grossman, 2010). CD is frequently overlooked as a diagnosis (Findling & Raff, 2005). Elevated spot serum cortisol and ACTH levels are suggestive but they are not independently diagnostic for CD. Elevations in spot morning urine fee cortisol levels were also found to be an unreliable indicator (Fujita, Hata, Ogata, & Kojima, 1991). Some authors suggest that the most sensitive indicator of CD is the loss of circadian rhythmicity (Alexandraki & Grossman, 2010; Melmed, 2002). Although a midnight sleeping serum cortisol is a sensitive indicator of CD, it is impractical to obtain. The assessment of late-night salivary cortisol is a simple and convenient outpatient proxy shown in meta- analysis to have a sensitivity of 92% and a specificity of 96% (Carroll, Raff, & Findling, 2009). Evidence of elevated 24 hour urine free cortisol levels (sensitivity 45-71% and specificity of 100%) together with the foregoing tests is more predictive of CD (Findling & Raff, 2005; Findling & Raff, 2006). A positive overnight 1mg dexamethasone suppression test or more complex combination testing using both 2-day dexamethasone suppression (of normal ACTH and Cortisol levels) and CRH stimulation to elucidate excess pituitary ACTH and consequent excess adrenal cortisol production, is diagnostic for CD (Melmed, 2002). Most clinicians use a combination of these tests to increase their diagnostic value and distinguish CD from pseudo-Cushing's states (Alexandraki & Grossman, 2010; Findling & Raff, 2006; Yanovski et al., 1993; Yanovski, Cutler, Chrousos, & Nieman, 1993; Yanovski, Cutler, Chrousos, & Nieman, 1998).

Procedures such as cavernous sinus sampling and inferior petrosal sinus sampling confirm a pituitary source of excess ACTH and lateralization of excess hormonal concentrations within the pituitary gland (Yanovski et al., 1997).

As in metabolic syndrome (MS), patient with CD present with central obesity and extremity sparing and the addition of muscle wasting. Other clinical issues in common include: hypertension (more than 70% of the patients), elevated serum triglycerides (20% of the patients), and low high-density-lipoprotein cholesterol, elevated fasting blood sugar and insulin resistance (Chanson & Salenave, 2010). In CD, high glucocorticoid (cortisol) levels lead to muscle and liver glycogenesis and adipocyte insulin resistance plus glucose metabolism abnormalities (21–60% and 20–47% of the patients have impaired glucose tolerance and diabetes respectively) (Chanson & Salenave, 2010; Greenman, 2010; Pivonello et al., 2010). Pseudo-Cushing's states occur as a result of alcoholism, depression and some psychiatric disorders (Rosales, Fierrard, Bertagna, & Raffin-Sanson, 2008). Providers are challenged to pursue further assessment for patients with apparent MS.

Structural and functional impairment of the skeletal system from glucocorticoid inhibition of calcium absorption from the gut limits bone formation and accelerates bone resorption. Pituitary hormone deficiencies (sex hormones and growth hormone) associated with CD contribute to poor bone density with the result that up to 70% of CD patients experience fractures such as vertebral fractures and avascular necrosis of the femoral head (Kaltsas & Makras, 2010). Treatment of glucocorticoid excess reduces or eliminates this risk.

As glucocorticoids are the central hormone in the stress response, psychopathology such as co-morbid major depression, mania and anxiety disorders are also reported. Although improved after treatment, premorbid level of functioning may not be restored. Persistent impairment in quality of life, cognitive function, and coping strategies have been reported despite long-term cure (Biller et al., 2008;

Pereira, Tiemensma, & Romijn, 2010; Psaras et al., 2010; Tiemensma et al., 2010; Tiemensma et al., 2010; Tiemensma et al., 2011).

Treatment:

Treatment for concomitant and persistent diseases may be necessary for disease control during and after treatment although evidence based literature is absent to direct this treatment (Munir & Newell-Price, 2010). Consensus Guidelines emphasized the need for multidisciplinary and individualized treatment (Biller et al., 2008). Recommended first line treatment of CD is surgical resection of the pituitary adenoma. Second-line treatments for surgical failures or recurrence includes more radical pituitary surgery, radiation therapy, medical therapy, and, lastly, bilateral adrenalectomy. Because of the mortality risk and significant morbidity associated with CD, early diagnosis and treatment is recommended (Arnaldi & Boscaro, 2009; Arnaldi et al., 2010; Biller et al., 2008).

Transnasal transsphenoidal (TSH) and endoscopic approaches to tumor removal are the most common with reported disease remission rates of 70-100% (Kelly, 2007). Long term remission rates vary by report for 43% to 57% over 9 years of follow-up (Fleseriu, Loriaux, & Ludlam, 2007). The higher rates are achieved in the hands of more experienced neurosurgeons (Kelly, 2007; Netea-Maier et al., 2006). Cure rates are compromised by inability to depict the tiny microadenoma, even on sophisticated imaging, when the sella turcica is small and the dural cover of the pituitary gland highly vascularized. These factors result in bleeding and poor tumor visualization during surgery. Craniotomy is performed in a few patients with large and extrasellar tumors (Buchfelder & Schlaffer, 2010).

Recurrence rates are reported in up to 27% of patients post resection with redo surgical resection performed at the risk of further pituitary damage (Fleseriu et al., 2007). Second TSH has been reported to improve the remission rate by a further 10-15% or between 50-85% of those with recurrence (Fleseriu et al., 2007; Liubinas, Porto, & Kaye, 2011; Patil et al., 2008; Porterfield et al., 2008). When primary and

secondary surgical options fail to remit the disease, alternatives such as medical therapies, bilateral adrenalectomy, stereotactic radiotherapy or radiosurgery are considered (Kelly, 2007; Netea-Maier et al., 2006). Nelson's Syndrome can develop after bilateral adrenalectomy and often requires both transsphenoidal surgery and radio-therapy to gain disease control (Kelly, 2007).

Bilateral adrenalectomy (BA) offers effective permanent treatment for CD (Smith et al., 2009) and laparoscopic procedures in the hands of experienced surgeons have minimized: blood loss, mean hospital stay, operative time and recovery time when compared to open procedures (Castillo et al., 2007; Goitein, Mintz, Gross, & Reissman, 2004; Porterfield et al., 2008). The patient is permanently, surgically adrenally insufficient and subsequently has a lifelong dependence on exogenous glucocorticoid replacement for survival (Melmed, 2002). No endogenous source of glucocorticoid and mineralocorticoid production risks adrenal crisis and death from vascular collapse, hypoglycemia and hyponatremia (Melmed, 2002).

Nelson's syndrome is variably defined but central features include a high level of ACTH and skin hyperpigmentation post bilateral adrenalectomy. This may be associated with growth or re-growth of a pituitary tumor that can be potentially a life-threatening condition. Visual field disturbances may be present if the tumor is large and compresses the optic apparatus above the pituitary. Reports estimated occurrence rates of between 8-50% of CD patients post adrenalectomy with presentation time of 0.5 to 24 years postoperatively (Gil-Cardenas, Herrera, Diaz-Polanco, Rios, & Pantoja, 2007; Vance, 2009). Both radiation therapy and redo pituitary tumor excision are the recommended treatments in these cases.

Radiation treatment (RT) to resolve hypersecretion of ACTH and arrest tumor growth can be delivered as single-dose Gamma Knife radiosurgery (GKR) which is a specific modality of stereotactic radiosurgery or fractionated radiotherapy (Castinetti & Brue, 2009; Castinetti et al., 2009; Castinetti & Brue, 2010). Gamma Knife requires a well-defined pituitary lesion on MRI for targeting and is not

suitable for lesions in the cavernous sinus or close to the optic nerves or optic chiasm (Jagannathan et al., 2007; Vance, 2009).

Hypersecretion of ACTH is controlled by RT in about 50% of cases and tumor volume is stabilized or decreased in 80-90% of cases (Castinetti & Brue, 2010; Mayberg & Vermeulen, 2007; Petit et al., 2008; Vik-Mo et al., 2009). The risk of radiation injury to normal neural structures is reportedly higher with single fraction compared to fractionated treatment (Minniti & Brada, 2007). Time to achieve remission is unpredictable and usually occurs within an average 60 months but tumor control can progress over 5-10 years (Castinetti et al., 2009; Mayberg & Vermeulen, 2007; Minniti & Brada, 2007; Minniti et al., 2007; Petit et al., 2008; Starke, Williams, Vance, & Sheehan, 2010; Vance, 2009). Until remission is achieved, additional treatment is required.

Hypopituitarism is the main side effect of radiotherapy and is reported in 20-50% of cases (Castinetti & Brue, 2009; Castinetti & Brue, 2009; Castinetti et al., 2009; Castinetti & Brue, 2010; Losa, Picozzi, Redaelli, Laurenzi, & Mortini, 2010; Minniti et al., 2007; Petit et al., 2008; Vance, 2009). Severe side effects of radiotherapy, such as optic neuropathy and radionecrosis, are uncommon (Losa et al., 2010). Relapse rates post GKR have been reported up to 20% over a period of 60 months with a further 50% of these patients responding to repeat GK intervention (Petit et al., 2008). Although the risk of developing a secondary neoplasia after radiosurgery is present, it is reportedly extremely low (Vik-Mo et al., 2009)

Medical therapies such as the alkylating agent, temozolomide has been used to effectively treat Nelson's syndrome in several case studies and appears to be well tolerated by the patient. Although more study is indicated this may prove a useful addition to the range of therapies available to treat this condition. (Barber et al., 2010; Moyes et al., 2009).

Available medical therapies for CD are useful when surgery is unsuccessful or contraindicated or as an adjunctive therapy until radiotherapy is effective (Feelders, Hofland, & de Herder, 2010; Pedroncelli, 2010). Available drugs include the adrenal-cortisol suppressive agent ketoconazole, neuromodulatory drugs and glucocorticoid receptor antagonists. Ketoconazole use is limited by hepatotoxicity (Feelders et al., 2010). ACTH producing adenomas have been shown to express dopamine (D2) and Somatostatin subtype receptors. DA agonists such as caberogline and bromocriptine, and the somatostatin analogue paseriotide have shown an inhibitory effect on ACTH secretion and/or a decrease of tumor size (Pedroncelli, 2010; Petrossians, Thonnard, & Beckers, 2010). Clinical trials of these agents alone and in combination are ongoing. Additionally, the glucocorticoid receptor antagonist, RU486 (mifepristone), has been determined to be a rapidly effective and well tolerated to block the actions of cortisol and clinical trials are progressing (Castinetti, Conte-Devolx, & Brue, 2010; Heikinheimo, Ylikorkala, & Lahteenmaki, 1990).

Hypercortisolism causes infertility but fertility can be restored after treatment and pregnancy remains possible after adrenalectomy. However, the mother and the fetus are exposed to higher mortality and morbidity risk (Trainer, 2002). During pregnancy the pituitary gland is enlarged as a result of lactotroph hyperplasia and hormonal changes may cause an increased risk of tumor growth (Karaca, Tanriverdi, Unluhizarci, & Kelestimur, 2010). Under normal circumstances maternal cortisol secretion increases from the beginning of the second trimester and in late pregnancy hormones of the Hyperthalamic- Pituitary -Adrenal (HPA) axis play a crucial role in parturition. Fetal exposure to excess glucocorticoid can result in intrauterine growth failure, and there is some concern that development of cardiovascular disease in adult life may be associated with excess intrauterine exposure (Trainer, 2002) . Control of cortisol levels during pregnancy and careful dose adjustments (particularly during labor) to avoid adrenal insufficiency, can result in a successful pregnancy outcome, with babies achieving a normal

birth weight. Patients should be followed closely throughout pregnancy for electrolyte abnormalities and signs of volume depletion as a result of increased rennin aldosterone activity (Karaca et al., 2010).

Case presentation:

At the age of 17 KF was diagnosed by her local physician with a presumed prolactin producing tumor. She had developed amenorrhea and some breast-milk production (galactorrhea), and recalled being told of a small pituitary tumor and an elevated prolactin level. Medical treatment was given and her prolactin level normalized with return of menses and she discontinued treatment. She subsequently had two normal pregnancies and breast fed successfully. However, after the birth of her second child and for the subsequent six years, until presentation at our clinic, she again experienced amenorrhea and some mild galactorrhea. She gained 35lbs, had rounding of her face, developed a hump on the back of her neck (dorsocervical hump) and developed exaggerated supraclavicular fat pads bilaterally. She complained of hirsutism, acne (particularly impacting her chest), and hair loss from her head, arms, legs and pubis. She denied facial plethora but had a dark complexion. She had been bruising easily with some thinning of her skin, darkening patches under her arms and breasts, and skin tags. She had not noticed any poor wound healing or violaceous truncal or extremity striae. She did have some stretch marks that were mildly pinkish in color. She had no history of bone fractures but noted some proximal muscle weakness and lower extremity edema. She had experienced recurrent upper respiratory tract and urinary tract infections, bouts of frequent nocturia and tachycardia. Her vision was blurred but she reported no visual field changes or deficits. She did not have gastroesophageal reflux disease or other gastrointestinal symptoms. In terms of neuropsychiatric symptoms, she had been having fatigue, depression, emotional lability, and sleep disturbance but felt she had adequate levels of concentration and short-term memory. She had no obvious neurological deficits. Her past medical history was significant for hypertension, fasting hyperglycemia with worsening insulin resistance treated with metformin.

She presented for evaluation at another facility and was diagnosed with Cushing's disease. Her initial workup revealed: an elevated 24-hour urine-free cortisol of 340 ug/dl with an upper range of 45, a morning cortisol of 28ug.dl, (upper range of 23ug/dl and did not suppress her cortisol below the expected 5ug/dl (patient level was 32) a morning cortisol level of 32ug/dl (normal < 5ug/dl) after a 1mg dexamethasone overnight suppression test, and a serum ACTH of 89 (9-52 pg/ml). MRI at this time indicated a pituitary tumor on the left anterior pituitary of 9mm.

KF presented to our clinic at the age of 31 years as an inpatient consultation for post-operative treatment of Cushing's disease. She had undergone an attempted transsphenoidal resection of her pituitary tumor at an outside institution that resulted in hemorrhage from damage to the right internal carotid artery. The patient was emergently transferred to OHSU and surgically stabilized. The histopathology from this resection confirmed an ACTH pituitary tumor.

KF's presenting symptoms were as previous described. She had no drug allergies and her only medications at the time of presentation were metformin and birth control pills. Her physical exam revealed a cushingoid habitus with facial rounding, acne, a dorsocervical hump, bilateral supraclavicular fat pad filling, central weight with relative extremity sparing, scattered ecchymoses with some thinning of the skin and multiple pink abdominal striae but <1cm in width with blanching. The remainder of her examination was negative. Her family history was non-contributory and negative for tumors or other chronic illnesses. She was married, with two healthy children ages 6 and 9 years and worked as a finance assistant in a local trucking company.

Nine months after surgery she had persistently elevated cortisol levels with a 24hour urinary cortisol level of 2.5 times normal (266ug/interval). She underwent a dexamethasone suppression and CRH stimulation test that was positive for a pituitary source of excess ACTH with a cortisol elevation of

5.7 times normal at 15minutes after CRH stimulation and a concomitant elevation of ACTH of 1.4 time normal at 65pg/ml. A cavernous sinus sampling was obtained to confirm a central source of ACTH and indicated elevated levels to 2001ug/dl and a gradient of greater than 3:1 (44:1) from the left side of the pituitary to the peripheral levels of ACTH. KF proceeded to a bilateral adrenalectomy for cure of Cushing's disease. Pathology confirmed adrenal hyperplasia, indicative of Cushing's disease and up-regulation of cortisol production under the influence of excess ACTH.

Post operatively KF progressed well. She was given tapered steroid supplementation for 3 months until her adrenal response normalized, after which glucocorticoid (hydrocortisone) was continued at a physiologic dose of 20mg each morning. Over the ensuing 12 months, her preoperative symptoms resolved, she had resolution of her headaches and lost 53lbs. Her hypertension and insulin resistance resolved, and all associated medication was discontinued. Aside from her surgical adrenal insufficiency and required replacement of glucocorticoids and mineralocorticoids, she had normal pituitary function with the return of menses within 6 months of adrenalectomy.

KF was followed post operatively with serial ACTH levels every 6 months and MR imaging yearly. Her ACTH remained within normal range and her MRI remained stable over the next 2 years. During this time KF achieved a quality of life she enjoyed. She returned to work and, with coaching during follow-up visits and phone consults, learned to identify and manage intermittent symptoms of adrenal insufficiency associated with stressors such as flying, injury, fevers, and illness and during the illness and death of her mother from a cerebral glioma.

After discussion with all her providers, two and a half years after bilateral adrenalectomy, KF elected to become pregnant. Prior to her pregnancy MR imaging indicated a right sellar mass of 5mm x 7mm with a 3-4 mm lesion on the left. Both lesions had been stable for 3 years. Her ACTH level was

normal. Her pregnancy progressed with normal fetal growth and movement. She had progressive symptoms of adrenal insufficiency with fatigue, pelvic pain, headache, nausea and dizziness requiring a steadily increasing dose of hydrocortisone as the pregnancy progressed. Her delivery was unremarkable and stress steroid doses were given, as recommended, throughout labor and delivery. She successfully delivered a healthy 3175 grams infant boy. She had difficulty breast feeding, despite lactation consultation and the baby thrived on bottle feeds.

MR imaging several months after delivery indicated some growth in the right residual pituitary tumor from 7mm to an overall size of about1.5 cm x1.7 cm x 1.2 cm, causing high grade stenosis of the distal right internal carotid artery. Her ACTH level climbed to 462pg/ml (range <46pg/ml) giving her Nelson's syndrome, despite adequate intake of hydrocortisone. She noted progressive skin fold darkening with darker patches under her arms and on the palms of her hands. She underwent immediate craniotomy for tumor debulking followed by radiation. The tumor pathology was again positive for pituitary adenoma with excess ACTH production. Somatoastatin 2a receptors were present in the tissue sample. Two months after surgery, and after receiving a total dose of 20 Gy of fractionated stereotactic radiation to the tumor bed, MRI indicated a decreased in size of tumor load to about 0.9 x 1.1 cm.

Several months post radiation KF complained of worsening headaches and fatigue. She had previously returned to work but was now finding it difficult to complete her daily routine and care for her children. She experienced recurrent upper respiratory infections and bronchitis. MRI was repeated and revealed an area of abnormal enhancement in the anterior right temporal lobe, which likely represented radiation necrosis. KF has had no other neurologic deficit and no seizure activity. She was counseled that because of the early appearance of these changes that the risk of progressive deterioration is greater. She underwent chemotherapy with Avastin (bevacizumab) to treat the necrosis. Based on a recent randomized controlled clinical trial, patients administered four doses of Avastin in the setting of radiation

necrosis given at 3-week intervals, showed improvement in both MRI and symptoms at the completion of treatment.

Nursing Care

Because of the mortality risks associated with CD, early diagnosis and management of concomitant diseases is important. There is evidence that this may avoid long term quality of life QoL changes that persist after treatment. Supporting the patient's coping skills and local support structure may aid in avoiding QoL changes long term. This should include the knowledge that 50% of patients will relapse within approximately 10 years of initial resection. Although the impact of regular monitoring has not been assessed, it is necessary for early identification and treatment of recurrent symptoms.

In line with all these data, patients with active CD (primary or recurrent) should be treated as having a prothrombotic disorder and consideration given to antithrombotic prophylaxis during procedures such as cavernous sinus (CSS) or inferior petrosal sinus sampling (IPSS).Measures should be taken in the immediate perioperative period in order to avoid thromboembolic events, such as the application of compressive stockings, early ambulation (Trementino et al., 2010). The risk of venous thromboembolism is enhanced in patients with CD by obesity and inactivity such as bed rest particularly with flying or driving long distances (Trementino et al., 2010). The patient and all caretakers need this information and instructions re thrombosis prophylaxis.

Bone mineral density (BMD) measurement at the lumbar spine should be performed as a screening test in all patients with CS due to the preferential loss of trabecular bone induced by GCs. For patients on chronic glucocorticoid replacement, regular measurement is recommended, although the measurement interval is unclear. Supporting diet and exercise, both for weight reduction and improved bone health, hypertension and glucose control require attention.

Surgically adrenally insufficient patients require much education and support in adapting their steroid dose to their physiologic need. Efforts are directed at mimicking the normal circadian pattern with higher doses in the am and tapered doses in the pm. Dosing is individual and may be given in one, two or three doses daily and from 15mg up to 40mg /day when heavy manual labor is involved (Melmed, 2002). The patient is instructed to increase their dose if they experience fever, vomiting, injury, or major illness. If symptoms persist after a double dose of glucocorticoid (hydrocortisone) treatment in an emergency room is recommended. This involves the evaluation and treatment of electrolyte disturbances, fluid resuscitation for hypotension and the intravenous administration of stress dose glucocorticoid (up to 100mg) to treat adrenal insufficiency. Furthermore, patients are instructed to purchase a medic alert bracelet to indicate their medical dependence of glucocorticoids as the result of surgical adrenalectomy.

KF's care was during pregnancy and in the post partum period required frequent and close communication with her pre-natal team. Pituitary clinic visits were coordinated with her prenatal visits and visit notes were immediately available in electronic records. This enabled lab draws to be coordinated and viewed by all providers and subsequent plans to be formulated jointly. The neuro-ophthalmologist and radiation oncologist regularly provide care to the pituitary disease population and an established path of communication allows again for coordination of care and visits. The patient was also in e-mail communication with all teams allowing more immediate responses to issues that arose during her pregnancy and subsequent radiation and oncology treatment.

Follow-up visits for KF included all immediate family members. She had a substantial support network of deeply involved friends and family. We discussed her need for respite from childcare, household infection control practices, and home management of upper respiratory tract infections. All family members have been instructed in the management of adrenal crisis, the recognition and management of seizures along with possible changes in KF's behavior if frontal lobe necrosis progresses.

Conclusion:

At the time of writing KF has had no further tumor growth. Her ACTH levels have maintained in the upper normal range, she has not developed further neurologic symptoms. Her fatigue and headaches have forced her to take a leave of absence from work although she is hoping to be able to return to work after 3 months. Her pituitary function has deteriorated and she has developed central hypothyroidism, amenorrhea and menopausal symptoms. She has stable replacement therapy for all hormonal deficits. She is likely growth hormone deficit but until her tumor has no further growth she is not a candidate for growth hormone replacement. However, she may receive future benefit from for growth hormone to improve her energy level and sense of well being.

KF's successful management can largely be attributed to timely responses and communication between disparate but contributory medical and nursing teams and the interaction of the patient. This reinforces for me the concept of coordinated care and the 'Medical home' concept.

Cushing's syndrome continues to pose diagnostic and therapeutic challenge at all levels of care. Diagnosis is only the beginning of a long term relationship between patient and multiple providers . Life-long follow-up and vigilance for complications is mandatory. Initially, ACTH is monitored every 6 months with yearly MRI. Changes that impact QoL may be minimized by early diagnosis and treatment. However, more study is required to determine specific changes, their impact on QoL, to identify their persistence over time and to address potential changes as they occur in the life cycle of this disease.

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Genomics Case Study MEN1

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Introduction

Theresa was a 23 year old woman who was referred to Pituitary clinic by her primary care provider for evaluation of a pituitary tumor in 2002. She was eventually diagnosed with Multiple Endocrine Neoplasia Type 1 (MEN1). This led to the diagnosis and treatment of other family members but more importantly led to the early diagnosis of her pancreatic malignancy that was successfully surgically removed before metastasis.

Familial MEN-1 is a rare autosomal dominant disease. Sporadic MEN1 mutations also occur with less frequency (Agarwal et al., 1997). It is estimated that by age 30, 87% of carriers have developed a MEN1-related neoplasm, and, by age 60, the majority of carriers have symptoms (Bassett et al., 1998). This case is interesting for its complexity and the wide reaching family implications. There are no effective treatments or cure for MEN1 cancers save early identification and resection (Agarwal et al., 2004). Half of all gastrinomas are estimated to have metastasized by the time of diagnosis (Brandi et al., 2001).

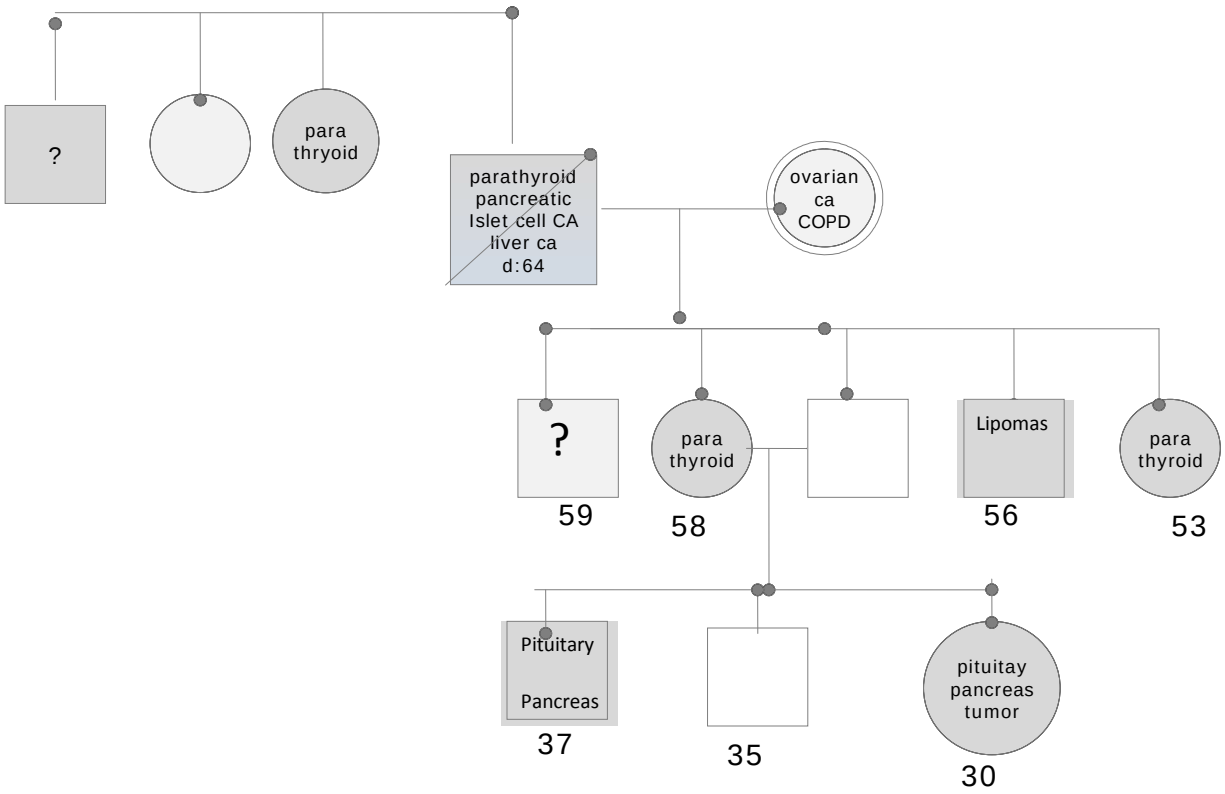
This patient was the youngest member of her extended family but refocused diagnosis and treatment for her siblings, mother, maternal aunts and uncles. This case exemplifies the need for early diagnosis and the clinical utility of a comprehensive family history.

Case Presentation

Theresa's pituitary tumor was discovered after a workup for amenorrhea in October 1994. An MRI of the brain showed a pituitary suprasellar and intrasellar of 7mm x4 mm. With a prolactin level of 200 (normal range 3-29ng/dl) she was diagnosed with prolactinoma. A trial of Bromocriptine, a dopamine agonist was initiated in order to treat the elevated prolactin and

shrink the tumor. Follow up MRI's in May 1995 and January 1996 showed an increase in the intrasellar component of the tumor. A transsphenoidal resection of the tumor was performed in February 1996. The pathology suggested the presence of a pituitary adenoma with cytologic atypia and increased mitotic rate indicating a more aggressive biologic nature of the tumor. A follow up MRI of May 1996 showed no further growth but serum prolactin level was mildly elevated at 32ng/ml but no dopamine agonist was prescribed. She had irregular menses and developed galactorrhea in 2001 and was restarted on Bromocriptine and birth control pills. Serial prolactin levels remained in normal range but a follow up MRI of the pituitary gland in late 2002, showed tumor growth to 1.8 cm. Two weeks prior to presentation at our clinic she developed headaches but denied any visual changes. She had no active breast discharge or tenderness. She had a history of anemia of unclear etiology elevated serum calcium levels but did not recall any specific workup being done. She had been evaluated for a lump in her right upper abdomen and was told this was a fatty lipoma.

Her family history was reviewed with her mother over several visits and revealed type 2 diabetes mellitus in her father and hyperparathyroidism in her mother, maternal grandfather and first degree maternal aunt. Her mother and aunt had undergone a parathyroid resection surgery for that purpose. The patient stated that her brother was diagnosed with multiple fatty subcutaneous tumors over the abdominal region and had been experiencing visual changes and headaches. To her knowledge, there was no other history of pituitary or pancreatic tumors in the family and no history of MEN1. (See pedigree chart below).



Theresa's social history included smoking one pack of cigarettes daily for 10 years with occasional alcohol and no other recreational drug use. Medications included Bromocriptine 2.5mg daily and Birth Control Pills Ovcon-35 daily. She had no known drug allergies.

On physical Exam she was, afebrile and normotensive with a BMI of 28. Her visual fields were normal to confrontation and the remainder of her exam was unremarkable with the exception of a right upper quadrant abdominal mass measuring 2.5 x 2 x 2.5 cm; firm, mobile, and non-tender.

An MRI of the pituitary revealed a 1.5cm x 1.8cm mass up to the optic chiasm. Labs were drawn to evaluate pituitary function, pancreatic function, liver function, Calcium and parathyroid function and for genetic testing for MEN-1. Laboratory results were remarkably all within normal limits.

Several weeks after this visit, Theresa presented to ED with visual changes and underwent an urgent transsphenoidal resection of her pituitary tumor that was pressing on her optic chiasm. After post operative follow up, she had genetic testing that indicated MEN1. She underwent further evaluation to determine is she harbored any other neuroendocrine tumors. Follow up neuroendocrine labs indicated elevated calcium; borderline parathyroid hormone levels and a significantly elevated glucagon level (see Table 1).

Table1

Component	Latest Reference Range	6/25/2003
MEAS ICA, WHOLE BLOOD	1.14 - 1.32 mmol/L	1.40 (H)
PH, WHOLE BLOOD		7.35
CALC ICA, WHOLE BLOOD	1.14 - 1.28 mmol/L	1.36 (H)
CALCIUM CONC, URINE	mg/dL	See cmnt
GLUCAGON	50 - 150 pg/mL	306 (H)
PARATHYROID INTACT, SERUM	10.0 - 65.0 pg/mL	65.0
GASTRIN	Low: < 101 pg/mL	47
	Low: < 17.1 uU/mL	8.4

In July of 2003 she underwent an abdominal CAT Scan (CT) scan for a suspected glucagonoma. CT revealed a 125- 160 HU dense lesion of 1.1cm in the tail of the pancreas. An ultrasound guided biopsy was performed and confirmed a diagnosis of malignant neuroendocrine islet cell tumor. No metastasis was noted but a total of 5 lesions were identified in the pancreas. She underwent tumor resection with a post operative course complicated by pulmonary emboli with bibasilar atelectasis and a Paralytic ileus.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant predisposition to tumors of the parathyroid glands, anterior pituitary, and pancreatic islet cells. Adrenocortical, thymic/bronchial and duodenal neuroendocrine tumors are also found (Lubensky et al., 1996) (Verges et al., 2002). The prevalence of MEN1 has been estimated at 1:30,000 with 2-4% of these presenting with primary hyperparathyroid tumors (Brandi et al., 2001). About 25% of all gastrinomas are associated with MEN1 (Agarwal et al., 2004; Brandi et al., 2001)}. A consensus

statement from an international group of endocrinologists recommends that MEN1 be defined as the presence of two of the three main MEN1 tumor types. Familial MEN1 is defined as an index MEN1 case with at least one relative who has one of the three main MEN1 tumors (Brandi et al., 2001).

Several studies have suggested that Familial Isolated Primary Hyperparathyroidism can represent a variant of MEN1 and recommend genetic testing in presenting individuals. A partial expression of MEN1 can present as different genotypes leading to the same phenotype (Miedlich, Lohmann, Schneyer, Lamesch, & Paschke, 2001; Perrier et al., 2002). Although malignant parathyroid tumors are uncommon, osteoporosis and nephrolithiasis commonly result from untreated parathyroid disease. If MEN1 is not considered for this population late diagnosis of other neuroendocrine tumors can lead to further morbidity and mortality.

Pituitary tumors in patients with MEN1 are often aggressive tumors that are discovered when large enough to cause pressure on the optic nerve and visual loss. This may reversible with tumor resection. Pituitary dysfunction can result and affect one or more of six axis functions including, pituitary/adrenal, thyroid, and gonadal, growth hormone, prolactin and vasopressin. Likewise, tumor hyperfunction and can result in the expression of excess pituitary hormones (Brandi et al., 2001). Hypothalamic/pituitary/adrenal axis deficiency results in adrenal insufficiency and can be life threatening, but hyperfunction results in Cushing's disease. Thyroid axis dysfunction results in metabolic disturbance and hypogonadism to poor bone density, sexual dysfunction, menstrual irregularities and infertility. Growth hormone deficiency in adults affects lipid metabolism, decreased lean muscle mass, memory deficits and psychological disturbances while excess leads to acromegaly bone growth, joint instability and soft tissue changes that affect cardiac and lung function. Posterior disturbances in vasopressin affect electrolyte balance

particularly hypernatremia or hyponatremia (Gomez, Steinhauslin, Crottaz, & Temler, 1987; Schneider et al., 2006).

The area of loss of heterozygosity (LOH) associated with the phenotype of MEN1 has been isolated to the gene encoding menin on chromosome 11q13 (Bystrom et al., 1990; Verges et al., 2002). As a result, down regulation of menin expression was initially thought to be the primary mechanism in the development of MEN1 tumors. However, approximately 20% of sporadic pituitary tumors show the same LOH (Asa, Somers, & Ezzat, 1998; Bystrom et al., 1990). Likewise, up to 30% of suspected MEN1 cases show no mutations in Menin (Pellegata et al., 2006). Using a rat model, Pellegata and colleagues (2006) identified a germ-line nonsense mutation in human CDKN1B gene found in an MEN1 (Menin gene) negative patient with parathyroid and pituitary tumors. This gene codes for the protein $p27^{Kip1}$. Findings indicate that a mutation in this protein is associated with the development of multiple endocrine tumors in rats. It is also known that down regulation of this gene plays a role in the development of a variety of human cancers supporting the theory that p27 plays an important role in neuroendocrine tumor suppression although this is not well studied (Pellegata et al., 2006). Recent studies have focused on the role of menin in altering epigenetic histone and chromatin structures (Gao, Hua, & Jin, 2008). Post translational modifications of histones have been cited as a factor in the development of hyperfunctioning pituitary adenomas (Minematsu et al., 2005) Likewise, epigenetic DNA methylation is thought to silence the hormone expression of an unmodified gene (Dudley, Revill, Clayton, & Farrell, 2009). A three to five fold greater incidence of the prevalence of pituitary adenomas in a province of Liege, Belgium has spurred further interest in the study of possible environmental or other epigenetic factors in the development of these tumors (Daly et al., 2006).

Knowledge of the role of affected genes and proteins in the development of MEN1 tumors provides the potential to develop targeted therapy to inhibit tumor growth. Identification of factors that may be involved in gene and protein mutations will require substantially more time and effort and centralization in data collection. Current knowledge only allows for the early identification of family members that carry the genetic mutations that can be followed for the development of neuroendocrine tumors and malignancies. The recognition of markers of aggressiveness of neuroendocrine tumors and the offer of genetic counseling to affected family members is currently the state and extent of the art in MEN1 prevention.

Case Analysis

Although her initial referral was for a probable recurrence of a prolactin producing tumor, her description of personal and family history led to a suspicion of a neuroendocrine genetic disorder. Theresa's primary provider had also elicited a family history of lipomas and had expressed concern of some unknown but possible genetic connection. Urgent resection because of visual field deficits delayed evaluation for MEN1 for this patient.

The patient presentation and the possibility of a family history of parathyroid disease triggered to need to elicit a more comprehensive family history. A pituitary biochemical workup is routine for all presenting patients. With a suspicion of MEN, testing for parathyroid, liver and pancreatic function was added. All screening biochemistries were normal.

A request for an interview with Theresa's mother stimulated the family to review their own medical history and family death certificates. This illuminated a trail of parathyroid disease and one death from a primary pancreatic tumor. This history mandated genetic testing for the

patient. Surgical pathology indicating an aggressive tumor coupled with the family history the enhanced this decision.

Once MEN1 mutation was confirmed for Theresa, it was recommended that other family members be evaluated, particularly those already diagnosed with hyperparathyroidism. Genetic consultation and counseling was offered at OHSU or recommended off campus and information was provided to the family as they approached the discussion with extended family members. At the time, a number of extended family members felt that further testing for them was not necessary. Theresa's subsequent diagnosis of a malignant pancreatic Islet cell tumor prompted screening in several affected family members.

Family members expressed concern regarding health care insurance, either fearing loss of or lack of eligibility if their genetic predisposition/ disease that would require lifelong medical surveillance. Some were concerned that being identified as the carrier of a genetic mutation, their ability to obtain health insurance in the future may be inhibited. Issues regarding the economic burden of ongoing screening and psychological concerns regarding the fear of developing a malignancy were also discussed. One uncle was estranged from the family and not interested in family contact. This opened old family wounds and unresolved interpersonal issues.

One of Theresa's brothers, diagnosed as paranoid schizophrenic, was incarcerated. Prison medical care provided for his evaluation and pituitary and pancreatic tumors were identified. They patient was scheduled for the removal of a large pituitary tumor but refused the procedure at the point of anesthetic induction. This became a significant ethical debate with respect to both the right to informed consent and his ability to consent. It was questioned if

beneficence was served if the patient was not mentally competent as a decision maker on his own behalf and subsequently died of a malignancy. This issue remains unresolved but medical surveillance continues.

Evidence based treatment includes yearly biochemical surveillance and early surgical intervention (Dekkers, Pereira, & Romijn, 2008). Literature reviews suggest 35% to 75% of genetically affected individuals develop neuroendocrine tumors (NETs) of the pancreas and duodenum (Lairmore et al., 2000). Surgical resection, using aggressive pancreatic resection, is reportedly the most effective in reducing metastasis and mortality (Lairmore et al., 2000) All NET's require lifelong follow up and interval imaging.

This case required patient approved involvement and coordination of multiple family members, genetic counselors, primary care providers, oncologists, general and neurosurgeons, medical ethicists and prison medical providers and officials. As discussed previously the treatment for MEN1 is limited to surveillance and resection of specific tumors that may develop. Expected outcomes are the early identification of hypersecretory and malignant tumors and the treatment of associated hormonal deficiencies. The need to ask the right questions regarding family history for all patient presentation is emphasized by this case. Stimulating family review of health information can either illuminate an hereditary disease or become data for future evaluation.

As a DNP the broader implication for standard care of my patient population includes the development of a graphic representation of pedigree as a standard part of an electronic record that can be adapted and updated by all care providers. This could provide a quick visual reference to stimulate further investigation as symptoms arise or as genetic knowledge improves.

The development of a provider algorithm for evaluation of patients who present with pituitary disorders and NET with known genetic implications may be a useful tool particularly in conjunction with a list of patient and provider resources.

Reflection on Practice

That the transcription of proteins may be enhanced or inhibited by a multitude of familial, historic and environmental factors is both exciting and disturbing. The possibility of improving public health environments to influence 'healthy' chromosome and protein expression, gives a whole new incentive to public health programs. Conversely, the concept that the environment of great grandpa or the fetal experience of grandma may have already influenced our genome and messed with our protein expression is quite disconcerting. My approach to health teaching and interventions with my patients has indeed changed. I have become more acutely environmentally conscious. Now, I add the need to be kind to your chromosomes, not only for the sake of the individual but also for that of possible future generations. Unfortunately, until there is more public education, this concept may be 'Star Trek' to many.

On the exciting side the possibility of targeted therapies to correct protein transcription errors, inhibition or over expression of proteins is encouraging. Enhancing tumor suppression has the potential to revolutionize the treatment of MEN1 and other NET sporadic tumors.

The identified of the MEN1 genetic mutation allows for testing at birth with early surveillance and early treatment or targeted therapies once developed. Concerns regarding health discrimination may need to be addressed legislatively for this to become an expanded effort from the current screening for inborn errors of metabolism.

I am now more aware of the need to develop, and revisit, family history. In past, this was considered a minimal part of history collection. Many patients are unaware of the implications and pay little attention to these family 'details'. I now encourage my patients to collect a family pedigree of health information that they keep with a compendium of their own health data. This is likely to be of greater use over the coming years as genomic information becomes more pertinent to diagnosis and treatment.

There is an imperative need for larger data bases with broad based data collection efforts that reflect collaborative scientific effort to advance knowledge of factors that influence gene mutation, expression and inhibition. I would add to this the need for quality information that conforms to a set of consensus developed criteria. There are multitude of peer review journals that catalogue much information, not all of which is useful, quality, reliable and reproducible data. Keeping up to date with current data is becoming increasingly difficult and the expansion of knowledge so rapid that online encyclopedic type sources of focused data may be useful and time saving for both research and practice.

Further development of critical evaluation skills and data mining techniques would be of benefit to me personally as more of this knowledge makes its way to my consciousness.

Summary/Conclusions

Neuroendocrine tumors can be sporadic or familial. There is clear evidence of a genetic mutation in familial MEN1. The involvements of genetic and epigenetic changes in histones and chromatin structures and the specific changes incurred in protein expression or inhibition are the focus of current studies. These changes appear to effect the development or suppression of specific tumor types. Further elucidation of these may pave the way for targeted gene or biochemical therapies to maintain tumor suppression or modify gene and/or protein expression.

There is a growing need for public policy and perhaps legislative protection of genetic information to guard against its misuse in individual and public health. As DNA banks collect more chromosomal information this becomes more imperative.

Mechanisms for sharing familial health genealogy so that this information can be available to all health providers in a dynamic fashion may help with the identification of potential inherited disorders and identify subjects for treatment in the future. Ethical issues with the collection and storage of this data will need to be addressed. Likewise, ethical issues particularly with respect to mental health in familial diseases will require more specialty attention and discussion.

Greater implications for public health may emerge in the coming years as more knowledge of environmental factors or the role of 'nurture on nature' becomes evident.

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Case Study: Infertility in a Hispanic Woman Presenting with a Prolactinoma

NUR 790

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Purpose: To outline a classic presentation of a patient with a prolactin producing pituitary adenoma.

Search Strategy: pituitary adenoma, prolactinoma, infertility, pregnancy, treatment, dopamine agonist, Hispanic.

Background.

Prolactin is an anterior pituitary hormone produced by lactotroph (or mammotroph) cells and controlled by tonic inhibition of dopamine from the hypothalamus (Kars, Dekkers, Pereira, & Romijn, 2010). This production is not age or sex dependent (S. Melmed, 2002). Prolactin producing cells represents 15-25% of the total compliment of pituitary cells, with a principle action to stimulate lactation after birth (Kars et al., 2010). To accomplish this, lactotroph hyperplasia normally occurs during pregnancy and resolves several months after delivery or after discontinuation of breast feeding. Serum prolactin levels are normally elevated during pregnancy and lactation. Prolactinomas or prolactin producing pituitary adenomas represent abnormal lactotroph hyperplasia with subsequent hypersecretion of prolactin and elevated serum prolactin levels in the non-pregnant state, and can occur in both males and females. Additionally, under the stimulation of high estrogen levels during pregnancy, abnormal prolactin production can be exacerbated, and hyperplasia of tumor cells can lead to the rapid growth of a pituitary adenoma during and/or after pregnancy (S. Melmed et al., 2011; Molitch, 2010). Prolactin synthesis and secretion is influenced by estrogen, thyrotropin releasing hormone, epidermal growth factor and dopamine receptor antagonists (S. Melmed et al., 2011). Most prolactinomas are thought to be the result of sporadic genetic mutations with inheritable genetic causes such as MEN-1 being rare (Colao & Loche, 2010).

Diagnosis is generally based on clinical symptoms of gonadal failure in both sexes. Women often present with amenorrhea or irregular menses and infertility. It was estimated that 25 % of women who initially present with amenorrhea, anovulation, infertility and galactorrhea have an associated prolactin

producing pituitary adenoma (Greenspan, Neer, Ridgway, & Klibanski, 1986; Klibanski et al., 1980). Women may also demonstrate vaginal-mucosal atrophy, lack of progesterone-induced uterine withdrawal bleeding, and serum estradiol levels comparable to those of postmenopausal women. Others may present with a relative estrogen deficiency, as serum estradiol concentrations may remain tonically fixed at levels found only during the early follicular phase of the menstrual cycle (Greenspan et al., 1986; Klibanski et al., 1980).

Males most often present with visual disturbances and headaches associated with compressive symptoms associated with a large macroadenoma (<1.0cm) (Colao & Loche, 2010). In men, hyperprolactinemia may lead to hypogonadism, decreased libido, erectile dysfunction, infertility, gynecomastia, and, in some instances, galactorrhea (Klibanski, 2010). Headaches are common for both genders and visual symptoms occur with macroadenomas that affect the optic apparatus. There have also been anecdotal reports of visual and olfactory hallucinations and episodes of "losing time," and apathy (Ali, Miller, & Freudenreich, 2010). Children may also present with growth delay (Colao & Loche, 2010).

Elevated serum prolactin levels can also be associated with breast stimulation and/or drugs that stimulate dopamine receptors on lactotroph cells. This includes, neuroleptics (metoclopramide, phenothiazides (Ali et al., 2010); drugs that inhibit hypothalamic control of dopamine such as monoamine oxidase inhibitors, tricyclic antidepressants, serotonin re-uptake inhibitors (Kars et al., 2010); and some antihypertensives (methyldopa, reserpine), estrogens, opiates calcium antagonists (verapamil). Other rare influences include severe head trauma, physical and psychological stress, primary hypothyroidism, chronic renal failure and liver cirrhosis, infiltrative diseases, cranial irradiation, and idiopathic causes (Colao, 2009; Klibanski, 2010).

Normal serum prolactin concentrations in women and men are dependent on the assay used but are usually below 25 ug/l and 20 ug/l, respectively. Mechanical and pituitary stalk disruption (stalk effect) that affects dopamine transport to the pituitary or drug effects in general result in mildly elevated serum

prolactin levels below 100ug/l. Likewise, those with prolactin secreting tumors usually demonstrate levels over 250ug/l. Higher levels are considered proportional to tumor mass with levels over 500ug/l diagnostic for macroprolactinoma (Colao, 2009; Kars et al., 2010; Klibanski, 2010; S. Melmed et al., 2011; S. Melmed, 2002). Those between these values present more of a challenge in diagnosis.

One caveat exists for mildly elevated prolactin concentrations known as 'hook effect'. This is an analytical artifact caused by lack of antibody-prolactin binding associated with the immunoassay when high levels of prolactin are present causing them to be read as falsely low. To obtain accurate levels, the sample is diluted and the adjusted concentration corrects for this effect (Kars et al., 2010; S. Melmed et al., 2011; S. Melmed, 2002). Asymptomatic patients with elevated prolactin levels should be evaluated for the presence of macroprolactin. In this circumstance, the bigger proportion of circulating prolactin is in the form of large, less bioactive prolactin molecules. It's estimated that 40% of patients presenting with elevated prolactin fall into this category. Further treatment is not considered necessary for this population (S. Melmed et al., 2011).

Epidemiology

Prolactinomas are the most common of the hormone secreting pituitary tumors and are estimated to account for 40% of all pituitary tumors (Arasho, Schaller, Sandu, & Zenebe, 2009; Colao, 2009; S. Melmed et al., 2011). Pituitary microadenomas (<1.0cm) are found in 10.9% of autopsies, with 44% of these reported as prolactinomas (Klibanski, 2010). They are the most common pituitary tumor in children and adolescents. However, their incidence is still largely unknown (Colao, 2009). Microadenomas are more common in women (up to 78%) aged 20-50 years and macroprolactinomas more commonly found in men over the age of 50 (Colao & Loche, 2010). The female-to-male ratio before age 50 is approximately 10:1(Ciccarelli, Daly, & Beckers, 2005). After 50 years the incidence is roughly equal for both genders.

Estimates of population prevalence vary from 100 per million population to 775 per million in one study done in Belgium (Colao, 2009; Daly et al., 2006; Gillam, Molitch, Lombardi, & Colao, 2006).

There is also some evidence that males often experience a more aggressive form of this disease, particularly those with positive Ki67 marker by tumor pathology (3.5+/-1.2 vs. 1.5+/-0.5%, p=0.0001) (Fainstein Day et al., 2010; Gillam et al., 2006).

Several explanations have been proposed for the higher incidence of microadenomas in women, and the incidence of macroadenomas in men. The simplest of these is amenorrhea, galactorrhea and resultant infertility is more apparent in childbearing women. Men, on the other hand, may ignore the symptoms of impotence and decreased libido, thereby delaying diagnosis until signs of chiasmal compression develop (Colao, 2009; Gillam et al., 2006). The other is that the development of prolactinomas is influenced by estrogen levels, although there is no conclusive evidence to this effect (S. Melmed, 2002).

Significance of the problem

Fertility is negatively impacted for both men and women with prolactinomas that coincide with peak childbearing years. Women with prolactin induced anovulation and amenorrhea have difficulty conceiving. In men, hypogonadism results in low sperm motility and consequent infertility. In children pubertal delay is found (Klibanski, 2010).

The prevalence of prolactinomas at a young age jeopardizes peak bone formation (particularly trabecular, vertebral bone) increasing the risk of osteopenia and osteoporosis. Gonadal deficiencies, estrogen and testosterone are proposed as causative of bone disease in adults (Kars et al., 2010; Klibanski, 2010). Spinal bone density is reported as decreased in approximately 25% of women with hyperprolactinemia, which persists in some cases despite normalization of prolactin levels (S. Melmed et al., 2011)

The apparent more aggressive nature of prolactinomas in men is still debated (Colao, 2009). However, it is known that the mean age of diagnosis for women is 10 years younger than for men (Bussade, Naliato, Mendonca, Violante, & Farias, 2007). Optic chiasm compression leading to visual

field deficits, 6th nerve palsies and permanent visual deficits are therefore more common in men than in women (Klibanski, 2010; S. Melmed et al., 2011; S. Melmed, 2002). In a retrospective review of 41 patients with macroprolactinoma, De Rosa and colleagues found that 17 (41.4%) had visual field defects (De Rosa et al., 2004). Those tumors with positive histological markers, Ki-67 index and p53 immunoreactivity, are correlated with more aggressive biological behavior and tumor (re)growth (Kars et al., 2010).

Quality of life has been found to be deficit, particularly in women with elevated prolactin. A US study of 50 women with microprolactinomas using SF-36 quality of life questionnaire, found that, compared with normal subjects, women with elevated prolactin levels (even after treatment) continued to experience lower quality of life (Cesar de Oliveira Naliato et al., 2008).

In an age matched controlled study of 22 patients (with newly diagnosed prolactinomas) and 20 healthy controls a strong association was found between hyperprolactinemia and platelet aggregation. This may increase the risk of mortality and morbidity from atherosclerotic and atherothrombotic events in patients with uncontrolled disease (Erem, Kocak, Nuhoglu, Yilmaz, & Ucuncu, 2010).

Pituitary apoplexy is a syndrome caused by hemorrhage or infarction of a pituitary tumor. This is a potentially life-threatening clinical condition associated with sudden onset of severe headache that may lead to loss of consciousness and vascular collapse from adrenal insufficiency. These patients may also develop visual field deficits if the optic chiasm is involved (Gillam et al., 2006). This is considered a medical emergency requiring the administration of stress dose steroids and surgical resection of the offending adenoma.

Management

When prolactin levels are elevated, an initial evaluation must first consider physiologic causes such as pregnancy (Klibanski, 2010). Prolactin levels can elevate 10 fold during pregnancy but usually normalize within 6 months after delivery in nursing mothers and within weeks in non-nursing mothers (S.

Melmed, 2002). Baring other causes for prolactin elevations (as previously discussed), MR imaging, using a pituitary protocol, should be obtained (S. Melmed et al., 2011). Full pituitary function testing is obtained to assess for pituitary dysfunction or co-secretion of more than one hormone, particularly growth hormone (Klibanski, 2010; S. Melmed et al., 2011).

Treatment goals include the normalization of prolactin levels, the restoration of gonadal dysfunctions and fertility, the reduction of osteoporosis, the reduction of tumor mass and the relief of visual field defects. Early treatment is aimed at the preservation of anterior pituitary function, the prevention of continuing tumor growth and/or the shrinkage of tumor mass and ultimately the improvement of quality of life (Kars et al., 2010; S. Melmed et al., 2011).

Treatment approaches include medical therapy, surgical tumor resection and radiation therapy. Medical therapies using dopamine receptor agonists (DA) have demonstrated efficacy in both normalizing prolactin concentrations, inducing tumor shrinkage and preserving anterior pituitary function (Acharya et al., 2009). In the US only two DA, Bromcriptine, and more recently Cabergoline, are available and are used as first line therapies ahead of surgical resection in most cases.

Bromocriptine-mesylate is a semisynthetic ergot derivative that has D2 receptor agonist properties and was the first medical therapy effective in the treatment of prolactinomas. It has a short half life and is dosed daily with therapeutic doses ranging from 2.5–15 mg/day (Gillam et al., 2006). The most common adverse effects are gastrointestinal with nausea (30%) and vomiting (20%), constipation (10%), dry mouth and dyspepsia, headaches and drowsiness. On initiation of Bromocriptine therapy, approximately 25% of patients experience postural hypotension and dizziness. Some patients complain of nasal stuffiness. Bromocriptine is reported to normalize prolactin levels in 80 to 90% of patients with microadenomas tumor shrinkage in 70% of patients with macroadenomas. Normalization of gonadal function, improvement in bone density and improvement in visual field defects can be achieved in the

majority of patients (Gillam et al., 2006). The use of Bromocriptine is disadvantaged by the frequent occurrence of side effects that lead to discontinuation of therapy.

Bromocriptine is the DA of choice in women desiring pregnancy in order to achieve ovulation (Colao, di Sarno, Pivonello, di Somma, & Lombardi, 2002). Although it is recommended that Bromocriptine is discontinue during pregnancy (S. Melmed et al., 2011; S. Melmed, 2002) in over 6000 pregnancies, bromocriptine has not been found to cause any increase in spontaneous abortions, ectopic pregnancies, trophoblastic disease, or multiple pregnancies, and the rate of congenital malformations compared favorably with the rate expected in the normal population. Comparable data for cabergoline is not available, but in 663 cases of pregnancy reported there has been no increased in spontaneous abortion, premature delivery, or multiple births and congenital malformation rate again compares favorably to the rate expected in the general population (Ionescu, Vulpoi, Ungureanu, Ionescu, & Zbranca, 2001; Molitch, 1998; Molitch, 2010).

Cabergoline, a potent D2 dopamine receptor agonist, achieves normalization of prolactin levels in 75 to 90% of the patients with micro- or macroprolactinomas, and an average decrease in tumor volume of 72 to 92% is reported (Bhansali et al., 2010; Kars et al., 2010; Klibanski, 2010; S. Melmed et al., 2011; S. Melmed, 2002). Cabergoline has been shown to be more effective than bromocriptine for both normalization of prolactin levels and tumor shrinkage and is generally better tolerated by patients (Colao et al., 2002; Gillam et al., 2006; S. Melmed et al., 2011). Although the side effect profile is similar to Bromocriptine, effects are usually shorter in duration and less severe (Gillam et al., 2006). The most common adverse effect is nausea or vomiting (35%), followed by headache (30%), and dizziness or vertigo (25%). Hypotension, with a median decrease of 10 mm Hg is experienced by approximately 50% of patients when therapy is initiated (Gillam et al., 2006). Therapy is usually initiated with 0.25 and increased to 0.5 mg twice a week although doses of up to 7 mg/wk have been required to achieve effect (Gillam et al., 2006).

With treatment, testosterone level is normalized, erectile function and sperm motility restored within 6 months (Colao et al., 2004; De Rosa et al., 2004). Colao and colleagues demonstrated, after 24 months of therapy, prolactin levels normalized in 75.6% of patients with macroprolactinomas and in 80% of those with microprolactinoma ($P = 0.9$). Galactorrhea disappeared in all patients; maximal tumor diameter was reduced by 22.6% in macro- and 28.3% in microprolactinomas ($P =0.91$), and in 30% of microprolactinomas ($P =0.37$) tumor disappeared. Visual field defects disappeared in 75% of patients with macroprolactinoma, and headache disappeared in 83% of patients with macro- and in 50% of patients with microprolactinomas. Anterior pituitary functions of growth hormone and ACTH secretion recovered in 62.5% and 60% of patients respectively (Aui-aree, Phruanchroen, Oearsakul, Hirunpat, & Sangthong, 2010; Colao et al., 2004).

Cerebrospinal fluid (CSF) leaks have been reported during treatment of adults using dopamine agonist (DA) therapy (bromocriptine and cabergoline), presumed to be due to tumor shrinkage which is thought to expose a pre-existing defect in the sellar floor (de Lacy et al., 2009; Gillam et al., 2006). CSF rhinorrhea and otorrhea have been reported with an incidence of 6-12% in various studies (Baskin & Wilson, 1982; Cappabianca et al., 2001; Hildebrandt et al., 1989; Hildebrandt, 1990; Kok et al., 1985; Teramoto, Takakura, Kitahara, & Fukushima, 1983). Symptoms of clear nasal and/or aural drainage and headache have been reported as early as after 3 doses of DA to as distant as 9 months after the start of treatment. Resultant pneumoencephalus and meningitis are risks that are reported in this literature.

Cardiac valvular insufficiency has been reported in patients with Parkinson's disease treated with high doses of cabergoline. Numerous studies have been undertaken with patients with prolactinomas. In six of seven studies involving 500 patients examined by the authors of Clinical Practice Guidelines for Hyperprolactinemia, no increased incidence of valvulopathy in those patients receiving standard doses, was found (Cawood, Bridgman, Hunter, & Cole, 2009; Cheung & Heaney, 2009; S. Melmed et al., 2011). An echocardiogram is recommended for patients treated with cabergoline long term, particularly in those

requiring elevated doses (Colao et al., 2004; Kars, Pereira, Bax, & Romijn, 2008; Kars, Pereira, Smit, & Romijn, 2009; Kharlip, Salvatori, Yenokyan, & Wand, 2009).

Withdrawal of DA therapy is recommended if the patient has been treated for at least 2 years, is free of symptoms, has tolerated taper of DA without consequent elevation in serum prolactin and has no evidence of tumor on MR imaging (S. Melmed et al., 2011). Some studies have indicated that this can be achieved in a subset of patients after treatment with cabergoline after duration of therapy of three to five years with tumor shrinkage demonstrated on MR imaging of at least 50% (Colao et al., 2004; Kars et al., 2010). However, one study demonstrated the risk of tumor recurrence over 60 months after DA withdrawal was 60% using these guidelines (Kharlip et al., 2009). More long term studies are required.

Resistance to DA has been reported in 10-25% of patients and may result in tumor growth (S. Melmed et al., 2011; S. Melmed, 2002). Some authors suggest that resistance to DA is usually apparent at the onset of treatment (Alberiche Ruano et al., 2010; Behan et al., 2009). Both resistance and intolerance represent failure of medical therapy.

Failure of medical therapies, along with apoplexy and optic chiasm compression, constitute indications for surgical resection of prolactinomas (Astaf'eva, Kadashev, Trunin, & Rotin, 2010; Gillam et al., 2006). Transsphenoidal approaches to the pituitary are now common using C-arm videofluoroscopy, MRI and frameless stereotactic intraoperative navigational imaging techniques for guidance to reach the sphenoid sinus and sell, and to assess the extent of a pituitary tumor resection. Endonasal endoscopic approaches have been shown to have favorable outcomes. However, surgical outcomes and ‘cure’ are highly dependent on the expertise of the neurosurgeon and the extent of the tumor invasion of the cavernous sinus, which is surgically inaccessible (Gillam et al., 2006). Long-term recurrence rates post surgically were reported as 18% for microprolactinomas, and 23% for macroprolactinomas (Kars et al., 2010). Adverse effect of transsphenoidal surgery includes the development of hypopituitarism, which is more common after surgery for macroprolactinomas. The

overall mortality rate following transsphenoidal surgery is less than 0.5% (Kars et al., 2010). Treatment with DA may still be required post surgically if ‘cure’ is not obtained (Colao, 2009).

Failed surgical resection or recurrent tumor post operatively warrants radiation therapy (Gillam et al., 2006). Several forms of radiation treatment are used, most commonly conventional fractionated external beam radiotherapy and stereotactic conformal radiotherapy (SCRT) to improve the precision of the delivery and reduce exposure to surrounding normal tissue. Some centers use single dose gamma knife radiotherapy. Radiation-induced hypopituitarism occurs in up to 50% of patients treated with effects that are cumulative over 10–20 years. There is also a risk of increased mortality from radiation-induced intracranial malignancies estimated at a cumulative risk of 2.0% at 10 years and 2.4% risk at 20 years post radiation (Gillam et al., 2006). In addition, the mean time to disease remission after radiation has been estimated in one study as 42.6 months (Castinetti et al., 2009). Continued treatment with dopamine agonists may be required until remission is achieved.

Follow up

Because prolactin levels usually, but not always, correspond to changes in tumor size, both prolactin levels and tumor size (assessed with the use of MRI) should be checked routinely (e.g., once a year for 3 years and then every 2 years if the patient's condition is stable, although data regarding optimal follow-up intervals are lacking (Klibanski, 2010; S. Melmed et al., 2011).

Case Presentation

A G 32-year-old Spanish speaking woman who presented accompanied by her English-speaking sister and husband for consultation and treatment of a pituitary macroadenoma with optic chiasm compression and an elevated prolactin level. Historically, AG’s menses were regular until the age of 25, when she became amenorrheic after discontinuing breast feeding her first child. She developed headaches at that time. A prolactin level was drawn by her primary provider which she reported as ‘elevated’. An MRI was done at that time and a pituitary tumor was described which was "chickpea" size. She was

started on the dopamine agonist, bromocriptine and, 3 months later, became pregnant. She discontinued bromocriptine after her pregnancy due to side effects (including headaches, nausea, and vomiting) and had no treatment for a period of about 2 years and reported having no significant symptoms. However, she began experiencing worsening headaches, amenorrhea and MRI revealed a 2.6 x2.1 cm pituitary macroadenoma with optic chiasm compression. She had no visual field deficits at that time and re-started dopamine agonist therapy with bromocriptine. Her menses were not restored. She sought consultation re possible stereotactic radiosurgery. However, the proximity of this tumor to the optic chiasm and the possibility of visual damage made her a poor candidate for this treatment. She was referred to the Pituitary Clinic for further evaluation.

At presentation, review of systems was negative other than as previously described. Her past medical history was unremarkable save for a recent diagnosis of hypertension for which no medication was prescribed. Her only surgical history was a C-section for the delivery of her first child 12 years previously. Her only medication was bromocriptine 5mg daily and she reported no known drug or environmental allergies.

Her family history was negative for tumors, but her mother had late onset diabetes and hypertension. AG was married with two living school aged children. She consumed 1 cup of caffeinated beverage per day, no alcohol, and she had never smoked, and she worked outside the home as a ‘picker’.

On physical examination she was normotensive with a blood pressure 122/68, pulse 80. Her BMI was 30. Her visual fields were normal to confrontation. The remainder of her exam was unremarkable. At presentation in clinic, a diluted prolactin level was 105 (normal range 3-13ng/dl) despite medical therapy. Her MRI revealed a left-sided adenoma about 7mm x 10 mm in close proximity to the optic chiasm. Assessment of anterior pituitary functions was found to be normal save an inappropriately low lutenizing hormone level (LH) and follicle stimulating hormone level (FSH).

AG consented to a trial of cabergoline. Consideration was given to surgical resection at this time and remained an option if she did not respond to treatment with Cabergoline. She returned to clinic for evaluation of prolactin level after 3 months, with minimal changes in diluted prolactin level. MRI showed tumor growth into the cavernous sinus. She proceeded to transsphenoidal tumor resection with an experience neurosurgeon. Pathology indicated a prolactin secreting adenoma.

Her post operative course was uncomplicated. She was discharged with controlled headaches. At follow up her anterior pituitary function was tested to be normal but diluted prolactin level had climbed to 276 ng/ml (3-29). She continued to have a milky breast discharge and frontal headaches some temperature dysregulation, weight gain, emotional lability and anxiety. She had not had the return of normal menses.

Given the patients symptoms, her intolerance to DA, her poor candidacy for radiotherapy and concerns re bone density in a young patient with persistently elevated prolactin level, she was offered a repeat surgery. Although AG was agreeable to this plan, her husband was angry and confused. He expressed economic concerns during the patient's disability and her inability to work to help support their family and lack of confidence that a second resection would be effective to control AG's symptoms.

AG returned to clinic four months later with worsening symptoms requesting a second surgical resection. She had discontinued cabergoline because of its economic burden. She underwent a orbitozygomatic craniotomy. The second pathology was negative for tumor and her post operative prolactin level was 311 (normal range 3-29).

Although continued treatment with a DA was recommended, the patient was lost to follow up for 4 years. She was re-referred by her primary care provider for treatment of a prolactin level of 158 (3-29) despite reported intermittent treatment with cabergoline. She did reported minimal headaches but had not had the return of menses. AG was referred for bone density measurement and echocardiogram but has not presented for these evaluations at the time of this report, six months later.

Nursing Care

Long-term success depends largely on the information provided to the patient and the patient's adherence to treatment (Delemer, 2009). Information and education were required for both AG and her husband regarding the short and long term implications of both treatment and lack of treatment. Without the use of a qualified medical interpreter, this information is difficult to convey. Language and cultural barriers were cited as a barrier for Latino/Hispanic couples being evaluated for infertility in a study by Nachtigall and colleagues (Nachtigall et al., 2009). This resulted in patients having difficulty both in understanding diagnoses and treatments and in communicating their questions, concerns, and experiences to providers.

Although it is easy to assume that information given is information received, this patient, nor her husband were ready to accept and comprehend the full implications, risks and benefits of medical and surgical therapies. Both parties may have benefited from improved coordination with her primary provider, a qualified interpreter and written, translated information.

A clear understanding of the cultural context of this patient was also absent from her treatment. There is little research into the use of traditional treatments and 'medications' used in the Hispanic/Latino communities that may have impacted AGs prolactin levels. A number of herbal treatments with varying active ingredients are shared between relatives and community members. These require more exploration with the patient and more academic research.

Likewise, exploration of the meaning of infertility was recommended for this couple. In an ethnographic study of Latino women and men, it was found that both believed that children were the basis of the marital relationship and that childless marriages were considered a failure (Becker, Castrillo, Jackson, & Nachtigall, 2006). The impact of AG's inability to conceive more children and access to infertility services requires culturally sensitive evaluation and assistance (Jain, 2006).

Although resources are available for medical assessment and surgical intervention for some uninsured patients, support for specific medication is not always readily available. Beyond medical costs,

the socio-economic impact of the loss of AG's income during her disability was beyond this family's means to cope. This, coupled with the issue of citizenship legitimacy and their ability to access ongoing health care was a much more pressing issue for this family than theoretical concerns about what may happen in the future. It was challenging to reframe AG's husband's anger in this light and attempt to address both AG's medical issues and the husbands concerns in order for AG to continue treatment.

Summary

In the care of patients where English is a second language, where significant knowledge gaps exist in traditional cultural medical therapies and responses to illness and where treatment environment is resource poor, the provider is challenged to support patient adherence to treatment. Although efficacious medical therapies are available for the treatment of the majority of patients with prolactinomas, treatment is usually required long term, is expensive, and treatment side effects can continue to disrupt quality of life. A percentage of patients are more resistant to medical treatment and require more aggressive invasive therapies that incur significant economic, social and emotional costs and morbidities. There is currently no way of predicting response to therapy which creates uncertainty and disruption to the lives of both patients and families.

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Lymphocytic Hypophysitis

Case Study 2

By

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Purpose: To outline the need for coordinated multi-focused care for a patient presenting with lymphocytic hypophysitis: a rare but clinically challenging pituitary disease.

Search Strategies: hypophysitis, lymphocytic hypophysitis, autoimmune pituitary diseases, pituitary diseases, pregnancy, and hypopituitarism.

Background

Hypophysitis is a rare inflammatory disease of the pituitary, considered to be autoimmune and classified either as primary or secondary disease. Primary disease is described as lymphocytic, granulomatous or xanthomatous, whereas secondary disease is identified by anatomical location or its effect upon the anterior pituitary (adenohypophysitis), the pituitary stalk or infundibulum (infundibuloneurophyophysitis) or all structures (panhyophysitis) (Karaca, Tanriverdi, Unluhizarci, Kelestimur, & Donmez, 2009; Molitch & Gillam, 2007). The disease is characterized by destruction of the pituitary tissue which is replaced with fibrosis (Molitch & Gillam, 2007). In lymphocytic hypophysitis (LH), the anterior pituitary architecture is mostly affected and more often occurs during the third trimester of pregnancy (Molitch & Gillam, 2007). LH may mimic a pituitary tumor and may enlarge the anterior pituitary sufficiently to affect the optic chiasm (Kerrison, Lee, & Weinstein, 1997; Nishioka, Shibuya, & Haraoka, 2010; Rumana, Kirmani, Khursheed, Besina, & Khalil, 2010; Yamaguchi, Kato, Takeda, Anzai, & Ikeda, 2005). Diagnosis is achieved through biopsy of the lesion but this can be difficult when the lesion is small, minimizing the size of the histologic specimen (Nishioka et al., 2010).

Epidemiology

The true incidence of lymphocytic hypophysitis is unknown (Molitch & Gillam, 2007). It is estimated that 1-2 patients per million of the general population are affected annually (Tritos, Byrne, Wu, Klibanski, & Medscape, 2011). Although originally reported in association with pregnancy, LH appears to affect both males and females (and has been reported in children), although females are more frequently affected at a ratio of 8.5:1 (Gellner, Kurschel, Scarpatetti, & Mokry, 2008; Kalra, Riel-Romero, & Gonzalez-Toledo, 2011; Molitch & Gillam, 2007). In females, an estimated 57%- 71% of cases are related to pregnancy or occur during the post-partum period (Bensing, Hulting, Hoog, Ericson, & Kampe, 2007; Crock, 1998; Gellner et al., 2008; Molitch, 1996; Molitch, 1998; Thodou et al., 1995). The mean age at the onset of the disease for women is estimated at 34.5 -37.7 years and 44.7 years for men (Gellner et al., 2008; Gutenberg, Buslei, Fahlbusch, Buchfelder, & Bruck, 2005; Thodou et al., 1995). By 2007, 400 cases of LH had been reported in the literature, but it is appreciated that many cases may go undiagnosed or are simply not reported (Molitch & Gillam, 2007).

LH has been reported as occurring in association with a number of inflammatory local conditions, including: Rathke's cleft cysts, inflammation of the lacrimal gland (dacroadenitis) (Lu et al., 2009), optic neuritis (Zoeller, Benveniste, Farhadi, & Bruce, 2010), eye pain and occulomotor nerve palsy (Moon & Kim, 2011). Other systemic autoimmune disorders such as thyroiditis (Lim, Elston, Swarbrick, & Conaglen, 2009), Wegener granulomatosis, sarcoidosis and systemic lupus (Crock, 1998; Gutenberg et al., 2005; Ray et al., 2010) have also been associated with this disease.

The role of pregnancy in the development of LH is not clearly understood. It has been posited that gestational unmasking of latent pituitary insufficiency occurs during the normal process of lactotroph hyperplasia in pregnancy. This normal enlargement of the gland may promote compressive injury to faltering cells and the release of pituitary antigens (Karaca, Tanriverdi, Unluhizarci, & Kelestimur, 2010). Others hypothesize that hyperestrogenemia and increased blood flow during pregnancy promotes susceptibility of the pituitary to the immune system activity (Karaca et al., 2010).

The role of humeral immunity in the pathogenesis of LH also remains unclear. It is theorized that lymphocytic invasion of pituitary cells induces a T cell mediated cytotoxicity that results in hypopituitarism. In a study by Gutenberg and colleagues, the number of T cells correlated significantly with fibrosis in an evaluation of tissue samples from 21 patients with LH (Gutenberg et al., 2005). Cytosolic proteins 22kDa and 49-kD (alpha-enolase) have been identified as the autoantigens targeted by the immune system in LH (Crock, 1998; Gutenberg et al., 2005). 49kDa has also been identified in the placenta and may explain the connection between LH and pregnancy (Siddique, Baskar, Chakrabarty, Clayton, & Hanna, 2007).

Although pituitary cell antibodies can be detected in patients with LH, 18% of normal pregnant women have been shown to have detectable antibodies in the postpartum period (Nishiki, Murakami, Ozawa, & Kato, 2001). In a study of 13 patients with LH, Nishiki and colleagues found antipituitary antibodies were present in a minority of patients. The measurement of autoimmune pituitary antibodies is difficult to perform and current evidence does not clearly establish their utility in diagnosis (Crock, 1998; Ezzat & Josse, 1997).

Furthermore, the presence of lymphocytes at biopsy is diagnostic and has been shown to be more predictive of a poor outcome than the presence of serum pituitary antibodies (Lupi et al., 2010). Japanese researchers recently identified IgG-4 in all of 5 cases of LH on histologic evaluation (Nishioka et al., 2010). IgG-4 diseases are associated with chronic inflammation and fibrosis. However, this is a marker of autoimmune inflammation and not be specific to the pituitary. More study of the mechanism of pituitary injury is indicated.

Presenting symptoms include headache (La Mantia & Erbetta, 2004) lactation (galactorrhea) (Karaca et al., 2009), visual field deficits (Kerrison et al., 1997), polyuria, polydipsia and nocturia (diabetes Insipidus) (Akahori & Sugimoto, 2010; Hamnvik, Laury, Laws, & Kaiser, 2010; Miyagi et al., 1997) and symptoms of adrenal insufficiency (weakness, lethargy, fatigue, anorexia, nausea, vomiting, arthralgias, myalgias, hyponatremia, symptomatic hypoglycemia, hypotension) (Melmed, 2002; Molitch & Gillam, 2007). The presence of hyperprolactinemia is a normal state during pregnancy and breast feeding, therefore information regarding pathologic elevated states is derived from males with LH and patients with no underlying cause of prolactin elevation (Thodou et al., 1995). Pituitary stalk compression is thought to be causative (Melmed, 2002).

Pituitary MR imaging in LH reveals gland enlargement with or without optic chiasm compression, (Akahori & Sugimoto, 2010; Baoke et al., 2009; Hamnvik et al., 2010; Honegger et al., 1997; Zoeller et al., 2010) stalk thickening and/or a loss of the characteristic “bright spot” in the posterior pituitary or neurohypophysis (Karaca et al., 2009; Kerrison et al., 1997; Lim et al., 2009; Moon & Kim, 2011). The enhancement of the gland tissue on MR imaging (after contrast

administration) is usually uniform or homogeneous helping to differentiate LH from a pituitary micro or macroadenoma (Karaca et al., 2009).

Significance of Problem

Pregnancy results in a normal hypertrophy of the lactotroph cells and a marked increase in the size of the pituitary gland (Melmed, 2002). This is differentiated in LH by the infiltration of the pituitary tissue by lymphocytes, plasma cells and some macrophages with the subsequent inflammation destructive of cells leading to functional damage and hormonal deficits. Up to 80% of cases of LH have been reported with at least one hormonal deficiency and up to 75% of cases with multiple deficiencies (Kalra et al., 2011; Thodou et al., 1995). Some sources estimate that about 15% of patients die from adrenal insufficiency (AI) that results from LH (Melmed, 2002). Autopsy reports of three pathologically confirmed cases of pituitary LH revealed adrenal atrophy, supporting AI as a likely cause of death associated with this disease (Thodou et al., 1995). Elevated prolactin levels result in amenorrhea and difficulty with subsequent fertility. Gonadotrophs, lutenizing hormone and follicle stimulating hormone can also be deficient and contribute to infertility. Induction of ovulation may be required if subsequent fertility is desired (Siddique et al., 2007). Growth hormone deficiency and thyroid deficiency can occur and require replacement. Blindness or persistent visual field deficits can occur if the disease is progressive or unresponsive to conventional treatments (Ezzat & Josse, 1997).

Although the course of this disease is not well known, there are also anecdotal reports after long term followups that suggest an increased likelihood of empty sella syndrome (Crock, 1998; Karaca et al., 2009). This syndrome occurs when a defect in the diaphragm above the

pituitary allows fluid to compress the pituitary gland or the gland itself shrinks and can result in one or more pituitary hormonal deficiencies. The incidence of pituitary deficiencies and hypopituitarism in empty sellar syndrome is reported in between 6-60% of cases (Giustina et al., 2010). There remains much debate regarding the cause of empty sella associated with LH. Likewise, it is debated if the presence of antipituitary antibodies after steroid treatment may simply be the results of massive doses of steroids or could indeed be the result of the natural course of LH (Karaca et al., 2009). More long term studies are needed to resolve these questions.

Management

Initial treatment is focused on the replacement of deficient pituitary hormones. Particularly urgent is the replacement of glucocorticoids in cases of ACTH impairment and adrenal insufficiency. Surgical biopsy to establish a diagnosis or for urgent decompression of the optic chiasm to preserve vision may be warranted (Karaca et al., 2010). Several case studies have demonstrated effective treatment of headache and optic chiasm compression using a high dose taper of glucocorticoids such as hydrocortisone, prednisone, methyl prednisone or dexamethasone. These have been used effectively to shrink the enlarged pituitary and relieve both visual field deficiencies and headaches (Baoke et al., 2009; Ezzat & Josse, 1997; Honegger et al., 1997; Jan & Destrieux, 2000; Kannappan et al., 2007; Karaca et al., 2010; Thodou et al., 1995; Tritos et al., 2011). However, there are reports of spontaneous remission without treatment (Molitch, 1996).

Although dopamine agonists have been postulated as an appropriate treatment, Thodou and colleagues demonstrated a lack of response to treatment with the dopamine agonist bromocriptine in 5 patients who presented with elevated prolactin levels and visual field changes (Thodou et al., 1995). There was no change in either the size of the pituitary mass on MR imaging or visual fields as would be expected in a prolactin secreting tumor. Stereotactic radiotherapy and Gamma knife surgery have reportedly been used successfully when other surgical and medical managements have failed (Ray et al., 2010).

Case Presentation

AC presented as a 29 year old female who was referred by her obstetrician for evaluation of visual changes. She complained of seeing "purplish grey spots" in both eyes. This started soon after giving birth to her first child two months prior to presentation. AC reported her pregnancy and delivery were both uneventful. However, she felt that the spots had become progressively darker. On further review, she had noted some blurriness during the end of her second trimester and early third trimester of pregnancy, but didn't pay this any attention. She was having daily headaches that she described as left frontal retro-orbital constant pain. She would wake with a headache but was not awakened by this. She did get temporary relief with aspirin, but her headaches would return quickly. She had no prior history of visual changes. She denied diplopia, visual field or peripheral vision deficits, eye pain, flashes or floaters during pregnancy. Her headaches stopped temporarily around the time she delivered her baby but returned shortly afterward. At that time she developed bilateral central visual deficits that

persisted in the same location despite her eye movement. Neuro-ophthalmologic exam revealed bitemporal visual field deficits.

Post delivery she experienced difficulty breast feeding and was seen by a lactation specialist for lactation failure and ceased attempting to breast feed at two weeks post partum. She also complained of numbness in her hands and fingertips and symptoms of carpel tunnel syndrome that began during pregnancy. These had progressed somewhat and were worse in her left hand.

History and Physical Examination and Medication

AC's past medical history was significant for depression, Human Papillomavirus (HPV) and Chlamydia. She had no reported surgical history. She did report some question in her late teens of a diagnosis of bipolar disorder but denied any treatment. Her medications at presentation were limited to prenatal vitamins with iron, fluoxetine (Prozac) 40 mg daily (discontinued during pregnancy due to cost) and docusate sodium 100 mg daily. She had no known drug allergies.

Historically her menarche was unremarkable at age 12 years with regular cycles and flow. She had an IUD placed prior to presentation. She has no significant or contributory family history with both parents and grandparents living and healthy. She has been an office worker but was unemployed at presentation. She had smoked about one pack of cigarettes but quit during pregnancy. She was unmarried but with a stable male partner who is the father of her child. Although the patient reported her partner was supportive, he did not present at any of her office visits. She lived in close proximity to her mother and grandmother who were both supportive.

Her mother was present at all visits. AC's sister was single and able to provide both support and respite child care. AC reported no other close friends, social or religious group affiliations.

Laboratory Data

MRI two months after delivery showed large pituitary enlargement, measuring 1.8 x 1.7 by 1.3 cm with compression of the optic chiasm. The contrast enhancement of the pituitary gland was homogeneous and without evidence of a discrete lesion. There was no evidence of cavernous sinus invasion. The infundibulum was not well visualized but appeared to be midline. Hormonal evaluation revealed a low free T 4 of 0.5 (0.6-1.2 ng/dl) with a low normal TSH of 1.16 (0.34 - 5.60 uIU/ml) suggesting central (pituitary) hypothyroidism. She had normal adrenal function after cortrosyn stimulation testing with 1ug of cortrosyn, normal FSH and LH and a slightly elevated prolactin level of 28 (3 - 20 ng/ml). Her IGF-1 (indicative of growth hormone) levels, electrolytes and renal function were all unremarkable.

She underwent an immediate transsphenoidal surgical biopsy to establish a conclusive diagnosis. AC was concerned about possible side effects of high dose steroids and elected to wait for the result of the biopsy before starting glucocorticoid therapy. She agreed to revisit this decision if she experienced deterioration in her vision prior to surgery but this proved unnecessary. The surgical pathology indicated non-neoplastic anterior pituitary cells with predominant T cell lymphocytes typical of reactive infiltrates. No cells showed lambda light chains, only a very small subset of B- cells showed kappa light chains. There was no evidence of a malignant disorder and no germ cells were detected. The final diagnosis was Lymphocytic Hypophysitis. AC was treated post operatively with Prednisone 20mg three times daily. This

dose was tapered by 10mg every two weeks over the next month. Over the counter Omeprazole (prilosec) was recommended for heartburn during the prednisone taper. She was also treated with levothyroxine 50mcg daily for hypothyroidism.

AC was advised about possible adverse effects of high dose glucocorticoid treatment. These include: hypothalamic adrenal axis suppression; immunosuppression with an increased potential for secondary viral and bacterial infections, myopathy (this usually occurs in patients with neuromuscular transmission disorders), Kaposi's sarcoma (usually after prolonged treatment with corticosteroids), and psychiatric disturbances including depression, euphoria, insomnia, mood swings, and personality changes. Steroids also have the potential to exacerbate pre-existing psychiatric conditions, heartburn, worsening hypothyroidism, increased hunger and weight gain, and promote sleep disturbance.

At her follow-up visit one month post surgery, AC felt she was able to tolerate the high dose Prednisone but complained of some mood problems, persistent blurry vision and visual field changes, weight gain, headaches and insomnia. Testing indicated mild HPA axis suppression and normalization of thyroid function with replacement doses of levothyroxine. She was instructed to maintain 20mg bid for a further two weeks then taper to 20mg daily.

MR imaging after two months of prednisone treatment indicated minimal decrease in the size of her pituitary, but there was still some contact with the optic nerve. She reported her sleep had improved and her mood disturbance was more stable. However, because of the persistent optic chiasm involvement, a second high dose steroid taper was recommended.

Three weeks after restarting high dose steroids, she placed an urgent call to the Pituitary Clinic to report she had developed severe mood swings and insomnia and expressed concerns about her ability to safely care for her infant. She reported vivid dreams of perpetrating violent acts and occasional thoughts of suicide. She denied having a suicide action plan or intent to carry it out. She was afraid of her impulsivity while on steroids and the risk to her baby. Her thoughts did include injuring her child. She continued to have bilateral visual deficits but was unsure about continuing treatment. She was now uninsured and felt she had no option for psychiatric evaluation. She refused to present to the emergency room for evaluation. With AC's permission, an urgent family telephone conference was held and respite child care and a daytime rotation of family support was organized so that she was never alone caring for her infant. Her family was in agreement that they would assist her to seek psychiatric evaluation and treatment while she continued to taper the prednisone. Her prednisone was decreased to 20mg daily for two weeks then tapered further to 10mg daily. She underwent immediate psychiatric evaluation and, after a joint consultation, was treated with Tramadol prn for headaches and lamotrignine (Lamictal) 200mg daily for a diagnosis of bipolar disorder.

Over the next 2 months she was tapered to physiologic dose steroids of 20mg hydrocortisone daily, and her mood stabilized. After 5 months of treatment her HPA axis remained suppressed, as did her thyroid function. Levothyroxine was increased to 75mcg daily. Imaging at 8 months of treatment indicated a further decrease in the size of her pituitary and visual field exam indicated a resolution of visual field deficits. HPA axis testing indicated normal function and glucocorticoid (hydrocortisone) treatment was discontinued. Likewise

thyroid function had improved. At six months after treatment was discontinued, AC's symptoms had resolved. Testing demonstrated normal HPA axis and MR imaging indicated a normal sized pituitary gland.

At all visits AC was encouraged to present with her infant and was supported at each visit by her mother. AC had appeared agitated and had minimal contact with her infant during initial visits, but this had resolved by the fifth month of steroid treatment. During each visit, both AC and her mother openly expressed their concerns. AC demonstrated insight and actively sought support. During each visit, plans for the safety of her son and herself were reviewed and revised as needed. At 16 months AC's son actively sought her attention and contact and she responded appropriately. Both mother and son appeared bonded. AC's MR images remained normal and she demonstrated no further deterioration of her pituitary function.

Prospects for future fertility were discussed with the patient and concerns for recurrent LH. At the completion of treatment, AC's menstrual cycle had normalized, as had her levels of lutenizing and follicle stimulating hormone. We have no reason to believe that pregnancy is not possible, and birth control was recommended. There is little evidence of the risk of recurrence of LH with subsequent pregnancies, but she will require regular monitoring. MR imaging and follow up pituitary testing is recommended yearly. There are no guidelines for the short or long term management of LH. Yearly follow up seems appropriate, given the risk of progressive fibrosis, empty sella syndrome and worsening pituitary function.

Summary

LH is a rare disease that can result in significant morbidity and mortality in a population largely of young, intra and post partum women. Apart from the temporality and gender preference of the disease, triggers and other risk factors are unknown. Although LH is known to be autoimmune in nature, little is known of its pathogenesis, and the outcome is dependent on early recognition and treatment. Responses to treatment are varied and the most effective treatment is yet to be determined. Psychiatric disturbances, as seen in this patient, are not documented and clearly present a significant concern and risk for both mother and infant. Clearly the practitioners caring for patients treated for LH should be aware of these risks and closely monitor for psychosocial and mental state changes in addition to biochemical and physical responses to treatment.

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DNP Clinical Inquiry Project Report & DNP Portfolio Approval

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Degree: Doctor of Nursing Practice

Title of Study:

DOMAINS OF LIFE FUNCTION SCALE FOR PATIENTS WITH PITUITARY ADENOMAS.

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