WEIGHT AND VISUAL FIELD STATUS AT DIAGNOSIS IN WOMEN WITH IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

by

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ABSTRACT

Title: Weight and visual field status at diagnosis in women with Idiopathic Intracranial Hypertension (IIH)

Purpose: Idiopathic Intracranial Hypertension (IIH) is a disease of elevated intracranial pressure (ICP) with no identifiable cause. Signs and symptoms of elevated ICP include swelling of the optic nerve (papilledema), visual field loss, severe headache, and blindness in some cases. Previous small retrospective and prospective studies have observed a relationship between weight gain prior to or during the course of disease and vision loss. In this study, a population of women with IIH is described and the association between weight in the year prior to diagnosis and visual field deficits at diagnosis is examined.

Methods: This cross-sectional study consisted of 159 females, age 13 to 65, who enrolled in the Intracranial Hypertension Registry (IHR) at Oregon Health & Sciences University between January 2003 and December 2005 and met study criteria for IIH. Study criteria expand the definition of IIH from the modified Dandy criteria to require the presence of papilledema and to include registrants with a highest lumbar puncture opening pressure of greater than or equal to 20 cm cerebrospinal fluid (CSF). Existing data from mailed questionnaires completed by registrants and their physicians at the time of entry into the registry and review of registrant medical charts were used to establish signs and symptoms around the time of diagnosis. Prevalence ratios were used to assess

the relationship between weight, weight gain, body mass index (BMI), and percent change in ideal body weight (IBW) during the year prior to diagnosis and abnormal visual field findings at diagnosis in either eye by formal perimetry.

Results: The mean weight of the study population (n=159) one year prior to diagnosis was 92 kg (SD 27 kg). Forty-five percent of study subjects (n=62) gained 3 or more kilograms in the year prior to diagnosis, with a mean weight gain of 5 kg (SD 13 kg). Visual field findings at diagnosis were abnormal in 84% (n=122) of study subjects. Those who weighed 110 kg or greater were 0.92 times as likely (95% CI: 0.63 to 1.33) as those who weighed less than 75 kg to have an abnormal visual field finding at the time of diagnosis. After adjustment for surgical intervention, study subjects in the highest weight category were still only 1.01 times as likely (95% CI: 0.65 to 1.55) as those in the lowest weight category to have an abnormal visual field finding. There was also no association between abnormal visual fields at diagnosis and higher BMI, weight gain in the year prior to diagnosis, or percent change in IBW ($p>0.05$ for all)

Conclusion: Neither weight, nor weight gain, in the year prior to diagnosis was associated with abnormal visual field status at diagnosis in this registry population of women with Idiopathic Intracranial Hypertension. Selection bias in may have resulted in a study population with more severe disease and with more obesity than other populations of women with IIH, which may have resulted in an inability to detect an association between weight and visual field deficits.

INTRODUCTION

Overview

Idiopathic Intracranial Hypertension (IIH) is a chronic disease of elevated intracranial pressure (ICP) that affects thousands of individuals worldwide, with a high prevalence in obese women. IIH is characterized by severe debilitating headache, and is accompanied by visual impairment in most individuals, resulting in deterioration of vision or blindness in as many as 10% of cases [1].

IIH, formerly known as Pseudotumor Cerebri (PTC), represents a subset of individuals within a larger category of those experiencing elevated ICP, termed Secondary Intracranial Hypertension (SIH) or undetermined Intracranial Hypertension (IH). Individuals within these categories experience the same symptoms of severe headache and vision loss, but either the source of their high ICP has been identified (SIH) or the neurologic or neuroimaging workup to rule out SIH has not been completed (unidentified IH). For those with IIH, the cause of elevated ICP is still unknown.

Female sex and obesity have been established as risk factors for IIH [1-3]. Other risk factors being investigated include thrombophilic disease and polycystic ovarian syndrome (PCOS) [4]. Attempts have been made as well to identify risk factors for disease severity among individuals diagnosed with IIH. Recent weight gain and obesity have been observed to occur more frequently in those with poor vision outcomes [1, 5, 6]. In this study, we identified a registry population of women

with Idiopathic Intracranial Hypertension (IIH) and examined the relationship between weight and visual field deficits.

Clinical Characteristics

Patients with IIH typically present with symptoms of elevated ICP, including vision changes, chronic daily headache, or intracranial 'noises,' described as pulsatile rushing, whooshing, pounding, or ringing in the ears (tinnitus). Loss of segments of vision (visual fields) occurs commonly as a result of elevated intracranial pressure, and loss of visual acuity less commonly [1]. Most patients experience improvement of symptoms over time, but many experience relapses [7]. Understandably, IIH can lead to disability and psychological stress [8].

Treatment modalities in IIH include attempts to relieve the elevated intracranial pressure by decreasing CSF volume, shunting CSF away from the confined intracranial environment, or surgically decreasing the pressure exerted on the optic nerve. Most IIH patients receive drug therapy with the carbonic anhydrase inhibitor acetazolamide, which is effective in reduction of CSF volume and intraocular pressure [9]. In some cases, optic nerve swelling is improved with corticosteroid administration [10]. Some patients continue to be treated with repeated lumbar punctures to reduce CSF volume, but this has not proven to be an effective method and has associated complications [11]. Surgery to relieve pressure on the optic nerve (Optic Nerve Sheath Defenestration, ONSD) has been effective for some patients with rapid vision loss or a refractory disease course [12, 13]. Shunting of spinal fluid to other fluid compartments in the body is

another effective surgical measure, but with high rates of obstruction and need for revision [14, 15]. Weight loss in obese patients has been beneficial in reducing disease signs and symptoms of IIH [16, 17].

Diagnostic Criteria

IIH is a diagnosis of exclusion, meaning that other types of intracranial hypertension must be ruled out. The diagnosis of IIH must establish evidence of elevated ICP and must rule out non-idiopathic causes such as medication-induced toxicity, chronic infection, malignancy, chronic systemic hypertension, or cerebrospinal fluid (CSF) obstruction, including sinus thrombosis, cerebral venous stenosis, congenital malformation, or previous traumatic or surgical changes (Appendix A). IIH diagnosis is established only after thorough neurological exam, magnetic resonance imaging (MRI) of the head, and CSF laboratory studies reveal no identifiable cause, and an ophthalmologic exam by an experienced ophthalmologist or neuro-ophthalmologist yields findings consistent with elevated ICP. There can often be a period of several months between the onset of symptoms and diagnosis of IIH.

The Modified Dandy criteria are a list of diagnostic criteria for IIH that have been utilized since 1985 to aid in diagnosis and evaluation (Table 1a). The criteria specify that an individual with IIH must have no localizing findings on neurological exam, and a normal neuroimaging exam by MRI or CT scan without evidence of venous obstruction or intracranial process that might lead to elevated intracranial pressure. There must be a finding of elevated CSF pressure greater than 25 cm

CSF with normal CSF constituents, the individual must be awake and alert, and no other cause for elevated ICP may be found. These criteria were updated in 2002 to specify the need for exclusion of other possible causes of elevated ICP (Table 1b) [18], which included specifying that if signs or symptoms were present, they were consistent with elevated intracranial pressure or papilledema. The revised diagnostic criteria include the presence of papilledema as a requirement for diagnosis of IIH, which was reflected in our study criteria (Table 2).

Epidemiology

Epidemiologic studies in the United States have reported an estimated annual age-adjusted prevalence of IIH of 0.9 per 100,000 individuals (Table 3). In females age 15-44, this proportion increased to 3.5/100,000, and was as high as 19.3/100,000 in obese women age 20-44 who weighed more than twenty percent above their height-adjusted ideal body weight [2]. Several studies worldwide support the trend of higher incidence of IIH in obese women of childbearing age [19-21].

Pathophysiology

Visual field impairment in IIH is related to the force exerted on the optic nerve by the high-pressure environment within the confined compartment of the brain. The optic nerve is in close communication with cerebrospinal fluid (CSF), which normally maintains a balance of pressure within the brain by controlled production and reabsorption into the venous circulation. In IIH, this balance is impaired, the exact mechanism for which is unknown.

The pathophysiological mechanism of elevated ICP present in IIH is poorly understood, but several hypotheses exist. The main theory describes the inability of CSF to be reabsorbed for venous drainage in the brain, due to either increased venous pressure or some obstruction to reabsorption. Possible obstruction might include micro-thromboses at the sites of CSF reabsorption at arachnoid granulations. Formation of cerebral venous sinus thrombosis is a recently identified mechanism for relative obstruction to venous flow, and thus CSF reabsorption [22]. Alternatively, increased cerebral vascular volume might lead to elevated ICP through cerebral edema, effectively reducing venous sinus drainage through compression [23]. There is much debate over whether elevated ICP is the cause of decreased CSF reabsorption, or is the primary factor in the disease [24]. Increased CSF production has also been hypothesized to explain the phenomenon, but has not been supported by evidence [25].

The pathophysiological relationship between obesity or weight gain and elevated ICP in women with IIH is thought to be either through a prothrombotic effect of higher levels of estrogen in obese women and thus reduced CSF reabsorption [4] or through compression of jugular venous return by central obesity, thus causing increased cerebral edema [26]. The prothrombotic model has been supported recently by several studies [4, 22, 27-29].

Obesity and IIH

Obesity has been shown to be consistently associated with IIH in several studies, especially in adult women [3, 20, 25, 30, 31]. The annual age-adjusted incidence of patients newly diagnosed with IIH appears to be related to the prevalence of obesity in some populations in prospective studies, with higher proportions occurring in countries with higher rates of obesity, such as the United States and Israel, and lower proportions in countries with less obesity, such as Italy, Japan, and Northern Ireland [20, 30, 32].

Obesity has been defined differently in various studies with the IIH patient population. The most commonly defined measure of obesity in these studies was a body mass index (BMI) greater than or equal to 30 kg/m^2 [33]. However, attempts have been made to standardize patients by their proportion of weight greater than their ideal body weight (IBW). Patients weighing greater than or equal to twenty percent above their calculated IBW have been considered obese, and patients whose weight is greater than or equal to 10 percent above IBW have been considered overweight [2, 34]. Some studies have relied on the clinician's impression of whether a patient was overweight or obese for some or all of the study subjects [21, 31].

Weight Loss and IIH

The relationship between obesity and IIH appears sensitive to even small amounts of weight changes. Weight loss appears to be helpful in ameliorating the symptoms of IIH, including improvement of visual field deficits and

papilledema, and decreasing headaches and tinnitus. One retrospective study identified 58 women who met criteria for IIH, did not undergo early surgical intervention, and had adequate documentation of visual status, papilledema, and weight at baseline and at six-month follow-up. Women were categorized depending on whether they lost 2.5 kg or more, or less than 2.5 kg during any 3-month interval over the follow-up period. At baseline, women all weighed greater than or equal to 10% above IBW and there were no differences in the visual findings between the two groups. Weight loss of at least 2.5 kg in this study was associated with more rapid recovery of papilledema and visual field deficits [16].

Surgical methods for weight loss have been very successful with improvement of the disease [35]. Two women with diagnoses of pseudotumor cerebri lost 107 lb (47%) and 130 lb (43%) as a result of bariatric surgery, which was effective in initiating remission of their disease [36]. Nineteen severely obese women diagnosed with pseudotumor cerebri who underwent bariatric surgery lost a mean of 45 kg, which corresponded to an average of 71% of their excess weight above ideal body weight. Their BMI decreased to a mean of 30 kg/m^2 and their percentage of ideal body weight improved to an average of 33% above mean ideal body weight, with resolution of headache and pulsatile tinnitus in all but one [17].

Weight Gain

Some cross-sectional studies have shown an association between weight gain and IIH. In a small preliminary retrospective study, Ireland et al. reported an

association between cases with IIH and recent weight gain and obesity (n=40) compared to age- and sex- matched controls (n=39) [37]. Recent weight gain was also more common in cases (n=50) than age- and sex-matched controls (n=100) in a cross-sectional study with an 83-item symptom questionnaire administered at the time of diagnosis. Cases, of whom 90% were female, gained an average of 19.7 lbs in the 12 months prior to diagnosis versus a 1.2 lb weight loss in controls ($p<0.01$). 90% of cases and 30% of controls were obese (OR 17.5, 95%CI: 5.6-50.2), with obesity defined as greater than 20% above IBW [34].

Weight and Disease Severity

Although weight loss has consistently been shown to improve disease status, the converse relationship between recent weight gain and disease severity has been less clearly established. Several definitions for disease severity have been used, focusing on vision loss or the presence of symptoms such as headache. Different measures for the assessment of weight gain have been employed as well, with the time course for weight gain ranging from several months prior to the onset of disease to several months after the onset of disease.

Definitions for disease severity have centered on vision outcomes, as they are the most debilitating and potentially irreversible aspect of the disease. Vision measures that are monitored in IIH include visual acuity by the Snellen test, visual field assessment, by Goldmann perimetry and/or Humphrey automated perimetry, and contrast sensitivity testing. Studies have consistently shown that visual field deficits are a more frequent outcome of the disease [24], though visual

acuity can be affected as well. Goldmann and Humphrey perimetry methods are used preferentially by different providers, but are highly correlated [1, 38]. Visual field deficits can be categorized as present or absent, and have been graded for easier classification in some studies (Appendix B).

Weight and Visual Field Loss – Previous Studies

Previous attempts to identify patients at risk for sustained vision loss have observed a more severe disease course in obese patients (Table 4) [5, 6]. Recent weight gain was associated with deterioration of visual field grade in a study by Wall and George in 1991 [1], in which patients recalled their weight in the year prior to diagnosis, but was not associated with visual field grade in a study by Rowe and Sarkies in 1999 [33], in which weight change was evaluated over a follow-up period after diagnosis. These studies bear further examination to evaluate whether weight gain is important as a risk factor for visual field deficits.

Wall and George studied 50 newly diagnosed patients (92% female) with IIH of which 94% were obese (BMI ≥ 30 kg/m^2) at the time of diagnosis. Patients were asked to recall their weight one-year prior to diagnosis (mean weight gain 7.7 kg) and were assigned a grade for their visual field deficits both at baseline and at their last follow-up exam (mean follow-up 1 year). Visual fields were assessed using both Goldmann and Humphrey perimetry methods. Patients whose visual field had deteriorated (n=5) were compared to all others (n=45), of which 30 had experienced improvement. Visual field deterioration was association with weight gain ($p<0.01$, independent t-test with Bonferroni adjustment) [1].

Rowe and Sarkies did not find a similar relationship between weight gain and visual field deterioration in their prospective study in which 34 newly diagnosed IIH patients (91% female) were followed an average of two years for weight change and visual field outcome. Seventy-one percent of patients in this study were obese (BMI ≥ 30 kg/m^2), and 9 patients (27%) experienced weight gain during the study period (mean weight gain 7.7 kg for all patients). No significant association was found between weight change over the study period and visual field deterioration (p=0.24, chi-square) [33].

Although Rowe and Sarkies studied weight change over the follow-up period, rather than prior to diagnosis, they did report 7 patients who had experienced recent weight gain, 3 prior to the initial presentation and 4 prior to a recurrence of disease symptoms. The average weight gain among these individuals was 16.5 kg (range 5-25 kg). These patients did not have a poorer visual outcome, expressed as visual field grade at follow-up, compared to other patients (p=0.6, independent t-test). However, patients were more likely to have poor visual outcome if they were morbidly obese (BMI ≥ 40 kg/m^2), compared to all other patients (p=0.05, independent t-test) [33].

Recent weight gain continues to be cited as a risk factor for visual loss in IIH [39]. In this preliminary study, we address the association between weight in the year prior to diagnosis and visual field status at the time of diagnosis in a registry population of women with IIH.

METHODS

Study Design

In this preliminary cross-sectional study, we identified a population of women with IIH within the Intracranial Hypertension Registry (IHR) who met diagnostic and study criteria. We investigated the relationship between weight in the year prior to diagnosis and visual field deficits at diagnosis in the study population. Secondary purposes of the study were to assess the relationship between other weight measures, including weight gain, body mass index (BMI), and weight change percentage of ideal body weight (IBW) with the presence of abnormal visual field findings at diagnosis, and to describe characteristics of the study population.

STUDY POPULATION

Study Subject Recruitment

Study participants were selected from a population of registrants who enrolled in the Intracranial Hypertension Registry (IHR) during the study period of January 1, 2003 through December 31, 2005. The IHR is based in Portland, Oregon, and solicits registrants through the website of an intracranial hypertension organization, the Intracranial Hypertension Research Foundation (IHRF) (http://www.ihrfoundation.org/), and directly through physicians who commonly treat IIH. Registrants were collected by self-referral through the IHRF or by

physician referral. Registrants were not required to submit a questionnaire for inclusion into the IHRF.

Study Criteria

Study subjects were adolescent girls and adult women with IIH, age 13 through 65, who were not pregnant at the time of diagnosis, lived in the United States, and had documented papilledema, a lumbar puncture opening pressure of 20 cm CSF or greater with normal constituents, a normal head-imaging study, a normal neurological exam other than findings consistent with elevated intracranial pressure (ICP), and had no other known cause for intracranial hypertension.

Study Subject Selection and Exclusions

Study subject selection occurred in two stages, first through registry designation of diagnosis and then through application of further study criteria (Table 2). First, the Intracranial Hypertension Registry (IHR) assessed registrants for the presence of Idiopathic or Secondary Intracranial Hypertension using the modified Dandy criteria (Table 1a). Chart review was conducted for all selected registrants suspected to have IIH by an ophthalmologist on the Steering Committee for the IHR. To meet criteria for IIH, there must have been documentation of a neurological exam with no abnormal findings other than papilledema or oculomotor dysfunction consistent with elevated ICP, such as sixth cranial nerve palsy [40]. There must have been a report of an MRI or CT scan of the head with no evidence of venous obstructive disease and no abnormal findings other than "empty sella syndrome" or posterior scleral

flattening, consistent with IIH. Additionally, there must have been no suggested process in the medical record that would result in elevated intracranial pressure, including history of head injury, intracranial mass lesion, hydrocephalus, other medical history, or use of medications known to cause Secondary Intracranial Hypertension.

Following selection by the IHR of registrants fulfilling criteria for IIH, female registrants who were United States residents, age 13 through 65, with lumbar puncture opening pressure (LPOP) greater than or equal to 20 cm CSF and documented papilledema were selected for study inclusion (Table 2). After selection for study inclusion, confirmation of documented papilledema was made through chart review. Those without appropriately documented papilledema, as well as registrants with findings on chart review suggestive of Secondary Intracranial Hypertension who had not been previously excluded were excluded from the study population. To avoid confounding by physiologic changes due to pregnancy, women were excluded from the study if they reported being pregnant at the time of diagnosis. Registrants with an intracranial process not consistent with causing a mass effect were included in the study population if they had strong evidence of papilledema (Table 5a).

Study Population

A total of 159 study subjects, 32% of the total registry population at the conclusion of the study period, were considered to have IIH and fulfilled the study criteria. The original registry population consisted of 502 individuals with

suspected Intracranial Hypertension. From this population, 89 registrants were excluded because they were male, 50 female registrants were excluded due to a non-United States address, and 2 registrants were excluded because they were pregnant at the time of diagnosis. A further 26 registrants were excluded due to age less than 13 or greater than 65 (Table 6).

The remaining 335 registrants underwent chart review by an ophthalmologist on the Steering Committee of the IHR to determine IIH diagnosis using the Modified Dandy criteria (Table 1a). Of this subset, 88 registrants were excluded due to having an incomplete record such that disease criteria could not be examined. Twenty registrants were excluded due to inability to distinguish between Idiopathic and Secondary Intracranial Hypertension due to conflicting medical records, and 19 registrants were excluded due to having Secondary Intracranial Hypertension. Eight registrants were excluded for having an LPOP of less than 20 cm CSF. At this point, records for 200 registrants with suspected Idiopathic Intracranial Hypertension were transferred to SPSS Version 14.0 for further analysis.

The 200 registrants identified as having IIH were examined more closely for fulfillment of study criteria (Table 2) and for absence of findings possibly suggestive of Secondary Intracranial Hypertension. Three stages of internal data verification were completed. First, 10% (n=20) of registrants were randomly selected for verification of height, weight, and headache variables. Next, chart review of the 200 registrants identified as having IIH was done to verify the

finding of papilledema on fundoscopic exam. Chart review was also used to fill in missing data for key variables and diagnostic criteria (weight, height, LP pressure, and neurological exam). Cases were removed if they no longer met disease or study criteria (n=41), but were retained despite other missing variables. Eleven registrants were excluded for having a medical history suggestive of possible intracranial or intraorbital mass effect, 17 were excluded due to no papilledema on fundoscopic exam, 9 were excluded for having questionable papilledema, and 2 were excluded for having no fundoscopic exam recorded (Table 5b). An additional 2 were excluded because chart review revealed an LPOP less than 20 cm CSF in one and the other was pregnant at the time of diagnosis, with the onset of papilledema coincident with a diagnosis of pre-eclampsia. Finally, blinded verification of visual field exam findings for all 159 selected study cases was completed by the IHR ophthalmologist and compared to those entered into the database, resulting in no further exclusions. A total of 343 consecutive exclusions were made, resulting in a study population of 159 cases of IIH (Table 6).

DATA SOURCES

Data Collection & Management

Questionnaires developed by the IHR Steering Committee were mailed to registrants and their treating physicians upon enrollment into the IHR. Registrants and physicians were also given the option of sending medical records in lieu of or in addition to survey completion. Returned questionnaires

were entered into the IHR database by the IHR Research Coordinator, in the data management system, *4th Dimension*, and were verified by double entry. All variables of interest for female IIH patients fulfilling disease and study criteria were transferred to SPSS Versions 14.0 and 15.0 for analysis.

All registrants were assigned a unique identification number by IHR staff. The data set was de-identified by removal of name, social security number, date of birth, and address prior to transfer into SPSS 14.0. The data set still included the unique identification number, the year of birth, and a variable indicating the referring physician. The Oregon Health & Science University Institutional Review Board approved this study.

When questionnaire data was incomplete for a registrant, or when only a medical chart was submitted, chart review was performed for database completion by study investigators. An ophthalmologist on the IHR Steering Committee reviewed all submitted medical charts to confirm the diagnosis of IIH. Where information was unclear regarding the diagnosis, attempts were made to collect original data from the treating physician. When a medical chart was sent to the registry in lieu of a completed questionnaire, the IHR Research Coordinator abstracted data from the chart for key variables.

Registrant Questionnaire

Registrants were asked about demographic information, symptom characteristics, past medical history, medication use, family history, and disease

course, including medical or surgical interventions. Two versions of the registrant questionnaire were used, which varied in the format and answer choices for some symptom questions. Each also included some unique questions, which were considered separately in analysis or condensed to approximate a response. Registrant Questionnaire Version 1 (RQV1) was sent to registrants from January 2003 until March 2004 and included 189 questions. Registrant Questionnaire Version 2 (RQV2) was sent beginning in March 2004 and included 171 questions.

Physician Questionnaire

Registrants indicated specific physicians involved in their care and completed appropriate release of information documents for survey data as well as a copy of their medical chart to be released through their physician to the IHR. Physicians were sent questionnaires specific to their specialty (neuro-ophthalmology/ophthalmology, neurology, neurosurgery, or primary care). Physicians were given the option of sending a registrant's medical chart in lieu of questionnaire completion.

All physicians sent medical charts or completed questions pertaining to a general physical exam, lumbar punctures, imaging studies, pertinent laboratory data, medications, and surgical management. Neuro-ophthalmologists and ophthalmologists were asked details of their initial and most recent ophthalmic exams and more specific questions regarding optic nerve sheath fenestration procedures. All physicians completing a questionnaire were asked to diagnosis

the patient as having Primary (Idiopathic) versus Secondary Intracranial Hypertension per the modified Dandy criteria (Table 1a). They were asked to determine between Definite and Probable Primary (Idiopathic) Intracranial Hypertension. These determinations were used by the registry to determine classification of registrants into Idiopathic versus Secondary Intracranial Hypertension prior to selection of registrants for the purpose of this study.

Registry files contained multiple physician questionnaires and medical charts for most registrants. For data pertaining to the general physical exam, including imaging studies, neurological exams, surgical data, and initial diagnosis, the choice of which physician record to use for a registrant was decided using the following algorithm: First, the most appropriate physician type, in descending order of neuro-ophthalmologist, ophthalmologist, neurosurgeon, neurologist, and other physician. After physician type, the second criterion used was the most complete exam. In cases where one physician record included physical exam information and another included surgical data, the records were combined to provide the more complete information possible for a registrant. For data pertaining to the visual field exam, the record closest to the date of diagnosis was selected using the following algorithm: First, the exam date closest to the date of diagnosis, then the most appropriate physician type, and next, the most complete exam.

Two versions of the physician questionnaire were developed, MDQV1 and MDQV2. Version 1 was intended for all physician types, included all exam

question sections and was distributed from January 11, 2003 through February 28, 2004. Version 2 questionnaires were distributed beginning in March 2004 that were specific to each physician type and included question sections pertinent to the physician specialty. In most cases, questions were exactly the same between the two versions.

DATA CATEGORIES

Overview of Variables

The primary independent variable was *weight (kg)* one year prior to diagnosis. *Body mass index (BMI) (kg/m^2)* one year prior to diagnosis, *weight change (kg)* in the year prior to diagnosis, and *percent weight change over ideal body weight (IBW) (%)* were secondary exposure variables. Other characteristics that were included as potential confounders were demographic variables, lumbar puncture opening pressure, surgical intervention, and treatment by Physician A, one referring physician. The primary dependent variable was *visual field status* at the time of diagnosis, classified as normal bilaterally or abnormal in either eye (Appendix C).

Demographic Characteristics

Gender, race/ethnicity, and state of residence were self-identified by each registrant. Gender choices were male or female. Race/ethnicity choices were the following: non-Hispanic/white, African American, Hispanic/Latino, Asian/Pacific Islander, Native American/Alaskan Native, or other (specify). State

of residence was self-reported with mailing address. A new variable, *Region* of residence was created using the four Census Bureau Regions: Northeast, Midwest, South, and West (Appendix D). One physician referred a large proportion of the study population so a variable was created, *Physician A*, to signify whether a registrant had been under the care of this physician.

Weight and Height Measures

Registrants were asked to report their current weight and height and to recall their weight at diagnosis and at one year prior to diagnosis on both registrant questionnaire versions. Weight and height were converted to metric measures. *Weight (kg)* at one-year prior to diagnosis was categorized into quartiles. *Body Mass Index (BMI)* was calculated using the formula: kg/m^2 for one year prior to diagnosis and categorized into quartiles and dichotomized. *Weight change (kg)* was calculated as the difference between a registrant's weight one-year prior to diagnosis and weight at diagnosis. *Weight change (kg)* was categorized into no weight loss or weight stable, and weight gain. *Ideal Body Weight (IBW) (kg)* was calculated using the Robinson formula for women of all frame sizes: [(ht in inches – 60)*1.65 kg/inch] + 48.67. The Robinson formula is much more robust for women of shorter heights than other IBW formulas, and was developed using population data [41]. *Weight change percent of IBW* (%) was calculated using the formula: [weight change (kg)/IBW (kg)]*100.

Symptoms

Registrants were asked to indicate the presence of headache, neck pain or stiffness, tinnitus (defined as whooshing/swishing/ringing/buzzing/noise in their ears), hearing loss, central vision, peripheral (side) vision, and diplopia (double vision) associated with the disease. Significant differences between the question formats were present between RQV1 and RQV2 that limit analysis (Appendix E). For example, in RQV1, symptom questions were headed, "With this illness, have you had...?" RQV2 asked, "At the time of diagnosis did you have...?" for questions regarding headache, neck pain/stiffness, and tinnitus. For questions regarding hearing loss, and vision symptoms in RQV2, the format was: "At the present time do you have...?"

Medical History

Registrant questionnaires asked numerous specific questions regarding medical conditions that have been known to be associated with elevated intracranial pressure (ICP). Answer choices for these conditions were: Yes, No or Not Sure. Registrants were also asked to identify whether a physician told them that their condition was caused by a medication or drug. Answering "yes" to either of these question types indicated that they might have an identifiable underlying cause for elevated intracranial hypertension. Medical chart review and review of these questions were used by the IHR ophthalmologist to identify registrants with likely or probable Secondary Intracranial Hypertension, and they were excluded from this study on that basis.

Reproductive Health

Only registrants who completed RQV2 answered questions about their reproductive health. One question asked, "Were you pregnant at the time of diagnosis?" Another asked, "Have you had PCOS (Polycystic Ovarian Syndrome)?" Answer choices for both questions were: Yes, No or Not Sure. Registrants who indicated they were pregnant at the time of diagnosis were excluded from analyses due to possible confounding of their weight data. Registrants with missing data or those who completed RQV1 were not excluded unless there was an indication revealed on chart review that they were pregnant at the time of diagnosis. Data regarding PCOS were reported separately for registrants who completed the RQV2.

Neurological Exam

Evidence of a neurological exam with no abnormal findings other than those attributable to elevated ICP was necessary for IIH diagnosis. MDQV1 asked all physicians to report whether a neurological exam was normal or abnormal, and to describe abnormal findings. Only the MDQV2 developed for neurologists asked this question. However, all MDQV2 physician questionnaires asked whether a registrant had no localizing findings on neurological exam in the diagnosis checkbox. This variable was verified for all registrants undergoing chart review prior to study inclusion.

All physician questionnaire versions included the same questions regarding neuro-imaging, which asked about the type of imaging study, whether it was abnormal, and the date performed. Imaging study choices included: magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), magnetic resonance venography (MRV), computed tomography (CT), positron emission tomography (PET), cerebral angiography, or other (specify). Physicians were asked to describe abnormal findings.

Elevated Intracranial Pressure (ICP) Measures

Elevated ICP is detected by measurement of CSF pressure, via lumbar puncture (LP), as it passes through a manometer or transducer. The pressure can be measured upon immediately accessing the subarachnoid space, termed lumbar puncture opening pressure (LPOP), or by continuous monitoring. LPOP is typically measured in a relaxed patient lying in the lateral decubitus position (on their side). ICP can also be measured via a transducer introduced directly into the brain. CSF pressure measured by LPOP has been shown to correlate well to direct measurements of ICP [42].

Several entries for CSF pressure measured by lumbar puncture opening pressure (LPOP) were recorded for each registrant. The highest LPOP in the database for each registrant was used for consideration of fulfillment of IIH disease criteria. All physicians were asked to record whether CSF constituents (RBC, WBC, proteins, or glucose) were normal or abnormal for the initial LP procedure, and to provide values if abnormal.

Overview of Ophthalmic Measures

Ophthalmologists and neuro-ophthalmologists completed ophthalmic exam questions regarding visual acuity, type of visual field exam used, specific visual field findings, motility, pupillary defects, biomicroscopy, fundoscopic exam, including Frisén's Grade, contrast sensitivity, color vision testing, Amsler charts, and optic nerve imaging. Physicians were asked to provide information from their initial most recent exam. For the purposes of this study, we focused on the fundoscopic exam and visual field findings for the exam date closest to the date of diagnosis. Visual acuity was not considered due to uncertainty about whether best-corrected vision was recorded in all cases.

Papilledema

Papilledema is swelling of the head of the optic nerve, which occurs as a result of elevated intracranial pressure. Elevation of ICP results in papilledema that should be recognized by a skilled practitioner. Though the presence of papilledema is not currently required for the diagnosis of IIH in revised criteria, the lack of papilledema in the presence of elevated ICP is suspicious for an etiology other than IIH, particularly when other symptoms of elevated ICP or visual signs are lacking [18]. Therefore, we required a diagnosis of either symmetric or asymmetric papilledema for study inclusion to improve the specificity of our disease criteria for IIH.

The answer choices for the initial and most recent exams began with a question of normal in both eyes or abnormal in either eye. Answer choices for abnormal findings followed, with OD (right) or OS (left) check boxes: chronic atrophic, papilledema, optic nerve atrophy, absence of venous pulsations, and optociliary shunt vessels. Under papilledema, sub-choices included: symmetrical (yes/no), and early, fully developed, or chronic (OD/OS for each). Physicians could alternatively write in the Frisén's Grade (Appendix F).

When fundoscopic exam findings from physician records conflicted, the following algorithm was used: first, the most qualified physician, and then the exam date closest to the date of diagnosis. Registrants with uncertain findings of papilledema, such as conflicting reports of papilledema from the same physician in the same period of time were included (n= 4). If no finding of papilledema was reported on fundoscopic exam (n=17), or there was no fundoscopic exam (n=2) the registrant was excluded from the study population.

Visual Field Status

Visual field findings at the time of diagnosis were the main outcome measure in this study. Visual field test-type answer choices included: tangent screen, Goldmann kinetic perimetry, or Humphrey static perimetry. Visual field finding answer choices included: normal, enlarged blind spot, generalized peripheral constriction, sectoral peripheral constriction, central, paracentral, arcuate, nasal step, and hemianopia. Subtypes of hemianopia were bitemporal, binasal, and

homonymous. Check boxes to indicate OD (right) and OS (left) eyes were presented for both initial and recent exams.

The visual field exam closest to the date of diagnosis was identified for each registrant using the previously mentioned algorithm. Visual field findings were condensed to improve statistical power and to establish the main outcome variable, *visual field (VF) status*, which identifies registrants with normal versus abnormal visual field findings at diagnosis. A finding of normal was considered valid only if there were no other abnormalities listed in either eye for that exam.

Five types of visual field deficits were identified for the purpose of this study: *enlarged blind spot (EBS), peripheral constriction*, *central/paracentral defect*, *arcuate/nasal step defect,* and *hemianopia*. A solitary visual field finding of *EBS* may represent a range of normal in some registrants, as we do not have information on the size of the blind spot. Therefore, *EBS* was considered separately as normal or abnormal in the main analyses when it was the only abnormal finding.

Surgical Interventions

A variable for *surgery* was created which signified whether a registrant had undergone any surgical interventions due to intracranial hypertension. All physician questionnaires asked detailed questions about each surgical intervention. Procedures considered surgical interventions for intracranial hypertension were: optic nerve sheath decompression, all CSF shunting

procedures (ventriculoperitoneal, lumboperitoneal, etc.), and subtemporal or suboccipital decompression.

STASTICAL ANALYSIS

Overview

The statistical analyses in this study were conducted in four stages: (1) descriptive analysis, (2) univariate analysis, (3) subgroup multivariate analysis, and (4) combined multivariate analysis. SPSS Versions 14.0 or 15.0 were used for all statistical analysis in this study, with confirmation of regression statistics in SAS. A p-value ≤ 0.5 was considered significant for all analyses. Because this was a cross-sectional study design with a high population prevalence of the outcome, (abnormal visual field status), the main outcome measure of interest was the prevalence ratio, rather than the prevalence odds ratio, to estimate relative risk [43-45].

Descriptive Analysis

Frequency analyses, including mean and standard deviation, were used to describe prevalence of weight change, demographic characteristics, symptoms, clinical findings, visual field findings, and use of surgical interventions. Distributions of each continuous variable were examined for normality and dichotomized or categorized to maintain logical divisions (Appendix C). We used contingency tables with chi square tests for independence and Fisher's Exact

test to examine the relations of demographic factors with *weight* one year prior to diagnosis in quartiles to assess for potential confounding (Table 7).

Regression Procedures

Poisson regression with robust error variances and a log-link function was used to estimate prevalence ratios as a measure of relative risk in this cross-sectional study [46]. Regression procedures were performed in SPSS Version 15.0 using Generalized Linear Models and confirmed in SAS with PROC GENMOD using both log-binomial regression and Poisson regression with robust error variance.

First, the association of each weight measure variable with *visual field status* was assessed in univariate models generating prevalence ratios with 95% confidence intervals (Table 8). Univariate analyses were performed in parallel with *enlarged blind spot* coded as either normal or abnormal in *visual field status*. Associations between other weight variables and visual field status were also examined using univariate analysis. Next, categorized characteristic variables were examined for distribution and compared to *weight* one year prior to diagnosis in univariate regression models to assess for potential confounding (Table 9). Then, univariate regression with *visual field status* and all characteristic variables was done to assess for independent associations.

Multivariate models containing the primary independent variable, *weight* one year prior to diagnosis and each other characteristic variable were evaluated and ranked using their delta G value. Delta G values for each model were calculated

by subtracting the –2 log-likelihood value of the model containing the independent variable and *weight* from the model containing only *weight*. If addition of a characteristic variable into the model containing *weight* changed the prevalence ratio more than 10%, it was considered a confounder and left in the model for adjustment. This process continued, adding the one characteristic variable with the highest delta G value into the model each round until there were no significant changes to the measure of association or all variables were included in the model.

Missing Data

Missing data for all independent variables was examined for the distribution between normal and abnormal visual field status. All analyses were conducted using listwise deletion for cases with missing data.

RESULTS

Study Population Characteristics

The study population of 159 female registrants with IIH had a mean age at diagnosis of 32 (14 to 64, SD 10 years). Ninety-two percent of the study population reported their race as non-Hispanic/white. Of those who completed a question about education level on the second version of the registrant questionnaire (n=114), 42% had completed college or a higher-level education. Diagnosis of IIH occurred between 1980 and 2005, and 38% of study subjects were diagnosed during the study period, between 2003 and 2005.

Study subjects lived in 36 different states, with 11% from the Northeast, 53% from the Midwest, 20% from the South, and 16% from the West. Ohio (n=71) and California (n=12) were the most common states of residence. Sixty-one study subjects (38%) were referred from one neuro-ophthalmologist, Physician A, who had treated 71% of the study subjects from the Midwest.

Disease Characteristics

The mean lumbar puncture opening pressure (LPOP) was 35 cm CSF (20 to 70, SD 10 cm). Only 10 registrants selected for the study had an LPOP between 20 and 25 cm CSF. Fifty-two percent of study subjects (n=68) had a surgical intervention related to intracranial hypertension (CSF shunting or optic nerve sheath decompression, not including repeated lumbar puncture). Patients of Physician A were more likely to have surgery compared to all other study

subjects. Sixty-five percent of study subjects under the care of Physician A had surgery, compared to 43% of all other study subjects (p=0.01, chi-square test of independence).

Symptom Data

A total of 95 study subjects (62%) completed Registrant Questionnaire Version 1 (RQV1), which specified symptoms 'with this disease,' while 59 study subjects (38%) completed the Version 2 (RQV2), which specified symptoms 'at the time of diagnosis.' Two study subjects completed unknown questionnaire versions. Most study subjects reported having headache, with 95% reporting the presence of headache either at diagnosis or associated with the disease. Of the registrants who completed RQV1 (n=59), 61% reported having a headache 'always' at the time of diagnosis, compared to 39%, who reported having a headache 'sometimes.' Only a total of 8 study subjects reported no headache associated with the disease.

Most study subjects also reported tinnitus. Of those who completed the questionnaire and did not mark 'not sure,' 90% (n=111) reported 'always' (41%) or 'sometimes' (48%) having tinnitus. Seventy-eight percent (n=100) reported neck pain or stiffness associated with the disease. Hearing loss was reported to occur 'always' (16%) or 'sometimes' (39%) in 55% of study subjects who did not indicate 'not sure.'

Symptoms of abnormal vision were reported in fewer than half of study subjects. Abnormal peripheral vision was reported in 77% (n=74) of study subjects. Central vision was abnormal for the left or right eye in 40% (n=44, 43), and double vision was reported by 35% (n=42). A large proportion of study subjects indicated 'not sure' for visual symptom questions, with hearing loss the most likely to be 'not sure,' reported by 18% (n=23) and peripheral vision next more frequent at 15% (n=19). All symptom questions had high rates of missing data, with 18% of responses missing for the peripheral vision question.

Although many registrants did not complete the RQV2 asking about a diagnosis or past history of polycystic ovarian syndrome (PCOS), chart review completed data for 108 registrants. A total of 24 registrants responded or had a chart review positive for a diagnosis of PCOS. This corresponded to 27% of all study subjects who responded to the question and did not indicate 'not sure' about PCOS (total n=88).

Prevalence of Visual Field Deficits

At the exam closest to the date of diagnosis, 84% (n=122) of study subjects had at least one abnormal visual field finding in either or both eyes. The most common visual field deficits were the presence of an enlarged blind spot (50%) or peripheral constriction (40%). Arcuate or nasal field deficits were present in 20% of individuals, central or paracentral deficits in 9%, and hemianopsia in 8%. Of those with abnormal findings, 46% (n=56) had only one category of deficit, 44% (n=54) had two categories, 7% (n=9) had three, and 2% (n=3) had four

categories. No study subjects had visual deficits in all five categories. A large proportion of those with abnormal visual field findings were attributed to having only the finding of an enlarged blind spot (19%, n=23). If having only the finding of an enlarged blind spot was considered normal, the prevalence of abnormal visual field deficits at diagnosis was 68% (n=99).

The majority of study subjects had visual field exams performed by a neuro-ophthalmologist (67%) or an ophthalmologist (32%). One study subject had a visual field exam reported by a neurologist, which was normal, and one by an optometrist, who reported an enlarged blind spot and peripheral constriction. However, the physician type was missing for 14% (n=23) of study subject records, of which 13 were also missing the visual field exam. Neuro-ophthalmologists were more likely than ophthalmologists to report an abnormal visual field exam (90% compared to 74%, p=0.02, chi-square test).

Most study subjects had visual field exams using either Humphrey static perimetry or Goldmann kinetic perimetry (59%, n=94), and only 9% (n=15) were examined using only Goldmann kinetic perimetry. The type of perimetry used was missing for 50 study subjects. The type of visual field exam was not associated with the diagnosis of an abnormal visual field finding, with 85% abnormal using Humphrey perimetry or both, and 93% abnormal using only Goldmann perimetry ($p<0.05$, Fisher's Exact test).

Weight Characteristics

Study subjects had a mean weight one year prior to diagnosis of 92 kg (44 to 218 kg, SD 27 kg), which corresponds to 204 lb (97 to 500 lb, SD 60 lb). Nineteen percent (n=27) of study subjects lost weight in the year prior to diagnosis, while 36% (n=50) had weight stable with 0 to 2 kg weight gain, and 23% (n=32) gained 3 to 9 kg. Thirty study subjects (22%) gained 10 kg or more. Mean weight change was 5 kg weight gain (-57 to 57, SD 13 kg). The mean weight at diagnosis was 100 kg (44 to 218 kg, SD 27 kg) (Table 8).

The mean BMI of the study population was 34.1 kg/m^2 (16.6 to 70.9, SD 9.1 kg/m^2) the year prior to diagnosis, and 36.7 kg/m^2 (16.6 to 73, SD 8.9 kg/m^2) at the time of diagnosis. For the year prior to diagnosis, 15% (n=21) were normal weight, with BMI less than 25 kg/m^2, 17% (n=24) were overweight with BMI 25 to 29 kg/m^2, 46% (n=66) were obese with BMI 30 to 39 kg/m^2, and 22% (n=32) were morbidly obese with BMI 40 kg/m^2 or higher.

Ideal body weight (IBW) was calculated for study subjects using height reported for the time of diagnosis. Mean IBW for the study population was 57 kg (47 to 72, +/- 4 kg). The year prior to diagnosis, study subjects were an average of 64% (-20 to 239, +/- 44 %) above their IBW. There was a mean change in IBW of 9% (-86 to 103, +/- 23%) from the year prior to the time of diagnosis.

Assessment of Potential Confounders

No significant correlations were found between weight one year prior to diagnosis and study population characteristics, including age at diagnosis, race, region, year of diagnosis, treatment by Physician A, or lumbar puncture opening pressure (Table 7). There was a relationship between weight one year prior to diagnosis and whether a study subject had a history of surgery (p=0.03, chi-square test of independence), however this was not a linear relationship (p=0.60, chi-square test for linearity).

There were correlations between visual field status at diagnosis and both Physician A and surgery (Table 9). These relationships were apparent whether an enlarged blind spot was considered normal or abnormal. Given the association between surgery and weight the year prior to diagnosis, surgery could be a confounder of the relationship between weight and visual field status.

Weight and Visual Field Status

There was no significant relationship between the prevalence of higher weight one year prior to diagnosis and abnormal visual field status at the time of diagnosis when the solitary finding of an enlarged blind spot was considered normal (Table 8a). Those in the highest weight quartile, 110 kg or greater, were 0.92 times as likely (95% CI: 0.63 to 1.33) as those who weighed less than 75 kg to have an abnormal visual field finding at the time of diagnosis. Study subjects in all other weight quartiles were just as likely to have abnormal visual field findings as those in the lowest weight quartile. When adjusting for surgery as a

potential confounder, study subjects in the highest weight quartile were still only 1.01 times as likely as those in the lowest weight quartile (95% CI: 0.65 to 1.55) to have an abnormal visual field finding (Table 10). This prevalence ratio is 9% higher than without adjustment for surgery, suggesting that surgery may be a confounder in the relationship, but the association is not significant.

The relationship between other weight characteristics and visual field findings at diagnosis were examined. When enlarged blind spot was considered normal, there were no significant associations between weight gain in the year prior to diagnosis or excess ideal body weight and visual field deficits (Table 8a). Those with weight gain of 10 kg or greater were 1.06 times as likely as those who lost weight (95% CI: 0.85 to 1.32) to have abnormal visual field findings at diagnosis. Those who experienced an increase in IBW greater than 20% were 1.14 times as likely as those who lost weight (95% CI: 0.80 to 1.62) to have abnormal visual field findings. Only when those with a BMI the year prior to diagnosis of greater than or equal to 40 kg/m^2 were compared to those with a BMI less than 40 kg/m^2, was the prevalence of abnormal visual field findings greater in the higher weight group. Those with a BMI of 40 kg/m^2 or higher were 1.31 times as likely as those with BMI less than 40 kg/m^2 (95% CI: 1.05 to 1.62) to have an abnormal visual field finding at diagnosis.

When enlarged blind spot was considered abnormal, there were no significant relationships for any of the weight characteristics with the prevalence of abnormal visual field findings at diagnosis (Table 8b). There was no association

between weight in the year prior to diagnosis and the prevalence of abnormal visual field status at the time of diagnosis (crude PR 0.98, 95% CI: 0.83 to 1.15). With adjustment for surgery, the prevalence of an abnormal visual field exam at diagnosis was 1.04 times as likely for those in the highest weight quartile compared to the lowest (95%CI: 0.87 to 1.24). Those with weight gain of 10 kg or greater were 1.06 times as likely (95% CI: 0.85 to 1.32) as those who lost weight to have abnormal visual field findings at diagnosis. Similarly, those with a BMI of 40 kg/m^2 or greater were 0.98 times as likely (95% CI: 0.86 to 1.13) to have abnormal visual field status at diagnosis than those with BMI of less than 26 kg/m^2. Having an increase in IBW greater than 20%, compared to weight loss, was also not significantly more likely to be associated with abnormal visual field status (PR 1.08, 95% CI: 0.87 to 1.34).

Stratified Analyses

Recruitment patterns and trends in treatment and diagnosis of IIH could have impacted the association between weight and abnormal visual field status. Prevalence ratios for the association between weight the year prior to diagnosis and visual field status at diagnosis when enlarged blind spot was considered normal were stratified by whether study subjects had been treated by Physician A (Table 11) and by date of diagnosis (Table 12). Stratification for either Physician A or date of diagnosis did not identify an association between weight and visual field status at diagnosis in this study population.

DISCUSSION

Summary

In this cross-sectional study of women selected from a registry population for a diagnosis of IIH and meeting study criteria, we find no difference in visual field status at diagnosis between those in the highest weight quartile, compared to the lowest, for weight the year prior to diagnosis, even when adjusting for a history of surgical intervention. This observation is consistent when considering other weight categorizations, including weight change, BMI, and percent change in ideal body weight, and when considering the sole finding of an enlarged blind spot as either a normal or abnormal visual field exam. Surgery appears to be a potential confounder in the relationship between weight and visual field status, as it is independently associated with both weight and abnormal visual field status. Stratification by date of diagnosis and by whether a patient had been treated by a physician who referred a third of the study population did not reveal any significant association between weight and visual field status at diagnosis.

Comparison to Previous Studies

Two previous studies have attempted to answer the question of whether weight gain is association with visual field outcome. Each study reached a different conclusion regarding the association between weight and disease severity, with Wall and George (1991) [1] concluding an association between rapid weight gain and visual field deterioration, and Rowe and Sarkies (1999) [33] concluding no association between weight gain and visual field deterioration, but a possible

association between morbid obesity and visual field deterioration. These two previous studies were small with poor statistical power to detect differences between groups with weight gain and loss. Study selection criteria for a disease definition of IIH was not as strict as the present study, and both study populations included males. However, both previous studies had the advantage of random selection of study participants, with both studies having recruited consecutive newly diagnosed cases at their institution.

Both previous studies examined different parameterizations of weight measures and visual field status time points than we have used in this study. These studies had the advantage of assessing change in visual field grade as their visual field outcome variable, and measured this finding after a follow-up period several months after diagnosis. However, both studies used a dichotomous variable to compare visual field grade deterioration to improvement or unchanged status on the basis of weight gain. Although this allowed both studies to describe disease progression, this may have obscured the ability to detect a difference between those with more severe versus less severe visual field grade, and may not have been clinically significant if the majority of visual field grade deterioration was in the lower visual field grade range which is not detectable by the individual (Appendix B).

Our study was larger than the previous studies with 159 study subjects, compared to 50 participants in the Wall and George study and 34 participants in the Rowe and Sarkies study, and had greater than 80% power to detect a

difference in visual field status between those with weight gain or weight loss. Study subject selection was much more strict than the previous studies, with selection limited to women, the requirement of papilledema, and exclusion of those with potential Secondary Intracranial Hypertension (SIH). However, study subject selection was biased toward those who self-selected into the registry. Although our study population might have been less likely to include those with SIH, it likely represented a subset of those with IIH with more severe disease and those more likely to seek information on the Internet.

We were not able to assess visual field outcomes in this study because of its cross-sectional design, and we did not have the benefit of visual field grade determination, but we attempted to show an association between weight measures and visual field status at the most standardized time-point for all IIH patients – the date of diagnosis. In this study, without taking into account either the visual field grade or the change over time, we found no increased prevalence of an abnormal visual field exam with ascending weight. This finding, along with limitations of the prior studies, makes it less likely that a true association exists between weight and visual field deficits. It is possible, however, that patterns of visual field deficits that are associated with weight prior to diagnosis could develop over a follow-up period that were not apparent in this study, but were evident in these two prior studies.

Study Limitations

Limitations of the study design could have resulted in the conclusion of a null association that may not reflect the true underlying association between weight and visual field status and may not be comparable to other populations of individuals with IIH. Selection bias potentially resulted in a study population with more severe visual field deficits than the true population of women with IIH. Misclassification of study subjects may have resulted in placement of study subjects into the wrong exposure or outcome category. Use of study criteria that are different from those used in previous studies limits the generalizability of study conclusions to other study populations and to the entire population of those with IIH. Additionally, the cross-sectional study design limits the ability to show a temporal relationship between weight and visual field deficits.

Selection Bias

Selection bias may have resulted in a study population that consisted of an overrepresentation of individuals with abnormal visual field findings and higher weight than the underlying population of those with IIH. This selection bias might have resulted in the finding of a null association because it would have been difficult to detect a difference between those with abnormal, compared to normal, visual field status on the basis of weight with such a high proportion of both in the study population. Weight data was categorized into quartiles based on the study population distribution, so despite there being adequate numbers of individuals for comparison in the lowest weight quartile with normal visual field findings, in

reality, there were few study subjects of normal weight with normal visual field findings. Only 4 study subjects were normal weight (BMI <25 kg/m^2) with normal visual field findings, compared to 74 who were overweight or obese (BMI 25 kg/m^2 or greater) with abnormal visual field findings.

Self-selection by study participants into the IHR may have resulted in a study population with more severe disease. It would be expected that those who seek more information and who are affiliated with organizations related to their disease might have more severe disease. Selection on the basis of severe disease also might have occurred when patients of Physician A were referred to the study. Study subjects who were referred by Physician A may have had more severe disease or had more history of surgery than other patients with IIH due to Physician A being a tertiary care specialist in the disease, particularly in the area of visual field deficits. Similarly, patients with less severe disease may not have responded to the questionnaire or may not have been referred because they were less likely to be concerned about their disease.

It is likely that selection bias occurred in this study and resulted in an overestimation of severe disease in the study population, including those with worse symptoms, more abnormal visual field deficits, and those who were more obese. If a true association exists between visual field deficits at diagnosis and recent weight gain or obesity, we might not have been able to detect this association in our study population.

Misclassification

Misclassification may have resulted in some study subjects being placed in the wrong weight categories or visual status category, but it is unlikely that misclassification occurred differentially, and would not have been likely to result in a null association. Missing data may have played a role in misclassification of study subjects by either weight status or visual field status. Most missing data was for symptoms, with approximately 19% missing, but 10% of weight data was missing as well (Table 13). The distribution of missing weight data was slightly differential with respect to visual field status, with 56% of cases with missing weight data having abnormal visual fields, compared to 25% with normal visual fields (19% with unknown visual field status). If there is a true association between weight and abnormal visual field status, and all those with missing weight data and abnormal visual fields would fall into higher weight quartiles, then missing data could have resulted in a null association.

Study Selection Criteria and Generalizability

Some differences exist between the criteria used here for study subject inclusion and criteria used in previous studies, which limits comparison to other populations with IIH. It is not likely that these selection criteria would have impacted the association of interest in this study, unless we inadvertently selected for or against sub-populations within IIH with different relationships between weight and visual field status. We used the presence of papilledema and the level of elevated ICP as key objective findings to establish the diagnosis

of IIH. We chose to require papilledema for study inclusion because it is closely associated with elevated ICP and is associated with vision loss, and a more lenient ICP measure was chosen in an attempt to improve sensitivity to detect true cases of IIH.

With our strict study criteria, we attempted to improve the ability to include only true cases of IIH. The exact sensitivity and specificity of each measure to detect true cases of IIH is difficult to establish due to a poor understanding of the true etiology of the disease. It is possible that we may have inadvertently included individuals with Secondary Intracranial Hypertension (SIH), particularly when medical records or health history were not complete for some individuals, or when mention of a medication associated with SIH, or a history of another cause of elevated ICP was missed. By our exclusion of registrants without papilledema, we may under-represent true cases of IIH, particularly types that might be chronic and intermittent. However, we were concerned with vision loss associated with IIH, which appears to be associated with the presence of papilledema [47, 48].

A lumbar puncture opening pressure (LPOP) of 20 cm CSF or greater was used for study subject selection in this study. Elevated LPOP is commonly considered a finding of greater than 25 cm of CSF, although some patients with IIH may have findings that are intermittently low, and some normal patients may have findings that are higher [49, 50]. The sensitivity of LPOP to detect elevated ICP in IIH patients is unknown. The possibility that a relapsing disease course of IIH

may lead to changes in ICP over time, which may not be measured at single, or even multiple, time points, led to our decision to include lower lumbar puncture pressure values.

Further Studies

It is likely that a relationship between obesity and IIH exists, given the high prevalence of obesity in women with IIH. However, no relationship has been demonstrated between weight and severity of disease at the time of diagnosis. Further studies examining the relationship between weight and vision changes over the disease course of IIH would be useful to answer the question of whether weight change could affect the long-term vision outcome of the disease.

Conclusions

We have found no association between weight one year prior to diagnosis of IIH and the presence of abnormal visual field findings at the time of diagnosis (adjusted PR=1.01, 95% CI: 0.65 to 1.55) in a registry population of women with IIH that had a prevalence of abnormal visual field findings of 84% and a mean BMI of 37 kg/m^2 at diagnosis. This population may have had more severe disease and have been more obese than other populations of women with IIH, which may have resulted in an inability to detect an association between weight and visual field deficits.

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Table 1. Idiopathic Intracranial Hypertension (IIH) criteria

1a. Modified Dandy criteria for Idiopathic Intracranial Hypertension (IIH)

Signs and symptoms of increased intracranial pressure (papilledema, headache, tinnitus, etc.):
AND

1. No localizing findings on neurological exam
2. Normal MRI/CT scan with no evidence of venous obstruction
3. Increased ICP > 25 cm cerebrospinal fluid (CSF), with normal CSF constituents
4. Awake and alert patient
5. No other cause of increased ICP found

1b. Revised criteria for diagnosis of Idiopathic Intracranial Hypertension (IIH) [18]

1. If symptoms persist, they may only reflect those of generalized intracranial hypertension or papilledema
2. If signs persist, they may only reflect those of generalized intracranial hypertension or papilledema
3. Documented elevated intracranial pressure measured in the lateral decubitus position
4. Normal CSF composition
5. Papilledema seen on fundoscopic exam by an appropriate physician
6. No evidence of hydrocephalus, mass, structural, or vascular lesion on MRI or contrast-enhanced CT for typical patients, and MRI or MR venography for all others
7. No other cause of intracranial hypertension identified

Table 2. Study inclusion criteria

1. Enrollment in Intracranial Hypertension Registry (IHR)
2. Female
3. Age 13 to 65
4. Not pregnant at diagnosis
5. Papilledema seen on fundoscopic exam by an appropriate physician
6. Normal neurological exam other than a sixth cranial nerve palsy
7. Normal MRI/CT scan with no evidence of venous obstruction or intracranial mass
8. Elevated ICP > 20 cm cerebrospinal fluid (CSF), with normal CSF constituents
9. Awake and alert patient
10. No other cause of increased ICP found

Table 3. Annual age-adjusted incidence of Idiopathic Intracranial Hypertension (IIH) from prior studies [2, 3, 19-21, 30, 32]

STUDY LOCATION	MINNESOTA	IOWA	LOUISIANA	BENGHAZI, LIBYA	ISRAEL	PARMA, ITALY	BELFAST, IRELAND	HOKKAIDO, JAPAN
Study period, years	1976-1990	1988	1988	1984-1986?	1998-1999	1990-1999	1991-1995	1993
Recruitment base population	Mayo Clinic	Specialist[a]	Specialist[a]	North-Eastern Libya	Specialist[b]	Neurologic care at 3 hospitals	Royal Victoria Hospital	221/230 hospitals
Study Design	Retrospective	Prospective	Prospective	Prospective	Retrospective	Retrospective	Retrospective	Retrospective
Population	70,000	2,914,000	1,481,000	519,000	5,970,000/ 6,100,000	?	?	5,780,000
No. Patients	9	27	48	18	91	10	42	2
Female/male ratio	8	8	4.3	1	14	4	?	1
Obesity %	70	67	69	74	57 (97.2% females)[c]	?	?	0
Incidence (annual age-adjusted)	0.9	0.9	1.07	1.7	0.94 (1998) 0.57 (1999)	0.28	0.5	0.03
Incidence female	1.6	--	--	3.6	1.82	--	0.9	--
Incidence female age 15-45 y	3.3	3.5	3.5	10.3	4.02	0.65	--	--
Incidence female reproductive age	7.9 BMI>26 kg/m^2	13 >10% IBW	14.85 >10% IBW	21.4 obese	--	2.7 obese	--	--

[a]Specialist defined here as ophthalmologist, neurologist, or neurosurgeon
[b]Specialist defined here as ophthalmologist or neurologist
[c]Obesity determined by clinician's impression

Table 4. The relationship between weight gain and visual field grade deterioration in prospective studies of individuals newly diagnosed with Idiopathic Intracranial Hypertension (IIH) [1, 38]

AUTHORS	WALL M, GEORGE D, 1991	ROWE FJ, SARKIES NJ, 1999
Study Design	Prospective	Prospective
Study Subject Selection	New diagnosis	New diagnosis
Number of Study Subjects	50	34
Age, mean (years)	31 (11-58)	28 (11-57)
Female, n	46 (92%)	31 (91%)
Follow-up, mean (months)	12.4 (2-39)	24 (6-48)
Weight Data Collection	Patient recall	Recorded
Obese, n (BMI 30+ kg/m^2)	47 (94%)	24 (71%)
Morbidly Obese, n (BMI 40+ kg/m^2)	NR	9 (27%)
Weight Gain, n	NR	9 (27%)
Weight Gain, mean	7.7 kg over 1 year prior	6 kg (1-15) over follow-up
Visual Field at Diagnosis	Abnormal	Abnormal
Patient report	13 (26%)	NR
Goldmann perimetry	48 (96%)	NR
Visual Field Outcome	Deterioration Same Improvement	Improvement
Goldmann field grade	5 (10%) 15 (30%) 30 (60%)	Improved from first to last visit (p<0.01, Wilcoxin test)
Blindness	2 (4%)	NR
Comparison Factor	Weight gain (continuous)	VF grade deterioration (yes/no)
Comparison Groups	VF grade deterioration (yes/no)	Weight gain/no weight gain
Conclusion	Weight gain associated with VF grade deterioration (p<0.01, independent t-test, Bonferroni adjusted)	No difference (p=0.24, chi-square)

NR=not recorded

Table 5. Study subject inclusions and exclusions on the basis of the presence of papilledema and intracranial or ocular findings; (a) Study subjects with intracranial or ocular findings and papilledema who were selected for study inclusion due to a low suspicion of elevated intracranial pressure as a result of the intracranial or ocular finding; (b) The presence of papilledema in study subjects excluded [a, b] due to intracranial or ocular findings

5a.

HEAD/EYE FINDINGS (ALL HAD PAPILLEDEMA)	
Chiari malformation	2
History of brain aneurysm	1
History of cerebrovascular accident	1
History of varicella virus at diagnosis	1
Melanoma of the iris	1
Optic nerve atrophy	1
Pituitary adenoma	1
Prolactinemia	1
Prolactinoma	1
Questionable infectious etiology	1
Recent pregnancy/pre-eclampsia	1
Recent pregnancy	1
Remote history of head trauma, scoliosis	1
Remote history of head trauma	3
TOTAL	**16**

5b.

	HEAD/EYE FINDINGS		NONE	TOTAL
Had papilledema	3	Orbital mass Coma/cortical hemorrhage Absent ethmoid bone	0	3
No papilledema	5	Arachnoid cyst Optic nerve aneurysm History of head trauma (2) Retinal hemorrhage	17	22
Questionable papilledema	3	Chiari malformation (2) Leptospirosis infection	9	12
Missing papilledema	1	Possible multiple sclerosis	1	2
TOTAL	12		27	39

[a] One additional registrant had LPOP <20 cm CSF who was missed on previous exclusion due to a missing LPOP value

[b] One additional registrant was pregnant right at diagnosis and missed on previous exclusion (presented with pre-eclampsia)

Table 6. Total consecutive study subject exclusions of a registry population of individuals with suspected intracranial hypertension

TOTAL REGISTRANTS DEC 31, 2005	**502**
Male Registrants	89
Non-U.S. Address	50
Pregnant at Diagnosis	2
Age <13 or >65	26
Registrants Who Underwent Chart Review I	**335**
Incomplete Diagnostic Criteria	88
Undetermined Intracranial Hypertension	20
Secondary Intracranial Hypertension	19
LPOP <20 cm CSF	8
Registrants Who Underwent Chart Review II	**200**
Findings Suggest Possible Mass Effect	11
No Papilledema on Fundoscopic Exam	17
Questionable Papilledema	9
No Fundoscopic Exam	2
Pregnant at Diagnosis	1
LPOP <20 cm CSF	1
Total Exclusions	*343*
Total Study Subjects	**159**

Table 7. Assessment of potential confounders in the relationship between weight and visual field status at diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH); weight (kg) one year prior to diagnosis is categorized into quartiles and compared to study population characteristics using the chi-square test of independence

WEIGHT ONE YEAR PRIOR (KG)	TOTAL N (%)	<75	75-84	85-109	110+	TOTAL N (%)	P-VALUE*
Age at Diagnosis							
13-24	35 (22)	10 (35)	7 (24)	4 (14)	8 (28)	29 (20)	0.27
25-29	35 (22)	5 (16)	8 (25)	15 (47)	4 (13)	32 (22)	
30-34	34 (21)	9 (28)	7 (22)	9 (28)	7 (22)	32 (22)	
35-39	19 (12)	3 (18)	4 (24)	3 (18)	7 (41)	17 (12)	
40-44	17 (11)	4 (29)	1 (7)	3 (21)	6 (43)	14 (10)	
45+	19 (12)	3 (16)	5 (26)	6 (32)	5 (26)	19 (13)	
TOTAL (MISS)	159 (0)	32 (24)	32 (22)	40 (28)	37 (26)	143	
Race							
Non-white	13 (8)	3 (25)	3 (25)	3 (25)	3 (25)	12 (8)	0.99
White	145 (92)	31 (24)	28 (22)	37 (29)	34 (26)	130 (92)	
TOTAL (MISS)	158 (1)	34 (24)	31 (22)	40 (28)	37(26)	142	
Region							
Northeast	18 (11)	2 (13)	4 (27)	5 (33)	4 (27)	15 (10)	0.98
Midwest	84 (53)	18 (23)	17 (22)	22 (29)	20 (26)	77 (54)	
South	31 (20)	9 (32)	6 (21)	7 (25)	6 (21)	28 (20)	
West	26 (16)	5 (22)	5 (22)	6 (26)	7 (30)	23 (16)	
TOTAL (MISS)	159 (0)	32 (24)	32 (22)	40 (28)	37 (26)	143	
Year of Diagnosis							
1980-1999	52 (33)	11 (23)	12 (26)	12 (26)	12 (26)	47 (33)	0.76
2000-2002	46 (29)	13 (33)	7 (18)	10 (25)	10 (25)	40 (28)	
2003-2005	61 (38)	10 (18)	13 (23)	18 (32)	15 (27)	56 (34)	
TOTAL (MISS)	159 (0)	34 (24)	32 (22)	40 (28)	37 (26)	142	
Physician A							
No	98 (62)	12 (22)	12 (22)	17 (31)	14 (26)	55 (38)	0.93
Yes	61 (38)	22 (25)	20 (23)	23 (26)	23 (26)	88 (62)	
TOTAL (MISS)	159 (0)	34 (24)	32 (22)	40 (28)	37 (26)	143	
Lumbar Puncture							
20-24 cm CSF	10 (6)	3 (30)	1 (10)	3 (30)	3 (30)	10 (7)	0.56
25-29 cm CSF	44 (28)	10 (26)	11 (29)	8 (21)	9 (24)	38 (27)	
30-34 cm CSF	38 (24)	5 (15)	9 (27)	11 (32)	9 (27)	34 (24)	
35-39 cm CSF	28 (18)	4 (16)	3 (12)	8 (32)	10 (40)	25 (17)	
40+ cm CSF	39 (25)	12 (33)	8 (22)	10 (28)	6 (17)	36 (25)	
TOTAL (MISS)	159 (0)	34 (24)	32 (22)	40 (28)	37 (26)	143	

Surgery							
No	63 (48)	8 (14)	17 (30)	18 (32)	13 (23)	56 (48)	0.03
Yes	68 (52)	19 (32)	9 (15)	13 (22)	19 (32)	60 (52)	
TOTAL (MISS)	131 (28)	27 (23)	26 (22)	31 (27)	32 (28)	116	

*p-value for chi-square test of independence

Table 8. The association between weight measures and visual field status at diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH) using prevalence ratios (PR) with 95% confidence intervals (CI) and separated into (a) consideration of a solitary visual field deficit of enlarged blind spot as a normal finding, and (b) consideration of a solitary visual field deficit of enlarged blind spot as an abnormal finding

8a. Solitary finding of an enlarged blind spot considered normal

WEIGHT MEASURES	VISUAL FIELD STATUS			PREVALENCE RATIO WITH 95% CI		
Weight Year Prior	Normal (%)	Abnormal (%)	TOTAL (%)	Crude PR	95% CI	p-value*
<75 kg	10 (31)	22 (69)	32 (24)	Ref		
75-84 kg	10 (37)	17 (63)	27 (20)	1.00	0.72, 1.38	0.64
85-109 kg	11 (29)	27 (71)	38 (29)	1.03	0.76, 1.41	0.84
110+ kg	11(31)	24 (68)	35 (27)	0.92	0.63, 1.33	0.99
TOTAL (%)	42 (32)	90 (68)	132			
Weight Difference						
<0 kg	8 (32)	17 (68)	25 (20)	Ref		
0-2 kg	16 (34)	31 (66)	47 (37)	1.09	0.77, 1.55	0.86
3-9 kg	9 (31)	20 (69)	29 (23)	1.01	0.71, 1.46	0.94
10+ kg	7 (26)	20 (74)	27 (21)	1.06	0.85, 1.32	0.63
TOTAL (%)	40 (31)	88 (69)	128			
BMI						
<25 kg/m2	4 (20)	16 (80)	20 (15)	Ref		
25-29 kg/m2	11 (52)	10 (48)	21 (16)	0.60	0.36, 0.98	0.04
30-39 kg/m2	22 (36)	39 (64)	61 (46)	0.80	0.60, 1.07	0.13
40+ kg/m2	5 (17)	25 (83)	30 (23)	1.04	0.79, 1.37	0.77
TOTAL (%)	42 (32)	90 (68)	132			
BMI – cutoff 30						
<30 kg/m2	15 (36)	27 (64)	42 (32)	Ref		
30+ kg/m2	27(30)	63 (70)	90 (68)	1.09	0.84, 1.42	0.53
TOTAL (%)	42 (32)	90 (68)	132			

BMI – cutoff 40						
<40 kg/m2	37 (36)	65 (64)	102 (77)	Ref		
40+ kg/m2	5 (17)	25 (83)	30 (23)	1.31	1.05, 1.62	0.02
TOTAL (%)	42 (32)	90 (68)	132			
Percent IBW						
<0%	4 (16)	21 (84)	25 (20)	Ref		
0-3%	4 (11)	32 (89)	36 (29)	1.02	0.72, 1.44	0.91
4-9%	5 (23)	17 (77)	22 (17)	0.67	0.39, 1.14	0.14
10-19%	1 (5)	20 (95)	21 (17)	1.26	0.92, 1.74	0.16
20+%	2 (9)	20 (91)	22 (17)	1.14	0.80, 1.62	0.48
TOTAL (%)	16 (13)	110 (87)	126			

*p-value for Wald test

8b. Solitary finding of an enlarged blind spot considered abnormal

WEIGHT MEASURES	VISUAL FIELD STATUS			PREVALENCE RATIO WITH 95% CI		
Weight Year Prior	Norm (%)	Abnorm (%)	TOTAL (%)	Crude PR	95% CI	p-value*
<75 kg	3 (9)	29 (91)	32 (24)	Ref		
75-84 kg	6 (22)	21 (78)	27 (20)	0.86	0.68, 1.08	0.19
85-109 kg	6 (16)	32 (84)	38 (29)	0.93	0.78, 1.11	0.42
110+ kg	4 (11)	31 (89)	35 (27)	0.98	0.83, 1.15	0.78
TOTAL (%)	19 (14)	113 (86)	132			
Weight Difference						
<0 kg	4 (16)	21 (84)	25 (20)	Ref		
0-2 kg	7 (15)	40 (85)	47 (37)	1.01	0.82, 1.25	0.90
3-9 kg	3 (10)	26 (90)	29 (23)	1.07	0.86, 1.32	0.55
10+ kg	3 (11)	24 (89)	27 (21)	1.06	0.85, 1.32	0.61
TOTAL (%)	17 (13)	111 (87)	128			
BMI						
<25 kg/m2	1 (5)	19 (95)	20 (15)	Ref		
25-29 kg/m2	5 (24)	16 (76)	21 (16)	0.80	0.62, 1.04	0.10
30-39 kg/m2	11 (18)	50 (82)	61 (46)	0.86	0.74, 1.01	0.06
40+ kg/m2	2 (7)	28 (93)	30 (23)	0.98	0.86, 1.13	0.80
TOTAL (%)	19 (14)	113 (86)	132			
BMI – cutoff 30						
<30 kg/m2	6 (14)	36 (86)	42 (32)	Ref		
30+ kg/m2	13 (14)	77 (86)	90 (68)	1.0	0.86, 1.3	0.98
TOTAL (%)	19 (14)	113 (86)	132			
BMI – cutoff 40						
<40 kg/m2	17 (17)	85 (83)	102 (77)	Ref		

40+ kg/m2	2 (7)	28 (93)	30 (23)	1.12	0.98, 1.27	0.09
TOTAL (%)	19 (14)	113 (86)	132			
Percent IBW						
<0%	4 (16)	21 (84)	25 (20)	Ref		
0-3%	4 (11)	32 (89)	36 (29)	1.06	0.86, 1.30	0.59
4-9%	5 (23)	17 (77)	22 (17)	0.92	0.69, 1.22	0.56
10-19%	1 (5)	20 (95)	21 (17)	1.13	0.93, 1.38	0.21
20+%	2 (9)	20 (91)	22 (17)	1.08	0.87, 1.34	0.47
TOTAL (%)	16 (13)	110 (87)	126			

*p-value for Wald test

Table 9. Study subject characteristics and visual field status at diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH) using prevalence ratios with 95% confidence intervals and separated into (a) consideration of a solitary visual field deficit of enlarged blind spot as a normal finding, and (b) consideration of a solitary visual field deficit of enlarged blind spot as an abnormal finding

9a. Solitary finding of an enlarged blind spot considered normal

VARIABLES	VISUAL FIELD STATUS			PREVALENCE RATIO WITH 95% CI		
Age at Diagnosis	Normal (%)	Abnormal (%)	TOTAL (%)	Crude PR	95% CI	p-value*
13-24	4 (13)	26 (87)	30 (21)	Ref		
25-29	7 (23)	24 (77)	31 (21)	0.97	0.66, 1.42	0.87
30-34	3 (10)	28 (90)	31 (21)	1.17	0.83, 1.65	0.37
35-39	6 (33)	12 (67)	18 (12)	0.97	0.61, 1.53	0.88
40-44	1 (6)	16 (94)	17 (12)	1.30	0.92, 1.85	0.14
45+	2 (11)	16 (89)	18 (12)	1.14	0.77, 1.69	0.52
TOTAL (%)	23 (16)	122 (84)	145			
Race						
Non-white	1 (9)	10 (91)	11 (8)	Ref		
White	45 (34)	88 (66)	133 (92)	0.73	0.58, 0.91	0.01
TOTAL (%)	46 (32)	98 (68)	144			
Region						
Northeast	3 (21)	11 (79)	14 (10)	Ref		
Midwest	21 (26)	61 (74)	82 (57)	1.02	0.61, 1.70	0.94
South	12 (44)	15 (56)	27 (19)	1.36	0.91, 2.04	0.13
West	10 (46)	12 (55)	22 (15)	1.44	0.90, 2.30	0.13
TOTAL (%)	46 (32)	99 (68)	145			
Year of Diagnosis						
1980-1999	12 (26)	34 (74)	46 (32)	Ref		
2000-2002	15 (38)	25 (63)	40 (28)	0.85	0.63, 1.14	0.27
2003-2005	19 (32)	40 (68)	59 (41)	0.92	0.72, 1.17	0.49
TOTAL (%)	46 (32)	99 (68)	145			
Physician A						
No	38 (45)	46 (55)	84 (58)	Ref		
Yes	8 (13)	53 (87)	61 (42)	1.59	1.28, 1.97	<0.01
TOTAL (%)	46 (32)	99 (68)	145			
Lumbar Puncture						
20-24 cm CSF	3 (30)	7 (70)	10 (7)	Ref		

25-29 cm CSF	12 (31)	27(69)	39 (27)	0.99	0.63, 1.56	0.96
30-34 cm CSF	10 (29)	25 (71)	35 (24)	1.02	0.65, 1.61	0.93
35-39 cm CSF	9 (36)	16 (64)	25 (17)	0.91	0.55, 1.51	0.73
40+ cm CSF	12 (33)	24 (67)	36 (25)	0.95	0.60, 1.52	0.84
TOTAL (%)	46 (32)	99 (68)	145			
Surgery						
No	25 (45)	31 (55)	56 (47)	Ref		
Yes	11 (18)	52 (83)	63 (53)	1.49	1.15, 1.94	<0.01
TOTAL (%)	36 (30)	83 (70)	119			

*p-value for Wald test

9b. Solitary finding of an enlarged blind spot considered normal

VARIABLES	VISUAL FIELD STATUS			PREVALENCE RATIO WITH 95% CI		
Age at Diagnosis	Normal (%)	Abnormal (%)	TOTAL (%)	Crude PR	95% CI	p-value*
13-24	4 (13)	26 (87)	30 (21)	Ref		
25-29	7 (23)	24 (77)	31 (21)	0.89	0.71, 1.13	0.35
30-34	3 (10)	28 (90)	31 (21)	1.04	0.87, 1.25	0.66
35-39	6 (33)	12 (67)	18 (12)	0.77	0.54, 1.10	0.15
40-44	1 (6)	16 (94)	17 (12)	1.09	0.90, 1.31	0.38
45+	2 (11)	16 (89)	18 (12)	1.03	0.83, 1.27	0.82
TOTAL (%)	23 (16)	122 (84)	145			
Race						
Non-white	1 (9)	10 (91)	11 (8)	Ref		
White	22 (17)	111 (84)	133 (92)	0.92	0.75, 1.12	0.41
TOTAL (%)	23 (16)	121 (84)	144			
Region						
Northeast	2 (14)	12 (86)	14 (10)	Ref		
Midwest	8 (10)	74 (90)	82 (57)	1.45	0.96, 2.18	0.07
South	4 (15)	23 (85)	27 (19)	1.53	1.07, 2.18	0.02
West	9 (41)	13 (59)	22 (15)	1.44	0.98, 2.11	0.06
TOTAL (%)	23 (16)	122 (84)	145			
Year of Diagnosis						
1980-1999	6 (13)	40 (87)	46 (32)	Ref		
2000-2002	7 (18)	33 (83)	40 (28)	0.95	0.79, 1.14	0.57
2003-2005	10 (17)	49 (83)	59 (41)	0.96	0.81, 1.12	0.58
TOTAL (%)	23 (16)	122 (84)	145			
Physician A						
No	21 (25)	63 (75)	84 (58)	Ref		
Yes	2 (3)	59 (97)	61 (42)	1.29	1.13, 1.47	<0.01
TOTAL (%)	23 (16)	122 (84)	145			

Lumbar Puncture						
20-24 cm CSF	1 (10)	9 (90)	10 (7)	Ref		
25-29 cm CSF	7 (18)	32 (82)	39 (27)	0.91	0.71, 1.18	0.48
30-34 cm CSF	6 (17)	29 (83)	35 (24)	0.92	0.71, 1.19	0.53
35-39 cm CSF	6 (24)	19 (76)	25 (17)	0.84	0.62, 1.14	0.27
40+ cm CSF	3 (8)	33 (92)	36 (25)	1.02	0.81, 1.28	0.88
TOTAL (%)	23 (16)	122 (84)	145			
Surgery						
No	14 (25)	42 (75)	56 (47)	Ref		
Yes	5 (8)	58 (92)	63 (53)	1.23	1.04, 1.45	0.02
TOTAL (%)	19 (16)	83 (70)	119			

*p-value for Wald test

Table 10. Crude and adjusted prevalence ratios for the association between visual field status at diagnosis and weight one year prior to diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH) where a solitary finding of an enlarged blind spot is considered normal; (a) model adjustment for each study subject characteristic; and (b) model adjustment for surgery with each other study subject characteristic

10a. Model adjusted for study subject characteristics

WEIGHT ONE YEAR PRIOR	VF ABNORMAL	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]
Model adjustment	Prevalence	Crude PR	+Race	+Region	+Phys A	+LPOP	+Age
<75 kg	0.69	Ref	Ref	Ref	Ref	Ref	Ref
75-84 kg	0.63	0.92 [0.63, 1.33]	0.90 [0.62, 1.31]	0.88 [0.61, 1.27]	0.89 [0.62, 1.27]	0.90 [0.62, 1.31]	0.92 [0.64, 1.33]
85-110 kg	0.71	1.03 [0.76, 1.41]	1.04 [0.77, 1.41]	1.00 [0.74, 1.36]	1.00 [0.75, 1.34]	1.03 [0.75, 1.41]	1.03 [0.75, 1.42]
110+ kg	0.68	1.00 [0.72, 1.38]	1.00 [0.72, 1.38]	0.97 [0.70, 1.33]	0.99 [0.73, 1.33]	1.00 [0.72, 1.39]	0.98 [0.70, 1.36]

10b. Model adjusted for surgery and other study subject characteristics

WEIGHT ONE YEAR PRIOR	VF ABNORMAL	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]	PR [95%CI]
Model adjustment	Prevalence	+Surgery	+Surgery	+Surgery	+Surgery	+Surgery	+Surgery
			+Race	+Age	+Region	+Phys A	+LPOP
<75 kg	0.69	Ref	Ref	Ref	Ref	Ref	Ref
75-84 kg	0.63	1.01 [0.65, 1.55]	0.96 [0.62, 1.48]	1.01 [0.66, 1.56]	0.96 [0.63, 1.47]	0.99 [0.65, 1.50]	0.96 [0.62, 1.48]
85-110 kg	0.71	1.28 [0.94, 1.73]	1.27 [0.94, 1.72]	1.28 [0.94, 1.74]	1.21 [0.90, 1.64]	1.21 [0.90, 1.62]	1.28 [0.94, 1.74]
110+ kg	0.68	1.06 [0.77, 1.47]	1.07 [0.77, 1.47]	1.05 [0.75, 1.47]	1.03 [0.75, 1.43]	1.03 [0.76, 1.40]	1.09 [0.79, 1.51]

Table 11. The association between weight one year prior to diagnosis and prevalence of abnormal visual field status at diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH) stratified for treatment by Physician A

	TREATED BY PHYSICIAN A				NOT TREATED BY PHYSICIAN A			
	Visual Field Status				Visual Field Status			
Weight 1 Year Prior	Abn (%)	Norm (%)	Crude PR	95% CI	Abn (%)	Norm (%)	Crude PR	95% CI
<75 kg	11 (92)	1 (8)	Ref	--	11 (55)	9 (45)	Ref	--
75-84 kg	9 (75)	3 (25)	0.82	0.57, 1.18	8 (53)	7 (47)	0.97	0.52, 1.80
85-109 kg	14 (82)	3 (18)	0.90	0.68, 1.88	13 (62)	8 (38)	1.13	0.67, 1.89
110+ kg	13 (93)	1 (7)	1.01	0.81, 1.27	11 (52)	10 (48)	0.95	0.54, 1.68
TOTAL (%)	47 (86)	8 (15)	55		43 (56)	34 (44)	77	

Table 12. The association between weight one year prior to diagnosis and prevalence of abnormal visual field status at diagnosis in a registry population of women with Idiopathic Intracranial Hypertension (IIH) stratified for year of diagnosis

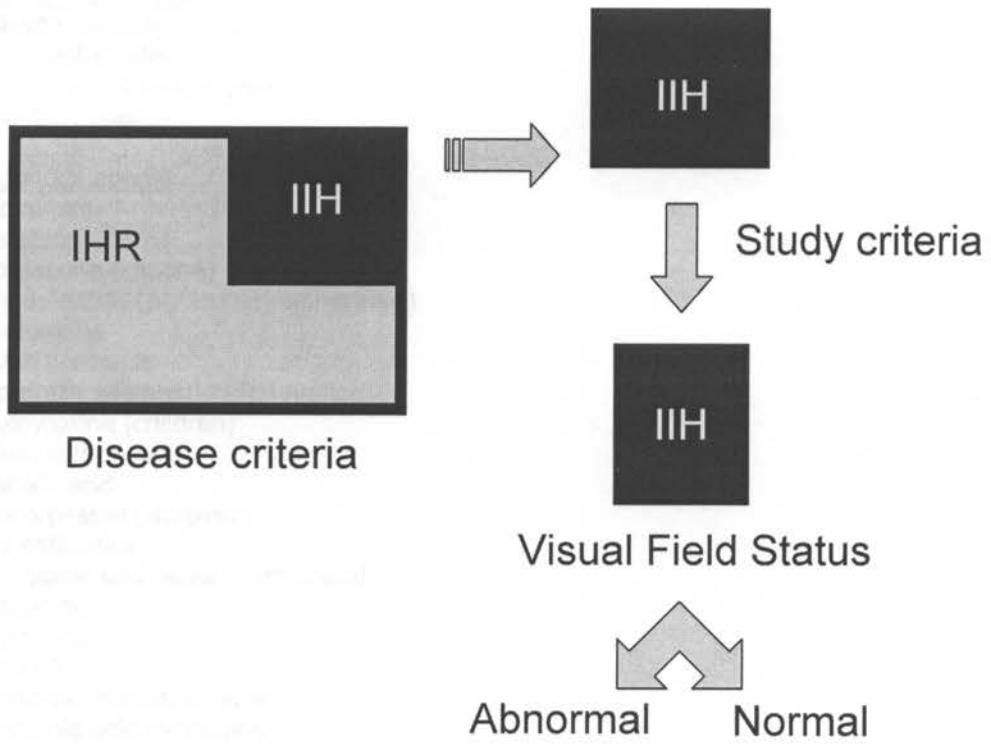
YEAR OF DIAGNOSIS	1990-1999				2000-2002			
	Visual Field Status				Visual Field Status			
Weight 1 Year Prior	Abnorm (%)	Norm (%)	Crude PR	95% CI	Abnorm (%)	Norm (%)	Crude PR	95% CI
<75 kg	6 (55)	5 (46)	Ref	--	7 (64)	4 (36)	Ref	--
75-84 kg	6 (67)	3 (33)	1.22	0.60, 2.49	2 (33)	4 (67)	0.52	0.16, 1.77
85-109 kg	10 (91)	1 (9)	1.67	0.94, 2.95	6 (60)	4 (40)	0.94	0.48, 1.85
110+ kg	9 (82)	2 (18)	1.5	0.82, 2.75	8 (89)	1 (11)	1.40	0.85, 2.31
TOTAL (%)	31 (74)	11 (26)	42		23 (64)	13 (36)	36	

YEAR OF DIAGNOSIS	2003-2005			
	Visual Field Status			
Weight 1 Year Prior	Abnorm (%)	Norm (%)	Crude PR	95% CI
<75 kg	9 (90)	1 (10)	Ref	--
75-84 kg	9 (75)	3 (25)	0.83	0.57, 1.23
85-109 kg	11 (65)	6 (35)	0.72	0.48, 1.08
110+ kg	7 (47)	8 (53)	0.52	0.29, 0.93
TOTAL (%)	36 (67)	18 (33)	54	

Table 13. Distribution by visual field status of missing study subject characteristic data that was excluded by listwise deletion from analysis of the association between weight and visual field status in a registry population of women with Idiopathic Intracranial Hypertension (IIH)

	TOTAL	MISSING	VF NORM	VF ABN	VF MISS
	N	N	N (% miss)	N (% miss)	N (% miss)
Visual Field Status	145	14	--	--	--
Headache	157	2	0	2 (100)	0
Neck Pain/Stiffness	129	30	3 (10)	27 (90)	0
Tinnitus	130	29	2 (7)	27 (93)	0
Hearing Loss	131	28	1 (4)	27 (96)	0
Central Vision (OS)	127	32	2 (6)	30 (94)	0
Central Vision (OD)	124	35	2 (6)	33 (94)	0
Diplopia	128	31	3 (10)	28 (90)	0
Peripheral Vision	131	28	1 (4)	27 (96)	0
US Region	159	0	0	0	0
Race	158	1	0	1 (100)	0
Year Dx	159	0	0	0	0
Age Dx	159	0	0	0	0
Phys A	159	0	0	0	0
Surgery	131	28	10 (36)	16 (57)	2 (7)
LPOP	159	0	0	0	0
Weight Year Prior	143	16	4 (25)	9 (56)	3 (19)
Weight Change	139	20	6 (30)	11 (55)	3 (15)
BMI	143	16	4 (25)	9 (56)	3 (19)
%IBW change	137	22	7 (32)	12 (55)	3 (14)

Figure 1. Study design for comparison of the association between abnormal visual field findings at diagnosis with weight prior to diagnosis of women with Idiopathic Intracranial Hypertension (IIH). Study subjects with a diagnosis of IIH were selected from the Intracranial Hypertension Registry (IHR) and study criteria were applied which refined the study population.



Appendix A. Conditions Associated with Pseudotumor Cerebri, adapted from Friedman, 2004 [51]

Obstruction to venous drainage
Cerebral venous sinus thrombosis
Aseptic (hypercoagulable state)
Septic (middle ear or mastoid infection)
Bilateral radical neck dissection with jugular vein ligation
Jugular vein tumor
Superior vena cava syndrome
Brachiocephalic vein thrombosis
Increased right heart pressure
After embolization of arteriovenous malformation

Endocrine disorders
Addison's disease
Hypoparathyroidism
Obesity, recent weight gain
Orthostatic edema

Exogenous agents
Amiodarone
Cytarabine
Chlordecone (kepone)
Corticosteroids (particularly withdrawal)
Cyclosporine
Growth hormone
Leuprorelin acetate (LH-RH analog)
Levothyroxine (children)
Lithium carbonate
Naladixic acid
Levonorgestrel (Norplant)
Sulfa antibiotics
Tetracycline and related compound
Minocycline
Doxycycline
Vitamin A
Vitamin supplements, liver
Cis-retinoic acid (Accutane)
All-trans-retinoic acid (for acute promyelocytic leukemia

Infectious or postinfectious
HIV infection
Lyme disease
After childhood varicella

Other medical conditions
Antiphospholipid antibody syndrome
Behc, et's disease
Occult craniosynostosis
Polycystic ovary syndrome
Sarcoidosis
Sleep apnea
Systemic lupus erythematosis
Turner syndrome

Appendix B. Goldmann Perimetry Visual Field Grading [33]

Grade 0 — Normal visual field

Grade 1 — Minimal visual loss – unlikely to be noticed by the patient
Isopter constriction; Step defects present that are less than 10° but greater than 5° in diameter
Defects not involving fixation;
Relative scotomas up to 20° x 20° in area outside 30°, or up to 10° in area inside 30°
Blind spot enlargement – encroaches central 10°

Grade 2 — Mild visual field loss – may be noticed by patient and usually compromises function
Isopter constriction; (1) Up to 20° in area; (2) 14e isopter inside 30° nasally, 50° temporally; (3) 12e isopter inside 20°
Defects not involving fixation;
Relative – less than 1 quadrant in size
Absolute – less than 20° x 20° in area
Defects involving fixation; VA of 6/9 or better

Grade 3 — Moderate visual field loss – nearly noticed by the patient which interferes with function
Isopter constriction; (1) Greater than 20° to any isopter but more than 50° of the field to the V4e target; (2) 13e isopter inside the blind spot; (3) 12e isopter inside 10°
Defects not involving fixation;
Relative – greater than 1 quadrant but less the 1 hemifield
Absolute – greater than 20° x 20° in diameter but less than 1 quadrant
Defects involving fixation; VA of 6/9 to 6/36

Grade 4 — Marked visual field loss
Isopter constriction; less than 50° but greater than 20° in diameter to V4e
Defects not involving fixation;
Relative – 1 hemifield or greater with more than 20° of field left to V4e
Absolute – greater than 1 quadrant with more than 20° to V4e
Defects involving fixation; VA of 6/36 to 6/60

Grade 5 — Blinding visual loss
Isopter constriction; less than 20° to V4e
Defects involving fixation; acuity worse than 6/60

Appendix C. Classification of variables examined for the association of weight in the year prior to diagnosis and visual field status at diagnosis

CHARACTERISTIC	DATA SOURCE	CLASSIFICATION GROUPS
Weight Variables		
Weight 1 year prior to Diagnosis (kg)	Self-report	<75 kg (ref)
		75-84 kg
		85-109 kg
		110+ kg
Weight at Diagnosis (kg)	Self-report	Same as wt 1 year prior
Weight Difference (kg)	Self-report	Weight loss (<0 kg) (ref)
		Weight stable (0-2 kg)
		Moderate weight gain (3-9 kg)
		Extreme weight gain (10+ kg)
BMI (kg/m^2) one year prior	Calculated, self-reported weight and height	Normal (<26 kg/m^2) (ref)
		Overweight (26-29 kg/m^2)
		Obese (30-39 kg/m^2)
		Morbidly obese (40+ kg/m^2)
		Non-obese (<30 kg/m^2) (ref)
		Obese (30+ kg/m^2)
		Non-morbidly obese (<40 kg/m^2) (ref)
		Morbidly obese (40+ kg/m^2)
Percent change in IBW (%)	Calculated, self-reported height	Weight loss (<0%) (ref)
		Weight stable (0-3%)
		Minimal weight gain (4-9%)
		Mod weight gain (10-19%)
		Extreme weight gain (20+ %)
Demographic Variables		
Age at Diagnosis (years)	Calculated using self-reported date of birth and date of diagnosis	13-24 (ref)
		25-29
		30-34
		35-39

		40-44
		45+
Region	Self-report	Northeast (ref)
		Midwest
		South
		West
Race/Ethnicity	Self-report	Non-white (ref)
		White/Non-Hispanic
Clinical Variables		
Year of Diagnosis	Self-report	1980 to 1999 (ref)
		2000 to 2002
		2003 to 2005
Lumbar Puncture Opening Pressure (cm CSF)	Physician report	20 to 24 (ref)
		24 to 29
		30 to 34
		35 to 39
		40 and above
Patient of Dr. A	Physician report	No (ref)
		Yes
Surgery Performed	Physician report	No (ref)
		Yes
Visual Field Variables		
Visual Field Status	Physician report and chart review	Normal (ref)
		Abnormal
Enlarged Blind Spot	Physician report and chart review	Absent (ref)
		Present
Peripheral Constriction	Physician report and chart review	Absent (ref)
		Present
Central/Paracentral Defect	Physician report and chart review	Absent (ref)
		Present
Arcuate/Nasal Step Defect	Physician report and chart review	Absent (ref)
		Present
Hemianopsia	Physician report and chart review	Absent (ref)
		Present
Symptom Variables		
Headache	Self-report	Yes, Always, Sometimes
		No, Never, Not Sure

Neck Pain/Stiffness	Self-report	Yes, Always, Sometimes
		No, Never, Not Sure
Tinnitus	Self-report	Never, Not Sure
		Always, Sometimes
Hearing Loss	Self-report	Never, Not Sure
		Always, Sometimes
Central Vision Loss	Self-report	No, Not Sure
		Yes
Peripheral Vision Loss	Self-report	No, Not Sure
		Yes
Double Vision	Self-report	No, Not Sure
		Yes

Appendix D. United States Census Bureau Regions

Region 1: Northeast

Connecticut
Maine
Massachusetts
New Hampshire
New Jersey
New York
Pennsylvania
Rhode Island
Vermont

Region 2: Midwest

Illinois
Indiana
Iowa
Kansas
Michigan
Minnesota
Missouri
Nebraska
North Dakota
Ohio
South Dakota
Wisconsin

Region 3: South

Alabama
Arkansas
Delaware
District of Columbia
Florida
Georgia
Kentucky
Louisiana
Maryland
Mississippi
North Carolina
Oklahoma
South Carolina
Tennessee
Texas
Virginia
West Virginia

Region 4: West

Alaska
Arizona
California
Colorado
Hawaii
Idaho
Montana
New Mexico
Nevada
Oregon
Utah
Washington
Wyoming

Appendix F. Symptom questions and answer choices for each registrant questionnaire

HEADACHES PRESENT	RQV1	WITH THIS ILLNESS, HAVE YOU HAD HEADACHES?	ALWAYS, SOMETIMES, NEVER, NOT SURE
	RQV2	At the time of diagnosis, did you have headaches?	Yes, No
NECK PAIN PRESENT	RQV1	With this illness, have you had neck pain or stiffness?	Always, Sometimes, Never, Not Sure
	RQV2	At the time of diagnosis, did you have neck pain or stiffness?	Yes, No
TINNITUS PRESENT	RQV1	With this illness, do you have tinnitus (whooshing/swishing/ringing/buzzing/noise) in your ears?	Always, Sometimes, Never, Not Sure
	RQV2	At the time of diagnosis, did you have tinnitus (whooshing/swishing/ringing/buzzing/noise) in your ears?	Always, Sometimes, Never, Not Sure
HEARING LOSS PRESENT	RQV1	With this illness, do you have hearing loss?	Always, Sometimes, Never, Not Sure
	RQV2	At the present time, do you have hearing loss?	Always, Sometimes, Never, Not Sure
CENTRAL VISION STATUS (OS=Left)	RQV1	Do you have normal central vision (20/20) in your eyes (with glasses or contacts, if you use them)?	Yes, No, Not Sure
	RQV2	At the present time, do you have normal central vision (20/20) in your eyes (with glasses or contacts, if you use them)?	Yes, No, Not Sure
CENTRAL VISION STATUS (OD=Right)	RQV1	Do you have normal central vision (20/20) in your eyes (with glasses or contacts, if you use them)?	Yes, No, Not Sure
	RQV2	At the present time, do you have normal central vision (20/20) in your eyes (with glasses or contacts, if you use them)?	Yes, No, Not Sure
DIPLOPIA PRESENT	RQV1	Do you have double vision?	Yes, No, Not Sure
	RQV2	Do you have double vision?	Yes, No, Not Sure
PERIPHERAL VISION LOSS PRESENT	RQV1	Do you have peripheral vision loss?	Yes, No, Not Sure
	RQV2	Do you have peripheral vision loss?	Yes, No, Not Sure

Appendix F. Frisén Papilledema Grading Scale [47]

Stage 0—Normal optic disc
- A. Blurring of nasal, superior, and inferior poles in inverse proportion to disc diameter
- B. Radial nerve fiber layer (NFL) without NFL tortuosity
- C. Rare obscuration of a major vessel, usually on the upper pole

Stage 1—Very early papilledema
- A. Obscuration of the nasal border of the disc
- B. No elevation of disc borders
- C. Disruption of the normal radial NFL arrangement with grayish opacity accentuating nerve fiber bundles
- D. Normal temporal disc margin
- E. Subtle grayish halo with temporal gap (best seen with indirect ophthalmoscope)
- F. Concentric or radial retinochoroidal folds

Stage 2—Early papilledema
- A. Obscuration of all borders
- B. Elevation of the nasal border
- C. Complete peripapillary halo

Stage 3—Moderate papilledema
- A. Obscuration of all borders
- B. Elevation of all borders
- C. Increased diameter of the optic nerve head
- D. Obscuration of one or more segments of major blood vessels leaving the disc
- E. Peripapillary halo–irregular outer fringe with finger-like extensions

Stage 4—Marked papilledema
- A. Elevation of entire nerve head
- B. Obscuration of all borders
- C. Peripapillary halo
- D. Total obscuration on the disc of a segment of a major blood vessel

Stage 5—Severe papilledema
- A. Dome-shaped protrusions, representing anterior expansion of the optic nerve head
- B. Peripapillary halo is narrow and smoothly demarcated
- C. Total obscuration of a segment of a major blood vessel may or may not be present
- D. Obliteration of the optic cup