VARYING LONG-TERM LIVER INVOLVEMENT IN PATIENTS WITH ALAGILLE SYNDROME IN A SINGLE CENTER STUDY

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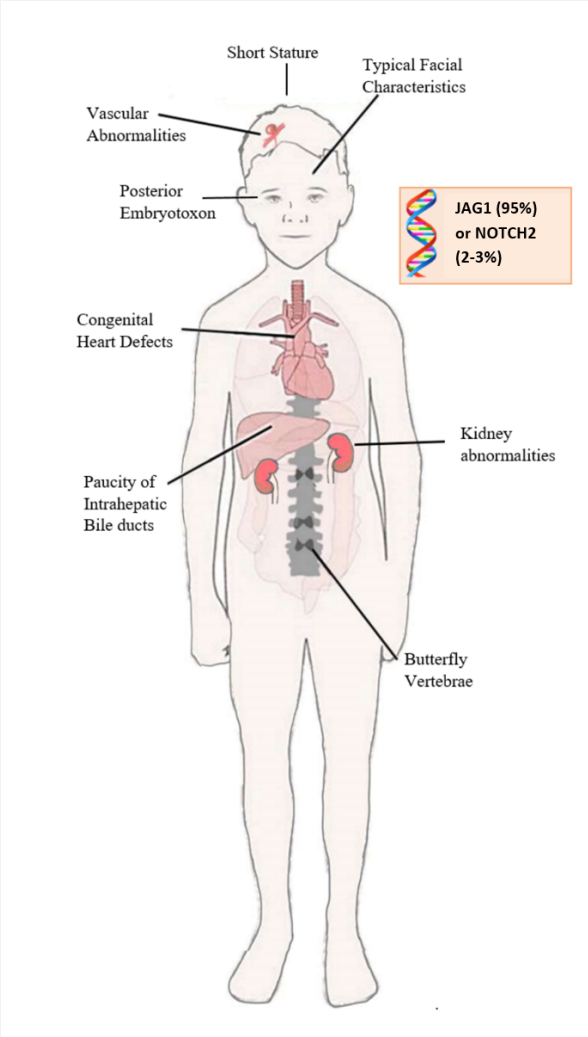
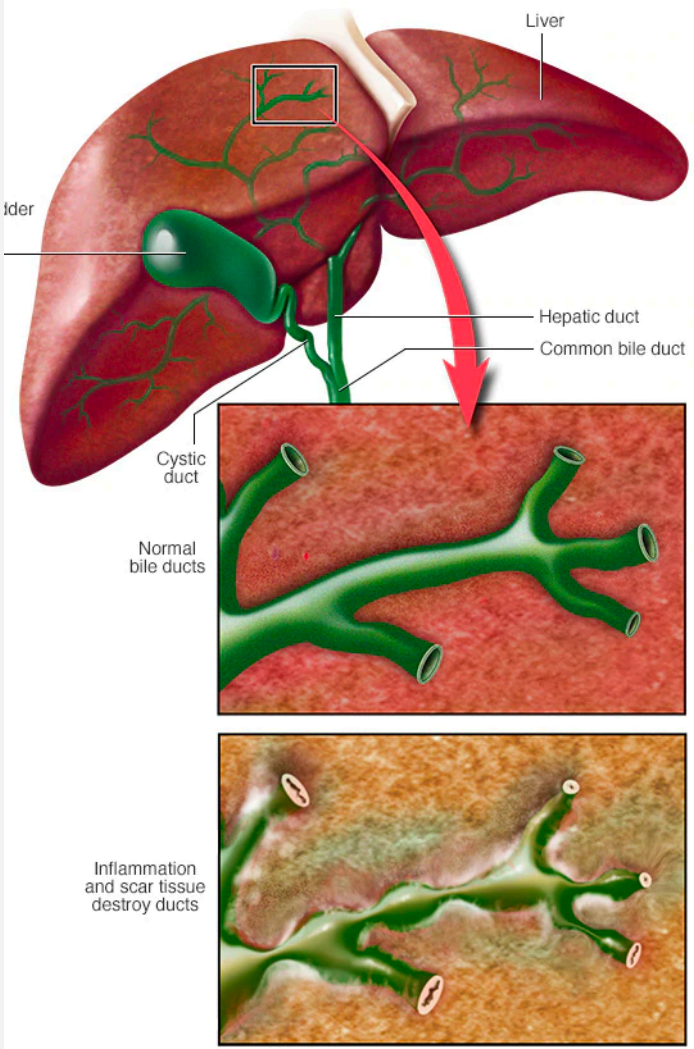
ALAGILLE SYNDROME

- ~1:30,000 – 1:50,000 births
- Diagnosed by genetic testing or clinical criteria
- Multisystem disorder
- Variable phenotype penetrance



LIVER DISEASE IN ALAGILLE SYNDROME

- Characterized histologically by bile duct paucity
- Liver involvement includes cholestasis, jaundice, pruritis, poor growth, xanthomas
- Typically presents within the first 3 months of life
  - Severity can range from subclinical disease to cirrhosis and liver failure
  - Severity of liver involvement can change with age
- No current predictor of progression to end-stage liver disease



LIVER DISEASE IN ALAGILLE SYNDROME

- Liver disease monitoring laboratory studies
  - Markers of cholestasis and bile duct damage (total and direct bilirubin, GGT)
  - Markers of liver damage and disease (AST, ALT, platelets)
- Treatment of cholestatic liver disease
  - Promote bile flow: ursodeoxycholic acid
  - Manage pruritis: rifampin, cholestyramine, antihistamines, naltrexone
  - Manage malabsorption and growth issues: supplemental vitamins and nutrients
  - For severe disease: biliary diversion and/or liver transplantation

Liver disease in Alagille Syndrome is variable

Mild course vs progression to ESLD unclear at diagnosis

Case series of varying long-term liver involvement at DCH

METHODS

- Retrospective case series of Doernbecher patients from 2003 - present
- Chart review to obtain laboratory values and ALGS characteristics
- Descriptive statistics to summarize clinical elements and severity of liver disease

PATIENT CHARACTERISTICS

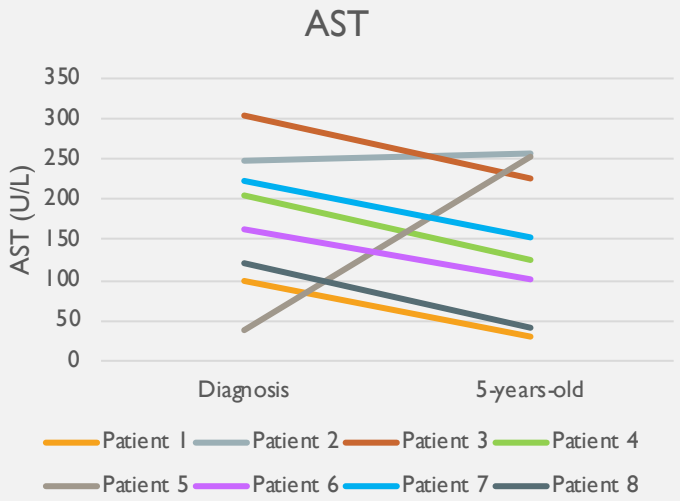
- 8 patients with Alagille Syndrome
- Average age of diagnosis: 18 months
- 3 patients with severe liver disease

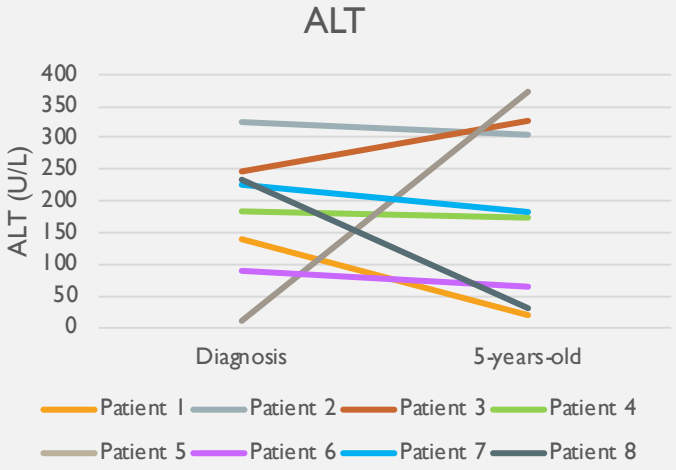
- JAG1 mutation: 6 patients
- NOTCH2 mutation: 0 patients
- 2 diagnosed by clinical criteria

Patient Number	1	2	3	4	5	6	7	8
Congenital heart defects	✓	✓	✓	✓	✓		✓	✓
Butterfly vertebrae	✓	✓						
Posterior embryotoxin			✓	✓	✓	✓	✓	
ALGS facies	✓	✓	✓	✓	unknown	✓	✓	unknown
Vascular Abnormalities	✓							

LIVER INFLAMMATION & DAMAGE TRENDS

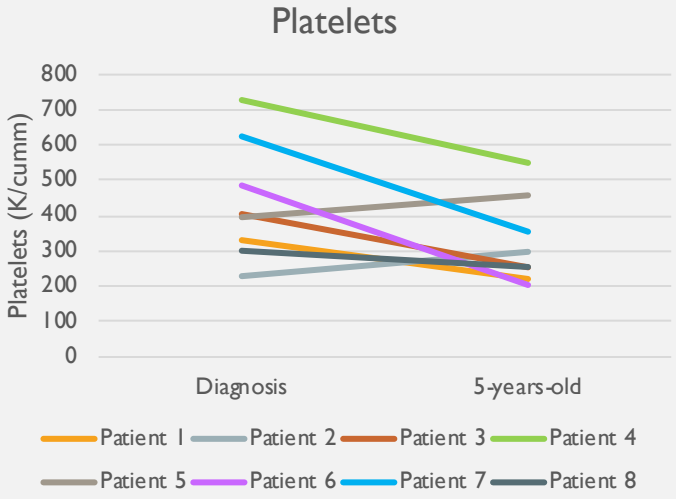
- Most patients had decreasing ALT, AST, and platelet values from diagnosis to 5- years-old





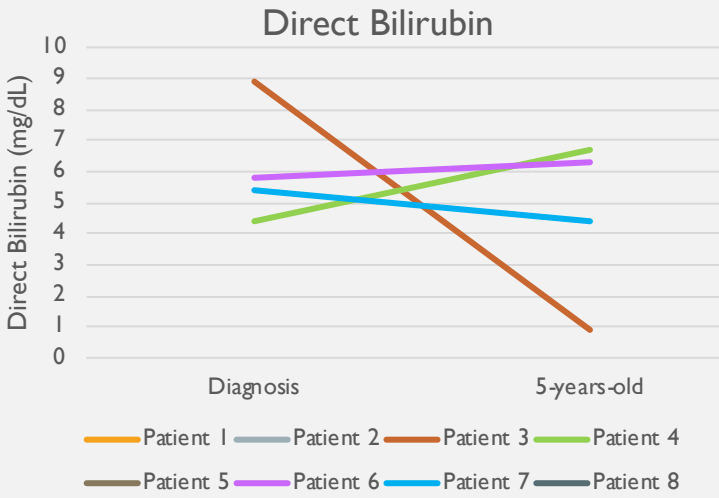
Normal ALT levels: 7-55 U/L
Normal AST levels: 5-40 U/L
Normal platelet levels: 150-400 K/cumm)

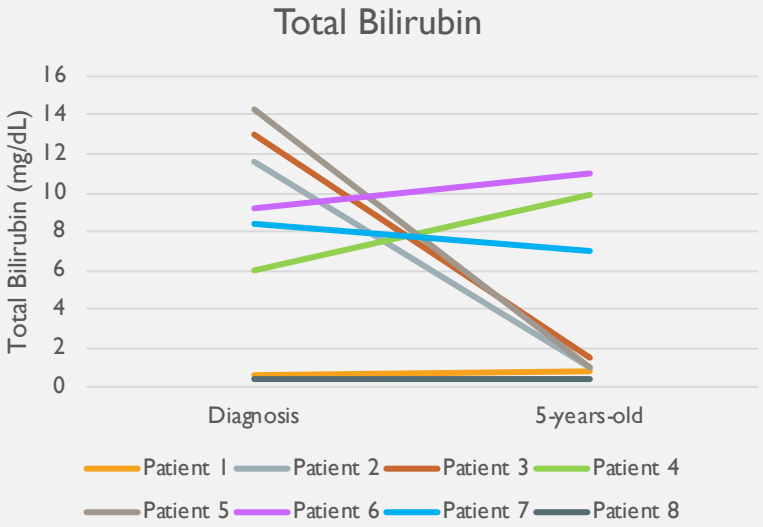
Patients 4, 6, 7 have severe liver disease



CHOLESTASIS AND BILE DUCT DAMAGE TRENDS

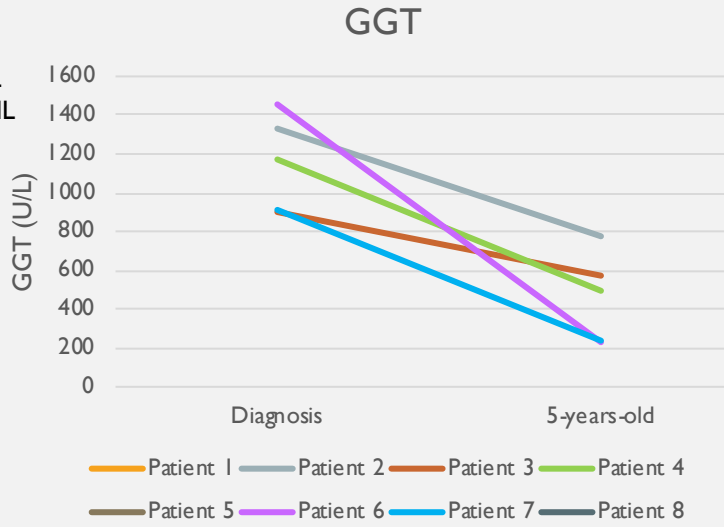
- Patients with mild liver disease had decreasing bilirubin levels
- Patients with severe liver disease had stably elevated or increasing bilirubin levels





Normal total bilirubin: 0.1 – 1.2 mg/dL
Normal direct bilirubin: 0.0 – 0.3 mg/dL
Normal GGT: <21 U/L

Patients 4, 6, 7 have severe liver disease



CONCLUSIONS & DISCUSSION

- Liver disease in Alagille Syndrome is variable
- Severity of liver disease at diagnosis does not necessarily predict progression to severe disease
- Of our eight patients, the three with severe disease had:
  - Elevated bilirubin, significant pruritus, and poor growth
  - Showed decreasing ALT, AST, GGT; decreasing platelets; and stably elevated or increasing total bilirubin and direct bilirubin
- Degree of cholestasis may suggest progression to severe liver disease

REFERENCES

Singh SP, Pati GK. Alagille Syndrome and the Liver: Current Insights. Euroasian J Hepatogastroenterol, 2018;8(2):140-147

Spinner NB, Gilbert MA, Loomes KM, et al. Alagille Syndrome. 2000 May 19 [Updated 2019 Dec 12]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1273/

QUESTIONS?

HEIGHT DATA

Patient Number	1	2	3	4	5	6	7	8
Current height %	28	11.5	43.6	0.5	26.9	12.3	0.08	12.7

LIVER TRENDS FROM DIAGNOSIS UNTIL 5 YEARS OF AGE

Patient Number	ALT (U/L)		AST (U/L)		Total Bilirubin (mg/dL)		Direct Bilirubin (mg/dL)		GGT (U/L)		Platelets (K/cu mm)	
	Dx	5 yo	Dx	5 yo	Dx	5 yo	Dx	5 yo	Dx	5 yo	Dx	5 yo
1	140	20	99	30	0.6	0.8	n/a	0.2	46	n/a	331	221
2	325	305	248	257	11.6	1	9.7	n/a	1331	776	229	298
3	247	327	304	226	13	1.5	8.9	0.9	901	573	405	254
4	184	174	205	125	6	9.9	4.4	6.7	1172	495	728	550
5	11	373	38	253	14.3	1	2.3	n/a	977	n/a	396	458
6*	90	65	163	101	9.2	11	5.8	6.3	1456	230	486	204
7	226	183	223	153	8.4	7	5.4	4.4	912	238	625	355
8	234	31	121	41	0.4	0.4	n/a	n/a	n/a	66	301	255

*patient was transplanted <5yo; "5 yo" values are just pre-transplant

Severe liver disease