Chronic Liver Disease in Urea Cycle Disorders

Lindsay C. Burrage, MD, PhD

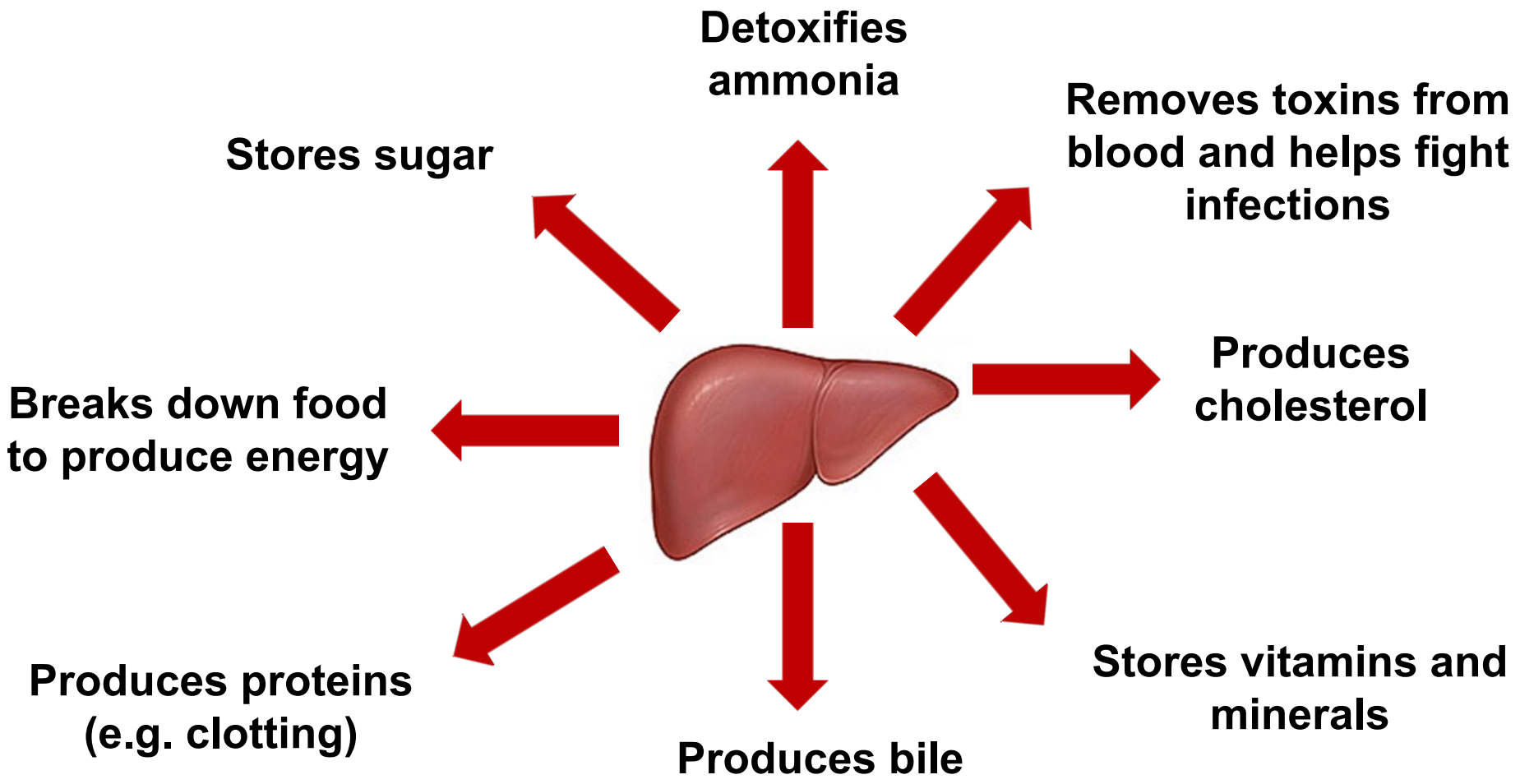
Investigator, Urea Cycle Disorders Consortium

RARE DISEASES CLINICAL RESEARCH NETWORK

Baylor College of Medicine

Urea Cycle Disorders Consortium

What Does the Liver Do?



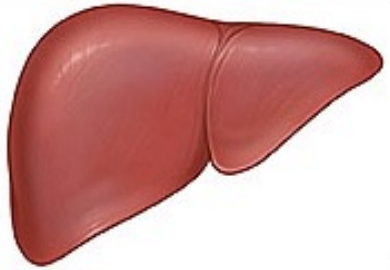
What Are the Signs and Symptoms of Severe Liver Disease?

- Yellow color to skin or eyes
- Abdominal pain and swelling
- Swelling in the legs and ankles
- Itchy skin
- Dark urine color
- Pale stool color, or bloody or tar-colored stool
- Chronic fatigue
- Nausea or vomiting or loss of appetite
- Easy bleeding or bruising

These signs or symptoms often do not occur unless the liver is severely damaged and milder liver disease may be associated with no signs or symptoms

Diagnosing Liver Disease in Urea Cycle Disorders

Acute liver failure



Chronic liver failure

Normal Liver

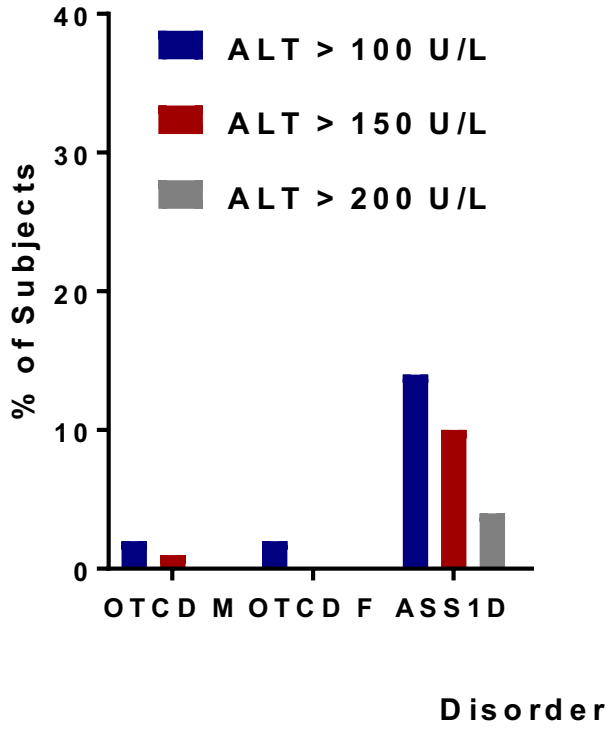
Elevated levels of liver enzymes in blood "AST" and "ALT"

Increased liver size

How Common Is Liver Disease in Urea Cycle Disorders?

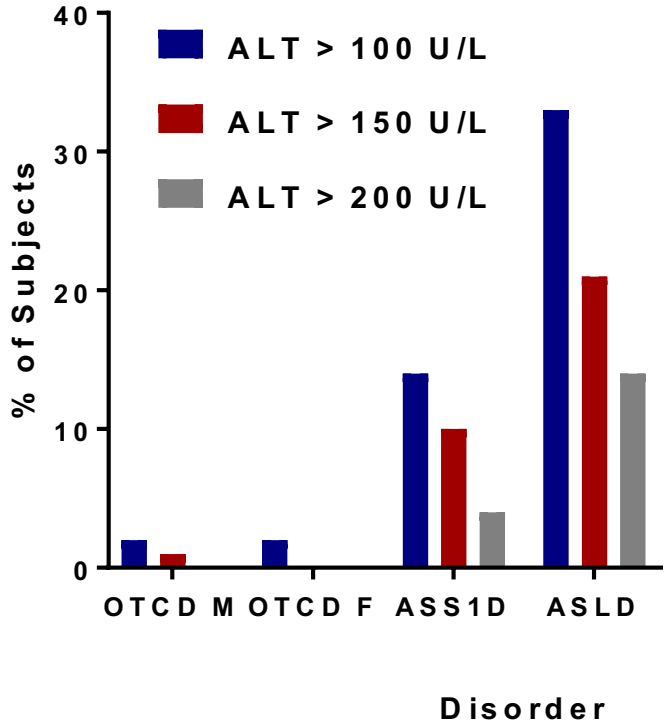
- We collected results from bloodwork collected at Longitudinal Study visits
- We determined how many patients with each urea cycle disorder had elevated levels of liver enzymes in the blood at 2+ visits
- Liver enzymes = AST and ALT

What Did We Learn?



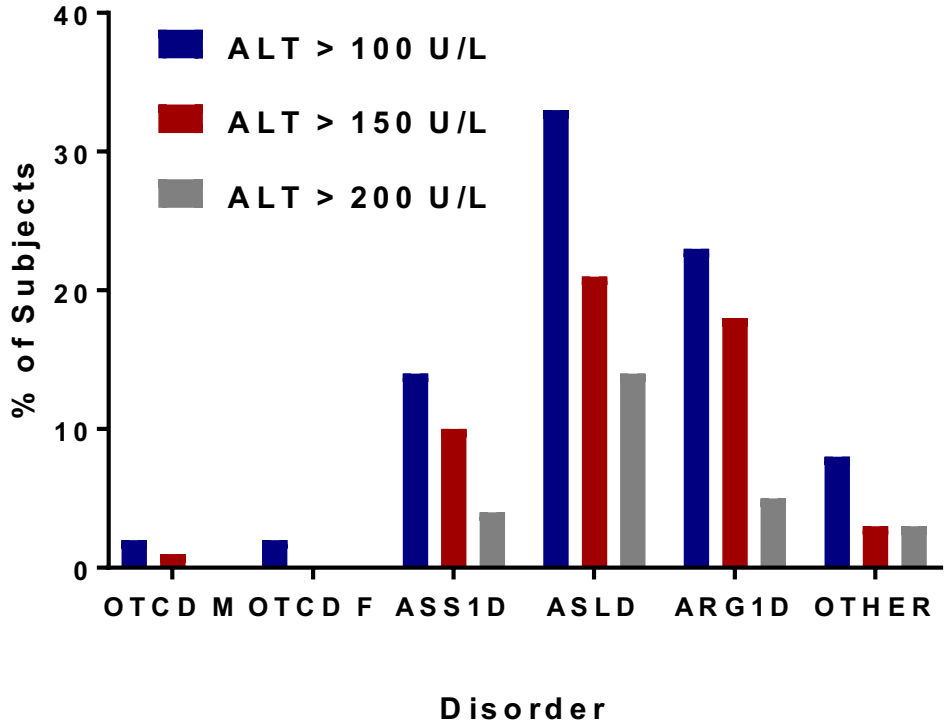
ASS1D = Citrullinemia

What Did We Learn?



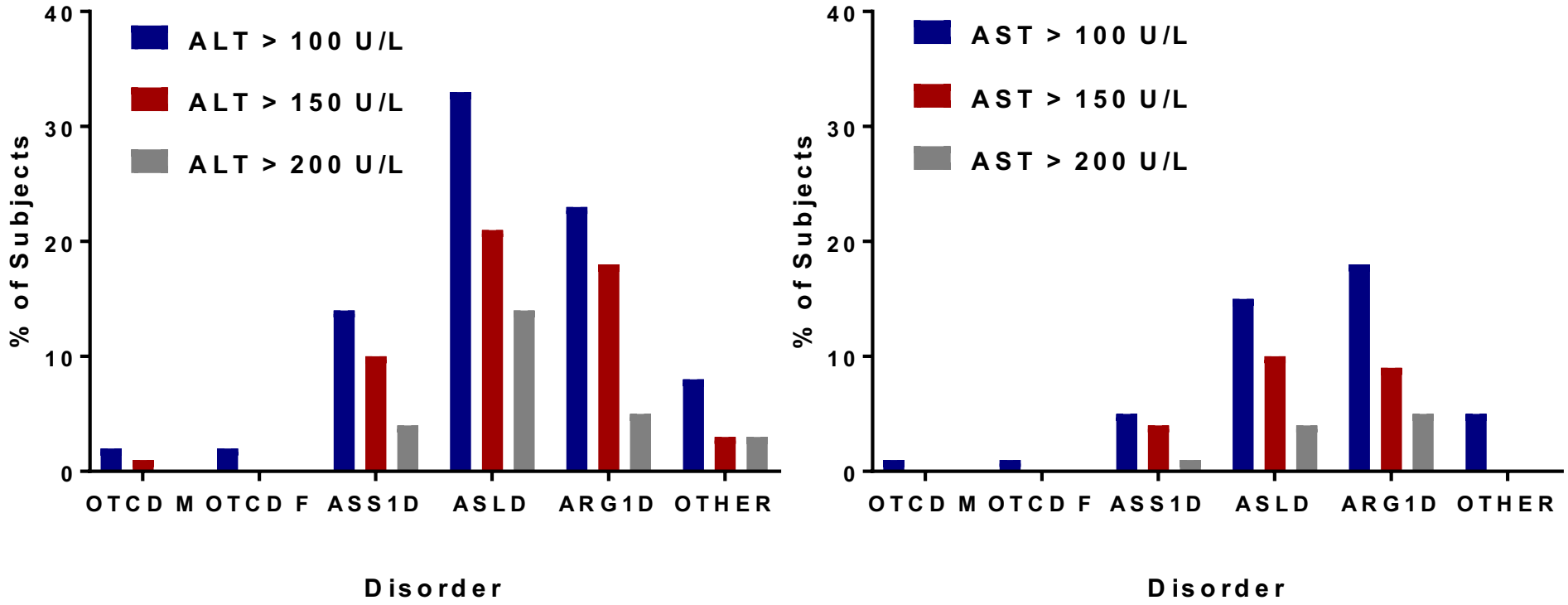
ASLD = Argininosuccinate Lyase Deficiency

What Did We Learn?



ARG1D = Arginase Deficiency

What Did We Learn?



Chronic elevation of liver enzymes is more common in distal disorders such as ASL deficiency and arginase deficiency

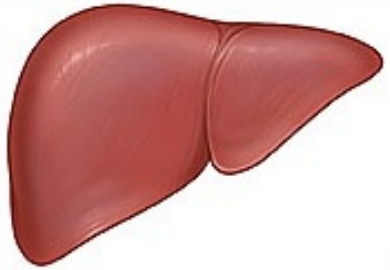
What Did We Learn?

- Patients with ASL deficiency who had a history of high ammonia level and need for medications were more likely to have elevated liver enzymes
- Elevated liver enzymes may be more common in patients with more severe forms of ASL deficiency
- The long-term effects of elevated liver enzymes are unknown

Diagnosing Liver Disease in Urea Cycle Disorders

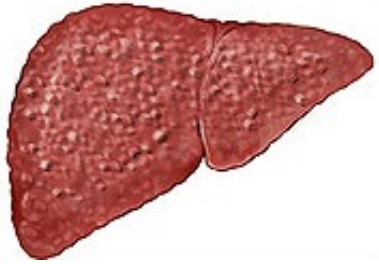
Acute liver failure

Chronic liver failure



Normal Liver

Elevated levels of liver enzymes in blood "AST" and "ALT"



Liver tissue sample to assess for hardening

Increased liver size

How Common Is Liver Disease in Urea Cycle Disorders?

Normal Liver

Stiff Liver
(Fibrosis---→ Cirrhosis)

We need to look at the liver under a microscope to know if an individual has fibrosis or cirrhosis and we only have such tissue after transplant (or biopsy, rarely)

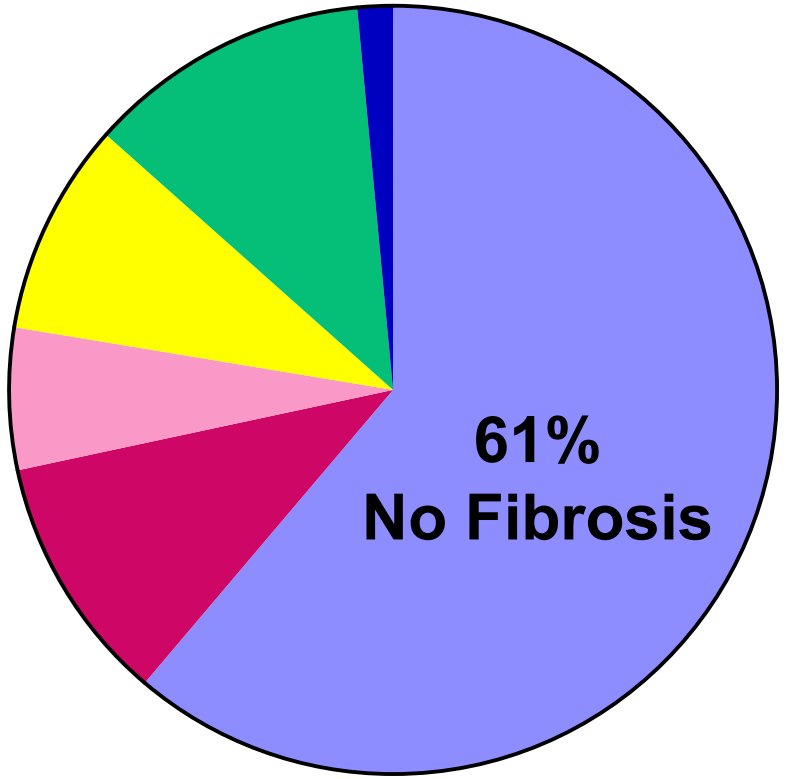
How Common Is Liver Fibrosis in Urea Cycle Disorders?

- We collected results from liver biopsies (rare) and tissue removed during liver transplants at Baylor and Stanford

- We determined how many people had liver stiffness in this liver tissue sample by looking at the tissue under a microscope

Hepatic Fibrosis in UCDs

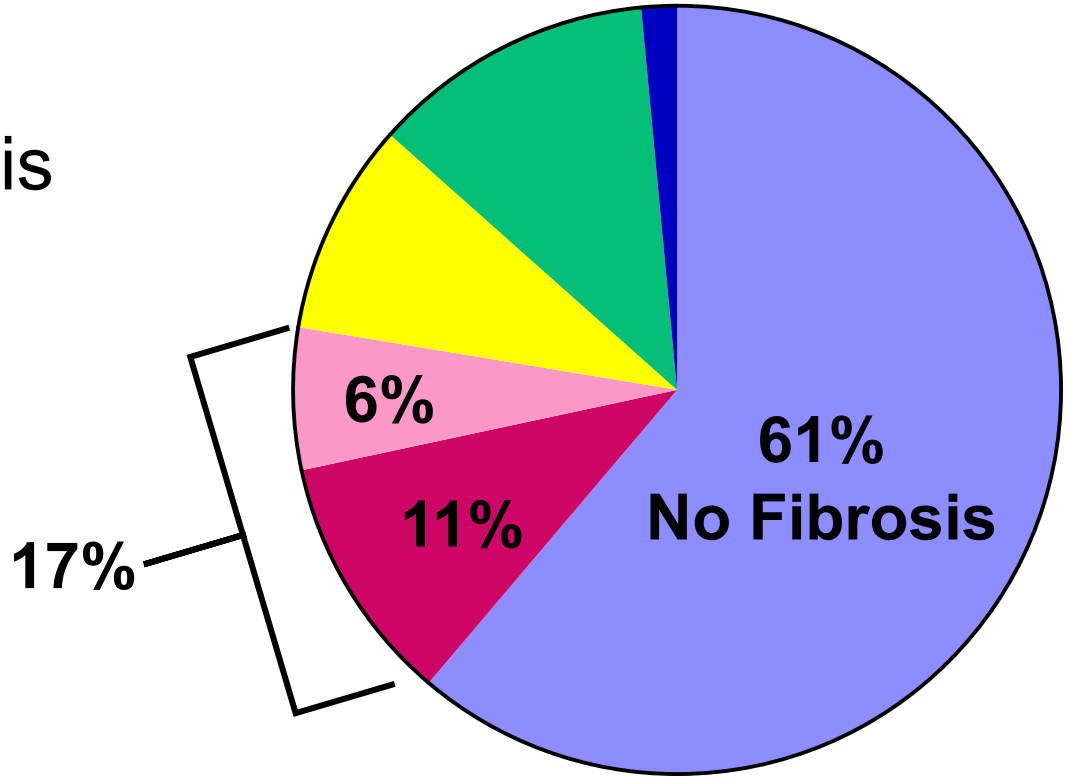
- 39% of individuals had any hepatic fibrosis



67 samples from 66 people

Hepatic Fibrosis in UCDs

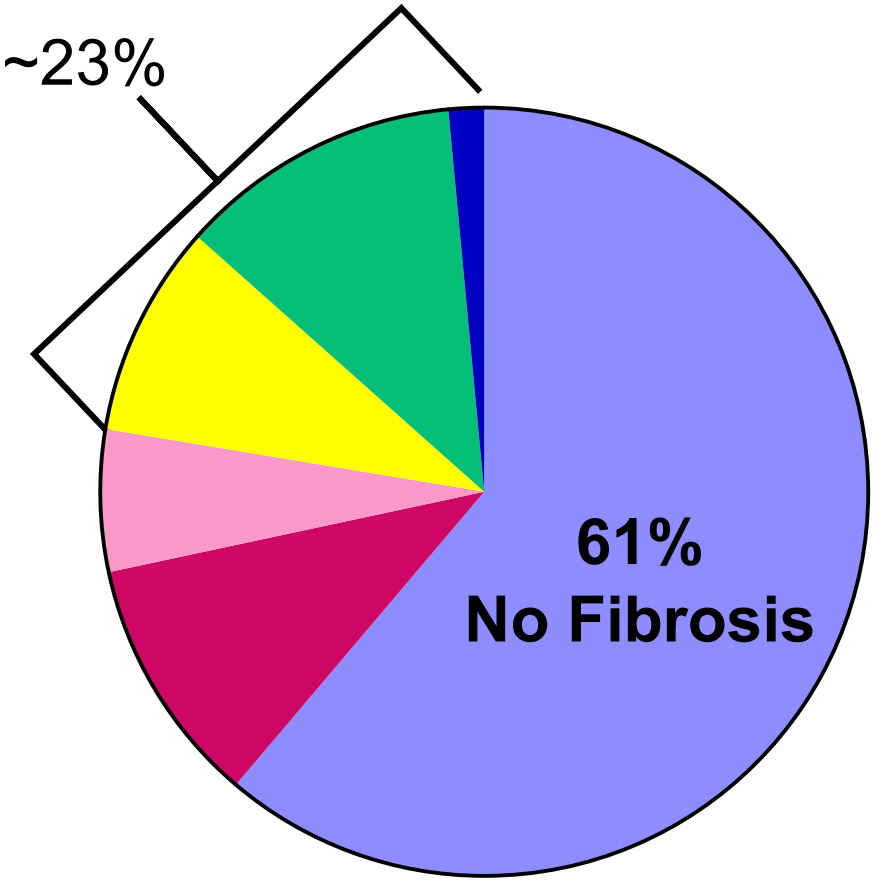
- 39% of individuals had any hepatic fibrosis
- 17% of individuals had very mild fibrosis



67 samples from 66 people

Hepatic Fibrosis in UCDs

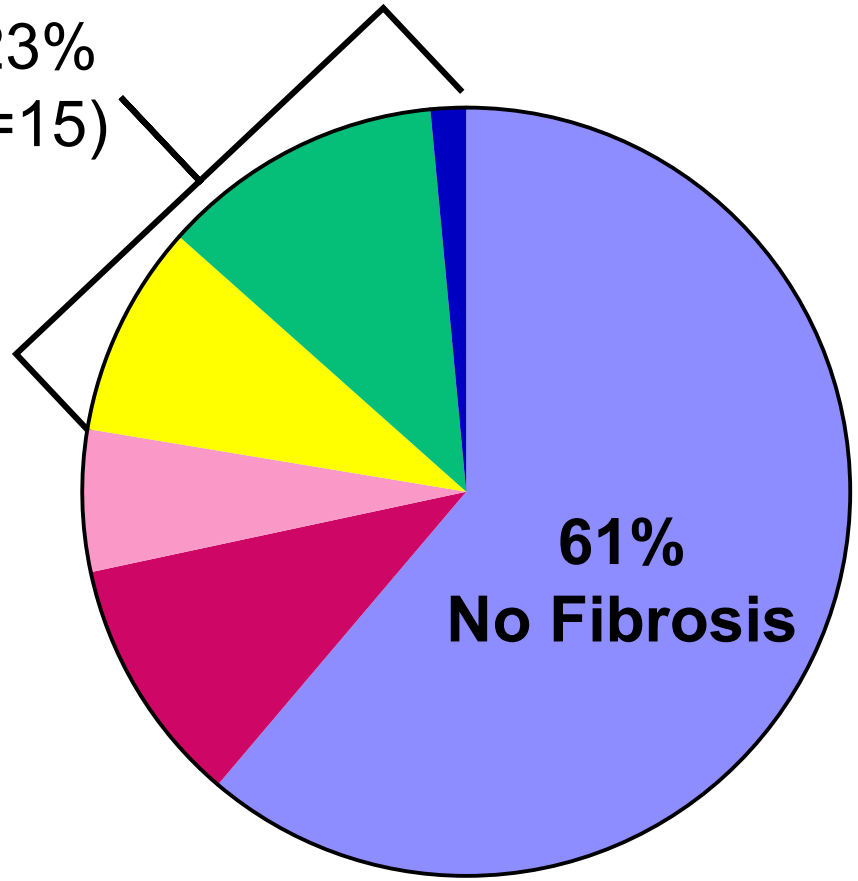
- 39% of individuals had any hepatic fibrosis
- 17% of individuals had very mild fibrosis
- 23% of individuals have significant fibrosis



67 samples from 66 people

Hepatic Fibrosis in UCDs

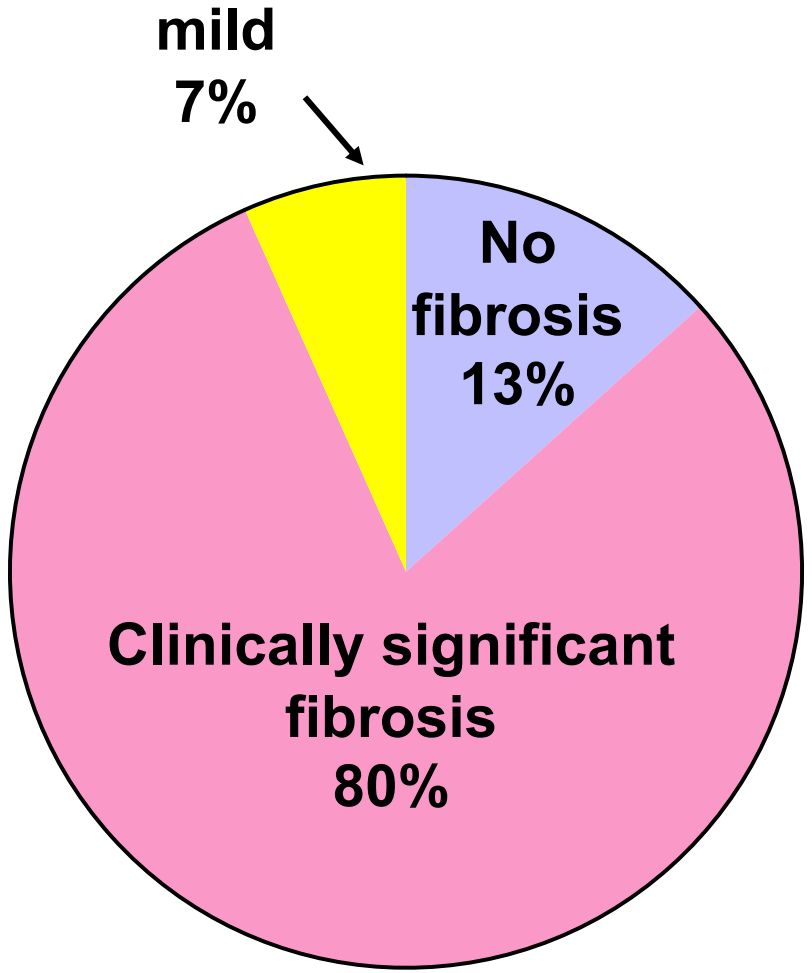
- 39% of individuals had any hepatic fibrosis
- 17% of individuals had very mild fibrosis
- ~23% of individuals have significant fibrosis
- 12 of the 15 individuals with significant fibrosis had ASLD



67 samples from 66 people

High Prevalence of Hepatic Fibrosis in ASLD (n=15)

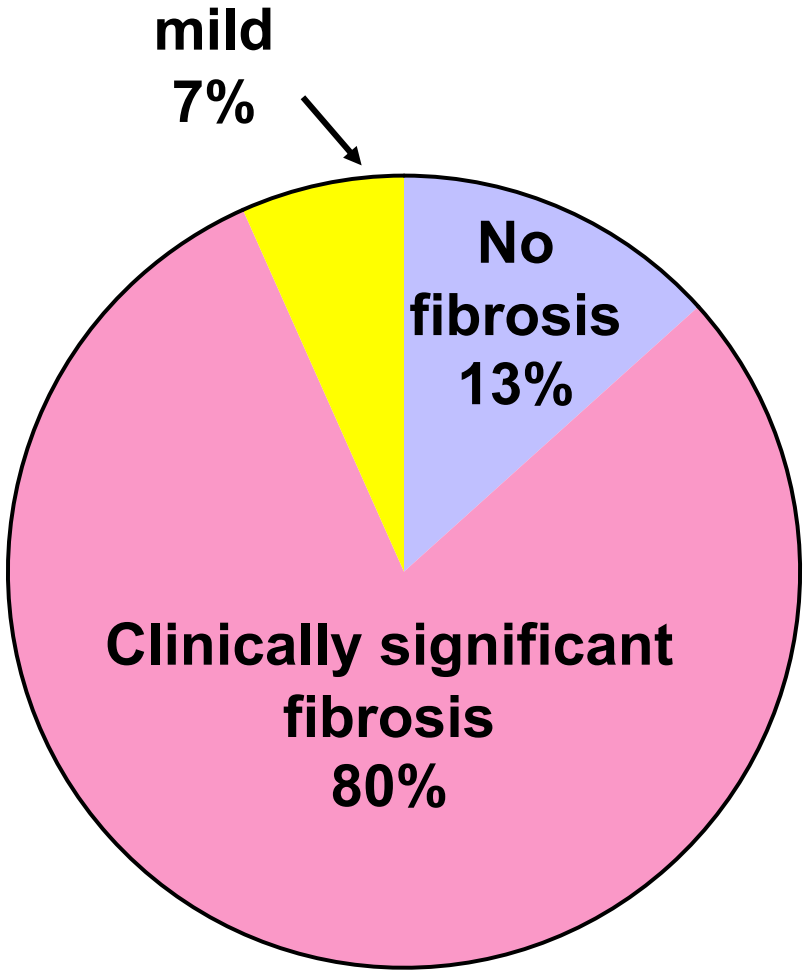
- 80% of all individuals (total n=15) with ASLD have clinically significant fibrosis (≥ F2)



N=15

High Prevalence of Hepatic Fibrosis in ASLD (n=15)

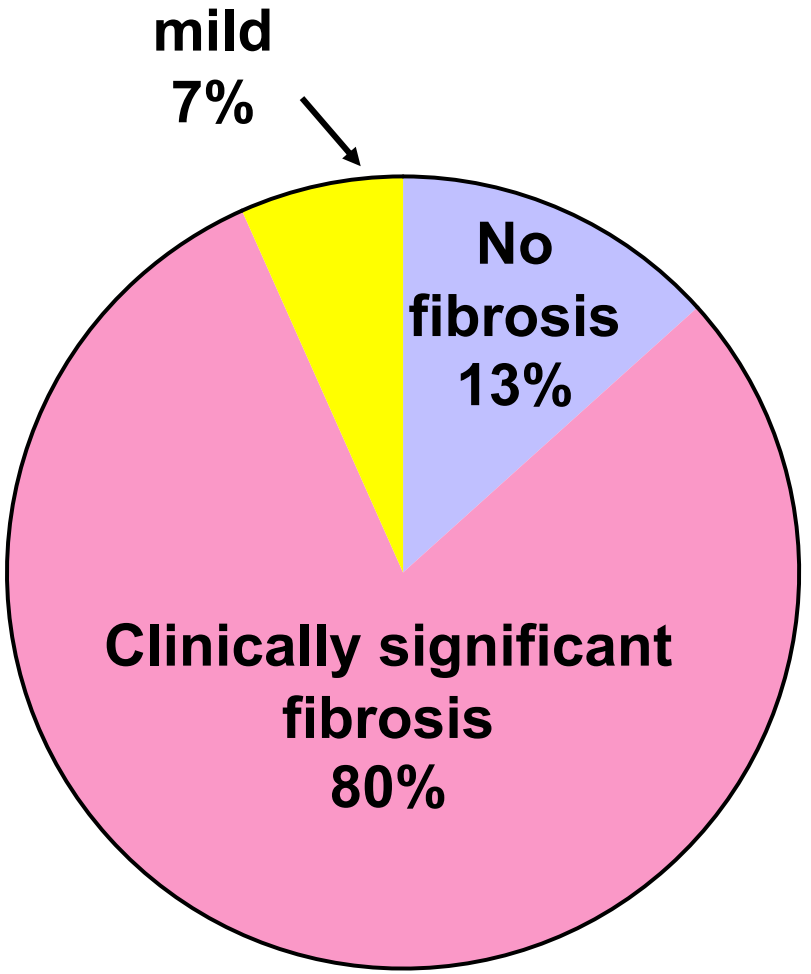
- 80% of all individuals (total n=15) with ASLD have clinically significant fibrosis (≥ F2)
- Clinical significant fibrosis was rare in other disorders



N=15

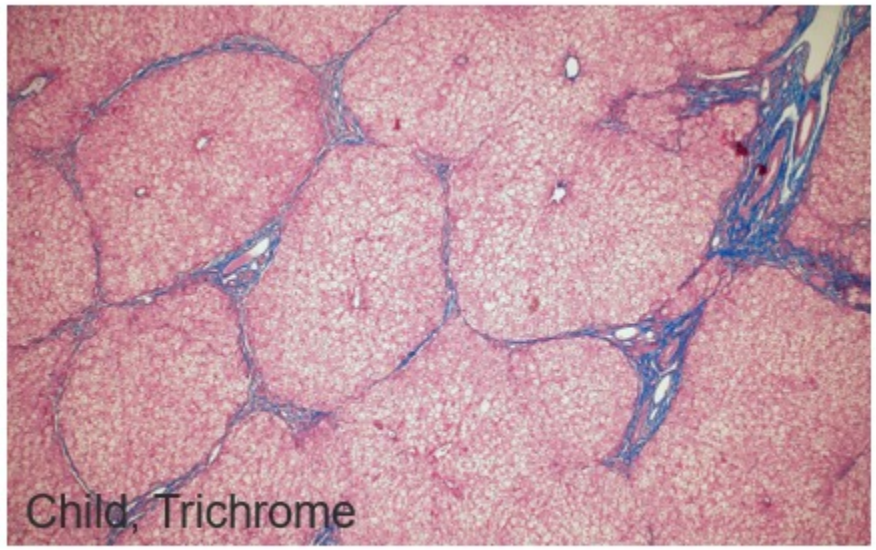
High Prevalence of Hepatic Fibrosis in ASLD (n=15)

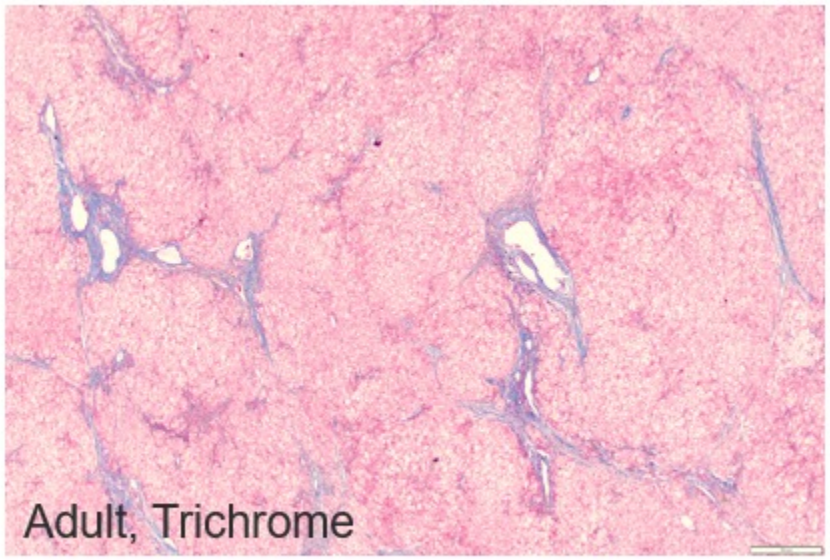
- 80% of all individuals (total n=15) with ASLD have clinically significant fibrosis (≥ F2)
- Clinical significant fibrosis was rare in other disorders
- Even the youngest patient (0.8 years) had F3 fibrosis!



N=15

Stiffening of the Liver or Fibrosis in Two Individuals with ASLD





What Did We Learn?

Patients with ASL deficiency appear to have a higher risk of elevated liver enzymes and hardening of the liver based on:

- *Liver enzyme elevation (bloodwork) – Easy to check*
- *Fibrosis in the liver (microscope) – Hard to check*

Does this mean other disorders are not associated with liver disease?

NO!

- Some individuals with other UCDs had evidence of liver disease in our studies

- We are not measuring every type of liver disease!

What Did We Learn?

Patients with ASL deficiency appear to have a higher risk of elevated liver enzymes and hardening of the liver based on:

- *Liver enzyme elevation (bloodwork) – Easy to check*
- *Fibrosis in the liver (microscope) – Hard to check*

Are there ways that we can measure liver fibrosis without taking a piece of liver and looking at it under the microscope?

Our next steps . . .

Testing New Tools for Investigating Liver Disease in UCDs

Our study of chronic liver disease in UCDs is exploring new tools for assessing the liver:

1.

Special Ultrasound with Elastography "Liver Stiffness"

2.

Bloodwork to test markers of liver fibrosis

Testing New Tools for Investigating Liver Disease in UCDs

This study is ongoing and hopefully we will have data from our work in coming years

1.

Special Ultrasound with Elastography "Liver Stiffness"

2.

Bloodwork to test markers of liver fibrosis

Summary

- All individuals with UCDs likely have some risk for liver disease
- For the two types of liver disease that we studied (elevated liver enzymes and stiffening of the liver), individuals with ASLD seem to have higher risk as compared to other UCDs
- We are exploring whether new tools that do not require taking a piece of liver tissue can be used to measure liver fibrosis in UCDs
- Individuals with UCDs may want to talk with their metabolic doctor about tips for keeping their liver as healthy as possible (e.g. immunizations, healthy body weight, etc)

Acknowledgements

Burrage Laboratory

- Saima Ali, N.P.
- Nathalie Aceves
- Haonan Zhouyao, Ph.D.
- Xiaohui Li
- Cher Sha
- Emily Chen

BCM/TCH

- Daniel Leung, M.D.
- Benjamin Shneider, M.D.
- Deb Schady, M.D.
- Shilpa Jain, M.D.
- John Goss, M.D.
- Shilpa Jain, M.D.
- Prakash Masand, M.D.

Stanford

- Gregory Enns, M.D.
- Florette Hazard, M.D.
- Aisha Nisar
- Thu Quan

CHOP

- Can Ficicioglu, M.D., Ph.D.
- Genevieve Neson
- Brittany Hoyle
- Mita Majumdar

Other participating sites:

- Seattle Children's
- Children's Hospital of Colorado
- Childrens' National

Urea Cycle Disorders Consortium

- Sandesh Nagamani, M.D.
- Andrea Gropman, M.D.
- Cindy LeMons
- Tresa Warner
- Shawn McCandless, M.D.
- Susan Berry, M.D.
- Anging Zhang, Ph.D.
- Jennifer Seminara
- Kia Bryan
- Consortium PIs and members

Funding Sources

NCATS
NICHD
NIDDK

NIH National Institutes of Health

Patients & Families

BURROUGHS WELLCOME FUND

O'Malley Foundation
Kettering Fund