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# Metabolic Diseases of The Liver: A Review



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## INTRODUCTION

Inherited metabolic liver diseases are a group of disorders caused by the pathologic accumulation of metals or misfolded proteins from disrupted normal metabolic pathways. The common diseases are hemochromatosis, Wilson disease (WD), alpha-1-antitrypsin deficiency (AAT) and glycogen storage diseases (GSD). New pathophysiologic understanding at the molecular level has changed clinical practice and research in recent years. This review article focuses on pathophysiology, clinical presentations, current management strategies and future directions.

## HEMOCHROMATOSIS

### Pathogenesis

Hemochromatosis is a well-defined syndrome characterized by toxic accumulation of iron in the parenchymal cells of the liver, heart and endocrine glands. In normal homeostasis, iron load will trigger an interaction between various signaling proteins including HFE, transferrin receptor 2 (TfR2) and hemojuvelin (HJV) leading to the expression of hepcidin, an

important hormone in iron homeostasis. Hepcidin binds to and causes the degradation of ferroportin (FPN) on the surface of duodenal enterocyte and macrophages.<sup>1</sup> When ferroportin is down regulated, iron will not be released from enterocytes and macrophages into the plasma thus keeping plasma iron levels low. Hepcidin also inhibits enterocyte iron absorption from the gut. If one or more components of this pathway fails, hepcidin will not be expressed in sufficient quantity and plasma iron will rise leading to hemochromatosis.<sup>2</sup> A defect to FPN will lead to hepcidin resistance and can result in hemochromatosis as well. In humans, hepcidin deficiency has been associated with HFE-associated, TfR2-associated and HJV associated hemochromatosis. Table 1.

The most well-known and most common form of hereditary hemochromatosis (HH) is HFE related hemochromatosis. This variant of the disease is associated with the homozygous polymorphic variant of the C282Y allele of the HFE gene. C282Y allele frequency is about 6%, and its prevalence of homozygosity among Caucasian is 1:2000 to 1:3000. A low penetrance of about 2% means disease manifestation is rare.

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**Table 1. Hemochromatosis Variants**

|                      |   |
|----------------------|---|
| HFE Hemochromatosis  | <ul style="list-style-type: none"> <li>• 40-50 year old Caucasian males.</li> <li>• Fatigue, dark skin, arthralgia</li> <li>• Elevated transferrin saturation (TS) and serum ferritin (SF)</li> </ul> |
| TfR2 Hemochromatosis | <ul style="list-style-type: none"> <li>• 30-40 year old male or female</li> <li>• Cardiomyopathy, endocrinopathy, liver disease</li> <li>• Elevated TS and SF</li> </ul>                              |
| HJV Hemochromatosis  | <ul style="list-style-type: none"> <li>• 15-20 year old male or female</li> <li>• Impotence/amenorrhea and/or cardiomyopathy</li> <li>• Elevated TS and SF</li> </ul>                                 |

Pietrangelo A. Hereditary hemochromatosis: Pathogenesis, diagnosis, and treatment. *Gastroenterology*. 2010;139(2):393-408.e2. doi:10.1053/j.gastro.2010.06.013.

## Clinical Presentation

The clinical presentation of hemochromatosis can vary widely depending on which organs are involved and the severity of iron overload. Symptoms range from simple laboratory abnormalities (elevated serum aminotransferase levels) to severe end organ damage (cirrhosis, liver fibrosis, hepatocellular carcinoma (HCC), restrictive cardiomyopathy, congestive heart failure, arrhythmia, gonadal dysfunction, glucose intolerance, diabetes). Environmental factors that could increase the risk of end organ damage includes excess alcohol consumption, pre-existing hepatic steatosis and coexisting viral hepatitis.<sup>3</sup> However, the classic presentation of diabetes, skin pigmentation and cirrhosis has become increasingly uncommon given more sensitive lab tests and increased awareness of the disease. Typical symptoms include malaise, fatigue, decreased libido, arthralgia and hepatomegaly. The majority of the cases of hemochromatosis are diagnosed after detecting elevated serum transferrin-iron saturation (TS) and serum ferritin (SF) levels. In general, males usually have worse manifestation of the disease. Their ferritin levels are usually higher (>200 ug/L for females and > 300 ug/L for male); excess tissue iron (>25 umol/g liver tissue) is more common in males.

## Diagnosis

The diagnosis of hemochromatosis should be considered in patients with the above non-specific symptoms and abnormal liver tests. Middle age men of Caucasian origin are especially susceptible. TS is almost always increased in affected patients. As the disease progresses, serum ferritin begins to rise indicating the accumulation of iron in tissue. If either test is abnormal (TS > 45% or ferritin above the upper limit of normal), then HFE

mutation analysis should be performed. Serum ferritin can also be elevated in other conditions such as infection, alcoholic liver disease, chronic hepatitis B and C and nonalcoholic fatty liver disease. If the HFE mutation analysis shows C282Y heterozygosity or non-C282Y mutation, one should exclude other liver/hematologic diseases and consider liver biopsy. Figure 1.

## Management

Once the diagnosis has been confirmed with genetic testing, the next step is to determine if liver biopsy is warranted. A ferritin level of > 1000 ug/L is associated with 20%-45% risk of having cirrhosis, therefore liver biopsy is recommended. Once the diagnosis has been confirmed, all first degree relatives should also be screened with gene testing.<sup>3</sup>

Despite the lack of randomized controlled trial of phlebotomy versus no phlebotomy, there is substantial evidence that early intervention will reduce morbidity and mortality of HH.<sup>4</sup> In a survey of 2500 patients, "86% of patients reported some or all symptom improvement with phlebotomy and 65% of patients agreed that benefits of treatment outweighed the difficulties".<sup>5</sup> Treatment should be initiated in: 1) symptomatic patients and 2) asymptomatic patients with homozygous C282Y and markers of iron overload or increased level of hepatic iron.<sup>6</sup> The removal of iron will relieve malaise, fatigue, skin pigmentation, abdominal pain, abnormal liver enzymes and even insulin requirements for diabetics.<sup>6</sup> However, certain features of the disease are irreversible such as arthropathy, hypogonadism and advanced cirrhosis. Patients with cirrhosis should be screened for HCC.

Phlebotomy should be performed as follows: one unit (500cc) of blood should be removed weekly

or biweekly with hemoglobin and hematocrit (H/H) check prior to avoid H/H from falling > 20% of the starting value. Ferritin should be checked every 10 phlebotomy sessions with a goal level of 50-100 ug/L. Most patients require maintenance phlebotomy to stay at goal. The frequency of maintenance therapy varies among patients. Dietary adjustments are not necessary in the treatment of hemochromatosis.<sup>3,6</sup>

## WILSON DISEASE

### Pathogenesis

Wilson disease is an autosomal recessive disease in which copper homeostasis is disrupted, leading to end organ damage from copper accumulation in tissues. Copper plays an important role in many cellular processes and serves as a co-factor for many enzymes such as cytochrome c oxidase (mitochondrial oxidation) and dopamine beta – hydroxylase (catecholamine production).<sup>7</sup> In its free form, copper has high redox potential, and it can degrade cellular structures if left unescorted by its chaperone proteins.

Central to copper homeostasis is the ATP7B gene which codes for a copper-transporting P type ATPase. The ATP7B protein is expressed most abundantly in the liver cells and has been localized to the trans-Golgi network within a cell. The ATP7B protein functions to incorporate free copper to apoceruloplasmin to form a 6 copper binding structure known as ceruloplasmin. Ceruloplasmin carries up to 90% of copper in the plasma and also stores copper in peripheral tissues.<sup>8</sup> Mutations to the gene can change the protein structure and functions that will lead to toxic accumulation of copper in the liver and brain. Wilson disease may present with hepatic, neurologic or psychiatric manifestations.

### Clinical Presentation

Similar to hemochromatosis, Wilson disease's clinical course is highly variable. In general, there are two forms of the disease; the predominantly hepatic form and the predominantly neurologic form. The hepatic form onset is usually earlier than that of neurologic form by several years, but most patients eventually develop both.<sup>7</sup>

The predominantly hepatic form affects about 40% of patients, and symptoms can vary from asymptomatic elevated liver enzymes, chronic hepatitis to liver cirrhosis and liver failure. It is often associated with a coombs-negative hemolytic anemia, acute renal failure and coagulopathy.<sup>9</sup> Initial presentation could

be as subtle as transient episodes of jaundice due to hemolysis.

In the predominantly neurologic form, initial symptoms may be mild and nonspecific. Characteristics symptoms include asymmetric tremors that can involve the trunk and head. Dystonia is another common symptom which presents in 10 to 60% of patients and is characterized by the abnormal posture of various body segments (involuntary head rotation, shoulder elevation, forceful eye closure, etc.). Memory decline, change in hand writing and lack of coordination have also been documented.<sup>7,9</sup>

Up to 10% patients exhibit non-specific psychiatric symptoms including attention deficit, depression, mood swings and even psychosis. Fortunately these symptoms may resolve with adequate therapy.<sup>7</sup>

### Diagnosis

The diagnosis of Wilson disease is challenging given the non-specific symptoms and variable clinical course. Clinicians should suspect Wilson disease in patients with liver abnormalities with or without typical neurologic symptoms. See Figure 2 for diagnostic algorithm. A liver ultrasound is needed to assess for signs of cirrhosis.<sup>7</sup>

### Management

All patients require lifelong drug therapy with liver transplant being the curative treatment in specific patient populations. Available treatments include chelators such as trientine and D-penicillamine or copper absorption inhibitors such as zinc salt.

D-penicillamine acts as copper chelating moiety. It also promotes urinary excretion of copper and induces production of metallothionein, an endogenous copper chelator. Trientine is another chelator that works by forming a stable complex with copper and promotes its urinary excretion. Zinc salt inhibits intestinal copper absorption by stimulating an endogenous copper chelator called metallothioneine.

Initial treatment focuses on having a negative copper balance with either of the chelators mentioned above. Treatment for this initial phase could last up to 6-12 months while aiming for a 24 hour urinary copper level of 800-1000 ug per day.<sup>10</sup> The maintenance phase of therapy is done with either low dose chelators (compared to initial treatment) or zinc salts with the aim of 24 hour urinary copper secretion being approximately

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200-500 ug per day. First degree relatives of any new patient must also be screened for Wilson disease.<sup>10</sup> Zinc is also recommended in the presymptomatic stage of Wilson disease given its favorable side effect profile.

Liver transplantation is the only curative treatment and it should be considered in patients with fulminant hepatic failure or end-stage cirrhosis. The effect of a low copper diet remains unknown. Gene therapy and stem cell research showed some early promise in animal studies but needs further study.<sup>7,9</sup>

## ALPHA 1 ANTITRYPSIN DEFICIENCY

### Pathogenesis

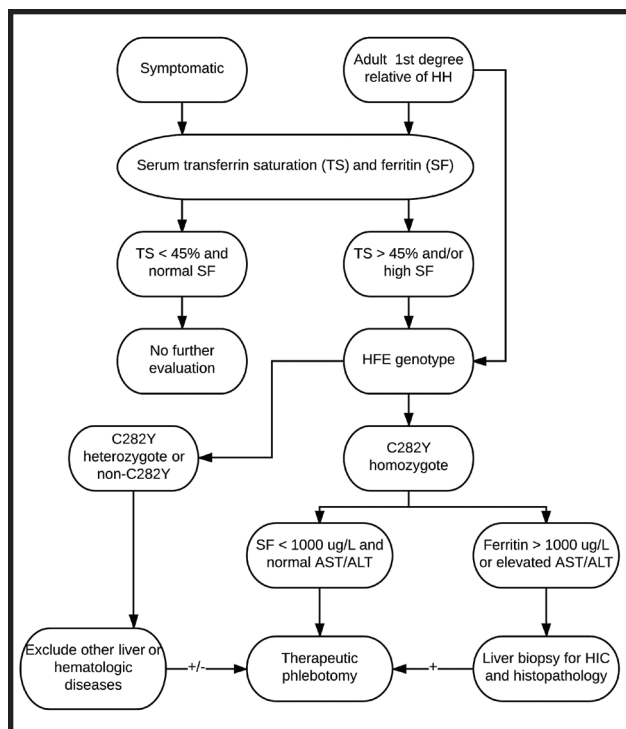
Alpha-1-antitrypsin (AAT) is a glycoprotein synthesized in liver cells and other tissues. It inhibits a wide range of proteases including pancreatic trypsin, cathepsin G and neutrophil elastase, which plays an important role in host defense.<sup>11</sup>

AAT deficiency is an autosomal co-dominant condition. AAT is encoded by the SERPINA1 gene (also known as Pi for protease inhibitor). AAT can be deficient either qualitatively or quantitatively. There are many Pi mutations both heterozygous and homozygous, that can lead to low level, non-functional or complete absence of AAT. The terminology Pi MM (protease inhibitor, genotype MM, Pi MZ, Pi ZZ) is used. AAT deficiency primarily affects the lungs and liver by two different mechanisms: polymerizations in the liver and elastase over activity in the lungs.<sup>12</sup>

In the lungs, Z or null mutation results in ineffective and low level of AAT leading to elastase over activity which causes emphysema. In the liver, the Z variant causes conformational changes in the AAT protein leading to their polymerizations and subsequent accumulation in hepatocyte endoplasmic reticulum. This accumulation of misfolded protein is thought to lead to apoptosis and cirrhosis, though the exact mechanism remains unclear. The proposed pathophysiology has been supported in animal models where the over expression of Z allele is associated with cirrhosis.<sup>13</sup> Table 2.

### Clinical Presentation

In the lungs, the most common presentation of AAT deficiency is early onset emphysema usually in the 4th or 5th decades of life, notably in patients without a significant smoking history. Emphysema from AAT deficiency disproportionately affects the lung bases and is usually panacinar in pathology.<sup>12</sup>



**Figure 1. Hemochromatosis Management Algorithm**

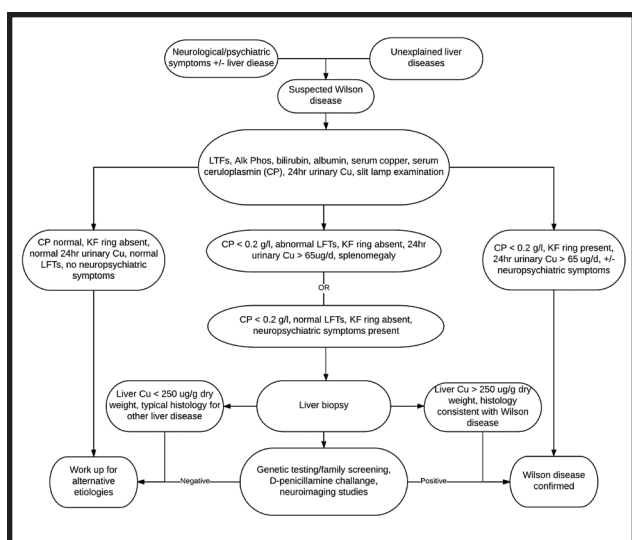
Pietrangelo A. Hereditary hemochromatosis: Pathogenesis, diagnosis, and treatment. *Gastroenterology*. 2010;139(2):393-408. e2. doi:10.1053/j.gastro.2010.06.013

In the liver, the disease follows a bimodal distribution of neonatal hepatitis and cholestatic jaundice in infants and chronic liver disease in adult. In infants, clinical symptoms include jaundice which can be easily mistaken for physiologic jaundice, bleeding diathesis, and change in urine color due to conjugated hyperbilirubinemia. Jaundice lasts for about 3 months on average. Other non-specific symptoms include slow weight gain, irritability and lethargy. Fortunately only 2-3% of PiZZ infants develop cirrhosis or fibrosis in childhood.<sup>14</sup> The jaundice eventually clears in the majority of these infants however some will continue to have abnormal liver enzymes, hepatomegaly or splenomegaly.<sup>15,16</sup>

In adults, AAT deficiency can present as asymptomatic abnormal liver function tests, cirrhosis (seen in up to one-third of adult PiZZ patients) or hepatocellular carcinoma.

### Diagnosis

The diagnosis of AAT deficiency can be confirmed by laboratory testing in three ways: AAT plasma or serum level, AAT phenotype, or AAT genotype. AAT



**Figure 2. Wilson Disease Management Algorithm**

Huster D. Wilson disease. *Best Pract Res Clin Gastroenterol.* 2010;24(5):531-539. doi:10.1016/j.bpg.2010.07.014.

deficiency testing should be performed in all patients with unexplained liver diseases.<sup>12,17</sup>

Serum AAT level can be measured accurately and is an acceptable initial test but has limitations. Heterozygous patients may have normal levels. AAT is also an acute phase reactant which can be elevated in inflammatory states. The gold standard of diagnostic testing is via phenotypic analysis, although there are drawbacks. Phenotyping is time consuming, not readily available and cannot distinguish between heterozygous and homozygous. Genotyping is generally more expensive but offers more information about the likelihood of clinical consequences.<sup>12</sup> Liver biopsy is not required for the diagnosis except in uncertain cases and when other conditions need to be ruled out. In older adult patients, once the diagnosis is confirmed, annual liver enzyme testing is recommended for monitoring. All first degree relatives should also be screened.<sup>17</sup>

## Management

AAT deficiency management depends on the severity and the organs involved. A major component of therapy consists of early detection and prevention of complications by reducing modifiable risk factors.

## Lung Diseases

In patients with COPD, management includes standard treatment with bronchodilators, inhaled corticosteroids, pneumococcal vaccine, influenza vaccine and smoking

cessation. Surgical treatment with lung volume reduction and transplant are available but clinical improvement remains inconsistent and controversial for the AAT deficient patients.<sup>12,17</sup>

Currently there are four different AAT augmentation therapies being investigated for the treatment of CODP: (1) intravenously human plasma derived augmentation, (2) augmentation by inhalation, (3) recombinant augmentation and (4) synthetic elastase inhibition.<sup>12</sup>

Injection of purified AAT protein has been shown to increase AAT level in the lungs of AAT deficient patients. However, only a modest reduction in FEV1 decline with weekly infusion was observed in a small, randomized trial<sup>18</sup>. Overall evidence for significant clinical improvement remains lacking.

## Liver Diseases

Besides the standard management for liver failure and associated complications, there is no specific therapy for AAT deficient patients. Effective preventive measures include: hepatitis A and B vaccination with avoidance of hepatotoxins such as alcohol. AAT augmentation therapy is not effective in AAT deficiency related liver diseases. To date, liver transplant remains the only curative treatment for AAT deficiency liver disease. AAT deficiency continues to be a leading indication for liver transplant in pediatric patients with 5 year survival rate up to 90%.<sup>19</sup> Liver transplant in adults occur less frequently but has a similar prognosis compared to liver transplant for other indications.<sup>12,19,20</sup>

The concept of chemical chaperones, where a synthetic compound would bind to the mis-folded AAT proteins to aid their secretion and avoid polymerization, have been explored. However the efforts were limited by the massive amount of drugs that would require for one to one binding. Currently, AAT liver gene silencing in animal models have been reported to be successful in suppressing liver damage and phase II trials have been announced.<sup>20</sup>

## Glycogen Storage Disease Pathophysiology

Glycogen storage disease (GSD) is a group of inherited heterogeneous disorders characterized by abnormal accumulation of glycogen in various tissues with an incidence of approximately 1 in 20,000 infants. Since glycogen usually serves as dynamic energy storage for muscle and liver, the disorders can be divided roughly into those that predominantly affecting the liver and

Table 2. Alpha 1 Anti-trypsin Genotype and Associated Risks

| Genotype    | Risk of COPD      | Risk of Liver Disease |
|-------------|-------------------|-----------------------|
| Pi ZZ       | Very Elevated     | Elevated              |
| Pi ZNull    | Very Elevated     | Unclear               |
| Pi MZ       | Possibly Elevated | Possibly Elevated     |
| Pi MNull    | Unclear           | None                  |
| Pi SZ       | Elevated          | Possibly Elevated     |
| Pi NullNull | Very Elevated     | None                  |

Silverman EK, Sandhaus RA. Alpha1-Antitrypsin Deficiency. *N Engl J Med.* 2009;360(26):2749-2757. doi:10.1056/NEJMcp0900449

those affecting muscle. These glycogen disorders are numbered in the order they were discovered and their severity with type I being the one discovered first and also the most severe variant. Based on prevalence, severity and liver involvement, this article will only discuss types I and III. The other two types, type IV and VI, also affect the liver but they are not as common and less severe.<sup>21,22</sup>

### GSD Type I

There are two subtypes of type I glycogen storage disease (GSD I), type Ia and Ib, both having autosomal recessive transmission.<sup>23</sup> Type I GSD typically presents early in infancy and was first discovered by von Gierke in 1929. The final step of gluconeogenesis and glycogen break down involves the translocation of glucose 6 phosphate (G6P) from the cytoplasm into the endoplasmic reticulum (ER) lumen where it is hydrolyzed into glucose and phosphate by glucose 6 phosphatase. GSD Ia is the true enzyme defect whereas GSD Ib is the transport defect.<sup>24</sup> Both processes lead to build up of G-6-P and hypoglycemia.

### GSD Type III

Similar to GSD I, GSD III is also an autosomal recessive condition with two subtypes, IIIa and IIIb, with an incidence of 1:100,000. The primary defect is a mutation in the AGL gene that leads to deficiency of the glycogen debranching enzyme (GDE). GDE participates in one of the last steps in converting glycogen to glucose-1-phosphate.

## Clinical Presentation and Diagnosis

### GSD Type I

Patients commonly present at 3-4 months of age with symptoms that include hepatomegaly, doll-like facies (fat deposit in the cheeks), growth failure and enlarged kidneys. Laboratory examination often reveals fasting lactic acidosis, hypertriglyceridemia, mild elevated LFTs and symptomatic hypoglycemia occurring 2-3 hours after meals.<sup>25</sup> Both types have abnormal platelet aggregation and there may be excessive bleeding. GSD Ib is moderately associated with inflammatory bowel disease and recurrent bacterial infections such as otitis media and pneumonia due to neutropenia and neutrophil dysfunction. The diagnosis is usually suspected clinically and confirmed with gene analysis. Liver biopsy is no longer required for diagnosis.<sup>24</sup> Long term complications include liver adenomas and renal disease. Progression to cirrhosis is rare though there has been case reports of liver cirrhosis in GSD Ib.<sup>26</sup>

### GSD Type III

The median age of first clinical symptoms is about 8 months. Early symptoms are very similar to GSD I; including hepatomegaly, hypoglycemia, failure to thrive and recurrent illness/infections. Kidneys are typically not enlarged. GSD IIIa affects both muscle and the liver while only the liver is affected in GSD IIIb. Unlike GSD I, progressive liver cirrhosis and failure may occur. Hepatic complication incidence of 11% has been reported in a study of 175 patients.<sup>27</sup> In the

(continued on page 34)

(continued from page 32)

same study, cardiac complications occurred in 58% of patients with ventricular hypertrophy being the most common. GSD IIIa patients often have minimal muscle weakness in childhood that can later progress to distal muscle wasting.<sup>21</sup> Diagnosis can be made via clinical symptoms and laboratory exam demonstrating deficient GDE in skin fibroblasts or lymphocytes.<sup>24</sup> Gene analysis can confirm the diagnosis and identify the subtype.

## Management

### GSD Type I

Management focuses on maintaining euglycemia through dietary therapy which includes a combination of continuous nasogastric tube feeding (CNTF), uncooked cornstarch (CS) and regular oral feeds high in complex carbohydrates evenly distributed over 24 hours. The management frequently requires a specialist dietician. Frequent blood glucose monitoring is crucial for well controlled GSD. Fructose and galactose are usually restricted since they cannot be converted into free sugar. CNTF should be started at the time of diagnosis with the aim of providing 8-10mg/kg/min of glucose in an infant and 5-7mg/kg/min in an older child. Traditionally, CS is ingested at bedtime and a trial of CS therapy is often introduced between 6mo and 1 year of age.<sup>28</sup> However consumption of cooked pasta, a more palatable alternative to CS and MCS, has been shown achieve adequate nighttime glucose control in older patients.<sup>29</sup> Common complications of the disease such as hyperlipidemia, high uric acid level, and microalbuminuria can be treated with HMG-CoA reductase inhibitor, allopurinol and ACE inhibitors respectively. In type Ib patients, granulocyte stimulating factor is added to treat neutropenia and neutrophil dysfunction. Liver and bone marrow transplantation can be considered in patients with extremely low fasting glucose tolerance and severe immune compromise.

### GSD Type III

Similar to GSD type I, the main stay of management is dietary. The regimen includes carbohydrates rich meals and nocturnal uncooked cornstarch. Unlike GSD type I, fructose and galactose do not need to be restricted. Some studies suggest that a high protein diet can help improve muscle strength and exercise tolerance besides and serve as substrate for gluconeogenesis.<sup>30</sup> In those studies, relative daily protein intake was increased from 18% to 25%.<sup>31</sup>

## CONCLUSION

Historically, metabolic diseases commonly presented with end organ damage, but with increased knowledge of these conditions and a high degree of suspicion patients can be diagnosed earlier. Various diagnostic criteria and screening methods, including sensitive blood tests and genetic testing, allow early treatment that can alter disease outcomes. As there may be a delay before these patients see a specialist, primary care physicians need to be familiar with the clinical presentations in order to send off the appropriate screening tests. The key is identifying abnormal liver tests in combination with non-hepatic disease presentations. These include endocrine and cardiac presentations with hereditary hemochromatosis, neuro-psychological with Wilson disease, and pulmonary with alpha-1-antitrypsin. We continue to make progress in our understanding at the molecular level in order to identify new potential targets of therapy. Finding curative treatments for many of these disorders remain challenging but gene therapy offers promise in glycogen storage disease, Wilson disease and alpha-1-antitrypsin.<sup>9,20,32</sup> ■

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