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Minireview

Adult liver disorders caused by inborn errors of metabolism: Review and update

Sirisak Chanprasert, Fernando Scaglia *

Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
Texas Children Hospital, Houston, TX, USA

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ABSTRACT

Inborn errors of metabolism (IEMs) are a group of genetic diseases that have protean clinical manifestations and can involve several organ systems. The age of onset is highly variable but IEMs afflict mostly the pediatric population. However, in the past decades, the advancement in management and new therapeutic approaches have led to the improvement in IEM patient care. As a result, many patients with IEMs are surviving into adulthood and developing their own set of complications. In addition, some IEMs will present in adulthood. It is important for internists to have the knowledge and be familiar with these conditions because it is predicted that more and more adult patients with IEMs will need continuity of care in the near future. The review will focus on Wilson disease, alpha-1 antitrypsin deficiency, citrin deficiency, and *HFE*-associated hemochromatosis which are typically found in the adult population. Clinical manifestations and pathophysiology, particularly those that relate to hepatic disease as well as diagnosis and management will be discussed in detail.

Contents

* Corresponding author at: Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA. Fax: +1 832 825 4294.
E-mail address: fscaglia@bcm.edu (F. Scaglia).

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1. Introduction

Inborn errors of metabolism (IEMs) are a group of genetic diseases characterized by abnormal processing of biochemical reactions, resulting in accumulation of toxic substances that could interfere with normal organ functions, and failure to synthesize essential compounds. IEMs are individually rare, but collectively numerous. The clinical presentations cover a broad spectrum and can involve almost any organ system. The age of onset is highly variable but IEMs afflict mostly the pediatric population. However, the increased awareness, the advances in management, and the new therapeutic armamentarium have resulted in improvement of patient care and increased survival. Altogether, individuals with IEMs have lived longer and many of them are in the period of transitioning from childhood to adulthood. Furthermore, IEMs may present their full blown clinical features in adulthood since the spectrum of clinical presentation in some of these disorders may be age-specific. The shift in the patient population with IEMs requires adult physicians to become knowledgeable about these conditions. In this review, the authors will focus on Wilson disease, alpha-1 antitrypsin deficiency, citrin deficiency, and *HFE*-associated hemochromatosis. These conditions are usually encountered in an adult-care setting and all of them have predominant hepatic phenotypes. Their clinical presentation, mechanisms of disease, and diagnostic and therapeutic approaches will be covered.

2. Wilson disease

Wilson disease is an autosomal recessive genetic disorder of copper metabolism [1]. It is characterized by an abnormal accumulation of inorganic copper in various tissues, most notably in the liver and the brain, especially in the basal ganglia [1]. The disease was first described in 1912 by Kinnier Wilson, and affects between 1 in 30,000 and 1 in 100,000 individuals. Clinical features are variable and depend on the extent and the severity of copper deposition. Typically, patients tend to develop hepatic disease at a younger age than the neuropsychiatric manifestations. Individuals with Wilson disease eventually succumb to complications of end stage liver disease or become debilitated from neurological problems, if they are left untreated. However, these events are now rare since, for the past decades, there has been significant progress in the recognition and treatment of this once universally fatal condition. The condition is caused by mutations in the *ATP7B* gene. This gene is expressed mainly in hepatocytes and encodes a protein that acts as a chaperone, facilitating intracellular copper transport and excretion [2]. The diagnosis of Wilson disease initially relies on biochemical testing to indicate excess copper accumulation, and is eventually confirmed by molecular genetic testing that is now widely available on a clinical basis.

2.1. Molecular genetics

The gene associated with Wilson disease was cloned and characterized in 1993 by three separate groups, and designated *ATP7B* [3,2,4]. It is located on 13q14.3, has 80 kB of genomic DNA and 22 exons, and is expressed mainly in the liver. This gene encodes the ATP7B protein which is a copper transporting P-type ATPase that functions as an intracellular copper transporter. More than 250 disease mutations have been reported. The vast majority of these mutations, approximately 58%–60%, are point mutations in the coding region critical for the protein function [5]. Small insertions and deletions are also common and occur in up to 27%, whereas splice site mutations or nonsense mutations are found only in 6%–7% [5]. Most of these mutations are isolated and unique among families. However, specific mutations appears to be more common in particular ethnic groups. The p.H1069Q is found in approximately 40% of Wilson disease patients of northern European descent [6], whereas the p.A778L mutation occurs in approximately 30% of Wilson disease patients of Asian descent. Data regarding genotype and phenotype correlation are conflicting. The study performed by Shah and colleagues has shown no correlation between homozygosity for p.H1069Q and clinical disease including age of onset, clinical manifestations, and biochemical features [6]. Whereas in another study, the earlier age of onset and predominant liver disease are associated with deletions or nonsense mutations causing a premature stop codon [7].

2.2. Clinical features

2.2.1. Hepatic disease

The clinical presentations of Wilson disease are varied affecting many organ systems. However, the overwhelming majority of cases display hepatic and neurologic symptoms. In general, patients with hepatic disease present between the first and second decades of life although patients as young as 3 years old or over 50 years old have also been reported [1]. The most common modes of presentations are acute self-limited hepatitis and chronic active hepatitis that are indistinguishable from other hepatic disorders although liver aminotransferases are generally much lower than in autoimmune or viral hepatitis [8]. Acute fulminant hepatic failure is less common but is observed in approximately 3% of all cases of acute liver failure [9]. Symptoms of acute liver failure include jaundice, coagulopathy, and hepatic encephalopathy. Cirrhosis can develop over time and may be clinically silent. Hepatocellular carcinoma (HCC) is rarely associated with Wilson disease, but may occur in the setting of cirrhosis and chronic inflammation [10,11].

In the early stage of Wilson disease, the accumulation of copper is associated with microsteatosis, macrosteatosis, and glycogenated nuclei [12]. These features will progress to periportal inflammation, mononuclear cell infiltration, lobular necrosis, and bridging fibrosis [13,14]. Cirrhosis almost invariably follows if left untreated. These histopathological features are similar to many forms of hepatitis including autoimmune and nonalcoholic steatohepatitis [12].

2.2.2. Other manifestations

Neurological and neuropsychiatric involvements are the presenting features in 40%–50% of patients with Wilson disease and these patients tend to be older than those who present with hepatic disease alone [15]. The clinical findings include akinetic–rigid syndrome similar to Parkinson disease, tremor, ataxia, dysarthria, dystonia, and spasticity