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Biochemical Diagnosis and Treatment of Cholestatic Syndrome in Children

Niyozova Durdona Shavkatovna

Bukhara State Medical Institute named after Abu Ali ibn Sino, Uzbekistan, Bukhara, st. A. Navoi

Abstract: Cholestatic liver disease causes significant morbidity and mortality in children. The diagnosis and management of these diseases can be complicated by an inability to detect early stages of fibrosis and a lack of adequate interventional therapy. There is no single gold standard test that accurately reflects the presence of liver disease, or that can be used to monitor fibrosis progression, particularly in conditions such as cystic fibrosis. This has lead to controversy over how suspected liver disease in children is detected and diagnosed. This review discusses the challenges in using commonly available methods to diagnose hepatic fibrosis and monitor disease progression in children with cholestatic liver disease. In addition, the review examines the mechanisms hypothesised to be involved in the development of hepatic fibrogenesis in paediatric cholestatic liver injury which may ultimately aid in identifying new modalities to assist in both disease detection and therapeutic intervention.

Keywords: Cystic fibrosis, Biliary atresia, Liver biopsy, Ultrasound, Hepatic fibrosis, Cirrhosis.

Introduction

Cholestatic liver disease is a significant cause of morbidity and mortality in infants and children. The inability to detect early stages of fibrosis and to monitor progressive hepatic injury hampers both the diagnosis and management of these diseases. Recent studies aimed at understanding the cellular and molecular basis of hepatic fibrogenesis in adult and paediatric liver disease have the potential to improve diagnostic capability and may lead to improved therapeutic intervention. This review details the difficulties associated with the use of commonly available methods to detect liver injury, diagnose hepatic fibrosis and monitor progression to cirrhosis in children with cholestatic liver disease, in particular in infants with biliary atresia and children with liver disease associated with cystic fibrosis, and examines the proposed mechanisms associated with the development of hepatic fibrogenesis in these conditions.

Common paediatric cholestatic liver diseases

The most common diagnosis in infants presenting with clinical or biochemical evidence of liver disease is benign Idiopathic Neonatal Hepatitis accounting for up to 40% of cases[1], with incidence rates reported between 1 in 4 800 and 1 in 9 000 live births[2]. Bilary Atresia is a liver disease of the newborn affecting the intra- and extra-hepatic bile ducts, with incidence rates reported to be between 1 in 8 000 to 1 in 21 000 live births (reviewed in[3]). Biliary atresia is the major indication for liver transplantation in children. The natural history of the disease is variable, with an unpredictable rate of progression and outcome. Diagnosis is complicated as infants have clinical symptoms which can be indistinguishable from Neonatal Hepatitis. A confirmed diagnosis of biliary atresia is made by operative cholangiogram, during which a liver biopsy is performed to assess the extent of hepatic fibrosis. If a diagnosis of biliary atresia is confirmed, then a portoenterostomy (Kasai procedure) is usually performed before 100 d of life. However, the successful establishment of bile drainage with this procedure is variable and up to 40% of children will develop significant fibrosis and progress to liver transplantation within the first few years of life[3-6]. The autosomal recessive disorder Alpha-1-antitrypsin deficiency affects 1 in 1 800 live births and is the most common genetic cause of liver disease in children. A mutation in the ATZ protein renders the molecule incapable of correct folding

resulting in the aggregation of misfolded protein in the endoplasmic reticulum, subsequently leading to liver damage[4]. However, not all patients with the ATZ mutation develop liver disease[5]. The natural history of the disease is variable suggesting that both host and genetic factors play an important part in the pathogenesis[4].

Diagnosis and monitoring CF liver disease

As the life expectancy of children and adults with CF has increased over the past decade, there has been a steady increase in the incidence of non-respiratory complications of CF such as liver disease[6]. The origin of the pathogenic lesion in CF is focal hepatic biliary fibrosis[7] which typically progresses slowly and unpredictably during childhood and adolescence. Clinical presentation with hepatomegaly and/or splenomegaly is usually around 10 years of age. Diagnosis of liver disease relies on a combination of clinical, biochemical, radiological and histological assessments; however, this is complicated by inconsistent use of definitions for what constitutes a diagnosis of liver disease[7-11].

It is estimated that up to 17% of children with CF will develop significant liver disease[8,9], with up to 10% developing cirrhosis, and prior to the advent of transplantation, end stage liver disease was the primary cause of death for 5% of patients with CF[10]. It has long been suspected that liver cirrhosis is also an important factor in premature death from other primary causes such as respiratory failure. However, the true prevalence of CF liver disease (CFLD) is unknown due to the poor sensitivity and specificity of available clinical tools used in diagnosis and monitoring disease progression. Based on radiological methods (ultrasound scanning), biochemical tests, clinical methods [presence or absence of hepato (± spleno) megaly] and histological assessment, the estimated prevalence of hepatic fibrosis and liver disease is proposed to be between 26%-45% in patients with CF[10-12]. However in studies undertaken at autopsy, the prevalence of significant liver disease is suggested to be as high as 10% in children, and 72% in adults[13]. Methods that are sensitive and specific enough to detect early evidence of cholestatic liver disease, and that can accurately monitor hepatic fibrosis progression are lacking[8]. This is particularly important in the setting of CF in which early detection of hepatic injury and fibrosis alerts the clinician to a more complicated future with further increased energy expenditure, impaired GI function and the need for more aggressive clinical management. It also allows for the timely commencement of ursodeoxycholic acid therapy which is proposed, though not demonstrated, to have a better efficacy earlier in the natural history of cholestatic liver diseases.

Diagnosis of liver disease using the presence of hepatomegaly and/or splenomegaly: Clinical liver disease is defined as an increase in volume and harder consistency of the liver, particularly of the right lobe with or without splenomegaly[14,15]. Studies using the presence of hepatomegaly, alone or in combination with splenomegaly, as indicative of liver disease report a prevalence rate of 4%-40%[7,12,16-18]. The use of hepato/splenomegaly as a method for the diagnosis of liver disease is inconsistent and controversial.

Biochemical markers of liver disease: In children with suspected CFLD, abnormalities in liver function tests (LFTs) are unreliable for the detection of significant liver disease and fibrosis[28-33], and hence are not useful to detect or measure the progression of fibrosis. Abnormal LFTs in CF are likely to be from more benign causes such as intercurrent infections, drug reactions and steatosis, and many children with advanced fibrosis have normal biochemistry. There is no consensus in the literature on a definition of “biochemically indicated liver disease” further complicating the assessment and use of biochemical markers of liver disease. The United States cystic fibrosis Foundation recommend that liver disease should be suspected if the child has any liver enzyme elevated by more than 1.5 times the upper limit of normal on two concurrent occasions and recommends more frequent testing of LFTs[8]. In comparison many clinical studies define biochemical liver disease as an elevation of LFTs for more than 2 years in patients who are > 4 years of age[10].

There is considerable evidence to suggest that children can have normal LFTs but underlying fibrogenesis[12,18,19]. When compared with fibrosis staged by liver biopsy, significant histological disease has been reported in up to 56% of patients with normal LFTs[15]. Abnormal LFTs are seen in 17%-80% of patients with CF, unrelated to the presence of neonatal cholestatsis[20], and in the

absence of overt histological involvement. Many children who present with biochemical liver disease do not go on to develop histological liver disease[10], but abnormal biochemical markers have been associated with future development of abnormal ultrasound or the presence of clinical hepato/splenomegaly in 75% of children[20]. In patients with CF, treatment with ursodeoxycholic acid leads to improvement of biochemical markers of liver disease (ALT/AST)[21], however there is little evidence that it changes the natural history of the disease, further supporting the idea that biochemical markers of liver disease do not accurately reflect the underlying pathogenesis.

Ultrasound imaging: Hepatic ultrasound scanning is a common clinical tool used to detect and diagnose liver fibrosis in children with cholestatic liver disease, specifically in children with suspected CFLD. Although widely used, ultrasound has poor sensitivity and specificity for detecting and staging fibrosis[22]. Between 18% and 35% of children with CF will display abnormalities detected by ultrasound scanning by age 6[20,23], irrespective of evidence of biochemical or histological liver disease. Abnormal ultrasound scores do not correlate with biochemical markers of liver disease or with the presence of hepatomegaly, with abnormal echogenicity frequently found in the absence of biochemical, or clinical indicators of liver disease[24].

A diagnosis of fibrosis based only on ultrasound may be erroneous because steatosis appears sonographically similar to focal fibrosis in the liver, both lesions being common in the setting of CFLD. A recent study examined the relationship between ultrasound scores and fibrosis staged by dual pass liver biopsy in children with suspected CFLD[22]. This study found that ultrasound scanning had poor sensitivity and specificity in diagnosing the absence of fibrosis but had some utility in confirming the presence of advanced liver fibrosis and cirrhosis. In children with indeterminate ultrasound scores, liver histology ranged from normal with no evidence of fibrosis to advanced stages of fibrosis including cirrhosis.

Because of poor sensitivity for early and moderate liver fibrosis, ultrasound is a poor predictor of the future development of serious liver complications. Children with normal hepatic ultrasound scores can still develop clinically significant liver disease and display evidence of fibrosis upon liver biopsy[22]. In most paediatric cholestatic liver diseases, ultrasound is a better diagnostic tool for detecting the presence of ascites, hepatic vein dilation, gallstones and common bile duct stones[8].

Ling and colleagues demonstrated that over a 4 year follow-up period, 92% of children with CF showed some evidence of liver abnormality determined by either biochemical tests, ultrasound or the presence of hepato/splenomegaly. Biochemical and ultrasound abnormalities were often intermittent suggesting a high rate of false positivity[33-39]. Biochemical testing, ultrasound scanning and the presence of hepatosplenomegaly are poor diagnostic indicators of sustained hepatic fibrosis and give a poor indication of the underlying fibrogenesis.

Conclusion

Detecting hepatic fibrosis and monitoring disease progression in paediatric cholestatic liver disease remains a challenge. The development of significant liver disease in children with CF is increasingly recognised but it is difficult to identify those likely to progress to cirrhosis and at risk of greater morbidity and mortality. Neonatal Hepatitis and biliary atresia are conditions with similar clinical presentation and thus difficult to differentially diagnose without an invasive operative cholangiogram. Commonly used clinical methods have poor sensitivity and poor specificity for detecting and staging fibrosis. While liver biopsy is the gold standard to detect fibrosis, it is not without limitations, particularly in focal diseases such as CFLD. New non-invasive serum marker panels or imaging technologies may provide a minimally invasive method to stage and monitor fibrosis progression. However, given the congestive nature of cholestatic liver diseases, transient elastography may not be a clinically useful alternative in children with suspected cholestasis. Significant advances have been made in understanding the biology of HSC and the interaction between HSC and cholangicytes, hepatocytes, Kupffer cells, inflammatory cells and progenitor cells. Understanding the cellular and molecular mechanisms associated with cholestasis-induced hepatocellular injury and fibrogenesis may provide novel markers to aid in better diagnosis of liver disease, detection of fibrosis and prediction of

outcome. The role of the endocrine growth factor intestinal FGF19 in regulating bile acid synthesis and the taurocholate-induced HSC chemokine MCP-1 in wound healing and fibrogenesis, have helped to identify previously unrecognised regulatory pathways of disease progression in paediatric cholestatic liver disease. Further investigation into the processes associated with wound healing will greatly assist in more accurate diagnosis and better management of infants and children with paediatric cholestatic liver disease, and ultimately aid in the development of more targeted therapeutic modalities.

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