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MINI REVIEW

Liver involvement in children with ciliopathies

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Summary Abnormalities in primary cilia lead to diseases called ciliopathies. Multiple organ involvement is the norm since primary cilia are present in most cells. When cholangiocyte cilia are abnormal, ductal plate malformation ensues leading to such conditions as congenital hepatic fibrosis, Caroli disease or syndrome, or other fibrocystic disease.

Introduction

Ciliopathies are a heteregeneous group of disorders due to cilia abnormalities. Ciliopathy without liver or kidney involvement is rare. In case of combined kidney and liver involvement, ciliopathies are also called hepatorenal fibrocystic disorders. The aim of this review is to briefly explain the pathophysiology of ciliopathies, the role of the ductal plate malformation in liver involvement and to offer a brief clinical overview focusing on congenital hepatic fibrosis (CHF), Caroli syndrome (CS), Caroli disease (CD) and other fibrocystic liver diseases.

Pathophysiology

Abnormalities of the primary cilia

There are two kinds of cilia: motile and immotile. In respiratory epithelium, fallopian tube epithelium, ependymal cells and sperm, cilia are motile and transport fluid along the epithelial surface through concerted movement. When motile cilia are non-functional, they cause primary ciliary dyskinesias with symptoms of bronchiectasis, situs inversus and infertility [1,2]. Most other cells possess primary cilia, which are non-motile. This sensory organelle extends outward from the cell surface and acts as a signal transducer between the extracellular and intracellular spaces [3]. Primary cilia abnormalities cause ciliopathies. Most polarized, eukaryotic cells are characterized by the presence of primary cilia, among which cholangiocytes, photoreceptors cells, and renal tubular epithelium are the cells most affected in human disease. It ensues that clinical features are variable and can involve several systems for any given mutation affecting a ciliary protein [1]. In addition to their role as signal transducers, primary cilia have multiple functions during development, tissue morphogenesis, and homeostasis [1]. Impaired ciliary function during embryogenesis explains the clinical and histological findings found in early onset human ciliopathies. Several recent reviews outline the multisystem involvement in ciliopathies. Here, we will focus on the ciliary defects underlying the forms presenting with liver disease in infancy and childhood [1,4,5].

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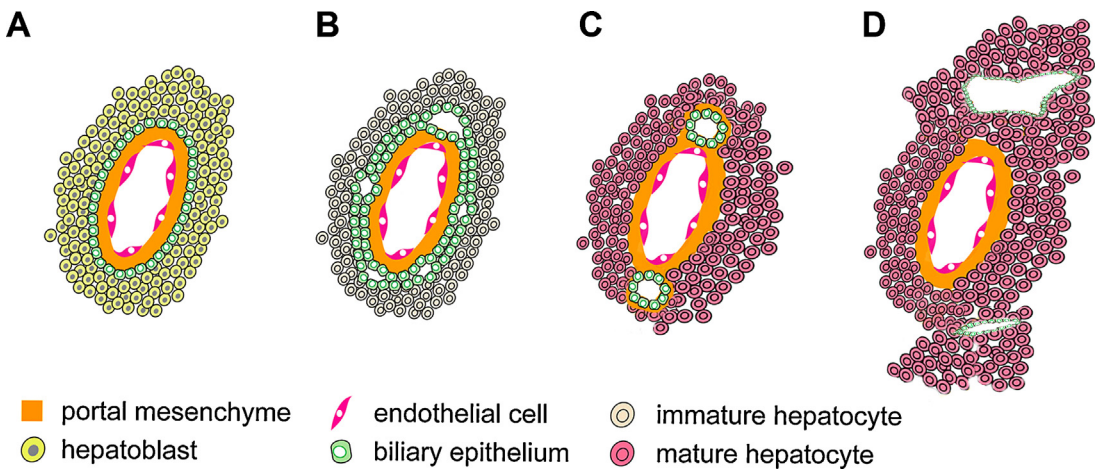

Figure 1 Biliary development and the ductal plate malformation. A. At 14 weeks of gestation, hepatoblasts in contact with portal vein mesenchyme adopt a biliary epithelial fate. B. At 17 weeks of gestation, biliary layer duplicates and focal dilatation within the layer leads to bile ducts formation. C. At birth, bile duct development is nearly completed, and the bilayer has involuted. Liver cells are either hepatocytes or hepatoblasts. D. Ductal plate malformation: abnormal ductal plate remodeling leads to saccular, biliary dilatations.
Modified from [14].

In cholangiocytes, the cilium is both a mecanoreceptor and an osmoreceptor. The cilium bends under the influence of biliary lumenal flow to which it responds by increasing intracellular calcium levels and decreasing cAMP. Polycystin 1 (PC1) and 2 (PC2) form a functional complex within the cilia: PC1 senses the bending and relays the information to PC2, which acts as a transmembrane calcium channel. In primary cilia defects, intracellular calcium is decreased and cAMP increased. Mutations in PC lead to impaired calcium signaling resulting in abnormal biliary development characterized by incomplete ductal plate remodeling. Histologically, this translates into cholangiocyte proliferation and abnormal extracellular matrix deposition [6—9]. These histological features are known as the ductal plate malformation.

Ductal plate malformation

The ductal plate appears between the 6th and 7th week of gestation. The ductal plate is a transient structure, which is normally only found in the embryo unless a developmental anomaly leads to its persistence post-natally. During normal embryogenesis, the ductal plate is a transient structure identified along the branches of the portal vein. The proximity of the portal vein branch triggers the differentiation and organization of neighboring hepatoblasts into primitive cholangiocytes and bile ducts. This is the accepted developmental paradigm for intrahepatic biliary development. The process of ductal plate remodeling begins during the 11th week of gestation and is illustrated in Fig. 1 [10,11]. During remodeling, a high rate of mesenchymal proliferation separates the bile ducts and liver parenchyma balanced by high apoptotic activity of hepatocytes and intrahepatic cholangiocytes. Impaired ciliary function due to a mutation in PC1 or PC2 leads to anomalous crosstalk between the extracellular and intracellular compartments [12]. This abnormal signaling leads to an imbalance between proliferation and apoptosis during ductal plate remodeling, whose abnormalities lead to the ''ductal plate malformation''. Persistence of ductal plate remnants post-natally results in the presence of abnormal bile ducts surrounded by an abundant dense, extracellular matrix [10—13]. When the ductal plate malformation affects the interlobular bile ducts, the disease is known as CHF. Larger bile ducts involvement is seen in Caroli disease and Caroli syndrome.

Ciliopathies

Over the last decade several genes associated with ciliopathies have been identified, and understanding their function has shed light on the pathophysiology of ciliopathies [1,5,15]. Generally, ciliopathies are multisystemic disorders, often sharing common features, such as polydactily, mental retardation, retinal defects, such as retinitis pigmentosum and polycystic kidneys. Table 1 summarizes the different types of ciliopathies. [4,5,16].

Liver involvement in ciliopathies

CHF and CD are the most common liver manifestations of ciliopathies in children. Here, we will describe CHF and Caroli disease and present other fibrocystic liver disorders in table form. In addition, we will elaborate on the group of ciliopathies known as hepatorenal fibrocystic disease for whom we will suggest a practical approach to diagnose liver involvement.

Congenital hepatic fibrosis and related diseases

Definition

CHF is characterized by the presence of abundant fibrous tissue between portal tracts and persistent ductal plate structure of interlobular ducts with normal lobular