Review article

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Ciliopathies in pediatric endocrinology

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Ciliopathies are a group of disorders that involve many organs and systems. In this review, we consider the role of the cilium in multiorgan pathology with a focus on endocrinological aspects. Identification of new genes and mutations is the major challenge in development of a tailored and appropriate therapy. It is expected that new mutations will be identified to characterize ciliopathies and promote new therapies.

Keywords: Ciliopathies, Cilia, Signaling

Highlights

- The term ciliopathy, popularised in the 21st century, describes human disorders caused by cilia dysfunction.
- There are different types of cilia that play a fundamental role in various organs and tissues .
- The study of ciliary function and the genes involved has made the classification of ciliopathies possible. However, further techniques are needed to analyse and describe new genes. This will make it possible to identify more diseases and design new drugs.

Introduction

Ciliopathies are complex diseases that are genetically inherited and involve numerous systems. More than 180 human genes have been identified, many of which have a role in the pathogenesis of complex diseases.[1,2] Ciliopathies are divided into mobile and primary (or immovable) diseases and are caused by cilium alterations and mutations in determinate genes.[3-5] Mobile ciliopathies (primary ciliary dyskinesia and Kartagener syndrome) are characterized by pulmonary alterations[6]; primary ciliopathies comprise organ-specific disorders or pleiotropic syndromes. These different phenotypes are the consequences of differences in structure and functions between primary and motile cilia.[7]

1. Cilia

Cilia are present on the surfaces of many cells and are necessary for vital functions of various organs. Cilia are generally classified as mobile (concentrated in the respiratory tract, middle ear, fallopian tubes, testicular vas deferens, and cerebral ventricles[8]), nonmobile, or primary and are the only organelle that acts as a sensory antenna and are located on the apical surface of nearly all cell types (cilia are not found on lymphocytes, granulocytes, or hepatocytes).[9]

Cilia are structurally composed of a microtubule backbone (the axoneme) surrounded by a matrix and are covered by the ciliary membrane, which is continuous with the plasma membrane. At the base of this structure, the basal body, which is composed of a specialized centriole, connects the cilium to the cell.[10] The axoneme of the primary cilium is composed of nine outer doublet microtubules (9+0 type); motile cilia have an extra inner pair of microtubules and an accessory structure involved in motility.[11]

Primary cilia are essential for tissue growth. They have numerous receptors, including sonic hedgehog, epidermal growth factor receptor, and platelet-derived growth factor receptor.[12]

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Therefore, migration, proliferation, differentiation, and apoptosis of cells are controlled by this pathway.[13,14]

The absence of primary cilia interferes with normal organ development and with connections between cells.[15-17] This altered transduction mechanism is the cause of ciliopathies.

2. Ciliopathies

The primary cilium is considered a cellular hub; its structural or functional defects involve important disorders, collectively named ciliopathies. Bardet-Biedl syndrome (BBS) was the first ciliopathy to be defined and is characterized by retinitis pigmentosa, intellectual disability, hypogonadism, and spastic paraplegia.

3. Clinical significance of primary ciliopathies

Primary cilia are present in all tissues and organs and comprise different phenotypes.

Clinical features in endocrinology

1. Joubert syndrome

Abnormalities in primary cilia have a complex role in the development of endocrine disorders. Joubert syndrome (JBTS) is a clinically heterogeneous group of disorders characterized by multiple congenital anomalies.[18]

Clinical hallmarks of JBTS include hypotonia, ataxia, facial dysmorphism, abnormal eye movement, irregular breathing patterns, and cognitive impairment; the molar tooth sign is pathognomonic. In addition to retinal dystrophy, hepatic fibrosis and polydactyly are also typical.[19] JBTS involves defects in the genes that codify proteins for primary cilia.[20]

Biallelic mutations in the KIF7 and KIAA0556 genes are rare but have been reported in a variable group of ciliopathies characterized by lethal hydrocephalus, polydactyly, craniofacial dysmorphism, and brain abnormalities.

Some patients have demonstrated a homozygous inactivating variant and a mild form of the JBTS phenotype including global development delays with variable hypotonia, transient tachypnea, variable cerebellar hypoplasia, and x-ray sign molar teeth.

Other patients exhibit panhypopituitarism with hypoplasia/aplasia of the anterior pituitary and an ectopic posterior pituitary. Other possible manifestations are described as hypotonia, developmental delay, hypoplastic pituitary, agenesis of the corpus callosum, oculomotor apraxia (but not coloboma), nystagmus, microphthalmia, and craniofacial dysmorphism.[21-23]

2. Bardet–Biedl syndrome

BBS is an autosomal recessive disease with an incidence of 0.7 cases per 100.000.[6] The clinical symptoms are early childhood obesity, retinal degeneration, polydactyly, hypogonadism, renal abnormalities, type 2 diabetes mellitus (T2DM), cardiovascular problems, and hypothyroidism. Hyperglycemia and insulin resistance have also been described as minor disorders.

The pathological mechanism of BBS is unknown. It is likely based on mutations in the genes that encode the proteins that form the BBSome and the BBS chaperone complex, which is responsible for proper functioning of cilia and for signaling pathways of body cells. The BBSome complex has an important role in molecular and vesicular transport.[4-8]

The diagnostic difficulties are related to the similarity of clinical features to those of other ciliopathies, such as Alström syndrome. Therefore, further studies will be important for understanding the causes of the diseases and are expected to allow earlier and more accurate diagnosis.[11]

3. Alström syndrome

A mutation in the *ALMS1* gene causes Alström syndrome (autosomal recessive pathology), a monogenic ciliopathy. This gene is located on the short arm of chromosome 2.[16,17] The symptoms of Alström syndrome present during infancy and childhood and include endocrine, cardiac, renal, and hepatic complications.[24]

ALMS1 is a protein of primary cilia; its absence results in failure of cilia formation.[20,25] In addition, the ALMS1 protein is related to energy metabolism homeostasis, cell differentiation, ciliary signaling pathways, cell cycle control, and intracellular trafficking.[17]

The main endocrine complications are related to growth, pubertal development, obesity, and T2DM.[26] Obesity and early onset T2DM are common complications. The ALMS1 protein is related to glucose transport through the actin cytoskeleton and assists in insulin-mediated glucose transporter type 4 transport.

Patients have high fasting and mixed-meal test (MMT) insulin resistance indices; higher MMT glucose, insulin, and C-peptide values; higher hemoglobin A1c, and a higher prevalence of T2DM.[27] Some studies have shown that patients affected by Alström syndrome have a growth hormone (GH) deficiency.[28]

Pubertal development is another endocrine complication. In males, hypogonadotropic hypogonadism and testicular fibrosis have been reported to halt or delay puberty.[29]

Currently, there are no specific treatments for Alström syndrome. Management focuses on preventing complications.[20,24] However, new mutations are being studied, which is expected to allow a more complete view of ciliopathies in endocrinology.[30] Identification of a genetic basis should help to highlight the molecular mechanisms of endocrinological alterations.[23,31]

Heterogeneity of ciliopathies

MC4R is a protein localized in the primary cilium that plays a key role in long-term regulation of energy homeostasis;

mutations in the MC4R protein are the most common cause of monogenic obesity. However, the precise molecular and cellular mechanisms that underlie the maintenance of energy balance within neurons that express MC4R are unknown.[32,33]

Several genetic studies have reported that cilia are crucial in neurons (which express MC4R) that control energy homeostasis. Cilia in the paraventricular nucleus of the hypothalamus (PVN) are essential for restricting food intake. Activation of the MC4R protein increased the activity of adenylyl cyclase (AC). Therefore, MC4R regulates the control of food intake and body weight via the cilia of the PVN neurons. Consequently, defects in MC4R ciliary localization lead to obesity in syndromic ciliopathies; inhibition of AC activity in the cilia of PVN neurons expressing MC4R thus causes hyperphagia and obesity.[34] Future studies will address how MC4R neurons integrate ciliary and synaptic communication.

In Alström syndrome, the main endocrine symptoms are related to growth, pubertal progression, and development of T2DM. The 2 main factors responsible for alterations in glucose metabolism in Alström syndrome are the insulin receptor and β-cell failure. A further endocrine complication is altered pubertal development. In males, hypogonadotropic hypogonadism and testicular fibrosis involve arrest or delay of puberty.[35] In females, however, insulin resistance results in low plasma gonadotropin concentrations, which may cause hirsutism, dysmenorrhea, amenorrhea, or precocious puberty. Limited studies have been conducted on male and female fertility in patients with ciliopathies.

New gene mutations are being investigated, and they should enable a more complete picture of ciliopathies and their implications in endocrinology. Abnormalities in inositol phosphate metabolism affect a wide range of systems and organs, such as congenital adrenal hyperplasia, which is due to 17-alpha-hydroxylase deficiency caused by a mutation in the *CYP17A1* gene.[36,37]

WDR proteins associated with ciliopathies

To date, mutations in at least 17 WDR proteins have been identified in ciliopathies. Members of the WDR protein family play important roles in many important cellular signaling pathways. Mutations in WDR proteins are associated with various human diseases, including neurological disorders, cancer, obesity, ciliopathies, and endocrine disorders.

WDRs are identified in the essential subunits of multi-protein complexes that participate in various signaling pathways that regulate DNA repair, cilia assembly and maintenance, and hormone biosynthesis.[38,39] Some patients with JBTS show GH or thyroid hormone deficiency. WDR proteins also have been associated with childhood obesity and T2DM. TBL1X is a member of the WDR protein family, and its associated mutation causes isolated congenital central hypothyroidism. However, the responsible molecular mechanisms are not well defined.[40]

Ciliopathies in the respiratory and digestive tracts

Ciliopathies affect not only the endocrine system, but also the respiratory and digestive systems. Primitive ciliary dyskinesia was the first ciliopathy to be described in 1976. It is a genetically inherited disorder characterized by abnormalities in the structure and function of the motile cilia. In this condition, the two most frequently mutated genes are DNAI1 and DNAH5, which code for components of the dynein arm complex in cilia.

Airway clearance and movement of secretions depend on coordinated beating of cilia.[41,42] Therefore, ciliary dysfunction causes chronic inflammation of the upper and lower airways.

Primary ciliary dysfunction (PCD) is characterized by neonatal respiratory distress, early onset and recurrent coughing throughout the year, nasal congestion, and situs inversus.[43] Kartagener syndrome occurs in approximately 50% of patients with PCD and is characterized by the triad of chronic sinusitis, bronchiectasis, and situs inversus.[44,45]

Due to the strong clinical heterogeneity, diagnosis is not immediate; genetic tests should be considered in the diagnostic process because 33 genes have been associated with primary ciliary dyskinesia. However, not all of them are included in the currently available genetic test panel. As genetic panels continue to develop, such tests will be considered valuable for diagnosis and research.

In the liver, primary cilia play an important role during embryogenesis in the formation of the ductal plate, which gives rise to the bile ducts.[46,47] Mutations in any component of this process may result in fibrosis of the portal tract and dilation of the bile ducts. The phenotype of the disease is heterogeneous and includes congenital liver fibrosis; Caroli disease, defined as dilated cystic ducts; and Caroli syndrome, which manifests as a combination of the 2 features: liver fibrosis and dilated cystic ducts. The 2 main consequences of liver fibrosis and dilated cystic ducts are portal hypertension and biliary stasis.[48]

Diagnosis

Beales and Kenny proposed a clinical diagnosis algorithm based on the clinical features of ciliopathies, which include renal and retinal involvement and/or polydactyly.[49] Today, there is still not a clear algorithm, but it is hoped that advances in genomic sequencing technologies may someday offer an accurate diagnostic method to optimize clinical management of these patients.

Therapy

The development of new therapeutic strategies is hindered by the multiplicity of ciliopathy syndromes, and there are no curative therapies. Treatment is based on the management of symptoms and varies according to clinical features.[50]

Many ciliopathies share symptoms in childhood or early adulthood. However, congenital ciliopathies are not able to

be treated. For example, primary microcephaly or cerebellar hypoplasia does not respond to any treatment. GH therapy has been administered to patients with Meier-Gorlin syndrome with a good response. The high genetic diversity of ciliopathies hinders effective treatment strategies.[51]

Conclusions

Knowledge about ciliopathies is limited. The use of exome sequencing will be fundamental in the discovery of new genes impacting ciliopathies. Each new study will improve our knowledge of the currently recognized ciliopathies.[52] However, much remains elusive. In the future, we hope to sequence new genes and to identify new ciliopathies to develop tailored therapies.[53]

Notes

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