The ciliopathies and their relationship with ophthalmology

Ciliopatías y su relación con la oftalmología

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The cells of highly evolved organisms exhibit a large variety of forms and shapes and their development is largely derived from the need to adapt to various environments or functions. One example is that of ciliated cells, characterized by having appendage-like structures on the surface similar to villi known as cilia (etimologically, from the Latin cilium: brow, or from the Greek κυλίς, kilis, eyelash). These are ubiquitous structures formed by the prolongation of the plasmatic membrane in a post-myotic cell. Cilia comprise a central organelle (or cilium) made up by almost 1000 types of proteins, surrounded by cytosol and the plasmatic membrane. Microtubules are arranged in the central area or axoneme and are perfectly structured. The cilia range in size between 10 and 15 μm. The cilia follow a pattern of movement similar to rowing to produce a propelling wave, and for this reason they are nearly always found in non-mobile cells. On the basis of microtubule configuration, there are four types of cilia: mobile with an axonemic configuration of “9+2”, nodal mobile “9+0”, sensory “9+2” and primary sensory “9+0”. From this latter type the modified cilia are derived, forming specialized structures such as photoreceptors. Additional microtubule configurations have been described, such as “9+1”, “9+3” and “9+4”. The functions of said cells are diverse, including as mentioned above the displacement of cells and structures, cleaning, filtering, locating and recognizing similar and different cells, as well as the regulation of the hydric balance. In addition, these cells participate in the transduction of a broad range of extracellular signals involved in cellular growth and polarity, differentiation, tissue maintenance and regeneration, including the important sonic hedgehog and Wnt pathways. Accordingly, ciliar receptors are able to receive a broad range of signals related to inputs of light, movements, osmolarity, temperature, hormonal and olfactory, among others. Mobile cilia are mainly found in the epithelial cells of the respiratory pathway, ependyma and reproductive organs, while the primary sensory cilia are found in a range of cell types including fibroblasts, neurons and osteocytes, among others.

Retinal cones and rods experience an extraordinary movement of proteins from the place of synthesis in the internal photoreceptor segments up to external segments to carry out phototransduction and the visual cycle. Specifically, the external segments have been related to a modification of primary sensory cilia and, as a result, variations in protein traffic dynamics in photoreceptor cilia can give rise to degenerative processes such as cone dystrophy, pigments retinitis or Leber’s congenital amaurosis.

The pathologies associated to cilia dysfunctions are called ciliopathies and respond to alterations in the genes involved in cilia formation and signaling. The phenotype of patients with ciliopathies is determined by 4 genetic mechanisms:

- Homozygote or double heterozygote mutations
- Multiple alleles
- Modifying genes


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• True oligogenicity (3 or more mutated alleles causing the phenotype are described, e.g., triallelic)

Of note among ciliopathies are some degenerative monogenic diseases, many of them with ophthalmological expression. These include some types of obesity, polycystic kidney disease, several types of cancer, the von Hippel–Lindau disease, various forms of nephropathies, some types of pigment retinitis (dominant, recessive and X-linked), some forms of Leber’s congenital amaurosis, ocu-lomotor apraxia and the following syndromes: Kartagener, Usher, Bardet–Biedl, Senior–Loken, Joubert, Meckel–Gruber, Jeune, Alström, COACH, Mainzer–Saldino and the orofaciocutaneous syndrome.3–5

In the case of autosomal dominant (as well as recessive) renal polycystic disease, the ciliopathy is derived from structural changes in polycystine and polycystein, two proteins which are crucial for the differentiation of renal tube cells.

In the autosomal dominant von Hippel–Lindau disease, the ciliary alteration originates in changes in the VHL protein and tubulin, predisposing to a large variety of benign and malign tumors in eyes, brain, pancreas and suprarenal glands.

Similarly, the Meckel–Gruber syndrome, which courses with cystic renal dysplasia, myelomeningoele, lung hypoplasia, microphthalmia and polydactyly originate in an alteration of MKS1 and meckelin proteins (coded by the TMEM67 gene).

The Kartagener syndrome is a primary ciliary dyskinesia which is genetically determined and characterized by ciliary movement alterations or absence which leads to reduced mucociliary clearing and expresses with chronic respiratory infections, male sterility due to sperm immobility and malformations (situs inversus).

The Bardet–Biedl syndrome, either recessive autosomic or triallele, is associated to cone and rod dystrophy, obesity, polydactyly, hypogonadism, renal dysfunction and intellectual disability. Some BBSome proteins participate in this syndrome. Protein NPHP6/CEP290 (290 kDa centrosome protein) is involved in this ciliopathy, but mutations in the NPHP6 are associated to a range of phenotypes including the Joubert syndrome, Leber’s congenital amaurosis or the Meckel–Gruber syndrome.

Some forms of pigment retinitis are also linked to connector cilium anomalies regulated by RP1 proteins (autosomic dominant) and RPGR (chromosome X-linked). The recognition of some retina dystrophies as ciliopathies and the identification of new genes with retinal expression associated to this kind of diseases are essential in order to design new forms of treatment.

The Joubert syndrome and its associated syndromes will be discussed in greater detail. This syndrome is characterized by the fact that patients exhibit cerebellar anomalies, intellectual disability and early retinal dystrophy or colobomas. It was first described by Marie Joubert in 1968 in 4 patients with partial or total agenesia of the cerebellar vermis, neonatal episodic apnea–hyperpnea syndrome, abnormal ocular movements, ataxia and mental retard. It must be taken into account that the prevalence of this rare disease is between 1/80,000 and 1/100,000 live births. As described by Joubert, the main neurological symptoms include hypotonia (typically in the neonatal period or infancy), delayed development with dyslalia and motor dysfunction, intellectual disability, ataxia and abnormal ocular movements which include ocu-lomotor apraxia and nistagmus in primary position. Some patients also exhibit neonatal breathing anomalies (apnea vs hyperpnea). Said characteristics can be associated to multior-gan involvement, mainly retinal dystrophy, nephronophthisis, liver fibrosis and polydactyly, with intra- and inter-familial variability. The syndrome is classified in 6 clinical subgroups: pure, with ocular defect, with renal defect, with oculorenal defect, with hepatic defect and with orofaciocutaneous defects. To date, 12 genes responsible for the Joubert syndrome have been identified. These genes code proteins of the primary cilia or their ultrastructure. The diagnosis should be suspected in children exhibiting the pathognomonic triad: hypotonia, abnormal ocular movements and delayed development (particularly breathing alterations). These children exhibiting neurological signs related to cerebellum involvement (ataxia, abnormal ocular movements, delayed development and intellectual disabil-ity), although alterations in other organs should also be assessed. Despite the large clinical variability, all patients have a common characteristic that expresses in evaluations by means of nuclear magnetic resonance, the molar tooth sign (MTS) of the mesencephallus, an image subsequent to hypoplasia/agenesis of the cerebellar vermis, narrow and elongated superior cerebellar peduncle (without decussation) and with deep inter-peduncle fossa in superior isthmus and bridges. Patients require multidisciplinary assessments and the differential diagnosis must be made with other ciliopathies, mainly with the Senior–Loken and Bardet–Biedl syndromes and with nephronophthisis, although other congenital defects of the spine-encephallus and cerebellum must be taken into account as well as several disorders that exhibit brain–eye–kidney expressions. Recently, 5 cases have been described with retinopathy, coloboma and Leber’s congenital amaurosis.6 The Joubert syndrome (and associated syndromes) is transmitted through the recessive autosomic form (with the exception of some recessive cases linked to chromosome X). The mutation analysis of the appropriate genes can be made although it is a difficult test accepted by only a few labs. Prenatal genetic diagnosis is essential, above all in couples at risk. Changes in the NPHP-JBTS–MKS have been identified in this disease. In addition, DNA sampling of patients affected by this syndrome (malformation and defec-tive development in various areas of the brain) has recently enabled scientists from the Principe Felipe Superior Research Centre (Valencia) to describe by means of electronic microscopic techniques and in cooperation with universities of several countries that mutations in the gene that produces the Tectonic 1 protein account for a form of said disease and therefore are a cause of human ciliopathies. Said protein is necessary for ciliogenesis and is involved in the adequate formation and signaling of cilia. In the clinical subtype with ocular defects, retinal dystrophy is expressed (with variable onset age and severity), including Leber’s congenital amaurosis. The most frequently associated gene is AH11 (approximately 25% of cases), and in the subtype with oculorenal defects (retinal dystrophy) about half exhibit mutations in the CEP290 gene. Patients affected by Joubert syndrome should be treated by multidisciplinary teams mainly comprised by pneumologists,
gastroenterologists, ophthalmologists, neurologists, psychologists, and rehabilitation experts. The prognosis will depend on the overall involvement and is subject to many variations between subgroups. In addition, it will depend mainly on the magnitude and severity of organ involvement.

Probably, the main reason for which ciliopathies are not better known in clinical practice is that most affected patients exhibit nonspecific prodromal symptoms and isolated or even negative symptoms, and a very small percentage exhibit the full range of symptoms, making early detection difficult. In many patients, a number of years elapse since prodromal onset without the pathology being detected even when in the last year they already exhibit clear symptoms. The period of time in which the disease is already in expression but undiagnosed is where action must be taken by means of biomedical research in order to discover molecular markers to resolve the situation. Ophthalmological assessment plays an essential role in diagnosing these patients. In addition, molecular medicine with its fledging “omic” disciplines associated to a massive analysis and computerized databases (genomics, proteinomics, transcriptomic, metabolomic), and specifically molecular ophthalmobiology, constitute an increasingly closer option to assist patients affected by ciliopathies.

The establishment of a connection between the new terminology in molecular medicine for ciliopathies and the genetic identification of cases is dependent on identifying the contribution made by each gene mutation to each clinical phenotype. Research on the ciliary protein networks and their functional interactions is crucial for designing new therapies applicable to different ciliopathies and not only to those focused on a specific mutation.

REFERENCES