Hypomyelination and congenital cataract: An overview of clinical, neuroimaging and genetic findings.

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Abstract

Hypomyelination and Congenital Cataract (HCC) is a rare autosomal recessive white matter disorder. It is characterized by the triad of bilateral congenital cataract, neurological impairment with peripheral neuropathy, and a typical hypomyelination pattern on brain magnetic resonance image. Most patients present with cataracts at birth or in the first month of life, followed by progressive neurologic impairment. In the presence of these clinical findings and characteristic brain magnetic resonance image features, HCC should be suspected, and mutation analysis of FAM126A should be performed. Genetic etiologies must be considered within the differential diagnosis in a patient with congenital cataracts and onset of progressive neurological impairment at the end of the first year of life.

Keywords: Hypomyelination, Congenital cataract, Hypomyelinating disorder, *FAM126A* gene.

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Introduction

Hypomyelination and Congenital Cataract (HCC) is a rare autosomal recessive white matter disorder within the hypomyelinating leukodystrophies group. It is characterized by the triad of bilateral congenital cataract, neurological impairment with peripheral neuropathy, and a typical hypomyelination pattern on brain Magnetic Resonance Imaging (MRI) [1,2].

Leukodystrophies are a large and heterogeneous group of uncommon genetic disorders, affecting primarily the white matter of the central nervous system.

Leukodystrophies are classically classified into broad categories, according to their main pathological finding: Hypomyelination, defined as lack or reduced myelin deposition; dysmyelination, defined as abnormal myelin development; demyelination, defined as loss or destruction of previously established myelin; and myelinolytic diseases [3,4]. A new classification was proposed by van der Knaap and Bugiani, based on pathological changes and pathogenetic mechanism, where leukodystrophies are categorized in five groups: Myelin disorders, Astrocytopathies, Leuko-axonopathies, Microgliopathies and Leuko-vasculopathies. In the Leuko-axonopathies category, white matter degeneration is secondary to an abnormal axo-glia interaction and includes different disorders, including HCC [4].

Clinically, it is difficult to differentiate between the various hypomyelinating disorders. Hypomyelination constitutes the largest single category among white matter disorders of unknown origin, representing a major diagnostic challenge [5,6]. Therefore, searching for distinctive key clinical findings, such as Congenital Cataract (CC), hypodontia, peripheral nerve involvement and extrapyramidal movement abnormalities, can facilitate the diagnosis of specific disease entities [6]. The association of CC and hypomyelination is typical of HCC.

CC are opacities in the lens of the eye detected at birth or at an early stage of childhood (within the first year of life) [7,8]. Its prevalence is variable; Sheeladevi, et al. reported 0.63 to 9.74 per 10,000 and Wu, et al. reported a global prevalence of 4.24 per 10,000 [7,9]. In more than 50% of CC cases, the cause is unknown [10]. Different etiologies have been described: Metabolic diseases, congenital infections, anterior-segment dysgenesis, preexisting posterior capsular defects, persistent fetal vasculature, or inherited CC. The latter can be classified as syndromic and non-syndromic. When systemic findings are present, syndromic CC should be suspected [8,11]. Therefore, it is crucial to expand the differential diagnosis and consider possible genetic etiologies in a patient with CC associated with other clinical findings, such as leukodystrophy or polyneuropathy [12].

Literature Review

Pathophysiology

HCC is a disorder caused by deficiency of a membrane protein called Hyccin. Its biological role is not completely understood, but it has been related to phosphatidylinositol 4-phosphate production in oligodendrocytes and myelination in both central and peripheral nervous system [13,14]. It has been hypothesized that Hyccin participates in neuron-to-glia signalling to initiate or maintain myelination process, as it is primarily expressed in neurons and its mutation leads to hypomyelination [1]. The specific role of Hyccin in HCC remains unclear, although it has been suggested that gap junction proteins may constitute a molecular link between myelination disorders and congenital cataract [13].

Hyccin is encoded by the *FAM126A* gene located on chromosome 7p21.3-p15.3 [13]. To date, 14 different pathogenic variants have been registered in Human Gene

Mutation Database (HGMD®). Missense/nonsense, splice site variants and small deletions are more frequently reported [15].

Clinical phenotype varies from a severe early-onset neurologic impairment to a relatively mild phenotype, even between patients carrying the same mutation. This variability is probably due to modifiers from the genetic background of each patient [6]. Peripheral neuropathy has been reported in all patients harboring splice-site mutations or deletions, whereas it is absent in patients carrying missense mutations. This suggests that missense mutations are likely to preserve a partial protein function without peripheral nervous system involvement, in contrast with splice-site mutations or deletions which cause the full HCC phenotype [2].

Clinical findings

HCC (OMIM #610532) is characterized by CC, slowly progressive neurological impairment, and hypomyelination of central and peripheral nervous systems. Patients usually have an unremarkable pregnancy and perinatal history. In the classical presentation, psychomotor development is normal or mildly delayed in the first year of life, achieving the ability to walk with support, followed by gradually neurological impairment, with loss of assisted gait and using a wheelchair for transfer, and mild to moderate intellectual disability. Two uncommon presentations have been described: an early-onset and a late-onset presentation. In the former, neurological impairment manifest on the newborn period, progressing with delayed psychomotor development, and early wheelchair dependency. In the latter, cataracts appear later in life, after the first year; and children tend to have a milder phenotype, acquiring independent gait, followed by sudden motor regression [6,16].

Most patients present with axial hypotonia; cerebellar signs like dysarthria, truncal ataxia, and intention tremor; pyramidal signs, such as brisk tendon reflexes and extensor plantar response; and peripheral nervous system involvement, evidenced by muscle weakness and wasting of the lower limbs. Only a few cases of seizures have been described [6,16].

Neurophysiological studies show different findings. In the electroencephalogram the findings include disorganization of background activity and multifocal epileptic discharges. In the Nerve Conduction (NC) study, motor NC velocity is decreased, compatible with a demyelinating polyneuropathy, in some cases with secondary axonal loss. The electromyography shows signs of denervation in the absence of spontaneous activity [12,16].

In the ophthalmology exam, most patients present with cataracts at birth or in the first month of life; however, some reports have described later cataract onset, after the first year of life. The vast majority have bilateral cataracts, but unilateral cataracts have been described [6,17]. Ugur and Tolun reported a case where a child developed bilateral cataract at age 9 years, and another child who had a persistent unilateral cataract at age 12 [17]. Additionally, nystagmus has been reported, but as a later feature [2,6]. Most children undergo cataract surgery in the first months of life [17].

Neuroimaging

Brain MRI demonstrates an hypomyelination pattern; in which supratentorial white matter, compared to the cortex, appears diffusely hyperintense in T2-weighted images and isointense to mild hypointense in T1-weighted images [18]. Rossi, et al. reported 2 children with spared subcortical white matter. Cortex and deep gray matter structures are preserved [18]. Areas of increased white matter water content have been described, with variable size, localized in frontal regions or extended to periventricular areas [18]. More uncommon features include thin corpus callosum, high T2 signal of corticoespinal tracts, hypoplastic pons, cerebellar atrophy and mildly increased cerebellar T2 signal intensity. Later on the disease course, patients present progressive white matter atrophy, demonstrated by diminishing white matter volume at older ages, atrophic gliotic white matter and enlargement of ventricular system and subarachnoid space [6,16,18].

Diagnosis

The diagnosis of HCC can be established in patients with suggestive clinical findings, characteristic brain MRI features and biallelic pathogenic variants in *FAM126A* gene identified by molecular genetic testing [19].

Patients with distinctive findings of HCC are likely to be diagnosed using single-gene testing. Sequence analysis of FAM126A should be the first diagnostic test, as it can detect small intragenic deletions/insertions and missense, nonsense, and splice site variants, which are the most frequently reported pathogenic variants [15]. If only one or no variant is detected by this method, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications [19]. Another option is to perform a multigene panel that includes *FAM126A* and other genes of interest, especially considering other hypomyelinating disorders that should be included in the differential diagnosis.

When the phenotype is indistinguishable from other inherited disorders with hypomyelination/leukodystrophy and/or cataracts, comprehensive genomic testing should be considered. Exome sequencing is the most commonly used test in this situation [19].

Considering the significant clinical variability, it is recommended to perform mutation analysis of FAM126A when there are characteristic MRI findings suggesting HCC, even in the absence of cataracts or with atypical clinical findings [6].

Differential diagnosis

The differential diagnosis with other hypomyelinating disorders should include Pelizaeus-Merzbacher disease, hypomyelinating leukodystrophy 2, TUBB4A-related leukodystrophy and POLR3-related leukodystrophy [19]. MRI changes are thought to be nonspecific [6]. However, it has been shown that subtle but consistent MRI abnormalities can help in differentiating hypomyelinating disorders [20].

In patients with HCC, hypomyelination is associated with areas of prominent T2 hyperintensity and T1 hypointensity in the periventricular and deep cerebral white matter, indicating focal lesions, with preservation of both cortical and deep gray matter structures, distinguishing HCC from other forms of hypomyelinating leukoencephalopathies [18,20]. Other hypomyelinating disorders, such as 4H syndrome and GM1 and GM2 gangliosidosis, may display T1 hypointensity of the deep cerebral white matter. However, what makes HCC distinct is the contrast with the more normal appearance of the subcortical white matter on T1-weighted images [20].

Conclusion

HCC should be suspected in children who present with CC and progress with delayed psychomotor development, polyneuropathy, or intellectual disability. In these cases, brain MRI should be performed. The presence of hypomyelination in association with increased periventricular white matter water content are very suggestive of HCC, even in the absence of cataracts or with atypical clinical findings. When HCC is suspected, sequence analysis of *FAM126A* gene should be performed as the first diagnostic approach.

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