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Review article

Childhood leukodystrophies: A literature review of updates on new definitions, classification, diagnostic approach and management

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Abstract

Childhood leukodystrophies are a growing category of neurological disorders in pediatric neurology practice. With the help of new advanced genetic studies such as whole exome sequencing (WES) and whole genome sequencing (WGS), the list of childhood heritable white matter disorders has been increased to more than one hundred disorders. During the last three decades, the basic concepts and definitions, classification, diagnostic approach and medical management of these disorders much have changed. Pattern recognition based on brain magnetic resonance imaging (MRI), has played an important role in this process. We reviewed the last Global Leukodystrophy Initiative (GLIA) expert opinions in definition, new classification, diagnostic approach and medical management including emerging treatments for pediatric leukodystrophies.

Keywords: Childhood leukodystrophy; Classification; Approach; Management

1. Introduction

There are many heritable and acquired disorders that involve the white matter of the central nervous system (CNS). In general, white matter disorders of the CNS are divided into two main categories: acquired myelin disorders and inherited myelin disorders [1]. Acquired melin disorders are indeed immune-mediated and

Abbreviations: ADLD, adult-onset autosomal dominant leukodystrophy; AGS, aicardi-goutieres syndrome; AMN, adrenomyeloneuropathy; AxD, alexander disease; CIC-2 related disease, chloride ion channel 2-related disease; CRMCC, cerebroretinal microangiopathy with calcification and cyst; CTX, cerebrotendinous xanthomatosis; GM1, GM1-gangliosidosis; GM2, GM2-gangliosidosis; H-ABC, hypomyelination with atrophy of basal ganglia and cerebellum; HBSL, hypomyelination with brainstem and spinal cord involvement and leg spasticity; HCC, hypomyelination with congenital cataract; HDSL, hereditary diffuse leukoencephalopathy with spheroids; HHHH (4H), hypomyelination, hypodontia and hypo gonadotropic hypogonadism; IEM, inborn error of metabolism; LBSL, leukoencephalopathy with brain stem and spinal cord involvement and lactic acidosis; L-2 HGA, L-2 hydroxy glutaric aciduria; LTBL, leukoencephalopathy with thalamus and brainstem involvement and high lactate; MLC, megalencephalic leukoencephalopathy with subcortical cyst; MLD, metachromatic leukodystrophy; MNGIE, mitochondrial neurogastrointestinal encephalopathy; MPS, mucopolysaccharidoses; MSD, multiple sulfatase deficiency; ODDD, oculodentodigital dysplasia; PBD, peroxisomal biogenesis disorders; PGBD, polyglucosan body disease; PMD, pelizaeus merzbacher disease; PMLD, pelizaeus merzbacher like disease; SLS, Sjogren–Larsen syndrome; VWM/CASH, vanishing white matter/childhood ataxia with central nervous system hypomyelination; X-ALD, X-linked adrenoleukodystrophy

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inflammatory diseases that cause destruction of normally developed myelin [2]. Poser named this category of myelin disorders "demyelinating or myelinoclastic diseases" in 1957 [3]. Disorders such as acute disseminated encephalomyelitis (ADEM), Schilder Disease, clinically isolated syndrome (CIS), Multiple Sclerosis (MS) and secondary CNS vasculitis belong to this category. On the other hand many metabolic and genetic disorders can affect the CNS myelin metabolism under titled inherited myelin disorders. Poser defined the term dysmyelinating white matter disorders for this category of myelin diseases [3]. Since the childhood leukodystrophies is an important and up growing category of inherited CNS white matter disorders; significant aspects of these disorders including new definition and classification, diagnostic tools and a brief review of new under study therapeutic plans are considered here. Acquired white matter disorders are not discussed in this article.

2. Method

The international leukodystrophy association known, as the Global Leukodystrophy Initiative (GLIA) is comprised of practitioners around the world that research heritable central white matter disorders specifically. We reviewed updates of childhood leukodystrophies mainly Based on GLIA expert opinions in addition of those articles that were focused on new classification of childhood leukodystrophies and their clinical manifestations, importance of magnetic resonance imaging (MRI) Pattern recognition and genetic studies in diagnostic approach of leukodystrophies, significance of biomarkers in diagnosis and clinical follow-up of leukodystrophy patients and finally we reviewed pharmacologic, medical and transplant-related methods of childhood leukodystrophy treatment in brief.

3. Definitions

In general, inherited central nervous system (CNS) white matter disorders can be divided into two main categories [4,5]:

1. *Classic leukodystrophies*: those disorders primarily affecting the CNS white matter with or without involvement of the peripheral nervous system myelin.
2. *Genetic leukoencephelopathies*: those in which CNS myelin is affected during a systemic metabolic disorder (Fig. 1).

Although there is an overlap between these two terms in that any classic leukodystrophy is a genetic leukoencephalopathy, this classification means that genetic defect in cell metabolism mainly affects the myelin sheath and cells that generate myelin in classic leukodystrophy, while in genetic leukoencephalopathy, genetic defects in cell metabolism are associated with systemic and neurologic manifestations and involve neuronal cells in addition to white matter structures [6].

The term "leukodystrophy" is defined as the degeneration of the brain's white matter (leuko means white and dystrophy means defective growth and nutrition). It was first introduced by Bielschowsky and Henneberg in 1928 [7].

Powers reported in 2004 that leukodystrophies are disorders that are characterized by these criteria: (a) a genetic basis; (b) a progressive condition; (c) a predominantly confluent involvement of the CNS white matter; and (d) a primary disease of myelin and myelin generating cells [7].

Based on the Global Leukodystrophy Initiative (GLIA) consortium consensus, the latest accepted definition of leukodystrophy is "heritable disorders affecting the white matter of the central nervous system with or without peripheral nervous system involvement" [8]. Although the main neuropathological sites in leukodystrophies are the myelin sheath and myelin generating cells, it is suspected that axonal damage is the starting point of destruction in some disorders [3,6,8]. In this consensus, two types of classic leukodystrophy have been defined:

A. Hypomyelinating leukodystrophies, in which magnetic resonance imaging (MRI) of the brain shows mild hyperintensity of white matter on the T2-weihted sequence (T2-W) sequence, but mild hypo-, iso-, or hyperintensity on the T1-weighted sequence (T1-W).
B. Demyelinating leukodystrophies, in which brain MRIs show prominent T2-W hyperintensity of white matter and hypointensity on the T1-W sequence [5,8].

Based on the expert opinion of the GLIA consortium, about 91 heritable disorders are known that affect CNS white matter, and their numbers are predicted to increase in the future. There are 30 disorders in the classic leukodystrophies group and about 61 disorders in the group of genetic leukoencephalopathies [8].

4. Mode of inheritance

The inheritance pattern depends on the type of white matter disorder and its related etiology. Although most heritable white matter diseases are inherited as an autosomal recessive pattern. Autosomal dominant, X-linked, and mitochondrial patterns have also been seen [6].

5. Incidence and prevalence

There have been few studies about the global incidence and prevalence of white matter disorders in