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Minireview

A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephelopathies

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ABSTRACT

Leukodystrophies (LD) and genetic leukoencephalopathies (gLE) are disorders that result in white matter abnormalities in the central nervous system (CNS). Magnetic resonance (MR) imaging (MRI) has dramatically improved and systematized the diagnosis of LDs and gLEs, and in combination with specific clinical features, such as Addison's disease in Adrenoleukodystrophy or hypodontia in Pol-III related or 4H leukodystrophy, can often resolve a case with a minimum of testing. The diagnostic odyssey for the majority LD and gLE patients, however, remains extensive – many patients will wait nearly a decade for a definitive diagnosis and at least half will remain unresolved. The combination of MRI, careful clinical evaluation and next generation genetic sequencing holds promise for both expediting the diagnostic process and dramatically reducing the number of unresolved cases. Here we present a workflow detailing the Global Leukodystrophy Initiative (GLIA) consensus recommendations for an approach to clinical diagnosis, including salient clinical features suggesting a specific diagnosis, neuroimaging features and molecular genetic testing. We also discuss recommendations on the use of broad-spectrum next-generation sequencing in instances of ambiguous MRI or clinical findings. We conclude with a proposal for systematic trials of genome-wide agnostic testing as a first line diagnostic in LDs and gLEs given the increasing number of genes associated with these disorders.

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Abbreviations: LD, Leukodystrophies; gLE, Genetic leukoencephalopathy; MR, Magnetic resonance; MRI, Magnetic resonance imaging; GLIA, Global Leukodystrophy Initiative; CNS, Central nervous system; SIMD, Society for Inherited Metabolic Disorders; VWM, Vanishing white matter disease; X-ALD, X-linked Adrenoleukodystrophy; AMN, Adrenomyeloneuropathy; 4H syndrome - Hypomyelination, hypodontia and hypogonadotropic hypogonadism syndrome; AGS, Aicardi-Goutières Syndrome; HCC, hypomyelination with congenital cataracts; CTX, Cerebrotendinous xanthomatosis; PMD, Pelizaeus Merzbacher disease; PMLD, Pelizaeus Merzbacher like-disease; SLS, Sjögren-Larsson syndrome; CRMCC, Cerebroretinal microangiopathy with calcifications and cysts; Pol III, Polymerase III; CMV, Congenital cytomegalovirus; Tay syndrome, Trichothiodystrophy; MLD, Metachromatic Leukodystrophy; FLAIR, Fluid-attenuated inversion-recovery; MRS, Magnetic resonance spectroscopy; CT, Computed tomography; NAA, N-acetyl aspartate; ADEM, Acute disseminated encephalomyelitis; NGS, Next-generation sequencing; WES, Whole exome sequencing; WGS, Whole genome sequencing; P, Pathogenic; LP, Likely pathogenic; CSF, Cerebrospinal fluid.

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1. Introduction and needs assessment

Leukodystrophies (LD) are genetic disorders affecting the white matter of the central nervous system (CNS) with or without peripheral nervous system involvement [1,2]. There are over thirty conditions typically categorized as primary LD and a number of other heritable conditions (genetic leukoencephalopathies- abbreviated here as gLE) that affect the white matter of the brain [2]. Primary LDs are those heritable conditions of the white matter that primarily effect glial cells, while gLE are disorders with either primary neuronal, vascular or systemic involvement, in which the white matter changes are felt to be secondary [2]. Depending on the etiology of the LD or gLE, inheritance can be by any known mechanism: autosomal recessive, (*de novo*) dominant, X-linked, mitochondrially-encoded, etc. These disorders include neonatal and adult presentations as well as the full spectrum through childhood and adolescence. Although individual features may vary, LDs and gLEs all share white matter abnormalities on imaging or pathology of the CNS, and most have motor deficits that often dominate the clinical picture, especially in younger individuals.

Due to challenges in diagnosis, the true prevalence and incidence of all LDs is not yet established. Estimates of their combined incidence range widely, from 1 in 50,000 to 1 in 7663 [3,4]. The early recognition of LDs can be challenging as they present insidiously, heterogeneously and are often not considered until neuroimaging shows abnormalities. Even then, they often remain undiagnosed or misdiagnosed, in part due to limited knowledge about their etiology. While advances in neuroimaging pattern recognition have improved diagnostic yield, curative treatments are currently limited and a definitive diagnosis is crucial for appropriate symptom management, prognostic and genetic counseling.

With the increasing number of LDs and gLEs a clinician must recognize, a simplified and standardized approach to facilitate identification of these diseases by child neurologists and geneticists is needed. The Global Leukodystrophy Initiative (GLIA) assessed clinicians' comfort in diagnosing LDs and gLEs and found that, despite the fact that these clinicians are members of the Society for Inherited Metabolic Disorders (SIMD) or Child Neurology Society, only a minority felt comfortable with the neuroimaging patterns and diagnostic approaches for LD and gLE patients (Table 1).

With the aim of providing clinicians with a simplified approach for diagnosing LDs and gLEs, here we (i) review the clinical presentations of various LDs and gLEs and highlight "red-flag" sine qua non neurologic symptoms along with extra-neurologic features, (ii) review established diagnostic algorithms for MRI pattern recognition, and (iii) present a decision tree workflow for molecular testing with specific attention to rapid diagnosis of treatable disorders and implementation of diagnostic genetic testing.

Table 1
Clinicians' comfort levels in the diagnosis of leukodystrophies.

Respondents by specialty	
Biochemical geneticists	43% (79)
Pediatric neurologists	34% (62)
Clinical geneticists	14% (26)
Other	9% (16)
Total	183
Comfort levels	
Very confident of providing a diagnosis [5 on a scale of 0–5]	16%
Moderately confident of providing a diagnosis [3 or 4 on a scale of 0–5]	36%
Very confident in providing a differential diagnosis of a leukodystrophies	15%
Moderately confident in providing a differential diagnosis of a leukodystrophies	36%
Access to resources	
Access to a regional leukodystrophy expert	76%
Cited a need for phone-based expert consult service	69%
Reported inadequate training in leukodystrophies	57%