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Case definition and classification of leukodystrophies and leukoencephalopathies

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ABSTRACT

Objective: An approved definition of the term leukodystrophy does not currently exist. The lack of a precise case definition hampers efforts to study the epidemiology and the relevance of genetic white matter disorders to public health.
Method: Thirteen experts at multiple institutions participated in iterative consensus building surveys to achieve definition and classification of disorders as leukodystrophies using a modified Delphi approach.
Results: A case definition for the leukodystrophies was achieved, and a total of 30 disorders were classified under this definition. In addition, a separate set of disorders with heritable white matter abnormalities but not meeting criteria for leukodystrophy, due to presumed primary neuronal involvement and prominent systemic manifestations, was classified as genetic leukoencephalopathies (gLE).
Interpretation: A case definition of leukodystrophies and classification of heritable white matter disorders will permit more detailed epidemiologic studies of these disorders.

Abbreviations: gLE, genetic leukoencephalopathy; CNS, central nervous system; MRI, magnetic resonance imaging; MSUD, Maple Syrup Urine Disease; ClC-2, Chloride Ion Channel 2; MLC, Megalencephalic Leukoencephalopathy with subcortical cysts; X-ALD, X-linked Adrenoleukodystrophy; NAA, N-acetyl-aspartate; GM1, GM1 gangliosidosis; GM2, GM2 gangliosidosis; NCL, neuronal ceroid lipofuscinosis; MCT8, monocarboxylate transporter 8; CRMCC, Cerebroretinal Microangiopathy with Calcifications and Cysts; CADASIL, Calcifications and Cysts and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; AGS, Aicardi Goutières syndrome; 4H syndrome, hypomyelination, hypodontia and hypogonadotropic hypogonadism syndrome; AxD, Alexander disease; H-ABC, hypomyelination with atrophy of the basal ganglia and cerebellum; IEM, inborn errors of metabolism

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1. Introduction

Leukodystrophies are a heterogeneous group of disorders with highly variable clinical manifestations and pathologic mechanisms. They are loosely grouped together, usually based on the initial findings of white matter abnormalities in the central nervous system (CNS), historically based on gross pathology, and now often based on neuroimaging. There has never been, however, a formal definition or classification for this group of disorders. The term leukodystrophy technically refers to disorders with wasting (dystrophy) of the brain's white matter (leuko) and is traditionally reserved for heritable disorders, however there is lack of consensus on how this term should be applied.

Further complicating the definition of leukodystrophies, the related but distinct term "leukoencephalopathy" exists in the literature. This term has characteristically been applied to disorders seen in the context of toxic, acquired vascular or infectious insults, as well as inherited disorders. In addition, disparate terms, such as hypomyelination, demyelination and dysmyelination are in use, and are a source of confusion.

Given today's modern neuroimaging, genetic and histopathologic techniques, we sought a more precise definition of these terms and classification of those disorders to which they apply. A case definition is an essential component of any epidemiologic study in a group of disorders. This may seem an esoteric goal when compared to the overwhelming need for improved understanding of disease mechanisms and potential therapeutic strategies in these devastating disorders. However, the number of funded studies in leukodystrophies is currently small, partially due to the perceived rarity of these disorders, and while recent studies [1] suggest that the incidence of leukodystrophies may be higher than previously thought, the lack of a precise classification scheme makes conclusive calculations difficult. There is therefore a pressing need for study into the distributions of leukodystrophies, in order to justify support for research into these disorders based on their relevance to public health.

Here, we report the results of an iterative consensus-building effort among a panel of leukodystrophy experts aimed at precisely defining the definition, descriptive terms, inclusion criteria and exclusion criteria that characterize leukodystrophies. In addition, this group comprehensively identified those disorders that meet this established definition, based on the current understanding of disease mechanisms. We also define the term "genetic leukoencephalopathy (gLE)," to describe disorders that are heritable and result in white matter abnormalities but do not necessarily meet strict criteria as a leukodystrophy. Of note, leukodystrophies are genetic leukoencephalopathies, but not all genetic leukoencephalopathies qualify as leukodystrophies. We also discuss specific applications of this definition and the classification as well as limitations of the proposed system.

2. Methods

2.1. Panel of experts and the modified Delphi method

Experts in inherited disorders of the white matter of the brain are located throughout the world. For this reason, this study utilized the modified Delphi method, a systematic internet based approach reaching a consensus regarding a specific topic using iterative surveys of expert opinion [2,3]. This approach permits consensus-building in circumstances where large face-to-face workgroups are not realistic.

Experts were selected based on their publication record and recognized expertise among their peers in heritable white matter disorders. Invitations were sent to fifteen experts in the leukodystrophy field, and thirteen elected to participate. Each panel member committed to full participation in all iterations of the survey process until the conclusion of the project.

2.2. Survey design and implementation

Surveys were generated using SurveyMonkey (www.SurveyMonkey.com, LLC; Palo Alto, California, USA), a web-based survey tool. Participants responded to surveys, which were summarized by a non-participating survey coordinator. Based on this summary, subsequent surveys were generated and summarized, each of which allowed panel members to revise previous responses and converge on a consensus.

In the initial survey, respondents were invited to provide a free text definition of the term "leukodystrophy." Answers to these questions were coded to quantify the frequency of keywords such as "inherited", "genetic", "myelin", "white matter", and "progressive". Based upon these answers, a preliminary definition was generated by the survey coordinator and respondents were asked to agree or disagree, and to provide commentary. Respondents were then asked to provide open-ended comment on possible inclusion and exclusion criteria for Leukodystrophies. Four rounds of surveys were required to reach consensus of the definition of Leukodystrophies and related terms. Once a consensus was reached, the final definition was reviewed in the format of this manuscript by all participants.

Additional surveys were used to review the classification of individual leukodystrophies and related disorders. A curated list of disorders was generated using PubMed searching for the terms "leukodystrophy" and "leukoencephalopathy," as well in established texts in these disorders [4,5]. Finally, the panel was provided with the opportunity to add disorders for review in the group. Complete consensus was reached on the first round of surveys for a small proportion of the disorders. A second survey was used to reach near consensus for a large proportion of disorders. For a smaller proportion, consensus was not reached under survey format, and email versions of text were used as a forum to discuss classification.

3. Results

3.1. Definition of leukodystrophy

The following definition was achieved by the consensus of all participating authors.

Leukodystrophies are heritable disorders affecting the white matter of the central nervous system with or without peripheral nervous system involvement. These disorders have in common glial cell or myelin sheath abnormalities. Where known, neuropathology is primarily characterized by the involvement of oligodendrocytes, astrocytes and other non-neuronal cell types, although in many disorders the mechanism of disease remains unknown, and in other cases is suspected to include significant axonal pathology.

In leukodystrophies, on magnetic resonance imaging (MRI), T_2 hyperintensity in the affected white matter is present and T_1 signal may be variable. Mildly hypo-, iso- or hyperintense T_1 signal relative to the cortex may be consistent with a hypomyelinating leukodystrophy. Demyelinating leukodystrophy leads to significantly hypointense T_1 signal.

Leukodystrophies do not include acquired CNS myelin disorders, such as multiple sclerosis and related acquired demyelinating processes, infectious and post-infectious white matter damage, toxic injuries and non-genetic vascular insults.

In addition, CNS diseases in which neuropathology shows primary involvement of neurons in cerebral cortex or other gray matter structures should not be characterized as leukodystrophies. Also, inborn errors of metabolism, in which the clinical manifestations of systemic illness, such as liver, muscle, or heart predominate, but in which brain MRI can detect significant abnormalities of white matter, should not be characterized as leukodystrophies.

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