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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.

Keywords

Leukodystrophy; Glia; Myelin; Genetic Leukoencephalopathy

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 make conclusive calculations difficult. There is therefore 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 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 amongst 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 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.

3.0 Results

3.1 Definition of leukodystrophy

The following definition was achieved by 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 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 grey 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.

3.2 Classification of disorders

Heritable disorders with white matter abnormalities (n= 91 disorders, Table 1 and Table 2) were reviewed to assess whether they met the criteria of this new definition. In a subset of disorders (n=10) complete consensus in favor of classification as leukodystrophies emerged immediately (Table 1). Other, often more recently described disorders, required thoughtful discussion to define features that met, or did not meet, criteria for inclusion or exclusion

(Table 1 for a complete list of disorders classified as leukodystrophy and % of respondents classifying them as leukodystrophy on early surveys). All disorders classified as leukodystrophy ultimately converged on complete consensus.

A second group of “genetic leukoencephalopathies” (Table 2) emerged in order to account for disorders with significant, if not primary, white matter abnormalities that did not meet criteria for inclusion as a leukodystrophy. Specific features that lead to this classification were strong evidence for primary neuronal involvement and prominent systemic manifestations which overshadowed the white matter abnormalities (Supplemental Table 2 for a description of these features).

3.3 Application of the definition in special circumstances

An important role of a definition is to provide the ability to prospectively categorize disorders. Thus, the authors illustrate the application of the definition to certain specific situations.

Novel leukodystrophies without neuropathologic data are able to be classified: In certain disorders, no neuropathologic data exists, and the workgroup was unable to establish CNS glial cell or myelin involvement on a histological level. However, predominant and persistent evidence of myelin deficits on neuroimaging without clear clinical signs of neuronal disease or evidence of systemic involvement, strongly suggest underlying glial cell or myelin abnormalities. As a result, the work group felt that these disorders could be characterized as leukodystrophies based on current knowledge. This characterization would be revised if future evidence demonstrated a lack of glial cell involvement in any of these disorders based on new molecular and neuropathologic data.

The definition does NOT discriminate based on which organelle is involved in the disease process: The definition specifically does not address subcellular involvement, in the form of specific organelles, as examples of both gLEs and specific leukodystrophies exist for most compartments of the cell (Table 3).

The definition DOES discriminate on whether the disease process is thought to be systemic versus originating within the glial cells. For example, there are a number of inborn errors of metabolism in which appropriate treatment of an underlying metabolic condition results in resolution of white matter abnormalities on neuroimaging. For example, in disorders such as Maple Syrup Urine Disease (MSUD), intra-myelin edema has been noted in multiple studies, but with the advent of treatment historically myelin abnormalities no longer play a large role in this condition. However, in addition, it is important to note that the abnormalities in myelin in MSUD relate to a metabolic condition that is systemic in origin and expression. This is of particular interest since several disorders classified by the group as leukodystrophies (Chloride Ion Channel 2 (ClC-2)-related disease, GlialCAM-related disease and Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)) also are primarily disorders of intra-myelin edema. Of note however, in each of these conditions, the defect occurs within a glial cell (astrocyte) versus the systemic defect seen in inborn errors of metabolism such as MSUD.

Thus, in many of the disorders classified as classic leukodystrophies but with a disturbance in small molecule and large molecule metabolism, it is important to note that there is a defect in intracellular processes within glial cells (transport of fatty acids into peroxisomes for X-linked Adrenoleukodystrophy (X-ALD), N-acetyl-aspartate (NAA) metabolism in Canavan disease, peroxisomal biogenesis disorders, and sialic acid storage disorders). Disorders resulting in substances toxic to the mammalian brain, but generated in a systemic fashion and then affecting the brain, such as L-2-hydroxyglutaric aciduria and many other inborn errors of metabolism, were not considered leukodystrophies.

The definition DOES discriminate based on which cell type is involved or thought to be involved primarily in the disorder. For example, primary gray matter or neuronal disorders, even with additional white matter abnormalities, are not classified as leukodystrophies. Several groups of disorders fall within this category. These include patients with malformations of cerebral development associated with congenital muscular dystrophy with severe secondary white matter abnormalities (such as in cases with *LAMA2* mutations). These also include progressive neurodegenerative disorders such as infantile variants of GM1 gangliosidosis (GM1), GM2 gangliosidosis (GM2), and neuronal ceroid lipofucinosis (NCL), which can have prominent white matter abnormalities in the periventricular region, presumed to occur because of secondary defects in myelination due to early onset axonal dysfunction. Another example of a neuronal disorder is Sanfilippo disease in which, during the course of the disease, progressive multifocal abnormalities are seen whereas the initial neuroimaging is usually normal. These patients may present early in life to the neurologist or geneticist for evaluation of a potential leukodystrophy, however their predominant neuronal involvement suggests that they are best characterized as gLEs. Other inborn errors of metabolism were classified as gLEs due to their severe neuronal involvement. Additionally, other primary neuronal disorders may have early defects in myelination (often resulting in globally delayed myelination on neuroimaging [6, 7]).

Of note, within the latter group, a very limited number of disorders could not be classified with complete consensus. These include the serine synthesis defect caused by 3-phosphoglycerate dehydrogenase deficiency and monocarboxylate transporter 8 (MCT8) related disorder, for which there was one dissenter each from otherwise complete consensus. In 3-phosphoglycerate dehydrogenase deficiency, in which clinical features suggest neuronal disorders, with severe epilepsy, mental retardation and microcephaly, the majority of respondents classified it as a gLE. On MRI affected patients lack myelin deposition in early stages of the disease, which has been attributed based on the clinical features to a primary neuronal dysfunction and secondary deficit in myelination; however the dissenting opinion expressed that there was insufficient evidence to definitively classify this disorder. Similarly patients with mutations in *MCT8*, in which initial myelination is severely delayed on neuroimaging, but continues to improve over time, were classified by the majority as a gLE. Although from a radiologic perspective, the myelin deficit appears to improve or resolve, it is unknown how the transporter encoded by *MCT8* may affect cells within the brain and how ultimately this disorder may be best classified. Both of these disorders were classified as gLEs based on the majority opinion.

The definition excludes disorders with vasculopathy as a primary disorder, even if these are inherited and have significant white matter abnormalities. Leukoencephalopathy with defects in *COL4A1* and *COL4A2*, Cerebroretinal Microangiopathy with Calcifications and Cysts (CRMCC) and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) are genetic disorders in which components of the vessel wall are abnormal. On neuropathology and neuroimaging, these disorders have multifocal white matter abnormalities reminiscent of classical vasculopathies such as amyloid angiopathy and hypertensive leukoencephalopathy. These are not classified as leukodystrophies.

In contrast, Aicardi Goutières syndrome (AGS), in which a microangiopathy is also seen, the pattern is that of a diffuse white matter disease, with superimposed calcifications. For AGS (initial classification 91.7% in favor of leukodystrophies), respondents noted that although current understanding of cellular targets in this disease limits definitive classification, the significant white matter abnormalities on neuroimaging, role of astrocytic interferon expression in disease pathology [8, 9] and limited systemic signs in this disorder justified its inclusion as a leukodystrophy.

The authors note that the definition does not include exclusions or inclusions based on whether the disorder is progressive. Disorders categorized as both gLEs and leukodystrophies are now recognized to have limited progression. This includes the remitting variant of MLC caused by dominant *HEPACAM* mutations, characterized by major improvement, and very slowly progressive disorders such as 4H (hypomyelination, hypodontia and hypogonadotropic hypogonadism) syndrome and the adult manifestations of certain disorders such as Alexander Disease (AxD).

4. Discussion

We describe a systematic effort among a panel of thirteen experts currently working in the field of leukodystrophy to establish a comprehensive definition of leukodystrophies, and to classify disorders according to that definition. In addition, we also sought to characterize a class of gLEs, hereditary diseases of the central white matter with predominant systemic manifestations and/or predominant neuronal involvement that include leukodystrophies but also include disorders that do not meet the strict criteria for leukodystrophies. The results of this effort will facilitate the epidemiologic study of these disorders in the general population.

While broad consensus was reached across a wide array of disorders, our study was constrained by various limitations. While this definition is based on involved cell types, the authors recognize that mechanisms of disease, and even primary neuropathologic data, are often lacking in these disorders. Novel findings and better neuropathologic data will continue to permit refinement of disease classification.

Additionally, the role of axonal pathology and its effect on glial cells and symptom development in leukodystrophies is poorly understood. Thus, the authors recognize that it is possible that secondary, and perhaps even primary, axonal involvement could occur in leukodystrophies. An example of this is Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC), in which the group rapidly converged on complete consensus in

favor of classification as a leukodystrophy. However, molecular definition of this disorder coincided with this consensus building exercise, and it is possible that, ultimately, we will understand *TUBB4A* mutations to result in primary neuronal dysfunction and secondary myelin disturbances. This same complex pathophysiology, affecting different cell types at different ages or based on differences in mutation, may be true across multiple other disorders currently understood as leukodystrophies. This point will need to be further clarified as mechanistic knowledge of these disorders advances.

An additional limitation is related to the difficulty of categorizing certain individual patients. Certain leukodystrophies have a spectrum of disease which includes patients that would not normally be classified as having a leukodystrophy, for example: *PLP1* mutated patients presenting with hereditary spastic paraplegia; Alexander disease patients presenting with a brainstem predominant phenotype; or patients with adrenomyeloneuropathy. These patients do not meet the radiologic criteria inherent to the definition. We therefore underline that the definition is intended to permit disease classification for epidemiologic purpose and not the clinical classification of individuals as belonging to certain nosologic groups.

Thus, it is important to note that this classification is a consensus effort based on the clinical expertise and evidence available to the experts to date. Inevitably, this classification will need to evolve to accommodate emerging information and insight on the causes, pathophysiology and pathology of the leukodystrophies and genetic leukoencephalopathies. In addition, new disorders with white matter abnormalities will continue to be defined and the pathways involved in these conditions will continue to shape our understanding of the definition and classification of the leukodystrophies.

Although not all heritable disorders with white matter abnormalities on neuroimaging met criteria to be classified as leukodystrophies, this by no means minimizes the impact on health or the importance of these non-leukodystrophy disorders to heritable white matter disease or genetic leukoencephalopathy overall. On presentation to the child neurologist or geneticists, general gLEs may initially be indistinguishable from the leukodystrophies, In addition, nearly half of all patients whose neuroimaging studies indicate white matter disease and whose clinical manifestations suggest a genetic etiology do not receive a specific diagnosis [10]. Therefore, the overall burden of heritable disorders of the white matter can only be appreciated if leukodystrophies, other gLEs and unsolved heritable disorders of the white matter are considered.

There is limited epidemiologic data available on the impact of leukodystrophies on population health. In addition, gLEs, while similar in clinical burden to leukodystrophies, are often not considered in epidemiologic studies of white matter disease. The proposed definition and classification of disorders may help in assessing the burden of inherited white matter disorders overall. Awareness of the frequency of these disorders may raise awareness of the need for further research into this group of disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 lipofucinosis
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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If accepted, we propose the following highlights

- Leukodystrophies are a heterogeneous group of disorders with highly variable clinical manifestations and pathologic mechanisms
- The lack of a precise case definition for leukodystrophies hampers efforts to study the epidemiology and the relevance to public health
- A consensus definition was achieved, taking into consideration the specific involvement of the white matter of the central nervous system
- 30 distinct disorders were defined as leukodystrophies based on the proposed definition
- A class of genetic leukoencephalopathies was characterized that may or may not include leukodystrophies

Table 1

Disorders Characterized as Leukodystrophy

Name of disorder	% of respondents classifying as a leukodystrophy on first surveys
Pol-III related disorders (4H syndrome (hypomyelination, hypodontia and hypogonadotropic hypogonadism))	83.3%
18q minus syndrome	71.4%
X linked Adrenoleukodystrophy (X-ALD)*	100%
Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia (including hereditary diffuse leukoencephalopathy with spheroids, HDLS, and Pigmentary type of orthochromatic leukodystrophy with pigmented glia, POLD)	70%
Aicardi-Goutières Syndrome (AGS)	91.7%
Alexander Disease (AxD)	91.7%
Autosomal Dominant Leukodystrophy with Autonomic disease (ADLD)*	100%
Canavan disease*	100%
Cerebrotendinous Xanthomatosis (CTX)	72.7%
Chloride Ion Channel 2 (ClC-2) related leukoencephalopathy with intramyelinic oedema	63.6%
eIF2B related disorder (Vanishing White Matter Disease or Childhood ataxia with central nervous system hypomyelination (CACH))	91.7%
Fucosidosis	83.3%
Globoid cell Leukodystrophy (Krabbe)*	100%
Hypomyelination with atrophy of the basal ganglia and cerebellum (H-ABC)	91.7%
Hypomyelination with Brainstem and Spinal Cord involvement and Leg Spasticity (HBSL)*	100%
Hypomyelination with congenital cataract (HCC)	91.7%
Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL)	91.7%
Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)	81.8%
Megalencephalic Leukoencephalopathy with subcortical cysts (MLC)*	100%
Metachromatic Leukodystrophy (MLD) and its biochemical variants*	100%
Oculodentodigital dysplasia	71.4%
Pelizaeus Merzbacher disease (PMD) *	100%
Pelizaeus Merzbacher like-disease (PMLD)*	100%
Peroxisomal Biogenesis disorders (including Zelleweger, neonatal Adrenoleukodystrophy and Infantile Refsum)	70%
Polyglucosan Body Disease (PGBD)	72.7%
RNAse T2 deficient leukoencephalopathy	72.7%
Sialic acid storage disorders (Salla disease, Infantile Sialic Acid Storage Disease and Intermediate form)	83.3%
Single enzyme deficiencies of peroxisomal fatty acid beta oxidation (including only D-Bifunctional Protein Deficiency; Sterol Carrier Protein X (SCPx) deficiency; Peroxisomal acyl-CoA-Oxidase Deficiency)	75%
Sjögren-Larsson syndrome*	100%
SOX10-associated PCWH: peripheral demyelinating neuropathy, central dysmyelinating leukodystrophy, Waardenburg syndrome, and Hirschsprung disease	70%

Name of disorder	**% of respondents classifying as a leukodystrophy on first surveys**
Total	More than 30 distinct Leukodystrophies

WM= white matter.

Disorders marked with an * denote disorders that met 100% consensus for classification as a leukodystrophy after the first survey round.

Table 2

Disorders Characterized as Genetic leukoencephalopathies (gLEs)

Inborn Errors of Metabolism	Vascular disorders
• 3-Phosphoglycerate dehydrogenase deficiency • Adenylosuccinate lyase deficiency • Aspartylglucosaminuria • Cerebral Folate Transport Deficiency (*FOLR1*) • D-2-Hydroxyglutaric Aciduria (D2HGA 1 and 2) • Dihydropterine reductase (DHPR) deficiency • Defects in N-Glycan synthesis • Defects in O-Glycan synthesis and other congenital muscular dystrophies • Disorders of glycoprotein degradation (alpha mannosidosis, beta mannosidosis and sialidosis, excluding fucosidosis) • Disorders of Branched Chain Aminoacids (BCAAS) and other Amino acid disorders (Including untreated propionic aciduria, methylmalonic aciduria, isovaleric aciduria, maple syrup Urine Disease (MSUD) (Excluding E3 subunit deficiency) • Fatty Acid Hydroxylase-Associated Neurodegeneration • Fumarate hydratase deficiency • Galactosemia type I • Glutaric aciduria type I (GA-I) • Glutaric aciduria type II (GA-II) or Multiple acyl-CoA dehydrogenase deficiency (MADD) • GM1 and GM2-Gangliosidosis, Infantile onset • Hereditary Homocystinurias • HMG-CoA lyase deficiency • L 2 hydroxyglutaric aciduria • Menkes disease • Molybdenum cofactor deficiency and isolated sulfite oxidase deficiency • Mucolipidosis type IV • Mucopolysaccharidosis including MPS type II (Hunter syndrome) and Sanfilippo syndrome • Multiple carboxylase deficiency, including biotinidase deficiency and holocarboxylase synthase deficiency • Neuronal Ceroid Lipofuscinoses (NCL), Infantile onset • Niemann-Pick C • Nonketotic hyperglycinemia • Phenylketonuria(PKU) • Ribose 5 phosphate isomerase deficiency • Succinic Semialdehyde	• Band-like intracranial calcification with simplified gyration and polymicrogyria, caused by mutations in *OCLN*, encoding a tight junction protein expressed in endothelia in the brain • Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) and Cerebral Autosomal Recesive Arteriopathy with Subcortical Infarcts and Leukoencephalopthy (CARASIL) • Cerebro Retinal Microangiopathy with Calcifications and Cysts or Coats Plus Syndome • *COL4A1* or *COL4A2* related disorder • Fabry disease • Labrune's Syndrome or Leukoencephalopathy with Calcifications and Cysts Mitochondrial and energy metabolism disorders • Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) • Mitochondrial neurogastrointestinal encephalopathy (MNGIE) • Pyruvate carboxylase (PC) deficiency • Pyruvate Dehydrogenase deficiency • Mitochondrial depletion syndromes (*POLG1* and others) • Succinate Dehydrogenase deficiency • Complex I deficiency such as *NDUFS1, NUBPL* • Mitochondrial aminoacyl-tRNA synthetases including *FARS2* (Alpers Encephalopathy) and *MARS2* (ARSAL or Autosomal Recessive Spastic Ataxia with Leukoencephalopathy Other • *AGC1* Related disorders • *AIMP1* related disorders • BCAP31 related disorder (X-linked phenotype with Deafness, dystonia and central hypomyelination) • Cockayne syndrome and trichothiodystrophy • CMTX (X linked Charcot Marie Tooth) • *DAG* related disorder • Dentatorubropallidoluysian atrophy (DRPLA) • Familial Hemophagocytic lymphohistiocytosis and other genetic disorders with macrophage activating syndrome • Fragile X Premutation • Giant Axonal Neuropathy • *GPR56* related disorders • *HSPD1* related disorders (or Mitchap60) • Hypomelanosis of Ito (HMI) (or incontinentia pigmenti achromians) • Incontinentia Pigmenti • *JAM3* related disorders • *LAMA2* related congenital muscular dystrophy

Inborn Errors of Metabolism	**Vascular disorders**
• Dehydrogenase (SSDH) Deficiency (or 4-Hydroxybutyric Aciduria) • Urea cycle disorders (Carbamoylphosphate synthetase I deficiency, Ornithine trans-carboxylase deficiency, Citrullinemia type I, Argininosuccinic-aciduria, Arginase deficiency, NAGS deficiency, HHH syndrome) Wilson's disease	• MCT8 (*SLC16A2*) related disorders • Myotonic dystrophy (DM) • Neuronopathic form of malignant infantile osteopetrosis • Oculocerebrorenal Syndrome of Lowe (OCRL) • Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) or Nasu Hakola disease • SPG11 and SPG15 • Spondyloenchondrodysplasia • Syndrome of Ravine (intronic mutations in *SLC7A2*) • Woodhouse Sakatai Syndrome
Totals: More than 61 Distinct Genetic leukoencephalopathies	

Table 3

Examples of leukodystrophies and other genetic leukoencephalopathies caused by inborn errors of metabolism

Organelle or cellular process	Disorders Classified as Leukodystrophy	Disorders Classified as Genetic Leukoencephalopathy
Lysosome	Globoid cell Leukodystrophy (Krabbe) Metachromatic Leukodystrophy Salla disease Fucosidosis	GM1 and GM2 gangliosidosis Neuronal Ceroid Lipofuscinosis Mucopolysaccharidoses
Peroxisome	Adrenoleukodystrophy D-Bifunctional Protein Deficiency SCPx deficiency Peroxisomal acyl-CoA-Oxidase Deficiency Peroxisomal biogenesis disorders (Infantile Refsum, Neonatal Adrenoleukodystrophy, Zellweger)	Not applicable, though disorders of the peroxisome not resulting in leukoencephalopathy exist
Mitochondria	Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (LBSL), Hypomyelination with Brainstem and Leukoencephalopathy with thalamus and brainstem involvement and high lactate (LTBL)	MNGIE (serious systemic manifestations) *PDH1A*, *POLG1*, MELAS (neuronal or cortical mantle involvement) [11, 12]. Succinate Dehydrogenase deficiency Complex I deficiency such as *NDUFS1*, *NUBPL* Mitochondrial aminoacyl-tRNA synthetases including *FARS2* (Alpers Encephalopathy) and *MARS2* (ARSAL or Autosomal Recessive Spastic Ataxia with Leukoencephalopathy
Errors of intermediary metabolism	Canavan disease Polyglucosan body disease L 2 hydroxyglutaric aciduria Cerebrotendinous xanthomatosis	Isovaleric aciduria, phenylketonuria, and homocystinuria, 3-phosphoglycerate dehydrogenase deficiency, in which the incidence of white matter abnormalities all but disappears with adequate treatment- see also Table 2 for other etiologies Non-ketotic hyperglycinemia

Caption: Among inborn errors of metabolism (IEM) with abnormalities of peroxisomal, mitochondrial, lysosomal or intermediary metabolism, those predominantly affecting the nervous system, with disorders of myelin or glial cells, and few systemic symptoms, were classified as leukodystrophies. In contrast, IEM that were felt to be better identified as “genetic leukoencephalopathies,” manifested serious, sometimes life-threatening systemic complications. We recognize that classification of this complex group of disorders is based on current knowledge and may change rapidly, as new disorders are identified. In particular, disorders with white matter abnormalities and a mitochondrial basis are rapidly being identified and several identified in the past months were too novel to have been included in our original sampling of disorders. [13]