

A diagnostic checklist of leukodystrophies and other genetic metabolic leukoencephalopathies

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The following **Table** is meant to help neurologists and neuroradiologists in the diagnosis of a leukodystrophy or leukoencephalopathy suspected to be of genetic origin. We have tried to classify the large number of possible causes according to different criteria:

- **Basic pathogenetic mechanism** (lysosomal, peroxisomal, or other molecular defects)
- **Recognizable neuroradiological criteria** (hypomyelination, cysts, calcifications, or other deformities)
- **Characteristic non-neurological findings** (such as bone or skin anomalies)
- **Miscellaneous genetic disorders.**

The table includes a few conditions that, from a neurological point of view, are not leukodystrophy-like but in which white matter changes may stimulate diagnostic thoughts.

The columns of the table contain the designation of the disorders and, where appropriate, their OMIM number [1], their mode of inheritance with incidence figures where available, the age at onset of symptoms, and suggestive findings from the medical history and clinical examination. Neuroradiological findings are restricted to prominent and helpful MRI features, with complementary findings of MR spectroscopy when important. For a comprehensive description of MR findings in myelin disorders, see, e.g. reference [2]. A further column lists basic defects and useful diagnostic tests. The references cited are thought to complement standard texts, e.g. [3].

Table 1
Leukodystrophies and other genetic leukoencephalopathies.

Disease ^a	Inheritance, incidence ^b	Gene, locus	Age at onset	Suggestive clinical findings	MRI, MRS ^c	Basic defect and diagnostic tests	References
<i>Lysosomal disorders</i>							
Metachromatic leukodystrophy (MLD) with arylsulfatase A deficiency #250100	AR	<i>ARSA</i> , 22q13.31-qter		Slowly progressive motor problems: ataxia, spasticity, dystonia, peripheral neuropathy; followed by mental decline	Demyelination begins in central and pv WM; tigroid pattern; Subcortical zones (U fibers) tend to be spared; corpus callosum is early affected; atrophy is a late sign; cerebellar white matter is affected in later course	Deficient activity of arylsulfatase A, urinary sulfatides elevated; CSF proteins elevated; nerve conduction velocity decreased	[4]
Late-infantile form	1/100,000 to 1/40,000		1–2 years	Starts mostly with gait disturbance, thereafter rapid motor deterioration, mental decline later			
Juvenile form Adult form			5–12 years Adolescence, adulthood	May start with motor or mental signs May manifest itself as psychosis			
MLD with activator defect #249900	AR	<i>PSAP</i> , 10q22.1		Similar to MLD with arylsulfatase A deficiency	Symmetric T2 hyperintensity in cerebral and cerebellar WM	Deficiency of saposin B (sphingolipid activator protein B); arylsulfatase A activity normal, urinary sulfatides elevated. Molecular genetic analysis helpful	[5]
MLD with multiple sulfatase deficiency #272200	AR	<i>SUMF1</i> , 3p26	Neonatal, infantile, juvenile	Similar to MLD, dysmorphic signs as in mucopolysaccharidoses, ichthyosis		Low activities of several sulfatases, abnormal granules in leukocytes, urinary glucosaminoglycans (mucopolysaccharides) elevated	[6]
Globoid cell leukodystrophy (Krabbe disease) with galactocerebrosidase deficiency #245200	AR, ~1/100,000	<i>GALC</i> , 14q31		Combination of symptoms of central and peripheral nervous system. Initially patients may have increased or decreased muscle stretch reflexes	T2 hyperintensity in WM, notably in parietal and central lobes; pattern of radial stripes; dental nucleus hyperintense in T2	Deficient activity of galactocerebrosidase; nerve conduction velocity mostly decreased	[7]
Classic infantile form			4–6 months	Rapidly progressive disease, starts with restlessness, irritability, progressive stiffness; convulsions, hyperacusis		CSF proteins elevated	
Late-onset forms			Children, young adults	Slowly evolving spastic paresis; cortical blindness, neuropathy		CSF proteins may be normal	
Globoid cell leukodystrophy with activator deficiency	AR	<i>PSAP</i> , 10q22.1	Infancy	One case reported		Deficiency of saposin A (sphingolipid activator protein A), cerebrosidase activity normal	[8]
Sialuria, Finnish type (Salla disease) #604369	AR	<i>SLC17A5</i> , 6q14-q15, frequent in Finland	Late infancy	Slowly progressive psychomotor deficits, hypotonia, cerebellar ataxia, mental retardation; visceromegaly and coarse features may develop	Hypomyelination; demyelination is some patients, thin corpus callosum	Deficiency of a carrier-mediated transport system in the lysosomal membrane. Increased urinary free sialic acid, light and electron microscope evidence of lysosomal storage on skin biopsy	[9,10]
Free sialic acid storage disease, infantile type, #269920	AR	Allelic variant of the above	Congenital or young infants	Failure to thrive, hepatosplenomegaly, severe mental and motor retardation, may have coarse facial features and dysostosis multiplex. Death frequently in first year of life			
Fucosidosis #230000	AR	<i>FUCA1</i> , 1p34	Infants	Progressive neurological deterioration, coarse facial features, dysostosis multiplex; variable phenotypes reported	Hypomyelination of supra- and infratentorial WM; pallidum hypointense in T2	Deficiency of alpha- L-fucosidase, detectable in leukocytes, fibroblasts	[11]
GM1-Gangliosidosis type 1 #230500	AR, rare, higher in Malta	<i>GLB1</i> , 3p21.33	Infants	Variable degrees of neurodegeneration and skeletal abnormalities, dysmorphies, hepatosplenomegaly, macular cherry-red spots; acoustic startle; ataxia and spasticity	Hypomyelination; thalamus hypointense in T2	Deficiency of β-galactosidase, detectable in leukocytes, fibroblasts	[12–14]
Tay Sachs disease, GM2-Gangliosidosis type 1, #272800	AR, high in Ashkenazi Jews	<i>HEXA</i> , 15q23-q24	3–10 months	Hyperacusis, arrest in intellectual development, macular cherry-red spots; convulsion	MRI findings change during evolution. Mainly grey matter changes. Late in the course marked brain atrophy and diffuse WM lesions	Deficiency of hexosaminidase A, detectable in leukocytes, fibroblasts	[15]
Fabry disease #301500	XR, 1/40,000	<i>GLA</i> , Xq22	Adolescents, adults	Intermittent burning pain in extremities, angiokeratomas, corneal opacifications	Cerebrovascular alterations, small hyperintense WM changes in T2, T1 hyperintensity in the pulvinar	Systemic disease due to vascular lipid deposits, deficiency of alpha-galactosidase A, detectable in leukocytes, fibroblasts	[16]
Mucopolysaccharidoses and mucopolidoses				May show typical dysmorphic stigmata	Perivascular spaces may appear enlarged	Urinary glucosaminoglycans elevated (not in mucopolidoses)	

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Table 1 (continued)

Disease ^a	Inheritance, incidence ^b	Gene, locus	Age at onset	Suggestive clinical findings	MRI, MRS ^c	Basic defect and diagnostic tests	References
Niemann–Pick disease type C #257220	AR	<i>NPCI</i> , 18q11-q12 or <i>NPC2</i> , 14q24.3	Variable	Highly variable, symptoms include vertical supranuclear gaze palsy, liver disease, psychiatric symptoms; late infantile course leads to spasticity Frequently multiple organs affected	Central WM changes mild and later in course	Cholesterol esterification and other studies in fibroblasts (filipin test); alternatively genetic diagnostic is available	[17]
<i>Peroxisomal disorders</i>							
Adrenoleukodystrophy (X-ALD) #300100	XR, 1/40,000	<i>ABCD1 (ALDP)</i> , Xq28		Variable; the disease may cause cerebral degeneration, or adrenomyeloneuropathy, or Addison disease only	T2 hyperintensity of pv WM; starts mostly in parieto-occipital WM; internal capsule early affected, 10–20% of the lesions start from the frontal lobe. MRS: choline-containing compounds elevated early Lesions frequently show a strong inflammatory component (contrast enhancement)	Very-long-chain fatty acids (VLCFA) generally elevated in plasma Deficient ATP-binding-cassette protein (ABC protein). VLCFA elevated, electrolyte imbalance and endocrinological findings of adrenocortical failure	[18]
			School age	The childhood cerebral form typically begins subacutely with loss of mental and emotional performance, followed by loss of motor performance and spasticity			[19,20]
			Adults	Adults rarely develop a cerebral form but adrenomyeloneuropathy (AMN) with progressive paraparesis, neuropathy and Addison disease; female carriers are asymptomatic or mildly affected		VLCFA may be normal in female carriers; in this case analysis of the <i>ABCD1</i> gene is required for diagnosis	
Spectrum of Zellweger syndrome and Zellweger-like disorders						Defects of peroxisomal biogenesis. VLCFA and other peroxisomal metabolites elevated	[21]
Zellweger syndrome (ZS) #214100	AR	Several different <i>PEX</i> genes involved in peroxisome biogenesis	Infancy	Typical face and skull anomalies (high forehead, huge fontanelle), severe hypotonia, visual and hearing loss, liver disease	Diffuse WM hyperintensity on T2; cortical abnormalities such as polymicrogyria		[14,22]
Neonatal adrenoleukodystrophy #202370	AR	Several different genes	1–3 months	Dysmorphic features, hearing deficit, hypotonia, hepatomegaly, seizures, retinopathy	Central and pv WM hyperintense on T2; cerebellum, BG, thalamus, corpus callosum may be affected; polymicrogyria		[14,23]
β-Oxidation defects #264470	AR	<i>ACO1</i> , 17q25	Infancy	Cranial dysmorphies, liver disease, developmental regression in later infancy	Mostly cerebellar WM involved	Only VLCFA are elevated	[24]
<i>Other molecular mechanisms</i>							
Canavan disease (Spongy Degeneration of Cerebral White Matter) #271900	AR, rare, higher in Ashkenazi Jews	<i>ASPA</i> , 17pter-p13	2–4 months	Failure of intellectual development, optic atrophy, hypotonia; macrocephaly; variants may start in newborns or adolescents	Global primary WM hyperintensity on T2; in the juvenile form only the BG hyperintense on T2. MRS: <i>N</i> -acetyl aspartate (NAA) peak elevated	Deficiency of aspartoacylase, <i>N</i> -acetyl aspartate elevated (urine, brain MR spectroscopy)	[14,25]
Alexander disease #203450	AR, Childhood forms mostly sporadic	<i>GFAP</i> , 17q21 and <i>NDUFV1</i> , 11q13			T2 hyperintensity of frontal-occipital WM; U-fibres affected; a periventricular rim of low signal intensity is seen on T2 and of high signal intensity on T1-weighted images; ependymal contrast enhancement in early course	Deficient glial fibrillary acidic protein (GFAP). The mutant protein accumulates into Rosenthal fibers. Sequencing of the <i>GFAP</i> gene is helpful. In a patient with a phenotype consistent with Alexander disease, a mutation in the <i>NDUFV1</i> gene was found	[26–30]
Neonatal form			1 month	Hydrocephalus due to aqueductal stenosis; epilepsy prominent	Swelling of BG		[31]
Infantile form			1–2 years	Most common form; progressive loss of mental capacities, ataxia and spasticity	Predominantly frontal demyelination		
Juvenile form			5–9 years	Prominent bulbar signs, spastic paresis	Focal brain stem lesions		
Adult form	AD			No macrocephaly	Diffuse demyelination with frontal predominance; coarsened pattern of sulci and gyri; subcortical cysts	Sequencing of the <i>GFAP</i> gene	
Vanishing white matter disease (VWM, Childhood Ataxia with CNS Hypomyelination, CACH) #603896	AR, not very rare	<i>EIF2B1-5</i>	Infancy through adulthood	Symptoms triggered by stress (head trauma, high fever), progressive spasticity, ataxia, dementia	T2 hyperintensity of central hemispheric WM; central WM signal becomes similar to that of CSF (Flair!); U-fibres affected, atrophy later in disease course	Mutations in genes coding for one of five subunits of translation initiation factor EIF2B	[32,33]
VWM-like leukodystrophy, adult onset, autosomal dominant (ADLD) #169500	AD	<i>LMNB1</i> , 5q23.3-q31.1	40–50 years	Slowly progressive pyramidal and cerebellar dysfunction	Symmetric demyelination of the CNS	Similar to VWM, duplications of the gene	[34–36]

Mainly hypomyelinating disorders

Pelizaeus–Merzbacher disease (PMD) #312080	XR	<i>PLP1</i> , Xq22	Infancy (rarely connatal)	Early symptoms are nystagmus, stridor, muscular hypotonia; later spasticity; initially not a progressive disorder. Brainstem auditory evoked potentials are of particular value in early diagnosis (normal wave 1 without subsequent waves)	Global hypomyelination with or without involvement of corticospinal tracts	Defective proteolipid protein; gene analysis	[40–42]
PMD-like disease type 1 (PMLD1) #608804	AR	<i>GJAI2</i> , 1q41–q42	Infancy	PMD-like (nystagmus, spasticity), but autosomal-recessive	Hypomyelination of central cerebral WM	Connexin (gap junction protein) defect	[43,44]
PMD-like disease type 2 (PMLD2)#260600	AR		Infancy	Early-onset nystagmus, seizures, resembling connatal PMD	Almost complete absence of myelin	Increased <i>N</i> -acetylaspartylglutamate in CSF	[45]
3-Phosphoglycerate dehydrogenase deficiency #601815	AR	<i>PHGDH</i> , 1q12jkmio	Newborns	Microcephaly, severe psychomotor retardation, intractable seizures	Hypomyelination, (reversible) attenuation of cerebral WM	Low concentrations of the amino acid serine in plasma and CSF	[46]
Hypomyelination with atrophy of basal ganglia and cerebellum (H-ABC)	Unknown, sporadic		2 months to 3 years	Delayed motor development followed by deterioration, spasticity, rigidity, ataxia, choreoathetosis, dystonia	Diffuse hypomyelination, hypoplasia/ progressive atrophy of BG, cerebellum		[47–49]
Hypomyelination and congenital cataract #610532	AR	<i>DRCTNBJA</i> 7p21.3–p15.3.	Infancy	Cataract, developmental delay, and slowly progressive spasticity, ataxia, tremor, mild-to-moderate mental retardation, peripheral neuropathy	Diffuse supratentorial hypomyelination	Motor nerve conduction velocity reduced	[50]
18q ⁻ syndrome #601808		Deletion of chromosome 18	Congenital	Variable malformations, mental retardation, short stature, hypotonia, hearing impairment, foot deformities	T2: poor differentiation of gray and WM	The chromosomal deletion includes the gene for myelin basic protein	[51,52]
Leukoencephalopathy with ataxia, hypodontia, and hypomyelination			Infancy	Progressive ataxia and hypodontia with delayed dentition	Hypomyelinated WM and cerebellar atrophy		[53,54]
Monocarboxylate Transporter 8 Deficiency (Allan–Herndon–Dudley syndrome) #300523	XR	<i>MCT8</i> , Xq13.2	Infancy	Hypotonia, weakness, reduced muscle mass, delay of developmental milestones. Spasticity later in life. Mild facial anomalies	Hypomyelinated WM	Thyroid anomalies (T3 resistance); gene analysis	[55]
<i>With intracerebral cysts and/or calcifications</i>							
Megalencephalic leukodystrophy with cysts (MLC) #604004	AR	<i>MLC1</i> , 22q13.33	Infancy to 10 years	Megalencephaly, very slowly progressive spasticity and dementia, high incidence in Asian Indians	Extensive WM changes with discrepantly mild clinical course, subcortical cysts		[56–58]
Aicardi–Goutières Syndrom #225750	AR	<i>AGSI-4</i> , 13q14.3	Early infancy	Severe postnatal encephalopathy, suggestive of intracranial infection	Intracerebral calcifications, especially in BG; pv and central WM hyperintensity on T2; later atrophy	Cell count and interferon levels in CSF elevated	[59–61]
Leukoencephalopathy with anterior temporal lobe cysts			Infancy	Delayed initial development, spasticity, normocephaly or microcephaly, no obvious progression	Cystic lesions in anterior temporal lobes, periventricular demyelination		[62,63]
Vacuolating glycine leukoencephalopathy			Infancy	Rapidly progressive neurological deterioration during first year of life, pulmonary hypertension	Extensive cerebral WM changes, sparing U-fibers	Defect of glycine cleavage system, high CSF/plasma glycine ratio	[64]
Progressive cavitating leukoencephalopathy			2 months to 3 years	Continuous or intermittent neurological deterioration	Patchy leukoencephalopathy with cavities, vascular permeability		[65]
Cerebroretinal microangiopathy with calcifications and cysts (CRMCC)#612199	Probably AR		Infancy to adolescence	Progressive extrapyramidal, cerebellar, and pyramidal symptoms and signs, dementia. May have features of Coats plus syndrome (bilateral retinal telangiectasia)	Diffuse WM abnormalities, parenchymal cysts, calcifications in BG, central WM, cerebellum		[66,67]
<i>With other neuroradiologic features</i>							
Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL) #611105	AR	<i>DARS2</i> , 1q25.1	Early childhood to adolescence	Slowly progressive, variable mental deficits, pyramidal and cerebellar dysfunction	Diffuse or spotty WM abnormalities, involvement of pyramidal tract, sensory tracts, cerebellar peduncles	MRS shows increased lactate	[68–71]
Leukoencephalopathy with hydrocephalus	AD?		Infancy	Macrocephaly, nystagmus, spasticity, nonprogressive	Obstructive hydrocephalus caused by enlarged cerebellum, abnormal cerebellar WM, progresses to atrophy		[72]
<i>With prominent features outside the nervous system</i>							
Leukoencephalopathy with polycystic osteodysplasia (Nasu–Hakola Disease) #221770	AR	<i>TYROBP (DAP12)</i> , 19q13.1 or <i>TREM2</i> , 6p21.2	Presenile adults	Pathologic fractures of often painful lesions, rapidly progressing dementia; diagnosis based on combination of neurological and bone changes	Sclerosing leukoencephalopathy	Radiographic changes may be confused with cystic angiomas, hemangiopericytoma, or Langerhans cell histiocytosis	[73]
Leukoencephalopathy with metaphyseal chondrodysplasia#300660	XR	Xq25–q27	2–3 years	Slowly progressive spastic paraplegia, later tremor, ataxia, optic atrophy, and tetraparesis; broad wrists and knees without significant contractures	Diffuse leukoencephalopathy	X-ray: bone and cartilage show mild metaphyseal chondrodysplasia	[74]

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Giant axonal neuropathy type 1 (GAN1) #256850	AR	<i>GAN</i> , 16q24.1	Childhood	Chronic polyneuropathy, kinky or curly hair, typical posture of legs	Progressive cerebral WM degeneration	Scanning electron microscopy: longitudinal grooves in hair; analysis of <i>GAN</i> gene	[75,76]
Trichothiodystrophy #601675	AR	<i>XPD</i> , 19q13.2-q13.3 or <i>XPB</i> , 6p25.3, 2q21	Infancy	Ichthyosiform skin, abnormal hair and nails, mental and growth retardation	Lack of myelination in the supratentorial WM		[77]
Sjögren–Larsson syndrome (SLS) #270200	AR	<i>ALDH3A2</i> , 17p11.12	Infancy	Ichthyosiform skin, slowly progressive dementia, spasticity, retinal abnormalities	Retarded myelination, mild persistent myelin deficit	Defect of fatty aldehydehydrogenase, detectable in fibroblasts. MRS: characteristic lipid peak in WM	[78–80]
<i>Miscellaneous genetic disorders</i>							
Leukodystrophy, adult onset #169500	AD	<i>LMNB1</i> , 5q23.3-q31.1	4th and 5th decades	“Multiple sclerosis-like”, symptoms include cerebellar, pyramidal, and autonomic abnormalities	Symmetrical demyelination with cavitation aspects		[35,81]
Leukodystrophy with ataxia and deafness			1–3 years	Slowly progressive ataxia, subsequently sensorineural deafness, no mental deterioration	T2: Diffuse hyperintensity of cerebral WM; corpus callosum and brain stem atrophy		[82]
Hereditary diffuse leukoencephalopathy with spheroids (HDLS)	AD		3rd to 6th decades	Begin with memory disturbance, behavioral mood disorder	Progressive, confluent, frontal-predominant leukoencephalopathy, cortical atrophy		[83]
Leukoencephalopathy with congenital muscular dystrophy			Infancy	Heterogeneous group of disorders		Evidence of muscular dystrophy	[84,85]
Mitochondrial Disorders			Variable	Very multifarious, frequently multisystem involvement	Central and pv WM hyperintensity on T2 is a sign especially of infantile forms; childhood and juvenile forms show typical striatal or pallidal signal changes (Leigh disease); cerebellar atrophy is seen in COX deficiency; infarct-like changes in MELAS syndrome; ¹ H-MRS shows elevated lactate	Lactate may be increased in serum and CSF; muscular biopsy may show ragged red or COX negative fibers; genetic diagnostics must take into account suitable tissues (e.g. muscle for PEO plus syndromes)	[14,86,87]
Amino acid and organic acid disorders							
Biotinidase deficiency #253260	AR	<i>BTD</i> , 3p25	Infancy	Seizures, hypotonia, ataxia, sensorineural deafness. Cutaneous features (erythematous exudative dermatitis, alopecia)	Delayed myelination, pronounced WM damage possible	Usually detectable by blood amino acid and urinary organic acid profiles	[88]
Cobalamin (vitamin B12)-related disorders			Infancy			Deficient recycling of biotin, a cofactor of multiple carboxylases. Lactate may be increased in serum and CSF. Abnormal urinary organic acids. Low enzyme activity in blood	[89–91]
Glucose transporter 1 deficiency syndrome #606777	AD	<i>GLUT1</i> , 1p35-p31.3	Infants	Seizures, developmental delay, ataxia, dystonia	Delayed myelination	Macrocytosis, methylmalonic acid elevated in urine, homocysteine and methionine abnormal in blood	[92]
Congenital Disorders of Glycosylation (CDG Syndromes), e.g., #212065			Congenital	A group of mostly multisystem disorders, some patients have dysmorphies	Cerebellar hypoplasia and hypomyelination may be present	Low glucose ratio in CSF/blood	[93,94]
Infantile neuroaxonal dystrophy (INAD) #256600	AR	<i>PLA2G6</i> , 22q13.1	Infancy	Psychomotor regression, relentlessly progressive to spasticity, visual impairment (optic atrophy)	Cerebellar atrophy. T2 hyperintensity of cerebellar cortex, some have marked cerebral WM hyperintensity	Atypical transferrins in serum	[95]
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) #125310	AD	<i>NOTCH3</i> , 19p13.2-p13.1	Mid-adulthood	Dementia	Multiple cerebral infarcts, WM lesions including the temporal poles	Fast EEG rhythms (“beta EEG”) and MRI are suggestive. Gene analysis. Axonal spheroids on skin biopsy	[96,97]
Cockayne syndrome type A #216400	AR	<i>ERCC8</i> , 5q11	Infancy	Progeria-like symptoms, light sensitivity, short stature, peripheral neuropathy, retinopathy; progressive symptoms typically apparent after the age of 1 year	Patchy central and sub-cortical WM changes; BG calcification	DNA repair mechanism disturbed; central and peripheral myelin affected;	[98,99]
Aluminum-associated leukoencephalopathy (genetic nature unclear)		Genetic cause not established	School age	One patient reported, vanishing white matter-like features (see VWM, above)	Diffuse WM changes	Brain biopsy showed aluminum accumulation in myelin	[100]

^a OMIM numbers where applicable.

^b Incidence figures are stated where available; AR: autosomal recessive; XR: x-linked recessive; AD: autosomal dominant.

^c BG: basal ganglia; MRS: proton magnetic resonance spectroscopy (only helpful findings mentioned); pv: periventricular; WM: white matter.

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