# 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 |
|---|---|---|---|---|---|---|---|
| *Lysosomal disorders* | | | | | | | |
| Metachromatic leukodystrophy (MLD) with arylsulfatase A deficiency #250100 | AR | *ARSA*, 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 | | | 5–12 years | May start with motor or mental signs | | | |
| Adult form | | | Adolescence, adulthood | May manifest itself as psychosis | | | |
| MLD with activator defect #249900 | AR | *PSAP*, 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 | *SUMF1*, 3p26 | Neonatal, infantile, juvenile | Similar to MLD, dysmorphic signs as in mucopolysaccharidoses, ichthyosis | | Low activities of several sulfatases, abnomal granules in leukocytes, urinary glucosaminoglycans (mucopolysaccharides) elevated | [6] |
| Globoid cell leukodystrophy (Krabbe disease) with galactocerebrosidase defiency #245200 | AR, ~1/100,000 | *GALC*, 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 defiency | AR | *PSAP*, 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 | *SLC17A5*, 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 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 | *FUCA1*, 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 | *GLB1*, 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 ß-galactosidase, detectable in leukocytes, fibroblasts | [12–14] |
| Tay Sachs disease, GM2-Gangliosidosis type 1, #272800 | AR, high in Ashkenazi Jews | *HEXA*, 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 | *GLA*, 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 mucolipidoses | | | | May show typical dysmorphic stigmata | Perivascular spaces may appear enlarged | Urinary glucosaminoglycans elevated (not in mucolipidoses) | |

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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 | *NPC1*, 18q11-q12 or *NPC2*, 14q24.3 | Variable | Highly variable, symptoms include vertical supranuclear gaze palsy, liver disease, psychiatric symptoms; late infantile course leads to spasticity | Central WM changes mild and later in course | Cholesterol esterification and other studies in fibroblasts (filipin test); alternatively genetic diagnostic is available | [17] |
| *Peroxisomal disorders* | | | | Frequently multiple organs affected | | Very-long-chain fatty acids (VLCFA) generally elevated in plasma | |
| Adrenoleukodystrophy (X-ALD) #300100 | XR, 1/40,000 | *ABCD1* (*ALDP*), 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 | 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 | Lesions frequently show a strong inflammatory component (contrast enhancement) | | [19,20] |
| | | | Adults | Adults rarely develop a cerebral form but adrenomyeloneuropathy (AMN) with progressive paraparesis, neuropathy and Addison disease; female carriers are asymtomatic or mildly affected | | VLCFA may be normal in female carriers; in this case analysis of the ABCD1 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 *PEX* genes involved in peroxisome biogenesis | Infancy | Typial 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 | *ACOX1*, 17q25 | Infancy | Cranial dysmorphies, liver disease, developmental regression in later infancy | Mostly cerebellar WM involved | Only VLCFA are elevated | [24] |
| *Other molecular mechanisms* | | | | | | | |
| Canavan disease (Spongy Degeneration of Cerebral White Matter) #271900 | AR, rare, higher in Ashkenazi Jews | *ASPA*, 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 iuvenile form only the BG hyperintense on T2. MRS: *N*-acetyl aspartate (NAA) peak elevated | Deficiency of aspartoacylase, *N*-acetyl aspartate elevated (urine, brain MR spectroscopy) | [14,25] |
| Alexander disease #203450 | AR, Childhood forms mostly sporadic | *GFAP*, 17q21 and *NDUFV1*, 11q13 | | | T2 hyperintenisty 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 *GFAP* gene is helpful. In a patient with a phenotype consistent with Alexander disease, a mutation in the *NDUFV1* 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 *GFAP* gene | |
| Vanishing white matter disease (VWM, Childhood Ataxia with CNS Hypomyelinization, CACH) #603896 | AR, not very rare | *EIF2B1-5* | 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 oset, autosomal dominant (ADLD) #169500 | AD | *LMNB1*, 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] |

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| *Mainly hypomyelinating disorders* | | | | | | | |
| Pelizaeus–Merzbacher disease (PMD) #312080 | XR | *PLP1*, 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 | *GJA12*, 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 *N*-acetylaspartylglutamate in CSF | [45] |
| 3-Phosphoglycerate dehydrogenase deficiency #601815 | AR | *PHGDH,* 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 | *DRCTNNB1A* 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 | *MCT8*, 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] |
| *With intracerebral cysts and/or calcifications* | | | | | | | |
| Megalencephalic leukodystrophy with cysts (MLC) #604004 | AR | *MLC1*, 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 | *AGS1-4*, 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] |
| *With other neuroradiologic features* | | | | | | | |
| Leukoencephalopathy with brainstem and spinal cord involvement and elevated lactate (LBSL) #611105 | AR | *DARS2*, 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] |
| *With prominent features outside the nervous system* | | | | | | | |
| Leukoencephalopathy with polycystic osteodysplasia (Nasu–Hakola Disease) #221770 | AR | *TYROBP* (*DAP12*), 19q13.1 or *TREM2*, 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 angiomatosis, hemangioendothelioma, 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 | *GAN*, 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 *GAN* gene | [75,76] |
| Trichothiodystrophy #601675 | AR | *XPD*, 19q13.2-q13.3 or *XPB*, 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 | *ALDH3A2*, 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] |
| *Miscellaneous genetic disorders* | | | | | | | |
| Leukodystrophy, adult onset #169500 | AD | *LMNB1*, 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 iuvenile 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 | | | | | | Usually detectable by blood amino acid and urinary organic acid profiles | |
| Biotinidase deficiency #253260 | AR | *BTD*, 3p25 | Infancy | Seizures, hypotonia, ataxia, sensorineural deafness. Cutaneous features (erythematous exudative dermatitis, alopecia) | Delayed myelination, pronounced WM damage possible | 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 | [88] |
| Cobalamin (vitamin B12)-related disorders | | | Infancy | | | Macrozytosis, methylmalonic acid elevated in urine, homocysteine and methionine abnormal in blood | [89–91] |
| Glucose transporter 1 deficiency syndrome #606777 | AD | *GLUT1*, 1p35-p31.3 | Infants | Seizures, developmental delay, ataxia, dystonia | Delayed myelination | Low glucose ratio in CSF/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 | Atypical transferrins in serum | [93,94] |
| Infantile neuroaxonal dystrophy (INAD) #256600 | AR | *PLA2G6*, 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 | Fast EEG rhythms ("beta EEG") and MRI are suggestive. Gene analysis. Axonal spheroids on skin biopsy | [95] |
| Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) #125310 | AD | *NOTCH3*, 19p13.2-p13.1 | Mid-adulthood | Dementia | Multiple cerebral infarcts, WM lesions including the temporal poles | | [96,97] |
| Cockayne syndrome type A #216400 | AR | *ERCC8*,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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