CHAPTER 13

LEUKODYSTROPHIES

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Abstract: Leukodystrophies comprise a broad group of progressive, inherited disorders affecting mainly myelin. They often present after a variable period of normalcy with a variety of neurologic problems. Though the ultimate diagnosis is not found in many patients with leukodystrophies, distinctive features unique to them aid in diagnosis, treatment and prognostication. The clinical characteristics, etiologies, diagnostic testing and treatment options are reviewed in detail for some of the major leukodystrophies: X-linked adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, Alexander disease, Canavan disease, megalencephalic leukoencephalopathy with subcortical cysts and vanishing white matter disease.

INTRODUCTION

Leukodystrophies are inherited disorders primarily affecting brain myelin development and maintenance. Although myelin is most prominently found in the white matter, many leukodystrophies also affect nonwhite matter regions of the nervous system. They have also been shown to be associated with axonal injury.[1] They must be distinguished from other causes of acquired myelin disorders that are often considered as part of a differential diagnosis: inflammatory conditions such as multiple sclerosis, infections such as progressive multifocal leukoencephalopathy (PML), toxin-mediated disorders and chromosomal disorders. An alternate term that has been suggested is *leukoencephalopathy*, though this is often used as a broader term to also include these other conditions. There are a large number of different leukodystrophies with different characteristics and etiologies, ages of onset, clinical courses and prognoses.[2]

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Leukodystrophies typically present after an initial period of normal development, though the age of clinical onset varies depending upon the specific disorder and normal development may not be seen in cases of infantile leukodystrophies. Behavioral changes and cognitive deterioration may be the initial presenting symptoms, progressing to regression of motor development and a variable array of findings including: spasticity (though hypotonia may also be seen), weakness, ataxia, nystagmus, swallowing dysfunction, enunciation difficulties, movement disorders, optic atrophy, neuropathy (if peripheral myelin is affected) and epilepsy.[3,4] Up to half of patients with leukoencephalopathies are never given a specific diagnosis.[5,6] Many leukodystrophies are well-defined and may be differentiated by distinctive characteristics in their clinical presentations and their associated biochemical, imaging and pathologic findings. While it is beyond the scope of this chapter to describe all leukodystrophies, we will highlight several of the most important and common types.

DEMYELINATING AND DYSMYELINATING DISORDERS

X-Linked Adrenoleukodystrophy

Clinical Characteristics

X-linked adrenoleukodystrophy (X-ALD) is one of the most common leukodystrophies, with a minimum incidence of 1 in 21,000 males.[7] The rapidly progressive childhood cerebral form is the most common type of X-ALD. These children typically present around 3-10 years of age with behavioral and cognitive deterioration, then follow a progressive course to profound neurodevelopmental disability within a few years. The other most common form of X-ALD presents in male adults as an adrenomyeloneuropathy (AMN), following a more slowly progressive course involving spastic paraparesis, sphincter dysfunction and sensory changes. All phenotypes of X-ALD will often involve a variable degree and timing of adrenocortical dysfunction. Some patients may present with an Addison-only form, whereas a small percentage of males—typically diagnosed after X-ALD is found in a family member—may be asymptomatic and show biochemical evidence but no clinical signs of disease.[2] Finally, a significant number of heterozygous female carriers will develop an AMN-like syndrome in adulthood, though cerebral and adrenocortical involvement in these patients is rare.[8-10]

Etiology and Pathophysiology

X-ALD is an X-linked recessive disease caused by mutations in the *ABCD1* gene. There is no clear correlation between genotype and phenotype, with a single kindred often displaying multiple manifestations of the disease.[11] The gene encodes the peroxisomal ATP-binding cassette trans-membrane transporter ALDP. The detectable biochemical abnormality is the accumulation in serum and all tissues of very long chain fatty acids (VLCFA) due to impaired peroxisomal degradation, though the primary effects are on the nervous system and adrenal cortex. Oxidative stress, inflammatory and autoimmune processes may all play a role in the various phenotypes of the disease.[8]

Diagnosis, Pathology and Imaging

The biochemical defect of elevated plasma VLCFA levels can be reliably found in untreated affected males, including during the neonatal period, and only 15% of heterozygote females may have a normal result.[12] Mutation analysis of *ABCD1* may therefore also be necessary in such patients or their family members. Neuroimaging often provides the primary information ultimately leading to diagnosis of X-ALD. The classic pattern of the cerebral form involves initial involvement of white matter spreading from the splenium of the corpus callosum to the parietooccipital lobes (Fig. 1); other described patterns (the differentiation of which can aid in prognostication) include primary involvement of the frontal lobes or genu of the corpus callosum, the corticospinal tracts (primarily in adults), cerebellar white matter and combined involvement of the parieto-occipital and frontal white matter.[13-15] U-fibers and cortex are typically spared. Proton MR spectroscopy demonstrates an abnormally reduced ratio of N-acetylaspartate (NAA) to choline that is apparent before the development of visible signal abnormalities on conventional MRI.[16,17] The pathologic findings in X-ALD comprise cytoplasmic inclusions of cholesterol esterified with VLCFA, with cerebral disease demonstrating perivascular inflammatory infiltrates behind an edge of confluent demyelination, while peripheral disease demonstrates a distal axonopathy with distal degeneration of myelin.[13]

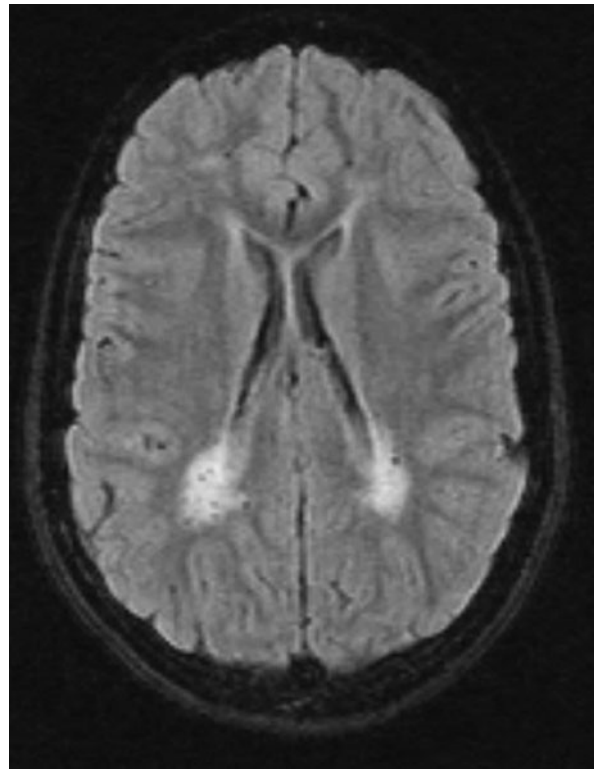

Figure 1. A 9 year-old boy with XALD. In this FLAIR sequence from a brain MRI there are marked T2/FLAIR hyperintense lesions in the white matter surrounding the occipital horns of the lateral ventricles.

Treatment

Patients with X-ALD must be carefully assessed for adrenocortical dysfunction and, if found, given hormone replacement therapy with glucocorticoids and sometimes mineralocorticoids. Treatment of patients with X-ALD with Lorenzo's oil, a 4:1 mixture of glyceryl trioleate and glyceryl trierucate and a reduced fat diet can normalize plasma levels of VLCFA. Although this does not affect endocrine function and has not been shown to alter neurologic disease progression in symptomatic boys, it may exert a preventive effect in asymptomatic boys with normal MRI findings.[8,18] Allogeneic hematopoietic stem cell transplant (HSCT), if performed at an early stage of disease when patients are free of neurologic and significant neuropsychological involvement and have only limited abnormalities on brain MRI, can arrest the cerebral inflammatory demyelination of X-ALD.[18,19] Autologous stem cell gene therapy techniques and valproic acid have also recently been investigated with initially promising results.[20,21]

Krabbe Disease

Clinical Characteristics

Krabbe disease, also known as globoid cell leukodystrophy is a progressive white matter disorder with three subtypes that have been delineated: infantile, juvenile and adolescent-adult forms. The infantile form is most frequent with an incidence of 1 in 70,000 to 100,000. The infantile can be separated into early and late forms based on the onset of the disease. In early infantile form, the clinical symptoms occur between 1 and 6 months of age and include hyperirritability, an exaggerated startle and dysphagia. These are followed by progressive spasticity, stagnation and regression of development, seizures, blindness, deafness, rapid motor and mental deterioration and death. Life expectancy varies between 5 months and 3 years of age. The late-onset infantile form usually presents before 18 months of age. The clinical symptoms of other late onset forms are heterogeneous, ranging from insidious isolated visual impairment to cognitive deterioration, gait abnormality, ataxia, hemiparesis and spasticity. The age of death of late onset forms varies from 18 months to more than 14 years.[1,22,23,15]

Etiology and Pathophysiology

Krabbe disease has autosomal recessive inheritance and is caused by a deficiency of galactocerebroside β galactosidase (GALC) activity. GALC is a lysosomal enzyme involved in the metabolism of important galactolipids found in myelin.[24,25] The accumulation of cerebrosides and psychosine results in the apoptotic death of oligodendrocytes and associated demyelination. Various mutations in the *GALC* gene, located on chromosome 14q31, have been identified.[26]

Pathology and Imaging Findings

Microscopic pathology reveals diffuse demyelination with loss of oligodendrocytes throughout the brain, but preservation of U fibers. Extensive fibrillary astrocytic gliosis replaces the lost oligodendrocytes and myelin. Infiltration of numerous macrophages, often multinucleated ("globoid cells"), is the unique feature of Krabbe disease. In areas

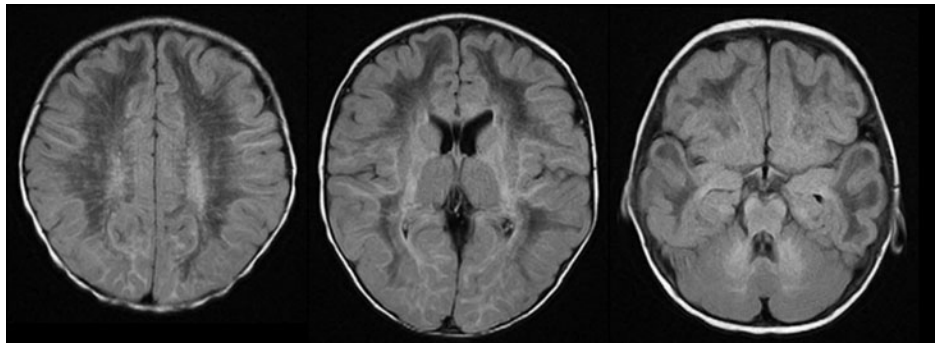

Figure 2. A 10 month old girl with infantile Krabbe disease. In this FLAIR sequence from a brain MRI there are T2/FLAIR hyperintense lesions in the predominantly parietooccipital periventricular and cerebellar white matter, the corticospinal tracts and the posterior corpus callosum. Grey matter structures in the basal ganglia are also involved. Courtesy of Jayne Ness, MD, PhD, The University of Alabama at Birmingham.

of demyelination, axonal degeneration typically is observed. Peripheral nerves also are involved in the disease process, with pathology demonstrating segmental demyelination.[27] MRI of infantile Krabbe disease (Fig. 2) typically shows T2/FLAIR hyperintense lesions of periventricular and cerebellar white matter and the pyramidal tracts. Posterior corpus callosum and parietooccipital white matter abnormalities are also seen and grey matter structures are commonly involved.[28] In the juvenile and adult forms white matter changes are characteristically confined to periventricular parietooccipital regions in the beginning of the disease. Proton MR spectroscopy has provided evidence of significant neuroaxonal loss in infantile globoid cell leukodystrophy, minor neuroaxonal damage in the juvenile form and nearly normal white matter and no evidence of neuroaxonal loss in adult globoid cell leukodystrophy, thus suggesting that axonal loss might be the marker of severe disease.[29]

Treatment and Outcomes

Umbilical cord blood transplantation has been shown to reduce the clinical severity if treatment is given in very young asymptomatic patients predicted to have a severe phenotype. However, children who underwent transplantation after the onset of symptoms had minimal neurologic improvement.[30]

Metachromatic Leukodystrophy

Clinical Characteristics

Metachromatic leukodystrophy (MLD) is an autosomal recessive lysosomal storage disease with an estimated incidence of 1 in 40,000 births.[2] It is divided into three subtypes based on age of onset after a period of initially normal development: late infantile, juvenile and adult. The late infantile form is the most severe phenotype and may present between 6 months and 2 years of age with motor developmental delay, weakness, hypotonia and ataxia. As the disorder progresses peripheral neuropathy occurs and worsens, speech and

cognition deteriorate, seizures may occur, hypotonia eventually transitions into a spastic quadriplegia, vision and hearing decline and the child eventually is left in a decerebrate state.[31,32] The juvenile form may have onset as either an early (4 to 8 years old) or late (6 to 16 years old) subgroup with the early subgroup resembling the late infantile form with predominantly motor involvement initially, whereas the late juvenile subgroup typically presents with behavioral and cognitive problems. The adult form may present anytime after 16 years of age and, like the late juvenile form, typically begins with emotional and intellectual dysfunction and may appear psychiatric in nature. As it progresses motor function is affected and peripheral neuropathy, to a varying degree, may be seen.[33,34] All forms of the disease follow a relentlessly progressive course that culminates in a profoundly debilitated state, with the pace of deterioration and progression to death increasing with later onset from within a few years to several decades after initial symptoms.

Etiology and Pathophysiology

MLD is caused by mutations in the *ARSA* gene causing deficiency in the lysosomal enzyme arylsulfatase A, which leads to accumulation of sulfatide.[2] Rarely, the disorder may be caused by mutations in the *PSAP* (prosaposin) gene, leading to deficient sphingolipid activator protein SAP-B (saposin B) that has a role in stimulating the action of ARSA.[35] This accumulation leads to demyelination from oligodendroglial and Schwann cell injury and death, although the mechanism by which this occurs is not completely understood. Greater than 150 distinct mutations in *ARSA* have been described. Those causing no enzyme activity are termed I-type alleles and those causing pathologically reduced enzyme activity are termed A-type alleles; there has been described some degree of genotype-phenotype correlation of allelic makeup with clinical subtype, although this is not universal and greatly varying ages of onset have been seen among siblings with identical mutations.[36-39]

Diagnosis, Pathology and Imaging

Although measurement of ARSA activity in leukocytes or cultured skin fibroblasts may demonstrate disease-causing reduction (typically from zero to 10% activity in MLD), it cannot differentiate between pathologic deficiency and ARSA pseudodeficiency that can occur in healthy individuals.[40] Measurement of urine sulfatide, molecular genetic testing of *ARSA* (or, if urine sulfatide is elevated but enzyme activity is normal, of *PSAP*), or biopsy of nerve or brain are therefore often undertaken as confirmatory tests. Pathologic examination of affected tissues reveals the characteristic metachromatically staining sulfatide deposited throughout the white matter and in Schwann cells and macrophages of peripheral nerve, while MRI demonstrates confluent, symmetric and non-enhancing white matter hypodensity that initially spares U-fibers and may start with occipital or frontal predominance (Fig. 3).[2]

Treatment

At present, HSCT is the only therapy available that has been clearly shown to alter the course of MLD involving the central nervous system, with greatest efficacy seen in patients with juvenile or adult forms still early in the course of the disease.[41] Other therapies currently under investigation include gene therapy techniques, warfarin (which

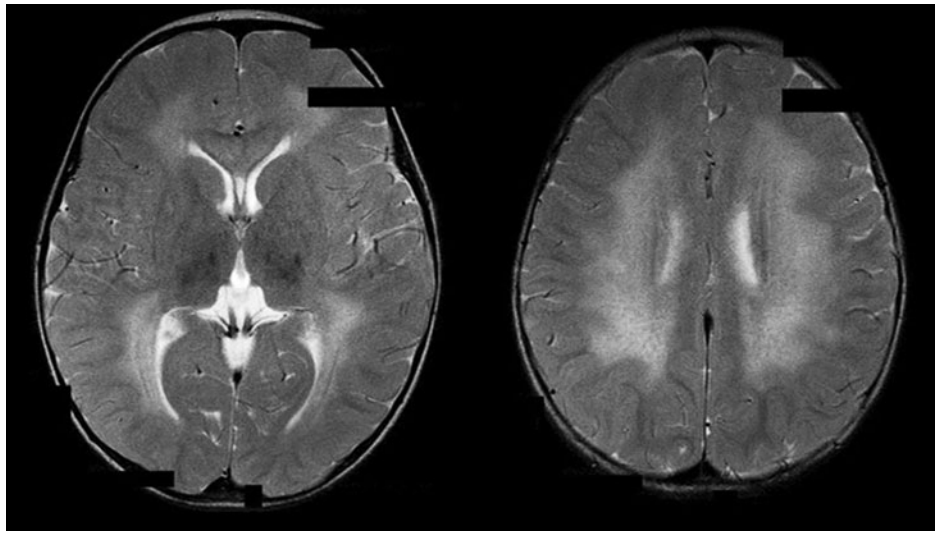

Figure 3. A 2-year, 10-month-old boy with the late-infantile form of metachromatic leukodystrophy. In this axial T2-weighted noncontrast MRI there are symmetric, confluent white matter abnormalities in all lobes that exhibit relative sparing of the subcortical U-fibers.

may affect the role vitamin K plays in sulfatide synthesis) and recombinant human ARSA (though this is not believed to cross the blood-brain barrier).[38,42,43]

HYPOMYELINATING DISORDERS

Pelizaeus-Merzbacher Disease

Clinical Characteristics

Pelizaeus-Merzbacher disease (PMD) is a rare disorder with an X-linked recessive mode of inheritance. Three forms have been delineated based on age and severity of presentation: classical, connatal and transitional. Children with the classical type (the most common form of the disease) present within the first year of life with irregular nystagmoid eye movements, hypotonia, severe developmental delay, microcephaly, growth retardation, ataxia and seizures. Spasticity, cerebellar signs and movement abnormalities including dystonia, choreoathetosis and hyperkinesis become more prominent with age. Very slow neurological deterioration occurs, usually noted after 10-12 years of age and they may survive until the 6th decade of life. Connatal PMD is the most severe form. Severe hypotonia, stridor, feeding impairment and nystagmus are noted during the neonatal period. Few, if any, developmental milestones are reached. The affected children undergo rapid progression and typically die during the first decade. Patients with the transitional form have overlapping features between the connatal and classic forms, with notable slower and later onset than the connatal form.[2,44] X-linked spastic paraplegia Type 2 (SPG2) is an allelic condition of PMD. The pure form of SPG2 may present with only a

spastic gait and ambulation problems, though there also exists a complicated form with additional nystagmus, ataxia and intention tremor.[45]

Etiology and Pathophysiology

PMD and SPG2 are caused by mutation in the *PLP* gene coding for proteolipid protein located on the long arm of the X chromosome (Xq21.33-Xq22).[46-48] The *PLP* gene encodes two proteolipid proteins in oligodendrocytes, PLP and DM20. While PLP is the prominent protein in CNS myelin, DM20 may be involved in oligodendrocyte differentiation and survival.[49-51] Many different mutations have been identified in *PLP*, with gene duplications being the most common cause of PMD. Clinical severity is correlated with the specific mutation. Mutations that affect only PLP, but not DM20, cause a milder clinical syndrome.[52] The most severe presentations of PMD are usually caused by missense mutations, although a broad range of clinical phenotypes may still be seen.[53] A benign form of PMD is seen in deletions or null mutations of the *PLP* gene.[52,54]

Pathology and Imaging Findings

In PMD central white matter is reduced in volume with signs of deficient myelination (Fig. 4). In the connatal form, central myelin is completely absent with reduced number of oligodendrocytes. In the classical form, the central white matter shows a patchy distribution of dysmyelination with preserved myelin islands, giving a "tigroid" appearance. Axons are relatively well preserved, though some axonal loss

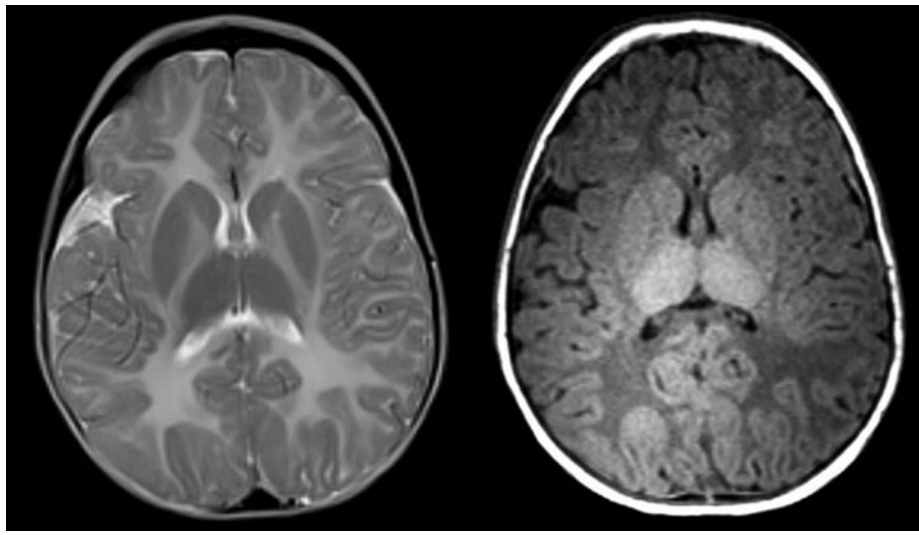

Figure 4. A 12-month-old boy with Pelizaeus-Merzbacher disease. T2 (left) and T1-MPR (right) axial sequences from a brain MRI show diffuse white matter signal intensity abnormalities with no evidence of myelination on the T1-MPR or T2 weighted images. There is bilateral, symmetric abnormal T2/FLAIR signal hyperintensity in the internal and external capsules.

may be seen in completely demyelinated areas. In SPG2, demyelination affects mainly the longitudinal spinal tracts.[55] The extent of axonal injury increases with age and may account for the progression of neurological signs and symptoms in patients with PMD.[52] It may be difficult to diagnose hypomyelination during the first few months of life, though the absence of myelin in the pons, cerebellum, posterior limb of the internal capsule, splenium of corpus callosum and optic radiations in the first 3 months in the right clinical setting may suggest PMD.[56] MRI patterns of PMD have been divided into 3 subtypes; Type I, diffusely hemispheric and corticospinal; Type II, diffusely hemispheric without brain stem lesions; and Type III, patchy in the hemispheres.[57] There is no clear relationship between MRI findings and clinical phenotype, but the degree of hypomyelination has been correlated with the severity of clinical handicap.[58] Magnetic resonance spectroscopy (MRS) results in patients with PMD are inconsistent: normal NAA/Cr ratio with decreased Ch/Cr ratio;[59,60] decreased NAA/Cr ratio with normal Cho/Cr ratio;[61] and increased NAA concentration.[62]

Treatment

There is currently no specific treatment available for PMD.

Alexander Disease

Clinical Characteristics

Alexander disease is a rare, mostly sporadic, progressive disorder of CNS, although familial cases have been reported. Based on the age of onset and severity of symptoms three subtypes have been described: infantile, juvenile and adult forms. The infantile form (birth to 2 years) is the most severe phenotype. Patients often present with macrocephaly, seizures, spasticity, motor and bulbar dysfunction. These children usually die within the first decade of life. Children with the juvenile form often present between 2 to 12 years of age with bulbar symptoms and signs followed by ataxia and spasticity. They typically survive into the 2nd to 4th decades of life. Adult-onset Alexander disease presents with gradually or episodically progressive symptoms of dysarthria, dysphonia, dysphagia, pyramidal signs, ataxia and palatal myoclonus or tremor.[63,64] The clinical course and survival of adult-onset Alexander disease are quite variable: the mean age of onset is in the late thirties, although an asymptomatic carrier over age 60 has been described.[65]

Etiology and Pathophysiology

The genetic basis of Alexander disease was established following discovery of mutations in different glial fibrillary acidic protein (GFAP) residues. *GFAP* mutations result in an over-expression of abnormal GFAP, which causes a lethal encephalopathy.[66] Another distinct pathological feature of Alexander disease is paucity of myelin, which is most pronounced and severe in the frontal white matter. In areas of myelin paucity, most axons are intact. In juvenile and adult forms, the pathology may be mainly limited to the brainstem and cerebellum.[67]

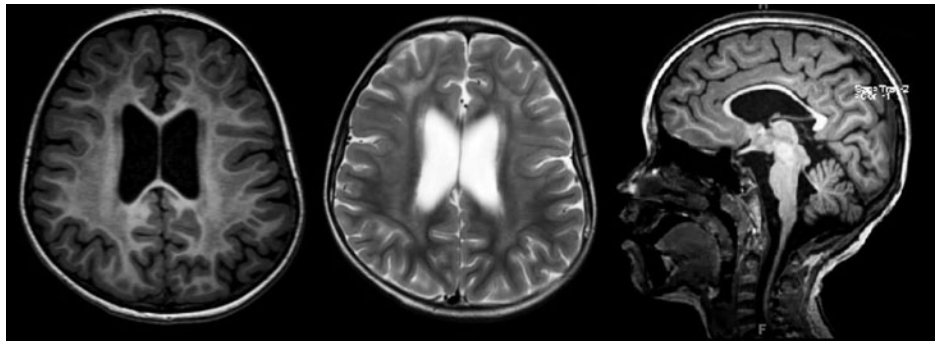

Figure 5. A 6 year-old girl with infantile Alexander disease. Axial T1-MPR (left) and T2 (center) images from a brain MRI show white matter changes with increased T2 and decreased T1 signal intensity, most prominent anteriorly and largely sparing the subcortical and periventricular white matter. There is a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images. Sagittal T1-MPR images (right) show corpus callosum, frontal and parietal cortical, cerebellar and pontine atrophy. Also noted is thickening of the inferior aspect of the tectum that may represent an incidental glioma.

Pathology and Imaging Findings

The most distinctive pathologic feature of Alexander disease is the presence and widespread deposition of cytoplasmic inclusions localized in astrocyte cytoplasm, termed Rosenthal fibers. They are mainly found in perivascular, perivenular and subpial spaces of cerebral hemispheres (mainly frontal), cerebellum and brainstem.[68] These Rosenthal fibers contain GFAP, which is now believed to modulate astrocyte motility and shape. GFAP also may be involved in glial cell adhesion, myelination and cell signaling.[69] Van der Knaap et al defined MR imaging criteria to diagnose Alexander disease (4 of 5 required): (1) extensive cerebral white matter changes with frontal predominance, (2) a periventricular rim with high signal on T1-weighted images and low signal on T2-weighted images, (3) abnormalities of basal ganglia and thalami, (4) brain stem abnormalities and (5) abnormal contrast enhancement. Although MRI (Fig. 5) is useful for diagnostic purposes and can document the extent of white matter disease, it does not always predict the severity and course of the disease.[64] The discrepancy between severe white matter changes on MRI and mild clinical features in some patients with Alexander disease may be explained by axonal preservation.[70] Decreasing NAA concentration over the time on proton MR spectroscopy may predict ongoing subclinical neuronal degeneration in these patients. This possibility is supported by research showing absent or severely reduced NAA in the oldest patients with the most severe clinical course.[70] These findings suggest that the degree and timing of the axonal degeneration may determine the phenotypic severity, rate of neurological decline and age of symptom onset in Alexander disease.

Treatment and Outcomes

There is no cure for Alexander Disease. The treatment for Alexander disease is symptomatic and supportive.

SPONGIFORM DISORDERS

Canavan Disease

Clinical Characteristics

Canavan disease is a rare autosomal recessive spongiform leukodystrophy most often seen in children of Ashkenazi Jewish descent.[71] It most commonly presents in infancy, with symptom onset between 3 and 6 months of age, although a congenital form may occur rarely and juvenile- and adult-onset forms, though controversial, may exist.[72,73] Initial symptoms include lethargy or irritability, a weak cry and suck, poor head control, hypotonia, decreased movement of the extremities and decreased visual responsiveness. Head growth is accelerated and macrocephaly develops and, as the condition progresses, spasticity and hyperreflexia develop, tonic extensor spasms occur, development arrests and regresses, blindness and optic atrophy are seen and about half of affected children develop seizures as they progress to a decerebrate state, with death typically occurring in childhood or the teenage years.[73]

Etiology and Pathophysiology

Canavan disease is caused by mutations in the *ASPA* gene leading to deficiency in aspartoacylase, the enzyme located in oligodendroglia that hydrolyzes NAA into aspartic acid and acetate.[74-77] Among the Ashkenazi population nearly all disease occurs due to only a few mutations, whereas in other patient groups different mutations of *ASPA* are found.[71,74] NAA accumulates in the CNS, causing dysfunction and injury to oligodendrocytes, vacuolation and spongiform changes and myelin destruction. The mechanism by which this occurs is not known, but there is increased water content in affected white matter and it has been suggested that, among other things, NAA may act as an osmoregulator and molecular water pump.[2,78]

Diagnosis, Pathology and Imaging

Biochemical diagnosis may be made by identifying elevated NAA in urine and serum (or amniotic fluid for prenatal testing) organic acid screening, while molecular genetic studies may be useful as confirmatory or prenatal tests. On pathologic examination, the brain is enlarged and extensive sponge-like vacuolation and demyelination is primarily seen in the subcortical and cerebellar white matter, although brainstem, globus pallidus, hypothalamus and thalamus are also affected.[2] MRI demonstrates symmetric, diffuse white matter involvement with T1 hypo- and T2 hyperintensity along with evidence of restricted diffusion in the deep white matter and brainstem (Fig. 6), whereas MR spectroscopy shows markedly increased levels of NAA.[79,80]

Treatment

No specific therapies are yet available and treatment is symptomatic and supportive. Investigational treatments include the use of gene therapy techniques and lithium, which may reduce the NAA content in affected white matter.[81,82]

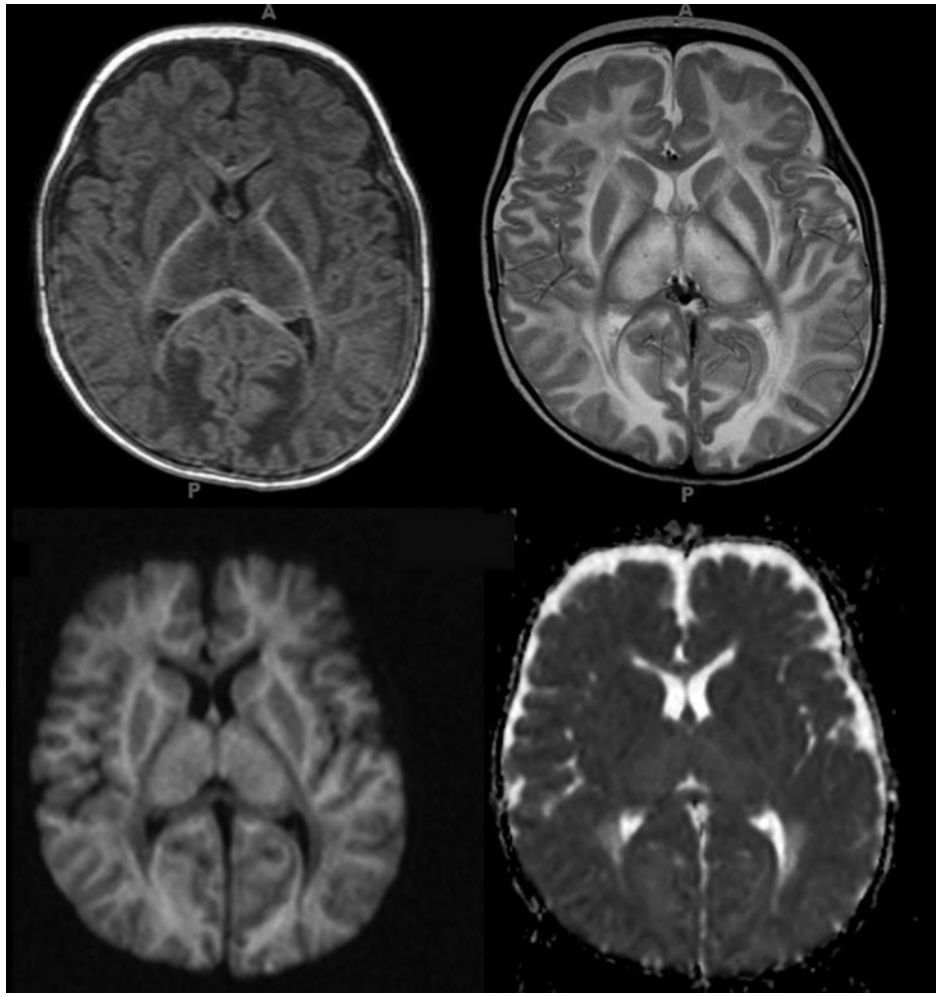

Figure 6. A 7-month-old boy with Canavan disease. Brain MRI T1-MPR (upper left) and T2 sequences (upper right) show diffuse signal abnormality throughout the bilateral cerebral white matter. Trace-diffusion (lower left) high signal and low ADC on the ADC map (lower right) indicate diffusion restriction within these regions. Note the preservation of myelin within the posterior limbs of the internal capsules and the corpus callosum.

Megalencephalic Leukoencephalopathy with Subcortical Cysts

Clinical Characteristics

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a recently described, rare, autosomal recessive disease that occurs with greater frequency in Turkish and Agarwal (an ethnic group in India) populations.[83] It presents with macrocephaly at

birth or within the first year of life, after which the growth rate normalizes, with initially normal neurologic exam and development in most cases.[84] Severity and course vary, but delayed and unsteady walking is seen early and is followed, over years, by the slow development of prominent ataxia, hyperreflexia, epilepsy, dysarthria, inability to walk and mild cognitive decline.[2]

Etiology and Pathophysiology

Mutations in *MLC1* genes are found in the majority of patients with MLC, although a significant percentage have typical MLC disease and no mutations.[85-87] The gene encodes for a transmembrane protein with unknown function.

Diagnosis, Pathology and Imaging

No measurable biochemical abnormalities have been identified and many patients do not have *MLC1* mutations (though genetic testing may be used prenatally or for confirmation in families with known mutations). Diagnosis of MLC is based on the clinical picture and imaging findings (Fig. 7), with MRI showing diffusely abnormal and mildly swollen cerebral white matter (with relative preservation of the corpus callosum, internal capsule and brainstem), mildly abnormal cerebellar white matter, increased white matter diffusivity, anterior temporal and frontoparietal cysts that may grow in size and number and eventual cerebral atrophy.[84,88,89] Brain pathologic findings were described in one patient and consisted of vacuolization and spongiform changes in the white matter, minor myelin degradation with splitting between the outer lamellae of the sheaths and normal cortex.[90]

Treatment and Outcomes

No specific treatment exists and therapy is supportive and symptomatic.

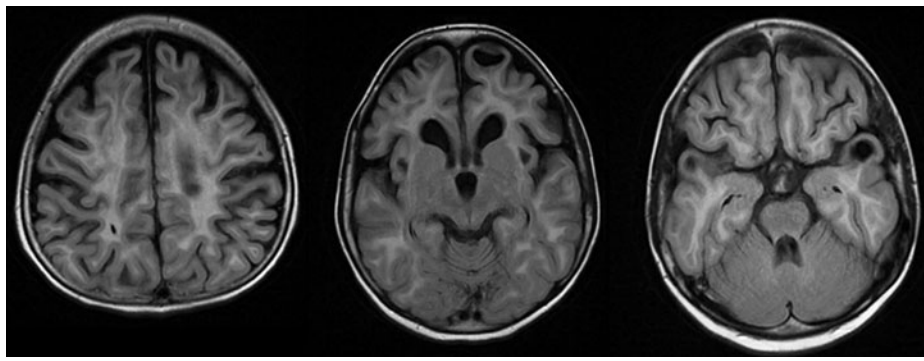

Figure 7. A 7 year-old girl with megalencephalic leukoencephalopathy with subcortical cysts. FLAIR sequence from the brain MRI shows diffusely abnormal cerebral white matter with relative preservation of the brainstem, mildly abnormal cerebellar white matter and primarily anterior temporal and frontoparietal cysts along with cerebral atrophy. Courtesy of Jayne Ness, MD, PhD, The University of Alabama at Birmingham.

CYSTIC DISORDERS

Vanishing White Matter Disease

Clinical Characteristics

Vanishing white matter disease (VWM, childhood ataxia with central nervous system hypomyelination, or Cree encephalopathy) is an autosomal recessive disease that is likely among the more common leukodystrophies.[91] VWM manifests a broad range of clinical presentations and ages of onset, from congenital forms with rapid neurological decline and death, to adult-onset forms with slow symptom progression; the classical and most common form presents between 2 and 5 years of age with progressive gait difficulties and mild cognitive impairment.[92] Characteristic of the disease are episodes of acute deterioration after minor head trauma, febrile infections, prolonged sun exposure and even fear that manifest as hypotonia, irritability, vomiting, seizures, unconsciousness that may progress to coma or death and lack of full recovery afterwards.[2] Extracranial involvement often includes ovarian dysgenesis in antenatal forms and ovarian failure in later-onset disease (termed ovarioleukodystrophy).[93]

Etiology and Pathophysiology

VWM and its varying presentations are caused by mutations in any of the five genes, *eIF2B1* through *eIF2B5*, that encode subunits (alpha through epsilon) of eukaryotic translation initiation factor 2B (eIF2B).[94,95] Regulation of the translation of mRNA to polypeptides involves eukaryotic transcription factors and mutant eIF2B in VWM may cause disease by disrupting the normal stress-elicited compensatory mechanisms that inhibit synthesis of new proteins and that induce signals promoting both cellular survival and apoptosis.[96] While members of the same affected family and individuals with the same mutation have been described to display significant phenotypic heterogeneity, some genotype-phenotype correlations have been noted.[94,97-101]

Diagnosis, Pathology and Imaging

No reliable routine laboratory abnormalities have been identified that aid in the diagnosis of VWM, though decreased CSF asialotransferrin to transferrin ratio and decreased lymphocyte eIF2B nucleotide guanine exchange (GEF) activity have both been proposed as possible markers of disease.[102,103] Molecular genetic testing of eIF2B subunits can be performed and is essential in infants with the antenatal or early infantile forms of VWM, but may not demonstrate a mutation in approximately 10% of patients with VWM.[104-106] Pathologic findings include vacuolation and "foamy" oligodendrocytes, white matter changes ranging from cystic to cavitary, variable degrees of axon loss and no significant inflammation.[2] MRI may show diffuse signal abnormalities in the cerebral white matter that may have a signal intensity near that of CSF, diffuse disappearance of the cerebral white matter, a fluid-filled space between the ependyma and cortex if all cerebral white matter has vanished, relative sparing of the temporal lobes, noncystic cerebellar white matter, no abnormal enhancement, radiating stripes within abnormal white matter on sagittal and coronal images and involvement of the inner (but sparing of the outer) rim of the corpus callosum.[97]

Treatment

There is no specific therapy for VWM, but avoidance and prompt treatment of possible stressors that may precipitate an episode is essential.

CONCLUSION

Patients with leukodystrophies, though often never given an ultimate diagnosis, can present in a wide variety of unique ways. Challenging and frustrating for both the clinician and the patient are the typically progressive natures of these diseases. The paucity of specific therapies available to treat them, and the often grim prognoses they carry, also contribute to the difficulty in caring for affected patients and families. Some promising tools for identification, evaluation and treatment of these diseases are under development, while many more are yet to be discovered and investigated. Continued research into genetic and pathophysiologic etiologies, distinctive biochemical and imaging features and potential avenues of treatment are all absolute necessities to improve the clinical care available for patients suffering from this difficult group of disorders.

REFERENCES

1. Mar S, Noetzel M. Axonal damage in leukodystrophies. Pediatr Neurol 2010; 42(4):239-242.
2. van der Knaap MS, Valk J, Barkhof F. Magnetic resonance of myelination and myelin disorders. 3rd ed. Berlin; New York: Springer; 2005.
3. Lyon G, Fattal-Valevski A, Kolodny EH. Leukodystrophies: clinical and genetic aspects. Top Magn Reson Imaging 2006; 17(4):219-242.
4. Costello DJ, Eichler AF, Eichler FS. Leukodystrophies: classification, diagnosis and treatment. Neurologist 2009; 15(6):319-328.
5. Bonkowsky JL, Nelson C, Kingston JL et al. The burden of inherited leukodystrophies in children. Neurology 2010.
6. van der Knaap MS, Breiter SN, Naidu S et al. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology 1999; 213(1):121-133.
7. Bezman L, Moser AB, Raymond GV et al. Adrenoleukodystrophy: incidence, new mutation rate and results of extended family screening. Ann Neurol 2001; 49(4):512-517.
8. Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol 2007; 3(3):140-151.
9. Restuccia D, Di Lazzaro V, Valeriani M et al. Neurophysiological abnormalities in adrenoleukodystrophy carriers. Evidence of different degrees of central nervous system involvement. Brain 1997; 120 (Pt 7):1139-1148.
10. Schmidt S, Traber F, Block W et al. Phenotype assignment in symptomatic female carriers of X-linked adrenoleukodystrophy. J Neurol 2001; 248(1):36-44.
11. Moser HW, Moser AB, Smith KD et al. Adrenoleukodystrophy: phenotypic variability and implications for therapy. J Inherit Metab Dis 1992; 15(4):645-664.
12. Moser AB, Kreiter N, Bezman L et al. Plasma very long chain fatty acids in 3,000 peroxisome disease patients and 29,000 controls. Ann Neurol 1999; 45(1):100-110.
13. Kim JH, Kim HJ. Childhood X-linked adrenoleukodystrophy: clinical-pathologic overview and MR imaging manifestations at initial evaluation and follow-up. Radiographics 2005; 25(3):619-631.
14. Kumar AJ, Rosenbaum AE, Naidu S et al. Adrenoleukodystrophy: correlating MR imaging with CT. Radiology 1987; 165(2):497-504.
15. Loes DJ, Fatemi A, Melhem ER et al. Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. Neurology 2003; 61(3):369-374.
16. Eichler FS, Barker PB, Cox C et al. Proton MR spectroscopic imaging predicts lesion progression on MRI in X-linked adrenoleukodystrophy. Neurology 2002; 58(6):901-907.
17. Eichler FS, Itoh R, Barker PB et al. Proton MR spectroscopic and diffusion tensor brain MR imaging in X-linked adrenoleukodystrophy: initial experience. Radiology 2002; 225(1):245-252.

18. Semmler A, Kohler W, Jung HH et al. Therapy of X-linked adrenoleukodystrophy. Expert Rev Neurother 2008; 8(9):1367-1379.
19. Cartier N, Aubourg P. Hematopoietic stem cell transplantation and hematopoietic stem cell gene therapy in X-linked adrenoleukodystrophy. Brain Pathol 2010; 20(4):857-862.
20. Cartier N, Hacein-Bey-Abina S, Bartholomae CC et al. Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. Science 2009; 326(5954):818-823.
21. Fourcade S, Ruiz M, Guilera C et al. Valproic acid induces antioxidant effects in X-linked adrenoleukodystrophy. Hum Mol Genet 2010; 19(10):2005-2014.
22. Crome L, Hanefeld F, Patrick D et al. Late onset globoid cell leucodystrophy. Brain 1973; 96(4):841-848.
23. Thomas PK, Halpern JP, King RH et al. Galactosylceramide lipidosis: novel presentation as a slowly progressive spinocerebellar degeneration. Ann Neurol 1984; 16(5):618-620.
24. Suzuki Y, Austin J, Armstrong D et al. Studies in globoid leukodystrophy: enzymatic and lipid findings in the canine form. Exp Neurol 1970; 29(1):65-75.
25. Suzuki K, Suzuki Y. Globoid cell leucodystrophy (Krabbe's disease): deficiency of galactocerebroside beta-galactosidase. Proc Natl Acad Sci USA 1970; 66(2):302-309.
26. Wenger DA, Rafi MA, Luzi P. Molecular genetics of Krabbe disease (globoid cell leukodystrophy): diagnostic and clinical implications. Hum Mutat 1997; 10(4):268-279.
27. Suzuki K. Twenty five years of the "psychosine hypothesis": a personal perspective of its history and present status. Neurochem Res 1998; 23(3):251-259.
28. Provenzale JM, Escolar M, Kurtzberg J. Quantitative analysis of diffusion tensor imaging data in serial assessment of Krabbe disease. Ann N Y Acad Sci 2005; 1064:220-229.
29. Brockmann K, Dechent P, Wilken B et al. Proton MRS profile of cerebral metabolic abnormalities in Krabbe disease. Neurology 2003; 60(5):819-825.
30. Escolar ML, Poe MD, Provenzale JM et al. Transplantation of umbilical-cord blood in babies with infantile Krabbe's disease. N Engl J Med 2005; 352(20):2069-2081.
31. Cameron CL, Kang PB, Burns TM et al. Multifocal slowing of nerve conduction in metachromatic leukodystrophy. Muscle Nerve 2004; 29(4):531-536.
32. Wang PJ, Hwu WL, Shen YZ. Epileptic seizures and electroencephalographic evolution in genetic leukodystrophies. J Clin Neurophysiol 2001; 18(1):25-32.
33. Felice KJ, Gomez Lira M, Natowicz M et al. Adult-onset MLD: a gene mutation with isolated polyneuropathy. Neurology 2000; 55(7):1036-1039.
34. Marcao AM, Wiest R, Schindler K et al. Adult onset metachromatic leukodystrophy without electroclinical peripheral nervous system involvement: a new mutation in the ARSA gene. Arch Neurol 2005; 62(2):309-313.
35. Wrobe D, Henseler M, Huettler S et al. A nonglycosylated and functionally deficient mutant (N215H) of the sphingolipid activator protein B (SAP-B) in a novel case of metachromatic leukodystrophy (MLD). J Inherit Metab Dis 2000; 23(1):63-76.
36. Arbour LT, Silver K, Hechtman P et al. Variable onset of metachromatic leukodystrophy in a Vietnamese family. Pediatr Neurol 2000; 23(2):173-176.
37. Berger J, Loschl B, Bernheimer H et al. Occurrence, distribution and phenotype of arylsulfatase A mutations in patients with metachromatic leukodystrophy. Am J Med Genet 1997; 69(3):335-340.
38. Fluharty AL. (Updated 2008/09/23). Arylsulfatase A Deficiency. GeneReviews at GeneTests: Medical Genetics Information Resource (database online) Copyright, University of Washington, Seattle:1997-2010. Available at http://www.genetests.org, Accessed 2010/09/15.
39. Polten A, Fluharty AL, Fluharty CB et al. Molecular basis of different forms of metachromatic leukodystrophy. N Engl J Med 1991; 324(1):18-22.
40. Barth ML, Ward C, Harris A et al. Frequency of arylsulphatase A pseudodeficiency associated mutations in a healthy population. J Med Genet 1994; 31(9):667-671.
41. Orchard PJ, Tolar J. Transplant Outcomes in Leukodystrophies. Seminars in Hematology 2010; 47(1):70-78.
42. Sevin C, Cartier-Lacave N, Aubourg P. Gene therapy in metachromatic leukodystrophy. Int J Clin Pharmacol Ther 2009; 47 Suppl 1:S128-131.
43. Sundaram KS, Lev M. Warfarin administration reduces synthesis of sulfatides and other sphingolipids in mouse brain. J Lipid Res 1988; 29(11):1475-1479.
44. Boulloche J, Aicardi J. Pelizaeus-Merzbacher disease: clinical and nosological study. J Child Neurol 1986; 1(3):233-239.
45. Hudson LD. Pelizaeus-Merzbacher disease and spastic paraplegia type 2: two faces of myelin loss from mutations in the same gene. J Child Neurol 2003; 18(9):616-624.
46. Willard HF, Riordan JR. Assignment of the gene for myelin proteolipid protein to the X chromosome: implications for X-linked myelin disorders. Science 1985; 230(4728):940-942.
47. Gencic S, Abuelo D, Ambler M et al. Pelizaeus-Merzbacher disease: an X-linked neurologic disorder of myelin metabolism with a novel mutation in the gene encoding proteolipid protein. Am J Hum Genet 1989; 45(3):435-442.

48. Hudson LD, Puckett C, Berndt J et al. Mutation of the proteolipid protein gene PLP in a human X chromosome-linked myelin disorder. Proc Natl Acad Sci USA 1989; 86(20):8128-8131.
49. Weimbs T, Stoffel W. Proteolipid protein (PLP) of CNS myelin: positions of free, disulfide-bonded and fatty acid thioester-linked cysteine residues and implications for the membrane topology of PLP. Biochemistry 1992; 31(49):12289-12296.
50. LeVine SM, Wong D, Macklin WB. Developmental expression of proteolipid protein and DM20 mRNAs and proteins in the rat brain. Dev Neurosci 1990; 12(4-5):235-250.
51. Yang X, Skoff RP. Proteolipid protein regulates the survival and differentiation of oligodendrocytes. J Neurosci 1997; 17(6):2056-2070.
52. Garbern JY. Pelizaeus-Merzbacher disease: Genetic and cellular pathogenesis. Cell Mol Life Sci 2007; 64(1):50-65.
53. Cailloux F, Gauthier-Barichard F, Mimault C et al. Genotype-phenotype correlation in inherited brain myelination defects due to proteolipid protein gene mutations. Clinical European Network on Brain Dysmyelinating Disease. Eur J Hum Genet 2000; 8(11):837-845.
54. Garbern JY, Yool DA, Moore GJ et al. Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. Brain 2002; 125(Pt 3):551-561.
55. Seitelberger F. Neuropathology and genetics of Pelizaeus-Merzbacher disease. Brain Pathol 1995; 5(3):267-273.
56. Barkovich AJ. Magnetic resonance techniques in the assessment of myelin and myelination. J Inherit Metab Dis 2005; 28(3):311-343.
57. Nezu A, Kimura S, Takeshita S et al. An MRI and MRS study of Pelizaeus-Merzbacher disease. Pediatr Neurol 1998; 18(4):334-337.
58. Plecko B, Stockler-Ipsiroglu S, Gruber S et al. Degree of hypomyelination and magnetic resonance spectroscopy findings in patients with Pelizaeus Merzbacher phenotype. Neuropediatrics 2003; 34(3):127-136.
59. Takanashi J, Sugita K, Osaka H et al. Proton MR spectroscopy in Pelizaeus-Merzbacher disease. AJNR Am J Neuroradiol 1997; 18(3):533-535.
60. Spalice A, Popolizio T, Parisi P et al. Proton MR spectroscopy in connatal Pelizaeus-Merzbacher disease. Pediatr Radiol 2000; 30(3):171-175.
61. Bonavita S, Schiffmann R, Moore DF et al. Evidence for neuroaxonal injury in patients with proteolipid protein gene mutations. Neurology 2001; 56(6):785-788.
62. Takanashi J, Inoue K, Tomita M et al. Brain N-acetylaspartate is elevated in Pelizaeus-Merzbacher disease with PLP1 duplication. Neurology 2002; 58(2):237-241.
63. Li R, Johnson AB, Salomons G et al. Glial fibrillary acidic protein mutations in infantile, juvenile and adult forms of Alexander disease. Ann Neurol 2005; 57(3):310-326.
64. van der Knaap MS, Naidu S, Breiter SN et al. Alexander disease: diagnosis with MR imaging. AJNR Am J Neuroradiol 2001; 22(3):541-552.
65. Balbi P, Seri M, Ceccherini I et al. Adult-onset Alexander disease : report on a family. J Neurol 2008; 255(1):24-30.
66. Brenner M, Johnson AB, Boespflug-Tanguy O et al. Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease. Nat Genet 2001; 27(1):117-120.
67. Spalke G, Mennel HD. Alexander's disease in an adult: clinicopathologic study of a case and review of the literature. Clin Neuropathol 1982; 1(3):106-112.
68. Quinlan RA, Brenner M, Goldman JE et al. GFAP and its role in Alexander disease. Exp Cell Res 2007; 313(10):2077-2087.
69. Tomokane N, Iwaki T, Tateishi J et al. Rosenthal fibers share epitopes with alpha B-crystallin, glial fibrillary acidic protein and ubiquitin, but not with vimentin. Immunoelectron microscopy with colloidal gold. Am J Pathol 1991; 138(4):875-885.
70. Dinopoulos A, Gorospe JR, Egelhoff JC et al. Discrepancy between neuroimaging findings and clinical phenotype in Alexander disease. AJNR Am J Neuroradiol 2006; 27(10):2088-2092.
71. Kaul R, Gao GP, Aloya M et al. Canavan disease: mutations among Jewish and nonJewish patients. Am J Hum Genet 1994; 55(1):34-41.
72. Adachi M, Schneck L, Cara J et al. Spongy degeneration of the central nervous system (van Bogaert and Bertrand type; Canavan's disease). A review. Hum Pathol 1973; 4(3):331-347.
73. Traeger EC, Rapin I. The clinical course of Canavan disease. Pediatr Neurol 1998; 18(3):207-212.
74. Kaul R, Gao GP, Balamurugan K et al. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. Nat Genet 1993; 5(2):118-123.
75. Kaul R, Gao GP, Balamurugan K et al. Canavan disease: molecular basis of aspartoacylase deficiency. J Inherit Metab Dis 1994; 17(3):295-297.
76. Matalon R, Kaul R, Casanova J et al. SSIEM Award. Aspartoacylase deficiency: the enzyme defect in Canavan disease. J Inherit Metab Dis 1989; 12 Suppl 2:329-331.

77. Matalon R, Michals-Matalon K. Biochemistry and molecular biology of Canavan disease. Neurochem Res 1999; 24(4):507-513.
78. Baslow MH. Brain N-acetylaspartate as a molecular water pump and its role in the etiology of Canavan disease: a mechanistic explanation. J Mol Neurosci 2003; 21(3):185-190.
79. Cakmakci H, Pekcevik Y, Yis U et al. Diagnostic value of proton MR spectroscopy and diffusion-weighted MR imaging in childhood inherited neurometabolic brain diseases and review of the literature. Eur J Radiol 2010; 74(3):e161-171.
80. Srikanth SG, Chandrashekar HS, Nagarajan K et al. Restricted diffusion in Canavan disease. Childs Nerv Syst 2007; 23(4):465-468.
81. Assadi M, Janson C, Wang DJ et al. Lithium citrate reduces excessive intra-cerebral N-acetyl aspartate in Canavan disease. Eur J Paediatr Neurol 2010; 14(4):354-359.
82. Janson CG, Assadi M, Francis J et al. Lithium citrate for Canavan disease. Pediatr Neurol 2005; 33(4):235-243.
83. Singhal BS, Gorospe JR, Naidu S. Megalencephalic Leukoencephalopathy With Subcortical Cysts. Journal of Child Neurology 2003; 18(9):646-652.
84. van der Knaap MS, Barth PG, Stroink H et al. Leukoencephalopathy with swelling and a discrepantly mild clinical course in eight children. Ann Neurol 1995; 37(3):324-334.
85. Leegwater PA, Yuan BQ, van der Steen J et al. Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megalencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 2001; 68(4):831-838.
86. Topcu M, Saatci I, Topcuoglu MA et al. Megalencephaly and leukodystrophy with mild clinical course: a report on 12 new cases. Brain Dev 1998; 20(3):142-153.
87. van der Knaap MS, Lai V, Köhler W et al. Megalencephalic leukoencephalopathy with cysts without MLC1 defect: 2 phenotypes. Annals of Neurology 2010; 67(6):834-7.
88. Itoh N, Maeda M, Naito Y et al. An adult case of megalencephalic leukoencephalopathy with subcortical cysts with S93L mutation in MLC1 gene: a case report and diffusion MRI. Eur Neurol 2006; 56(4):243-245.
89. van der Voorn JP, Pouwels PJ, Hart AA et al. Childhood white matter disorders: quantitative MR imaging and spectroscopy. Radiology 2006; 241(2):510-517.
90. van der Knaap MS, Barth PG, Vrensen GF et al. Histopathology of an infantile-onset spongiform leukoencephalopathy with a discrepantly mild clinical course. Acta Neuropathol 1996; 92(2):206-212.
91. Schiffmann R, Boespflug-Tanguy O. An update on the leukodsytrophies. Curr Opin Neurol 2001; 14(6):789-794.
92. Fogli A, Boespflug-Tanguy O. The large spectrum of eIF2B-related diseases. Biochem Soc Trans 2006; 34(Pt 1):22-29.
93. van der Knaap MS, van Berkel CG, Herms J et al. eIF2B-related disorders: antenatal onset and involvement of multiple organs. Am J Hum Genet 2003; 73(5):1199-1207.
94. Fogli A, Wong K, Eymard-Pierre E et al. Cree leukoencephalopathy and CACH/VWM disease are allelic at the EIF2B5 locus. Ann Neurol 2002; 52(4):506-510.
95. Ohlenbusch A, Henneke M, Brockmann K et al. Identification of ten novel mutations in patients with eIF2B-related disorders. Hum Mutat 2005; 25(4):411.
96. van der Voorn JP, van Kollenburg B, Bertrand G et al. The unfolded protein response in vanishing white matter disease. J Neuropathol Exp Neurol 2005; 64(9):770-775.
97. van der Knaap MS, Pronk JC, Scheper GC. Vanishing white matter disease. Lancet Neurol 2006; 5(5):413-423.
98. Fogli A, Rodriguez D, Eymard-Pierre E et al. Ovarian failure related to eukaryotic initiation factor 2B mutations. Am J Hum Genet 2003; 72(6):1544-1550.
99. Fogli A, Schiffmann R, Bertini E et al. The effect of genotype on the natural history of eIF2B-related leukodystrophies. Neurology 2004; 62(9):1509-1517.
100. van der Knaap MS, Leegwater PA, van Berkel CG et al. Arg113His mutation in eIF2Bepsilon as cause of leukoencephalopathy in adults. Neurology 2004; 62(9):1598-1600.
101. Li W, Wang X, Van Der Knaap MS et al. Mutations linked to leukoencephalopathy with vanishing white matter impair the function of the eukaryotic initiation factor 2B complex in diverse ways. Mol Cell Biol 2004; 24(8):3295-3306.
102. Vanderver A, Hathout Y, Maletkovic J et al. Sensitivity and specificity of decreased CSF asialotransferrin for eIF2B-related disorder. Neurology 2008; 70(23):2226-2232.
103. Horzinski L, Huyghe A, Cardoso MC et al. Eukaryotic initiation factor 2B (eIF2B) GEF activity as a diagnostic tool for EIF2B-related disorders. PLoS One 2009; 4(12):e8318.
104. Labauge P, Gelot A, Fogli A et al. Autosomal dominant leukodystrophy and childhood ataxia with central nervous system hypomyelination syndrome. Ann Neurol 2006; 60(4):485; author reply 485-486.
105. van der Knaap MS, Scheper GC. Non-eIF2B-related cystic leukoencephalopathy of unknown origin. Ann Neurol 2006; 59(4):724.
106. Labauge P, Fogli A, Castelnovo G et al. Dominant form of vanishing white matter-like leukoencephalopathy. Ann Neurol 2005; 58(4):634-639.