Genetic Disorders Affecting White Matter in the Pediatric Age

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Pediatric white matter disorders can be distinguished into well-defined leukencephalopathies, and undefined leukencephalopathies. The first category may be subdivided into: (a) hypomyelinating disorders; (b) dysmyelinating disorders; (c) leukodystrophies; (d) disorders related to cystic degeneration of myelin; and (e) disorders secondary to axonal damage. The second category, representing up to 50% of leukencephalopathies in childhood, requires a multidisciplinary approach in order to define novel homogeneous subgroups of patients, possibly representing “new genetic disorders” (such as megalencephalic leukoencephalopathy with subcortical cysts and vanishing white matter disease that have recently been identified). In the majority of cases, pediatric white matter disorders are inherited diseases. An integrated description of the clinical, neuroradiographic and pathophysiological features is crucial for categorizing myelin disorders and better understanding their genetic basis. A review of the genetic disorders affecting white matter in the pediatric age, including some novel entities, is provided. © 2004 Wiley-Liss, Inc.

KEY WORDS: myelin; magnetic resonance imaging; demyelination; genetic diseases

INTRODUCTION

The increased use of magnetic resonance imaging (MRI) in children with neurological impairment has expanded our knowledge about genetic disorders affecting white matter. By using a specific “MRI pattern recognition study” [van der Knaap and Valk, 1995], some new genetic diseases, such as megalencephalic leukoencephalopathy with subcortical cysts and vanishing white matter/childhood ataxia with central hypomyelination (CACH), have recently been identified. Furthermore, increased knowledge on the role of structural proteins of myelin, on astrocyte-oligodendrocyte interaction, and on oligodendrocyte-neuron interaction during myelin formation has widened the concept of hypomyelinating disorders. Recent advances in understanding the genetic basis of Alexander disease and glial fibrillary acidic protein (GFAP) have led to consider this disease the first example of a primary genetic disorder of astrocytes [Brenner et al., 2001]. Different classifications of myelin disorders are available (based on either pathological, biochemical, genetic data, or combined clinical and histological/biochemical criteria). By using an integrated MRI and pathophysiological approach, as recently proposed by van der Knaap (2001), white matter disorders may be categorized into the following categories: Hypomyelinating disorders: (i) due to a primary disturbance in the formation of myelin, and (ii) due to a failure of myelination secondary to neurons or astrocytes dysfunction (including abnormal interaction between oligodendrocytes and neurons). Disorders characterized by delayed and disturbed myelination. Disorders characterized by progressive demyelination (leukodystrophies). Disorders related to myelin splitting: (i) with myelin loss, and (ii) without myelin loss. Disorders secondary to axonal damage.

Leukencephalopathies of unknown etiology represent up to 50% of leukencephalopathies in childhood. A multidisciplinary approach (clinical, neuroradiological and electrophysiological) is crucial for defining homogeneous subgroups of entities in order to identify their molecular or biochemical defects.

A review of the genetic disorders affecting white matter in the pediatric age is provided; Table I summarizes MRI findings of the described disorders. Genetic white matter diseases with exclusive onset in adult age and acquired white matter disorders will not be considered herein.

Before discussing white matter disorders, a brief summary on myelin structure and function and on myelination will be reviewed.

MYELIN: STRUCTURE AND FUNCTION

Myelin sheath is a modified plasma membrane that is wrapped in a spiral fashion around a portion of an axon. Each myelin sheath is composed of multiple segments of myelin, which are modified extensions of oligodendroglial cell process. Each oligodendrocyte can contribute myelin to as many as 50 different axons. The sections of myelin are separated from each other by small segments in which the bare axon is exposed to the interstitial space. These segments, called nodes of Ranvier, are location of multiple sodium channels. Electrical impulse cannot flow through the high resistance myelin sheath, but flows out through and depolarizes the axonal membrane at the next node. This saltatory conduction is fast and at a lower energy cost. Myelin sheath is composed of multiple layers that have a protein-lipid-protein-lipid-protein structure. The lipid layer is composed of cholesterol, phospholipids, glycolipids, and hydrocarbon chains. Glycolipid (galactocerebroside and sulfatide) and cholesterol are in the outer layer of the membrane, exposed to the extracellular space. Phospholipids are hydrophobic and are located in the inner (cytoplasm) side of membrane. The area between outer and inner membrane
layers is composed primarily of hydrocarbon chains (long chain fatty acids).

The two major structural proteins of myelin are proteolipid protein (PLP) and myelin basic protein (MBP). Both proteins play a role in maintaining stability and periodic structure of myelin. A few other myelin proteins have been identified: myelin-associated glycoprotein (MAG) which is mediator of the axonal-glial contact, essential for the initiation of myelination; 2,3-cyclic nucleotide 3-phosphodiesterase, myelin oligodendrocyte glycoprotein, and oligodendrocyte-myelin glycoprotein.

Most of the process of myelination occurs in the first two years of life and results from a close interaction between oligodendrocytes, axons, astrocytes, and many soluble factors.

**Hypomyelinating Leukoencephalopathies**

This group of disorders includes conditions due to a primary disturbance in the formation of myelin (such as Pelizaeus-Merzbacher disease (PMD) that may be considered the prototype of hypomyelinating diseases), and other conditions leading to hypomyelination secondary to neurons or astrocytes dysfunction (such as Cockayne syndrome, Tay syndrome, Salla disease, GM1 and GM2 gangliosidoses, and infantile neuronal ceroid lipofuscinosis).

**PMD (OMIM 312080).** PMD (Fig. 1) is an X-linked recessive disorder caused by mutations in the PLP gene [Boespflug-Tanguy et al., 1994]. Different mutations in this gene cause a spectrum of phenotypes ranging from PMD to spastic paraplegia type 2 (SPG2), thus leading to the concept of PLP-related disorders [Cailloux et al., 2000]. PMD shows a variable onset age ranging from birth (connatal PMD) to childhood (classic PMD) [Inoue et al., 1999]. The connal form is characterized by horizontal, vertical or pendular nystagmus, hypotonia, and feeding difficulties. In the classic form, usually at onset in the first year of life, nystagmus, developmental delay, ataxia, limb spasticity, and choreoathetosis are evident. Children with the severe form may not survive the first decade; the others with classic form may live into adult age. Evoked-potential studies are abnormal with loss of rostral waves on the brainstem-evoked potentials. EMG and peripheral nerve conduction

### TABLE 1. MRI Findings

<table>
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<th>Disorder</th>
<th>MRI findings</th>
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<tr>
<td>Pelizaeus–Merzbacher disease</td>
<td>Arrested myelination (however normal for that stage); high signal intensity on T2-weighted images within unmyelinated WM; reduced WM volume, enlarged ventricular system, thin corpus callosum; brain atrophy mainly in the brainstem and cerebellum; abnormally high signal intensity on T2-weighted images throughout the hemispherical white matter; late involvement of the subcortical fibers; abnormal hyperintensity on T1-weighted images in the basal ganglia corresponding to calcification</td>
</tr>
<tr>
<td>Cockayne syndrome</td>
<td>Abnormal high signal intensity of subcortical white matter on T2-weighted images; global volume reduction of the supratentorial WM; extremely hypoplastic corpus callosum; cortical and cerebellar atrophy in severe cases; abnormal signal intensity in the cerebellar white matter</td>
</tr>
<tr>
<td>Salla disease</td>
<td>Extensively abnormal WM with swollen appearance and cavitations, namely in the frontal lobes; abnormalities of basal ganglia, thalami, and brainstem; positive enhancement</td>
</tr>
<tr>
<td>Alexander disease</td>
<td>Extensive WM lesions in the occipital regions with involvement of the splenium of the corpus callosum and sparing of the occipital arcuate fibers; early involvement of the pyramidal and occipito-parieto-temporo-pontine tracts are involved early</td>
</tr>
<tr>
<td>X-linked adrenoleukodystrophy</td>
<td>Demyelination of the deep WM, progressively involving the subcortical white matter. Calcifications within the thalami, basal ganglia, and corona radiata shown by CT scan</td>
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<tr>
<td>Globoid cell leukodystrophy</td>
<td>Symmetrical periventricular WM abnormalities; early sparing of the arcuate fibers; involvement of the corpus callosum; brain atrophy in the advanced stages of disease</td>
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<tr>
<td>Metachromatic leukodystrophy</td>
<td>Subcortical cerebral and cerebellar WM are predominately involved with a swollen appearance; later involvement of the central WM; bilateral involvement of the globus pallidus and of the thalamus with sparing of the caudate nucleus and putamen; cerebral and cerebellar atrophy; marked increased NAA peak on MR spectroscopy</td>
</tr>
<tr>
<td>Canavan disease</td>
<td>Multiple symmetrical foci of high signal intensity within the subcortical WM with sparing of the central WM on T2-weighted images; atrophy of the caudate nucleus and cerebellum; abnormal signal intensity of the dentate nuclei; normal cerebellar WM</td>
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<tr>
<td>1-2-Hydroxyglutaric aciduria</td>
<td>Diffusely abnormal, swollen cerebral WM with subcortical cysts in the anterior-temporal regions; sparing of the central WM; normal gray matter structures</td>
</tr>
<tr>
<td>Megalencephalic leukoencephalopathy with subcortical cysts</td>
<td>Symmetric, diffuse involvement of the cerebral hemispheric WM, including the central tegmental tracts; cystic degeneration of WM that is replaced by CSF; cerebellar atrophy</td>
</tr>
<tr>
<td>Vanishing white matter</td>
<td>Symmetric, diffuse involvement of the cerebral hemispheric WM, including the central tegmental tracts; cystic degeneration of WM that is replaced by CSF; cerebellar atrophy</td>
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</table>

WM, white matter.

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velocities are usually normal, except for cases showing a PLP null mutation who present with peripheral neuropathy and without nystagmus [Inoue et al., 1999]. The majority of classic PMD cases results from duplication of PLP gene; the other variants are due to mutations of PLP gene. Either an over-expression of PLP gene or a deficiency of PLP results in a disturbed formation of myelin. In addition, it has been suggested that accumulation of misfolded proteins in oligodendroglia, may trigger oligodendrocytes apoptosis and consequent demyelination [Koeppen and Robitaille, 2002].

**Cockayne syndrome (OMIM 216400).** Cockayne syndrome is an autosomal recessive disease due to a DNA repair defect (Fig. 2). Patients show psychomotor developmental delay, dwarfism, progeroid appearance, microcephaly, deafness, pigmentary retinal degeneration, optic atrophy, and photosensitivity. Abnormal peripheral nerve conduction is due to a demyelinating polyneuropathy.

**Tay’s syndrome or trichothiodystrophy (OMIM 601675).** Trichothiodystrophy or Tay’s syndrome is an autosomal recessive disease due to a DNA repair defect. Mutations in the genes XBP or XPD encoding helicases of the transcription/repair factor TFIIH have been found. Clinical findings are growth and mental retardation, microcephaly, congenital ichthyosis, and brittle hair. Frequent infections are related to secondary immunodeficiency. Some patients display photosensitivity. MRI shows a diffuse hypomyelination resembling MR picture of PMD [Barkovich, 2000].

**Salla disease (OMIM 604369).** Salla disease is an autosomal recessive neurodegenerative disorder characterized by psychomotor developmental delay, slightly dysmorphic facial features, hypotonia, and ataxia usually appearing during the
first year of life. It is prevalent in the Finnish population. A
defective proton-driven transport mechanism of N-acetylneur-
aminic acid sialic acid across the lysosomal membrane of
cytoplasm causes abnormally high urinary sialic acid level and
free sialic acid storage in fibroblasts. Mutations of the gene
SLC17A5 encoding a transport protein called sialin are the
primary cause of sialic acid storage diseases [Verheijen et al.,
1999]. In more than 95% of Finnish patients, a homozygous or
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cytoplasm causes abnormally high urinary sialic acid level and
of the infantile form of
gangliosidoses, and infantile
neuronal ceroid lipofuscinosis. Although these dis-
orders have been traditionally considered as “gray matter
diseases,” white matter is affected not only secondary to
Wallerian degeneration, but also for an impaired process of
myelination including both hypomyelination (related to the
abnormal interaction between oligodendrocytes and dysfunc-
tional neurons) and demyelination.

Among the GM1 gangliosidoses, severe white matter in-
volve-ment is exclusive of the infantile type 1 GM1 gang-
lisisosis and of the infantile form of GM2 gangliosidosis.
In infantile neuronal ceroid lipofuscinosis, severe brain
atrophy is associated with progressive volume reduction of the
white matter due to both a delayed/disturbed myelination and
myelin loss. In late infantile and juvenile neuronal ceroid
lipofuscinosis, in addition to cerebral atrophy (more prominent
within the cerebellum), a rim of high signal intensity around
the lateral ventricles has been described [Vanhanen et al.,
1985; Autti et al., 1996].

H-ABC syndrome (hypomyelination with atrophy of the
basal ganglia and cerebellum). It is a recently iden-
tified autosomal recessive syndrome [van der Knaap et al.,
2002], clinically characterized by prominent extrapyramidal
movement abnormalities.

Disorders Characterized by Delayed
and Disturbed Myelination

This group of disorders is characterized by an irregular
pattern of myelination as a consequence of an abnormal
process of myelination (i.e., the normal sequence of myelina-
tion is altered). An additional component of hypomyelination is
usually present [van der Knaap, 2001].

Deletion 18q (18q-syndrome). 18q-syndrome is charac-
terized by mental retardation, dysomorphic features, growth
failure, and neurological manifestations including seizures,
hypotonia, nystagmus. White matter involvement has been
described in many cases, either as diffuse, symmetric deep
white matter high signal intensity [Loevinger et al., 1996], or as
a non-specific pattern of delayed myelination/incomplete myelina-
tion [Gay et al., 1997]. Since the gene for the MBP is located
near the telomere of chromosome 18q (18q22-qter), a failure of
expression of the MBP gene, due to haploinsufficiency, is likely
to be responsible for impaired myelination [Gay et al., 1997].

Untreated aminoacidopathies and organic acidi-
durias. Untreated aminoacidopathies and organic acidurias
may be associated with white matter changes and irregular
hypomyelination. It has been suggested that accumulation of
organic acids may interfere with oligodendroglial development
either directly (stimulating the AMPA/kainate receptors) or
indirectly (through neuronal damage) [Kölker et al., 2002].

Disorders Characterized by Progressive
Demyelination (Leukodystrophies)

In this group of disorders, the composition of the myelin
membrane becomes progressively abnormal, leading to myelin
instability and finally to myelin loss.

X-linked adrenoleukodystrophy (ALD) (OMIM
300100). It is due to mutations of the gene (ABCD1) encoding
a peroxisomal membrane protein, the ALD protein (ALDP)
(Fig. 3). The ABCD1 is a member of the ATP-binding cassette
(ABC) transporter superfamily that translocates a wide vari-
ety of substrates across extra- and intracellular membranes.
The ALD is required for the peroxisomal localization of very
long chain fatty acids (VLCFA). The consequence of this defect
is inability to metabolize VLCFA into shorter chain fatty acids.
In normal individuals, shorter chain fatty acids compose
bilaminar membrane of myelin. In ALD patients, VLCFA are
incorporated into bilaminar membrane of myelin instead of
shorter chain fatty acids, resulting in destabilization of the
membrane [Moser, 1997]. An inflammatory response by dys-
functional microglia is characteristically present and is unique
to ALD among the metabolic leukoencephalopathies. Although
the cause of inflammation is not clear, both biochemical and
immunological mechanisms have been postulated: the inflam-
mation process seems to be a secondary phenomenon (in con-
trast to multiple sclerosis) and this is supported by the location
of the inflammatory cells in the second zone of the lesion (see
below). The clinical phenotype of ALD can be divided into
the following types: childhood cerebral, adolescent cerebral,
late-infantile, adrenomegaly-neuropathy, and Adalid syndrome.
Heterozygote females may develop symptoms of adrenomeyo-
leuropathy. No genotype-phenotype correlation is known.
Childhood onset is between 4 and 8 years with subtle cognitive
delay. An acute onset with focal seizure may be observed.
Spasticity, pseudobulbar signs, dementia, cortical distur-
bances of vision, and hearing subsequently develop. Adreno-
cortical insufficiency is also present. Death results after a few
months to several years.

Other peroxisomal disorders. Other peroxisomal dis-
orders showing white matter involvement are Zellweger
syndrome (OMIM 214100), neonatal ALD (NALD) (OMIM
202370), and Reufs disease (OMIM 266500).

Krabbe’s disease (globoid cell leukodystrophy) (OMIM
245200). Krabbe’s disease is an autosomal recessive disorder
due to a deficiency of the lysosomal enzyme galactocerebro-
dase (galactocerebroside-β-galactosidase) that catalyzes the
first step of cerebroside (galactosyl ceramide) degradation,
splitting cerebroside into galactose and ceramide. Cerebroside
is almost exclusively found in oligodendrocytes, Schwann cells,
and myelin sheaths and its metabolism is related to the meta-
bolism of myelin. Accumulation of cerebroside into phagocytic
cells is responsible for transformation of these cells into globoid
cells. The deacylated form of cerebroside, called psychosine, is
a cytotoxic substance that accumulates within oligodendro-
cytes causing their death and therefore myelin sheaths loss. In
the classic early-onset infantile form, symptoms begin before
6 months of age with irritability and crying followed by rigidity
and tonic spasms; peripheral velocity nerve conduction is
reduced and brainstem auditory-evoked are often disrupted.
In the late-infantile onset form, symptoms appear between
5 months to 3 years of life with ataxia, weakness, spasticity,
and dysarthria. In the juvenile onset form, symptoms appear
between 4 and 19 years with optic atrophy, progressive spastic
tetraplegia, and peripheral neuropathy; approximately half of
patients have preserved mental function. An adult onset form
has also been described.

Metachromatic leukodystrophy (MLD) (OMIM
250100). MLD is an autosomal recessive disorder that, in
the majority of patients, is due to a deficiency of the enzyme
arylsulfatase A that catalyzes degradation of sulfatides
(the sulfate ester of cerebroside). Different mutations of the
arylsulfatase A gene are associated with phenotypes of dif-
fente severity [Gieselmann et al., 1994]. A deficiency in the
sphingolipid activator protein, saposin B or SAP-1, is the cause
of disease in a minority of patients whose clinical and
neuroradiological picture is the same of MLD. Arylsulfatase A removes the galactose-3-sulphate group from glycolipids; its deficiency leads to an accumulation of sulphatide and to a reduction of cerebroside (both these substances are normally present in myelin sheaths). The resulting abnormal myelin composition leads to myelin instability and demyelination. Furthermore, oligodendrocytes dysfunction and death occur due to both storage of sulphatide and to releasing of highly toxic substances from lysosome degeneration. Three subtypes of MLD are known: the late infantile, the juvenile, and the adult type. The most common type is the late infantile MLD characterized by gait abnormalities, ataxia, hypotonia, and peripheral neuropathy at onset after the first year of life. Spasticity leading to spastic tetraplegia, bulbar and pseudobulbar symptoms, and mental regression subsequently develop.

Another variant, the multiple sulphatase deficiency or Austin’s variant, combines features of MLD and of mucopolysaccharidosis. Arylsulphatase A, B, and C are absent and both mucopolysaccharides and sulphatides are found in urine.

Disorders Related to Myelin Splitting
(With or Without Myelin Loss)

Disorders related to myelin splitting with myelin loss. Canavan disease (OMIM 271900). Canavan disease is an autosomal recessive disorder due to aspartoacylase deficiency (Fig. 4). Two mutations of the gene for human aspartoacylase account for about 98% of the alleles of Ashkenazi Jewish patients [Sistermans et al., 2000]. Many non-Jewish mutations have been reported. In non-Jewish patients of European origin, the A305E mutation accounts for 50% of alleles [Sistermans et al., 2000].

Patients with Canavan disease show delayed psychomotor development by 3 months of age. In the first year of age macrocephaly appears. Seizures and optic atrophy become evident in the second year of age. Most patients die in the first decade of life. Clinical variant without macrocephaly or with late onset have been described. Diagnosis is based on demonstration of N-acetylaspartate in urine. Although the pathogenesis has not been completely elucidated, it has been suggested that the deficiency of aspartoacylase in the white matter causes accumulation of N-acetylaspartate and of its precursor, N-acetylaspartylglutamate that may be responsible for intramyelinic edema, extensive vacuolization, and oligodendrocyte failure [Kölker et al., 2002].

Mitochondrial disorders. Mitochondrial diseases are a heterogeneous group of disorders caused by impairment of the mitochondrial oxidative phosphorylation system. The clinical phenotypes are variable. The presence of significant basal nuclei or brainstem abnormalities has been described in the majority of cases. However, in a few cases, with a defect of respiratory chain complexes, either isolated or multiple, as well as with a pyruvate dehydrogenase deficiency, diffuse white matter abnormality without other MRI findings has been reported [Moroni et al., 2002].

1-2-Hydroxyglutaric aciduria (OMIM 236792). 1-2-Hydroxyglutaric aciduria is an autosomal recessive disorder whose metabolic defect is still unknown (Fig. 5). The biochemical
marker is a massive urinary excretion of L-2-hydroxyglutaric acid. Clinically, children show a progressive slow mental regression after the first years of age, seizures, ataxia, pyramidal, and extrapyramidal signs. Macrocephaly may be present.

Disorders related to myelin splitting without myelin loss. Megalencephalic leukoencephalopathy with subcortical cysts (OMIM 604004). Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a recently described autosomal recessive disorder due to mutations in the MLC1 gene encoding a putative membrane protein [Lee et al., 2001a] (Fig. 6). The onset is during the first year of life with macrocephaly, and slowly progressive deterioration of motor functions with pyramidal signs and ataxia. Mental abilities are relatively spared. Seizures, easily controlled with antiepileptic drugs, occur in most patients.

Disorders Secondary to Axonal Damage

Giant axonal neuropathy (OMIM 256850). Giant axonal neuropathy is an autosomal recessive disorder caused by mutations in a gene encoding a ubiquitously expressed protein, named gigaxonin. It is characterized by chronic polyneuropathy, with variable CNS involvement, including diffuse white matter abnormalities consistent with demyelination [Lampl et al., 1992].

Other White Matter Disorders

Alexander disease (OMIM 203450). Alexander disease is a genetic disorder due to a defect in the gene encoding for GFAP (Fig. 7). Heterozygous mutations of GFAP gene have been reported in the majority of patients. Mutations occur de novo and are predicted to act in a dominant way [Brenner et al., 2001]. GFAP is an astrocytic protein and Alexander disease represents the first example of a primary genetic disorder of astrocytes. The failure of myelin deposition due to the astrocyte dysfunction illustrates the role of astrocytes in the process of myelination. Clinically, the most common form of Alexander disease is the infantile variant at onset at around 6 months of age, with developmental delay, macrocephaly, seizures, and progressive spasticity. Neonatal, juvenile, and adult variant have also been described. In the juvenile variant, the onset is between 6 and 15 years with bulbar dysfunction, slowly progressive gait disorders, ataxia, spasticity. Cognitive decline and behavioral changes occur only late in the disease. All the three subtypes of Alexander disease have been shown...
to be caused by mutations in the GFAP gene [Brenner et al., 2001; Namekawa et al., 2002; Sawaishi et al., 2002]. The pathological hallmark of all forms of Alexander disease is the presence of Rosenthal fibers which are astrocytic inclusions containing the intermediate filament protein GFAP in association with small heat-shock proteins.

**Vanishing white matter disease (OMIM 603896).** Vanishing white matter disease, also called CACH, is a recently described autosomal recessive disease, due to mutations in all five gene subunits encoding the eukaryotic translation initiation factor eIF2B [Leegwater et al., 2001b] (Fig. 8). This factor is a regulator of translation initiation (i.e., the final step of proteins production, in which mRNA is translated into proteins) under circumstances of mild stress. Clinically, after an initial normal or mildly delayed psychomotor development, patients show a neurological picture whose course is chronic progressive with additional episodes of rapid deterioration following minor infection and minor head trauma that may lead to lethargy or coma. Cerebellar ataxia and spasticity are the main neurological signs. Optic atrophy and seizures may occur. Mental impairment is relatively mild, and usually less severe than motor dysfunction. Phenotypic variation is wide.

Pathological abnormalities primarily involve the axons. It has been suggested that an abnormal stress reaction (related to the dysfunction of eIF2B that plays a crucial role in regulating protein synthesis under mild stress conditions) may cause deposition of denaturated proteins within oligodendrocytes leading to hypomyelination, loss of myelin, and subsequent cystic degeneration.

**Congenital muscular dystrophies (CMD).** CMD are a heterogeneous group of congenital myopathies that may or may not be associated with CNS abnormalities. White matter involvement, appearing either as hypomyelination or as abnormal white matter signal, is found in the Fukuyama type of CMD (OMIM 253800), muscle-eye-brain disease (OMIM 253280), Walker–Warburg syndrome (OMIM 236670), and merosin deficient CMD (OMIM 602771) (Fig. 9).

**Sjogren–Larsson syndrome (OMIM 270200).** Sjogren–Larsson syndrome (OMIM 270200) is an autosomal recessive disease due to fatty alcohol:NAD$^+$ oxireductase deficiency (FALDH), characterized by congenital ichthyosis, mental retardation, and spastic diplegia. MRI shows diffuse hemispheral cerebral white matter changes, with sparing of the arcuate fibers [Di Rocco et al., 1994].

**Cerebrotendinous xanhtomatosis (CXT) (OMIM 213700).** CXT (OMIM 213700) is an autosomal recessive disorder due to a deficiency of the sterol 27-hydroxylase enzyme. Although, the classic clinical triad is tendon xanthoma, cataract, and nervous system dysfunction, some patients may have only neurological changes without cataract and xanthomas. Neurological manifestations include behavioral problems, mental retardation and dementia, pyramidal signs, cerebellar ataxia, seizures, and peripheral polyneuropathy. MRI shows high signal intensity on T2-weighted images.

Fig. 6. Megalencephalic leukoencephalopathy with subcortical cysts (8-month-old boy). Axial T2-weighted image (A) shows diffuse swelling of the cerebral white matter which is diffusely hyperintense with involvement of the subcortical fibers, as well as of the capsules. The corpus callosum is spared. Axial FLAIR image (B) shows hypointensity of the white matter of the frontal lobes, extreme capsules, and temporal poles suggesting cavitation.
within the cerebellar hemispherical white matter and cerebellar atrophy, and periventricular white matter changes supratentorially.

**Leukodystrophy with polyol metabolism abnormality.** Leukodystrophy with polyol metabolism abnormality has been described in a patient showing both central and peripheral white matter involvement, and increased levels of polyols [van der Knaap et al., 1999].

Another disorder involving both the central and the peripheral myelin has been reported in patients with Waardenburg-Hirschprung disease (WS4) and a SOX10 mutation [Pingault et al., 2000].

**UNDEFINED LEUKOENCEPHALOPATHIES**

About 50% of patients with white matter abnormalities remains without diagnosis. Therefore a specific protocol for studying and categorizing these patients is crucial. **Clinical information** concerning familiarity, onset of symptoms, neurological examination, presence of non-neurological symptoms, progression of disease should be integrated with **neurophysiological studies** as well as **neuroimaging evaluation** based on the systematic analysis proposed by van der Knaap and Valk [1995]. MR spectroscopy and new MR techniques will provide further information. The integrated description of the clinical, neuroimaging and pathophysiological features is crucial for categorizing myelin disorders and defining novel disorders.

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**Fig. 7.** Alexander disease (2-year-old boy). Axial T2-weighted image shows abnormal hyperintensity of the white matter in the frontal lobes with involvement of the U fibers and global swelling. Hyperintense signal tracts posteriorly along the external and extreme capsules. The posterior periventricular white matter shows subtle signal increase.

**Fig. 8.** Vanishing white matter (27-year-old woman). Axial FLAIR image (A, 25 years) shows diffuse hyperintense white matter with multiple foci of decreased signal intensity affecting the deep portions bilaterally. Axial FLAIR image (B, 27 years) shows marked increased of the deep hypointense areas which are now merging consistent with progressive vacuolization.
homogeneous subgroups of patients. This is the basis for better understanding the basic processes involving the white matter and the genetic basis in the case of an undefined leukoencephalopathy.

REFERENCES


