Review Article

Update on Genetic Disorders Affecting White Matter

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The classification of diseases affecting white matter has changed dramatically with the use of magnetic resonance imaging. Classical leukodystrophies, such as metachromatic leukodystrophy and Krabbe’s disease, account for only a small number of inherited diseases that affect white matter. Magnetic resonance imaging has clarified genetic disorders that result in white matter changes or leukencephalopathies. The term leukencephalopathy is used to reflect the broader number of diseases that may cause as either primary or secondary changes in myelin development. This review attempts to categorize white matter disorders into classes such as lipid, myelin protein, organic acids, and defects in energy metabolism, in addition to other causes. © 2001 by Elsevier Science Inc. All rights reserved.


Introduction

The concept of a “leukodystrophy” has changed considerably from its original pathologic definition, which was first introduced by Bielschowski and Henneberg in 1928 [1]. The sensitivity of magnetic resonance imaging (MRI) in demonstrating abnormalities in myelin development has also expanded our concept of the disorders affecting myelin. The understanding of the pathophysiology of leukodystrophies is evolving and the classification of the leukodystrophies must continue to be arbitrary. The term leukodystrophy should be restricted to inherited diseases that affect myelin development and should not include disorders such as multiple sclerosis or other demyelinating disorders that are associated with inflammatory lesion-affecting myelin or toxic disorders, such as organic solvent exposure. The term leukencephalopathy may be a more accurate term because many genetic diseases affect white matter development and even the primary leukodystrophies may involve nonwhite matter regions of the nervous system. The pathologic classification of the leukencephalopathies can be divided into the following: (1) dysmyelinating (abnormally formed myelin); (2) hypomyelinating (decreased myelin production); and (3) spongiform (cystic degeneration of myelin) (Table 1).

A biochemical classification can also be used to classify leukencephalopathies (1) lipid disorders, (2) myelin protein disorders, (3) organic acids disorders, (4) defects of energy metabolism (associated with lactic acidosis), (5) other causes, and (6) unknown causes (Table 2). These classifications will certainly change as the molecular mechanisms for more of the leukencephalopathies become elucidated.

It is important to remember that the classification of diseases into disorders primarily affecting gray matter and disorders “primarily affecting white matter” is quite artificial. Although conceptually easier to consider, neurologic diseases often cannot be easily separated into highly compartmentalized disorders.

Leukoencephalopathy Associated With Lipid Abnormalities

Adrenoleukodystrophy. The first description of a male with adrenoleukodystrophy (ALD) was reported by Schilder in 1913, but the first complete study of what we refer to as the X-linked ALD is attributed to Siemerling and Creutzfeldt in 1923 [2,3]. The clinical phenotype of ALD can be divided into the following: childhood cerebral, 48%; adolescent cerebral, 5%; adult cerebral, 3%; adrenomyeloneuropathy, 25%; and Addison only, asymptomatic and presymptomatic, 8% [4]. The disease may also affect

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Received May 25, 2000; accepted August 30, 2000.

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PII S0887-8994(00)00232-0 • 0887-8994/01/$—see front matter

10-15% of heterozygote females who may develop symptoms of AMN in the third to fifth decades. MRI demonstrates a predilection for the parieto-occipital white matter (Fig 1). The cerebral features appear to be related to the perivascular lymphocytic infiltration affecting white matter and causing demyelinating lesions beginning in the parieto-occipital white matter. The clinical features are dependent on the age of presentation, with children having primarily visual and cerebral features and adults having a more slowly progressive spinal cord symptom complex.

The genetic understanding of ALD began in 1963 when the X-linked inheritance was observed [5]. The biochemical elucidation of ALD began with the identification of an excess of very long chain unbranched fatty acids (VLCFA) C24-C30 chain length, especially C26:0 and C25:0 in the cholesterol ester fraction of white matter and adrenal cortex for ALD cases [6]. Accumulation of VLCFA is widely used in plasma as a diagnostic test for ALD and other peroxisomal diseases [7].

Despite the wide range of clinical presentations the disease is always associated with the accumulation of VLCFA. The basis for the VLCFA accumulation has been the basis for much speculation. Before VLCFA can be oxidized in the beta-oxidation pathway, the fatty acids are activated into VLCFA-CoA through the enzyme VLCFA-CoA synthetase (ligase) [8]. All patients with ALD have decreased activity of the VLCFA-CoA synthetase enzyme but do not have mutations in the gene encoding this protein [9]. The mutated gene in ALD patients is responsible for encoding the ALD protein (ALDP). ALDP is required for the peroxisomal localization of VLCFA-CoA synthetase enzyme and, without appropriate localization to the peroxisome, this enzyme is unable to properly function [10]. ALDP is a part of a family of ABC transporters and this protein has at least three other homologs that include the PMP70, ALD-related protein (ALDRP), and P70R [10]. There is some similarity in these proteins because ALD patient cells treated with 4-phenylbutyrate exhibit increased expression of ALDRP and lowering of the VLCFA [11].

The gene encoding the ALDP is localized to Xq28 near a locus for color vision and was cloned in 1993 [12]. Several mutations of this gene have been identified in patients with ALD [13]. Mutations in the ALDP gene, however, do not correlate well with the clinical phenotype, suggesting a more complicated genotype/phenotype arrangement [9].

Treatment for ALD has been attempted over the years. Dietary treatment was begun using a combination of glycerol trioleate (GTO) and glycerol trierucate (GTE) because of the observed lowering of very long chain fatty acids in culture using these oils. Unfortunately, dietary trials using these oils did not improve the clinical course for symptomatic patients with the cerebral form or adrenomyeloneuropathy form of ALD [14]. It remains to be proven whether asymptomatic ALD individuals will develop a less-severe course if they are placed on the GTO/GTE oils [15]. The one therapy demonstrated to be effective is bone marrow transplantation.

**Globoid Cell Leukodystrophy (Krabbe’s Disease)**

Globoid cell leukodystrophy is considered one of two autosomal-recessive inherited glycosphingolipid storage disorders primarily causing a leukodystrophy. Children begin symptoms before 6 months in approximately 80% of
the cases with 25% occurring before 3 months [16]. The classic clinical presentation frequently consists of extreme irritability and crying followed by rigidity and tonic spasms. Peripheral nerves are affected early in the course, causing a reduction in the nerve conduction velocities. Cerebrospinal fluid (CSF) examination is remarkable for the elevation of protein, typically above 70 mg/dL. The CSF protein is frequently not increased [16]. The lifespan of individuals with the late-onset variant may vary, but survival beyond 24 years of age has been reported [22].

The disease is caused by a deficiency of the lysosomal enzyme galactosylceramide β-galactosidase, which is required to degrade the lipid galactosylceramide and is an important glycolipid in myelin structure [23,24]. This disease is unique among the lipid storage diseases because there is no increase of lipid in the brain except within specialized microglial cells referred to as globoid cells. Biochemical studies of total brain lipids did not reveal the expected increase in galactosylceramide but rather a lowering of total cerebroside and sulfatide and a reduced sulfatide-to-cerebroside ratio [25]. Only a fraction of brain lipids enriched in the globoid cells demonstrated an increase in galactosylceramide [26]. Psychosine (galactosylsphingosine), a related glycolipid also broken by the galactosylceramide β-galactosidase enzyme, is thought to be the metabolite responsible for the pathogenesis of this disorder because it is known to be toxic to oligodendrocytes [27].

The gene for the galactosylceramide β-galactosidase enzyme has been mapped to chromosome 14 and the cDNA encoding galactosylceramide β-galactosidase was cloned [28,29]. The cDNA is 3.8 kb in length and contains a 2007-bp open reading frame that codes for 669 amino acids, representing an nonglycosylated protein with a molecular weight of 72,781 [29]. The entire gene structure and organization has been determined to consist of nearly 60 kb with 17 exons and 16 introns [30]. The promoter region, located at the −149 to −112 nucleotide region from the initiation codon, contains three GC-boxlike sequences and one YY1 binding site [31].

Molecular analyses have demonstrated at least 60 mutations, including base transitions, polymorphisms, and deletions that are associated with Krabbe’s disease. In infantile patients with Krabbe’s disease with Northern European ancestry, approximately 40-50% of cases have a mutant allele that has a 30-kb deletion beginning in intron 10 and extending past the 3’ end of the gene [32]. In addition to the deletion on this allele, there is an invariable C → T transition at position 502, which is a polymorphism witnessed in only about 4% of the population. Most of the mutations causing infantile-onset disease are located on the region coding for the 30-kd subunit of the enzyme, suggesting that this subunit is critical for the normal functioning of the enzyme [21]. Adult-onset cases may also have the 502/del mutation on one allele but many other mutations including missense mutations, such as a homozygous T185C, nonsense mutations, deletions and insertions, have been reported in the older onset population [33-35].

Despite the significant advances in the molecular understanding of globoid cell leukodystrophy, therapy for this
disease has not progressed as quickly. Hematopoetic stem cell transplantation was initially discounted for use in Krabbe’s disease, but recent studies have suggested some ameliorating effects from this therapy, especially if used early in the course or ideally in a presymptomatic condition [36].

Metachromatic Leukodystrophy

Metachromatic leukodystrophy (MLD) is the second example of a lysosomal storage disease involving glycosphingolipid metabolism that causes a leukoencephalopathy with an estimated frequency of 1 in 40,000. The name is derived from the neuropathologic description of metachromatic staining, which consists of a brownish or reddish color compared with the blue color of cell nuclei when stained with cresyl violet or toluidine blue (Fig 2). This disease is associated with lipid accumulation in several cell types, such as hepatocytes, Kupffer’s cells, epithelium of bile ducts, galbladder epithelial cells, and renal tubular epithelium. In the central and peripheral nervous system the accumulation of lipid can be noted in oligodendrocytes and macrophages throughout the white matter and in selected neurons and retinal ganglion cells. Only in brain and peripheral nerves, however, is the sulfatide storage associated with pathology. The cause for the demyelination is not completely understood, but storage of sulfatides in Schwann’s cells and oligodendrocytes precedes the development of demyelination. Other hypotheses to explain the demyelination include unstable myelin sheaths resulting from sulfatide accumulation and, as in the “psychosine hypothesis for Krabbe’s disease,” toxic effects of a sphingosine (sulfogalactosylsphingosine) [27]. This disease is included in the dysmyelinating category of leukoencephalopathies.

The clinical phenotype depends on the cause of the leukodystrophy. Three etiologies for sulfatide accumulation and leukodystrophy have been identified. These include the most common etiology, arylsulfatase A deficiency, which may present in late infancy, late childhood, or adult ages [16]; a deficiency of the sphingolipid activator protein saposin B; and multiple sulfatase deficiency. The late infantile-onset children usually have normal milestones, but ataxia and difficulty with walking develop in the later half of the second year of age [37]. Eventually spasticity and loss of speech occurs followed by quadriplegia and cortical blindness. Juvenile-onset cases are characterized by a less-distinct phenotype that may vary greatly in age of onset, ranging from early childhood to late adolescence. The peripheral nerve involvement may predominate in young children, but in older children school problems and behavioral difficulties may be key features [38]. The rate of progression of the disease may vary from very rapid to indolent. Adults appear to have psychiatric problems as a major feature of the disease but may also have peripheral nerve and other findings [39].

Arylsulfatase A (ASA) Deficiency

The major cause for metachromatic leukodystrophy is a deficiency of ASA that catalyzes cerebroside 3-sulphate. The enzyme removes the galactose 3-sulfate group from the glycolipid and its deficiency results in the lysosomal accumulation of cerebroside 3-sulphate. The gene for arylsulfatase A is located on chromosome 22q13 and contains about 3 kb of genomic sequence and encodes for a 507 amino acid ASA polypeptide [40]. Three different species of mRNA are produced by the ASA gene, which are 2.1, 3.7, and 4.8 kb in length. All three transcripts encode the identical 507 amino
acid polypeptide but differ in the length of the 3’-untranslated sequence with the 2.1 transcript accounting for approximately 90% of the total ASA mRNA [41]. There are well over 70 mutations identified in the ASA gene responsible for metachromatic leukodystrophy [42]. Most of these mutations are found in individual patients but two mutations—a splice donor mutation at the exon 2/intron 2 border and a Pro426Leu substitution—account for approximately 25% of cases with another mutation, Ile179Ser, accounting for an additional 5% [40].

**Pseudodeficiency of Arylsulfatase A Activity**

A cause of difficulty in diagnosing patients with metachromatic leukodystrophy is the frequent occurrence of a benign decrease in the arylsulfatase A enzyme activity, which approaches levels seen in MLD patients. It is estimated that approximately 1% of the population has this nonpathogenic decrease in ASA activity with approximately 10% of the population carrying the ASA pseudodeficiency (ASA-PD) allele [41]. Two mutations are responsible for the occurrence of ASA-PD allele. These mutations are caused by two A→G transitions; the first resulting in a substitution of serine for a glycosylated asparagine at amino acid 305 and the second mutation that alters the polyadenylation signal in the major 2.1 kb transcript [41]. The first mutation may result in a small reduction in enzyme activity by changing the catalytic properties or targeting signal of the protein. The mutation causing the polyadenylation signal defect results in a 90% reduction in transcript production, causing the overall enzyme levels to fall to approximately 8% of normal values [41]. Further diagnostic confusion may result from the pseudodeficiency state because compound heterozygotes of the MLD and ASA-PD alleles, which are clinically normal, will have mildly elevated sulfatide excretion in urine [43]. Quantitative urine sulfatide measurements or radiolabeled sulfatide degradation in fibroblasts are chemical methods used to differentiate among asymptomatic ASA-PD states, carriers of MLD, presymptomatic MLD cases, and compound heterozygotes [43], but molecular testing is becoming a more commonly used method to identify ASA-PD.

**Saposin B Deficiency (Sphingolipid Activator Deficiency)**

Patients with normal ASA gene structure rarely may have a deficiency of the ASA enzyme activity. Typically these patients will have a clinical phenotype and MRI appearance that is compatible with a juvenile-onset form of MLD but will have apparently normal enzyme activity by customary fluorescent substrate analysis. The defect results from a mutation in the cerebroside sulfate activator protein (saposin B) that is mapped to chromosome 10 and one of a family of four genes (prosaposin gene) required for the hydrolysis of several lysosomal enzymes [44]. The saposin B protein will also enhance the degradation of several other lipids such as G_{34} ganglioside, globotriaosylceramide, and sphingomyelin suggesting a possible function for saposin B in the lysosomal hydrolases G_{34} ganglioside β-galactosidase, α-galactosidase, and sphingomyelinase [45]. Despite the role of saposin B in many lysosomal hydrolases, a deficiency of this protein resembles the clinical phenotype of MLD and not other storage diseases [44].

**Sjögren-Larsson Syndrome**

Sjögren and Larsson [46] first described the genetic syndrome that consists of the clinical triad of congenital ichthyosis, mental retardation, and spastic di- or tetraplegia. The MRI and clinical findings are consistent with a leukoencephalopathy associated with a lipid abnormality. The primary enzymatic defect in Sjögren-Larsson syndrome is deficient activity of the fatty aldehyde dehydrogenase component of fatty alcohol:NAD⁺ oxidoreductase [47]. Enzymatic studies may determine genetic carriers for Sjögren-Larsson syndrome [48] and allow prenatal diagnosis [49]. The gene for fatty aldehyde dehydrogenase is cloned and patients with Sjögren-Larsson syndrome have mutations of various types [50].

The clinical features of Sjögren-Larsson syndrome consist of three major signs: congenital ichthyosis, mental retardation, and spastic di- or tetraplegia [46]. The neurologic features usually begin before 1 year of age and consist of motor and language delay. Spastic diplegia is more common than tetraplegia, and many patients either never walk or require leg braces [51]. The degree of mental retardation tends to correlate with the severity of spasticity, and most patients are moderately or profoundly retarded with intelligence quotients less than 50. Many patients have speech defects of various types, and one third of the patients have an associated seizure disorder [51,52]. Unlike most other lipid disorders, patients with Sjögren-Larsson syndrome generally do not demonstrate neuroregression. A loss of ambulation can occur with age, but it is usually a result of progressive contractures. Most patients with Sjögren-Larsson syndrome have short stature, usually because of leg contractures and decreased leg growth. Kyphoscoliosis is not uncommon, particularly in severely spastic patients. Nerve conduction studies are normal [51]. Brain MRI demonstrates white matter disease involving primarily the parietal and frontal lobes [53,54].

The ichthyosis in Sjögren-Larsson syndrome is usually apparent at the time of birth, but a small proportion of patients first develop ichthyosis after several months of age or later [55]. The ichthyosis tends to be mild-to-moderate in severity. Scales can be fine and dandrufflike, larger and more lamellarlke or even thick and dark brown in appearance. The ichthyosis is generalized and typically affects the flexures, trunk, abdomen, back, extremities, nape of the neck, and dorsal areas of the hands and feet. Less severely affected are the palms and soles, whereas the
face is usually spared. A collodion membrane is rarely seen in this disease [56].

Ophthalmologic abnormalities of the retina have been reported in Sjögren-Larsson syndrome [57]. The most consistent finding is the presence of glistening white dots on the fundus, usually present in the foveal and perifoveal areas. These glistening white dots were observed in all 35 Swedish patients who were examined, including young children [57], but they have been reported in a lower percentage of non-Swedish patients. Retinal pigmented changes and macular degeneration have also been seen in some patients but corneal opacities or cataracts are not associated with Sjögren-Larsson syndrome [56].

Sjögren-Larsson syndrome is inherited in an autosomal-recessive fashion [46] and the gene is localized to chromosome 17p11.2 [58,59]. The cDNA for fatty aldehyde dehydrogenase is cloned and several mutations have been identified in this gene [50]. At present, more than 50 different mutations, including missense and nonsense mutations, deletions, insertions, and splice-site alterations have been reported [50,60-63]. Many patients of Swedish and northern European descent carry an identical missense mutation (943C→T; Pro315→Ser), and haplotype studies indicate that they share a common ancestor [60,61]. Most Swedish patients are homozygous for this mutation, which is consistent with their consanguineous history. A second deletion mutation, 1297-1298delGA, is frequently seen in European patients [63]. Approximately one half of European Sjögren-Larsson syndrome patients carry 943C→T or 1297-1298delGA.

Cerebrotendinous Xanthomatosis

The clinical triad of cerebrotendinous xanthomatosis (CTX) are tendon xanthomata (especially of Achilles tendons), juvenile ocular catarracts, and nervous system dysfunction. The central nervous system abnormalities may consist of behavioral problems, mental retardation, dementia, pyramidal weakness, cerebellar ataxia, seizures, psychiatric disorders and, rarely, parkinsonism [64]. Juvenile catarracts are observed in more than 90% of CTX patients and may be the presenting symptom of the disease [65]. Tendon xanthomas are found in 85-90% of patients with CTX. There is a strong preference for the Achilles tendon, but xanthomas and tuberous xanthomas are observed also in the tendons of other extensor muscles [64]. Typically, bananalike swellings of the Achilles tendon develop that can be documented by X-ray, CT scanning, and MRI.

Neuroimaging (CT and MRI) demonstrates in CTX diffuse brain and spine atrophy, white brain matter hypodensity above and especially below the tentorium, and, in some patients, focal lesions [66]. The white matter of the cerebellum appears to be particularly affected in CTX. Because some patients may only have the central nervous system changes without the cataracts or tendon xanthomas, CTX may be frequently overlooked as a diagnosis. Patients with degenerative central nervous system degeneration and white matter changes on MRI primarily affecting cerebellum should be screened for CTX.

The brains of patients with CTX were discovered by Menkes et al. [67] to have increased amounts of cholestanol. Cholestanol is the 5-α-dihydro-derivative of cholesterol and is present in small quantities associated with cholesterol in virtually every tissue and plasma. In normal subjects cholestanol represents about 0.1-0.2% of the cholesterol. In contrast, cholestanol is increased 10-fold to 100-fold in CTX. The biologic basis for CTX is a deficiency of the sterol 27-hydroxylase enzyme. This enzyme is responsible for the production of bile acids. Recently, mutations in the sterol 27-hydroxylase gene on the human chromosome 2 were determined to be the cause of CTX. Many mutations in the sterol 27-hydroxylase gene have been identified [68].

CTX may be diagnosed after finding increased plasma and tissue cholestanol concentrations and low or normal plasma cholesterol levels. Because CTX results from an inherited defect in bile acid synthesis, treatment with the bile acid chenodeoxycholic acid has been used in CTX. Chenodeoxycholic acid appears to reverse the metabolic encephalopathy before destructive xanthomas appear in the brain [69]. Long-term treatment with chenodeoxycholic acid (750 mg/day) suppresses abnormal bile acid synthesis, as evidenced by the almost total replacement of chenodeoxycholic acid in the enterohepatic pool and the disappearance of bile alcohol glucuronides from bile, plasma, and urine [70]. Plasma and cerebrospinal fluid cholestanol concentrations decline to normal levels. The neurologic improvement is better when treatment is started in young patients [71].

Myelin Protein Disorders

Pelizaeus-Merzbacher Disease (PMD). The best example of a hypomyelinating leukoencephalopathy is PMD. This disorder is X-linked leukoencephalopathy first described clinically by Pelizaeus in 1885, and the pathologic and clinical description of the same family by Merzbucher in 1910 [72,73]. The classic and connatal presentation of PMD begins in infancy and consists of horizontal, vertical, or pendular eye movements (nystagmus), stridor, feeding difficulties, hypotonia, titubation of the head, developmental delays, ataxia, spasticity, and choreoathetosis. Although PMD was thought initially to represent a leukodystrophy, Zeman et al. [74], in 1964, suggested that it was a disorder that “affects the deposition rather than the maintenance of myelin” and correctly predicted a defect in proteolipid protein or other myelin proteins. The proteolipid gene was linked to the Xq22 region in 1985 and defective biosynthesis of proteolipid protein in PMD patients was confirmed in 1987 [75,76]. In 1989, three independent observations confirmed mutations in the proteolipid gene associated with PMD disease [77-79]. It is of interest that an alternatively spliced gene, DM20, is also
derived from the PLP locus. The DM20 gene has been implicated in the maintenance of oligodendrocytes and myelin assembly, and mutations that affect the transport of both PLP and DM20 are associated with the severe connatal variant of PMD [80].

The MRI appearance of PMD indicates a diffuse increase in the signal of white matter on T2-weighted images that is characteristic for children over 1 year of age (Fig 3) [81]. In young children the MRI is less specific because of delays in myelination. Evoked-potential studies are also abnormal with loss of rostral waves on the brainstem-evoked potentials [17]. EMG and nerve conduction velocities are usually normal but some abnormalities have been reported [82,83].

The genetics of PMD have helped delineate the full clinical spectrum. The majority of classic-onset cases appear to result from a duplication of the proteolipid gene [84,85], although in one family an increase in gene dosage was noted without a duplication [86]. Interphase fluorescent in situ hybridization has been developed to screen patients for duplication of the PLP gene [87]. The approximate number of mutations or small deletions has approached 60 (June 1999), but these probably account for only 15-20% of the diagnosed PMD patients. There still remains an estimated 20-25% of patients in which no identified gene defect can explain the PMD phenotype. An expanded phenotype has occurred after molecular diagnosis because familial spastic paraplegia type 2 (SPG2) was found to be an allelic variant of PMD [88]. Classic PMD has been identified in families with the SPG2 variant [89]. As in many other inherited diseases, the genotype does not always predict the phenotype in PMD, although mutations in the same codon have led to speculation about genotype/phenotype correlations [90]. Small deletions or null mutations are believed to cause peripheral nervous system involvement because approximately 1% of PLP is present in peripheral nerve, especially in Schwann’s cells [87]. The genotype/phenotype correlation in patients with duplications is complicated because of varying lengths of the duplications reported [87].

**Myelin Basic Protein Deficiency (MBP)**

A deficiency of MBP has been described in a mouse model, the myelin-deficient mutant. A deletion of the 18q 22.3-qter region containing the locus for MBP was found in a 25-year-old female who demonstrated symptoms of involuntary movements, ataxia, and mild mental retardation [16]. MRI demonstrated abnormal myelination. The woman’s 18-month-old son was also affected. Children with the chromosomal deletion syndrome, the 18q-syndrome, have been described as having decreased myelination in the brain. MRI scans demonstrate a diffuse decrease in central white matter, which is thought to be related to a reduction in the MBP gene [16,91].

**Organic Acid Disorders**

**Canavan’s Disease.** Canavan’s disease is an autosomal-recessive neurologic disorder associated with macrocephaly and spongiform degeneration of brain. The eponym is derived from the first neuropathologic description of a leukodystrophy associated with spongy degeneration of brain written by Myrtelle Canavan in 1931 [92]. The clinical description and inherited basis of Canavan’s disease was first recognized by van Bogaert and Bertrand in 1949 [93]. In this report, five Jewish patients developed macrocephaly and severe mental retardation associated with spongiform degeneration of brain. In 1988, Canavan’s disease was identified as a

Figure 3. MRI indicating diffuse signal abnormalities in white matter in 6-year-old male with Pelizaeus-Merzbacher disease (TR = 3000/TE = 90).
deficiency of aspartylacylase, which causes an increase in N-acetyl aspartic acid (NAA) in brain and urine. The molecular basis of Canavan’s disease was elucidated in 1993 with the cloning of the gene and the identification of a common missense mutation [94].

The clinical triad of hypotonia, head lag, and macrocephaly is characteristic for Canavan’s disease. Infants with Canavan’s disease do not have distinctive clinical features in the first few months of life but begin to exhibit delayed development by 3 months of age. Macrocephaly may not be apparent in the first few months, but the head enlarges to above the ninetieth percentile within 6 months to 1 year of age. Head control remains poor, and the child never develops the ability to support the head. Seizures and optic atrophy frequently develop in the second year of life. Irritability and sleep disturbances are frequent clinical symptoms. In time, gastroesophageal reflux becomes prominent and swallowing deteriorates, leading to feeding difficulties and poor weight gain. Nasogastric feeding or permanent feeding gastrostomy is often required. Most patients with Canavan’s disease die in the first decade of life. However, with improved medical and nursing care, a larger number of children survive beyond the first decade [95]. The congenital, infantile, and juvenile variant forms of Canavan’s disease were described before the discovery of the enzyme that makes assessing the frequency of these subtypes difficult [96].

The clinical diagnosis is confirmed after identifying elevated NAA in urine or by the measuring NAA on magnetic resonance spectroscopy (MRS). The MRI reveals a diffuse leukoencephalopathy that extends to subcortical white matter (Fig 4).

The gene for human aspartoacylase is localized to the 17p13-ter region and spans 29 kb of the genome [97]. The transcript is 1.8 kb in length and contains an open reading frame on the cDNA, which is 939 bases long and predicts a 313 amino acid residue [95]. The identified mutations can be divided into Ashkenazi Jewish and non-Jewish mutations. Two mutations account for 97% of the mutant alleles in Jewish families. These two mutations include the most frequent mutation, which causes a substitution of glutamic acid for alanine at codon 285 (Glu285Ala), and another common mutation that results in a nonsense mutation changing a tyrosine at codon 231 to a stop codon (Tyr231ter) [98]. In the non-Jewish families, an alanine to glutamic acid substitution at codon 305 (Ala305Glu) occurs in approximately 36% of identified mutations. In the non-Jewish families only 70% of mutations have been identified so far with a total of 24 additional mutations being characterized [98]. If a mutation has been identified for a pregnancy at risk for the disease, mutational analysis can be performed on chorionic villus sampling to aid in diagnosis. Prenatal diagnosis of Canavan’s disease is complicated because cultured amniocytes or chorionic villus samples have low levels of aspartoacylase activity, making enzyme analysis unsatisfactory for disease detection in the fetus [99].

Figure 4. Diffusely increased signal of white matter, extending to the subcortical region, on T2-weighted MRI of a 6-month-old female with Canavan’s disease (TR = 3000/TE = 90).

At present, there is no treatment available for affected children with Canavan’s disease. An experimental gene therapy protocol, implanting into the central nervous system an expression vector containing the aspartoacylase cDNA, has begun but the efficacy and safety of this nascent treatment remains to be evaluated [100].

Defects in Energy Metabolism

Mitochondrial Disorders. It is understood that defects in energy metabolism, primarily defects in mitochondrial function, may present a leukodystrophy. The disorders include: MELAS, Leber hereditary optic atrophy, ubiquinone deficiency, Complex I deficiency, Complex III deficiency, cytochrome oxidase deficiency, and mitochondrial deletions [101]. It must be stressed that these diseases are part of a greater defect in energy metabolism that usually affects other areas of brain and systemic organs but at times may appear as a primary white matter disorder. Mitochondrial encephalopathy, lactic acidosis, and stroke (MELAS) is the best known of the mitochondrial diseases that may affect white matter structures. Typically, this disorder involves a mutation in a mitochondrial encoded
tRNA Leucine and results in strokelike episodes that involve a nonvascular distribution territory affecting both white and gray matter structures (Fig 5). Other features, such as short stature and basal ganglionic calcifications, are usually present in MELAS patients.

A characteristic MRI finding for the mitochondrial diseases includes the presence of "cavitary lesions" in the abnormal white matter. MRS will often demonstrate lactate in brain or CSF. CSF obtained after lumbar puncture will often have increased lactate.

**Other Causes of Leukoencephalopathy**

**Cerebral Autosomal-Dominant Arteriopathy Subcortical Infarcts and Leukoencephalopathy (CADASIL).** CADASIL is an interesting cause of leukoencephalopathy primarily affecting adults. The entity was described in 1977 as a familial multi-infarct dementia, although the disease is recognized more often because of the leukodystrophy noted on MRI [102]. The phenotypic spectrum usually begins after age 40, but asymptomatic at-risk individuals may have MRI abnormalities noted at times in childhood. The clinical manifestations consist of ischemic deficits, cognitive loss, including dementia, migraine, psychiatric disturbances, and, rarely, seizures [103]. The clinical course is unrelenting and occurs very slowly over decades. The MRI pattern consists of hyperintensities on \( T_2 \)-weighted images in periventricular regions, deep white matter, basal ganglia, and infratentorial areas, which increases with age [104]. The cerebral pathology consists of white matter gliosis and a small vessel angiopathy with PAS positive material in the media of the vessel [105]. Although confined to the central nervous system, CADASIL is a systemic vascular disease. The pathologic hallmark of the disease is a nonamyloid non-atheroslerotic microangiopathy. Because of the ubiquitous nature of the vasculopathy, electron microscopy of skin can be used as a diagnostic tool. Electron microscopy of small arterioles in the skin demonstrates characteristic granular osmophilic material in the basement membranes, which indent the surface and appear to rise as flames of electron dense material [105].

The genetic basis for this autosomal-dominant disease was elucidated in 1993 when the gene was mapped to chromosome 19p13.1 and clarified further in 1996 when mutations in the Notch3 were discovered [106]. The Notch3 gene encodes a 300-kd transmembrane protein with a receptor and cell signal transduction function that is important to embryonic development for many species. The gene contains 33 exons and contains 33 EGF-domains. As yet, the exact mechanism in which Notch3 mutations cause the CADASIL phenotype is not understood. The mutations in Notch3 appear to be very stereotyped, involving missense mutations with either a gain or loss of a cysteine residue [107]. It is hoped that mutational analysis will greatly aid in diagnosis and improve the sensitivity of testing.

**Merosin deficiency.** An important cause for a leukoencephalopathy noted on MRI is merosin deficient form of congenital muscular dystrophy or laminin-\( \alpha_2 \) deficiency [108]. These children often have dramatic and unexpected white matter findings but no evidence of upper motor neuron signs and minimal cognitive findings. The clinical picture consists of hypotonia and gross motor delays caused by the muscle disease or at times peripheral neuropathy. The disease may be severe, with the child never gaining the ability to walk, or mild, with the child gaining the ability to walk between 2 and 3 years of age. The disorder does not appear to be progressive. The MRI usually reveals a diffuse white matter signal increase on the \( T_2 \)-weighted image, but the cortex is not involved. The disease is associated with mutations in the laminin-\( \alpha_2 \) gene that is located on chromosome 6q2 [109]. Laminin-\( \alpha_2 \) is associated with \( \alpha \)-dystroglycan in muscle, but the protein is also found in central nervous system (CNS) and Schwann’s cells within the basal lamina.

**Glycogen Storage Disease Type IV (Branching Enzyme Deficiency).** Glycogen storage disease type IV (branching enzyme deficiency) (GSD IV) usually presents in infancy with severe liver disease, causing cirrhosis, portal hypertension, and early death [110]. Myopathy may be the presenting feature in many children and cardiomyopathy has been reported in some individuals [111]. A late-onset variant of GSD IV, referred to as adult polyglucosan storage disease, consists of progressive weakness and spasticity of the legs that may progress to quadriplegesis, urinary incontinence, and a peripheral neuropathy. Cognitive impairments may be present and a leukodystrophy has been noted in many patients. The branching enzyme is 1,4-glucan 6 glucosyltransferase. The gene expressing this
enzyme has been identified and mapped to chromosome 3. The cDNA is 3 kb in length and encodes a protein of 702 amino acids [112]. One mutation (Tyr329Ser) in the gene encoding the branching enzyme has been reported in a series of Ashkenazi families with adult polyglucosan storage disease [113].

**Unknown Causes**

**Childhood Ataxia with Diffuse CNS Hypomyelination (CACH; Vanishing White Matter Disease).** CACH is becoming an ever-important cause of previously undiagnosed leukodystrophies. The entity has been characterized in the last few years by a number of investigators. This disorder was described in four females with ataxia and spasticity but without peripheral nerve or cognitive involvement [114]. MRI demonstrated a diffuse confluent abnormality in white matter that was noted early in the course of the disease (Fig 6). MRS performed on this cohort revealed a reduction of NAA, choline, and creatine in white matter only. Brain biopsies in two of these patients indicated a generalized reduction in myelin-specific proteins and lipids but no evidence of any storage material. Three other patients were described with a relatively mild clinical course but with diffuse hypomyelination and a mildly swollen appearance of white matter [115]. In a later study, nine other children were identified and the term *vanishing white matter* was used to describe the entity [116]. The MRI findings were similar to previous reports, but on proton-density studies the white matter had an intensity similar to CSF. The MRS also confirmed the reduction in NAA, choline, and creatinine but, in addition, lactate and glucose peaks were observed in white matter. On postmortem examination of one patient from this series of children the histopathology demonstrated a cavitating leukoencephalopathy with replacement of white matter between ependyma and U fibers that was replaced by CSF. In areas with some preservation of white matter, astroglisis and macrophage proliferation were present. Mild elevations of CSF glycine have been noted in several patients with CACH, and linkage to chromosome 3q27 has been found in a cohort of Dutch families with vanishing white matter disease [117,118].

A set of criterion were suggested by van der Knaap et al. [119] to identify children with CACH (vanishing white matter disease):

1. Normal or mildly delayed initial psychomotor development.
2. Neurologic deterioration with a chronic progressive and episodic course. Deterioration may follow infection or minor head trauma and may lead to lethargy and coma.
3. Presence of cerebellar ataxia and spasticity with relative preservation of mental function. Optic atrophy and epilepsy may occur.
4. Diffuse symmetric white matter involvement on MRI with all or part of white matter exhibiting a signal intensity similar to CSF on proton density, FLAIR, and $T_2$-weighted and $T_1$-weighted images. Cerebellar atrophy may also occur.

**Vacuolating Leukoencephalopathy (Leukoencephalopathy, Megalencephaly, and Mild Clinical Course).** Vacuolating leukoencephalopathy (VLE) is a recently described disease that consists of the triad of (1) leukoencephalopathy; (2) megalencephaly; and (3) mild clinical course. Because of the length of the original name for this disease, the term VLE has been suggested to correlate with neuro-
pathologic changes seen in this disorder [120]. The first description was likely by Harbord et al. [121] when two siblings with megalencephaly and dysmyelination were reported, but van der Knaap et al. [122] and Goutieres et al. [123] have characterized the clinical and radiographic aspects of this disease. The clinical features consist of macrocephaly occurring in the first year of life with a relatively mild neurologic symptoms consisting of delays in gross motors skills, pyramidal signs, cerebellar ataxia, and occasionally seizures [122,123]. MRI demonstrates diffuse supratentorial white matter increased signal on T2-weighted images and hypodensity on T1-weighted images. In older patients, cystic changes occur in temporal and parietal white matter regions. The brainstem and cerebellum appear largely unaffected. MRS at times reveals a slightly lower NAA to creatine ratio.

Although VLE may share some characteristics with other leukoencephalopathies causing macrocephaly, it appears to be a unique disorder. There has been a spongiform leukoencephalopathy without cortical involvement reported on brain biopsy in one patient [120]. Most vacuoles were covered by single five-layered membranes, representing single myelin lamellae, and some vacuoles were partially covered by multilamellar myelin sheaths or oligodendrogial cell extensions [120]. Although VLE has some pathologic similarities to Canavan’s disease, no abnormality of NAA is present. Also, unlike what is found on brain biopsy in Alexander’s disease, there are no Rosenthal fibers in VLE. CACH or vanishing white matter disease differs from VLE by the presence of macrocephaly in the first year, and the MR changes in CACH that are not cystic but are more diffusely decreased density over time on T1, T2, and FLAIR images [119]. No definitive biochemical changes have been noted and there is no genetic linkage as yet on these patients. The disease is presumed to be inherited in an autosomal-recessive pattern.

**Alexander’s Disease.** Alexander’s disease usually presents during infancy with the typical features of developmental delay, macrocephaly (resulting from megalencephaly), and seizures [124,125]. The disease usually begins in the first or second year of life resulting from but rarely occurs as late as 6 years of age. Although initial reports suggested a male predominance, both sexes are equally affected. As the disease progresses, cognitive decline, feeding problems, and spastic quadriapresis become apparent. Some infants present acutely in the first year with hydrocephalus and increased intracranial pressure [126]. In a few cases, megalencephaly may be present from birth, and, rarely, megalencephaly is never present. Death usually occurs between the ages 2 and 10 years.

Juvenile-onset Alexander’s disease usually begins between 6 and 15 years of age but may begin as early as infancy [125,127,128]. Unlike the infantile onset, megalencephaly is usually not present in these later-onset children. Symptoms consist of bulbar dysfunction, especially dysphagia, and a slowly progressive gait disorder manifested by ataxia and progressive spasticity, which usually begins in the lower extremities. Cognitive decline occurs only late in the disease. These children may survive beyond 10 years of age.

The pathology of Alexander’s disease is unique among the leukodystrophies. On histologic appearance widely distributed astrocytic inclusions called Rosenthal fibers are found in the brain. There appears to be a pronounced paucity of myelin. The frontal lobes are the most severely affected with a discoloration of the white matter, and frequently cystic degeneration and cavitation are present. The lesions extend to involve the subcortical U fibers. The basal ganglia and thalami are also affected, but there is relative sparing of the occipital lobes and the cerebellum [129].

Alexander’s disease is suspected on the clinical history, but MRI may be very helpful in establishing the diagnosis. Lesions are typically located in the bilateral frontal regions and consist of frontal cystic changes, usually partially sparing the occipital lobes and cerebellum [125,130]. In one adolescent patient, some paramagnetic substances were noted in the basal ganglia and thalamus [130].

The genetic and biochemical basis for Alexander’s disease remains unknown. Only rarely has the disease been described in the same family, making the genetic inheritance pattern difficult to prove but suggestive of a sporadic inheritance. A preliminary study also found spontaneous mutations in the gene for GFAP in 11 of 12 patients with infantile, juvenile, and adult forms of Alexander’s disease, which would explain the usually sporadic inheritance pattern. There has also been some recent reports concerning the presence of GAP aggregates in the brains of Alexander’s patients and alpha B-crystallin and heat shock protein 27 in CSF, but to date no firm biochemical marker is present [131,130]. There is one report of a patient with Alexander’s disease associated with a chromosomal deletion involving the long arm of chromosome 11, but this child did not have a deletion affecting the alpha B-crystallin gene [132].

**Aicardi-Goutieres Syndrome.** Aicardi-Goutieres syndrome was first identified in 1984 by Aicardi and Goutieres [133]. They reported eight infants from five families who suffered from an early-onset familial encephalopathy with chronic CSF lymphocytosis and basal ganglia calcifications mimicking an intrauterine infectious process but with negative TORCH investigations [133]. Clinically, the patients exhibited bilateral spasticity, dystonia, ocular jerks, and acquired progressive microcephaly with a rapid course toward profound deterioration and death. In addition, CT scan demonstrated diffuse and progressive brain atrophy and deep white matter hypodensities. The authors suggested a probable genetic condition with autosomal-recessive inheritance.

Leukoencephalopathy is often noted on MRI, which may lead to diagnostic confusion. CT scan reveals white matter hypodensities located mainly around the ventricles. These hypodense lesions appear as hyperintense on MRI T2 sequences but they are not constant, and a diffuse leukodystrophic aspect is uncommon [134]. Signs of severe and progressive brain atrophy with enlarged ven-
tricles and sulci increasing on successive examinations are a constant finding on CT and MRI.

The diagnosis is confirmed by the identification of CSF lymphocytosis, clinical picture, and MRI and CT findings especially basal ganglia calcifications. The inheritance is presumed to be autosomal-recessive but no gene identification has been determined.

References

[43] Lugowska A, Tylik-Szymanska A, Berger J, Molzer B, Ele-


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