Invited Article: An MRI-based approach to the diagnosis of white matter disorders

Raphael Schiffmann, MD
Marjo S. van der Knaap, MD, PhD

Address correspondence and reprint requests to Dr. Marjo S. van der Knaap, Department of Child Neurology, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands
ms.vanderknaap@vumc.nl.

ABSTRACT

Background: There are many different white matter disorders, both inherited and acquired, and consequently the diagnostic process is difficult. Establishing a specific diagnosis is often delayed at great emotional and financial costs. The pattern of brain structures involved, as visualized by MRI, has proven to often have a high diagnostic specificity.

Methods: We developed a comprehensive practical algorithm that relies mainly on the characteristics of brain MRI.

Results: The initial decision point defines a hypomyelination pattern, in which the cerebral white matter is hyperintense (normal), isointense, or slightly hypointense relative to the cortex on T1-weighted images, vs other pathologies with more prominent hypointensity of the cerebral white matter on T1-weighted images. In all types of pathology, the affected white matter is hyperintense on T2-weighted images, but, as a rule, the T2 hyperintensity is less marked in hypomyelination than in other pathologies. Some hypomyelinating disorders are typically associated with peripheral nerve involvement, while others are not. Lesions in patients with pathologies other than hypomyelination can be either confluent or isolated and multifocal. Among the diseases with confluent lesions, the distribution of the abnormalities is of high diagnostic value. Additional MRI features, such as white matter rarefaction, the presence of cysts, contrast enhancement, and the presence of calcifications, further narrow the diagnostic possibilities.

Conclusion: Application of a systematic decision tree in MRI of white matter disorders facilitates the diagnosis of specific etiologic entities. *Neurology*® 2009;72:750–759

GLOSSARY

FLAIR = fluid-attenuated inversion recovery; **LBSL** = leukoencephalopathy with brainstem and spinal cord abnormalities; **T1W** = T1-weighted; **T2W** = T2-weighted.

White matter disorders or leukoencephalopathies comprise all disorders that exclusively or predominantly affect the white matter of the brain. Leukodystrophies are genetically determined leukoencephalopathies. There are many different leukoencephalopathies, which can occur at all ages, be progressive or static, and be genetic or acquired.[1,2] The diagnostic workup is complicated. Many tests are performed, at high financial and emotional costs and often with disappointing results.[3]

MRI has proven to be pivotal in the diagnostic workup of patients with leukoencephalopathies.[2] First, the presence of white matter abnormalities is usually established with MRI. CT may show white matter hypodensity, but it is much less sensitive than MRI and gives no details. Secondly, it has been shown repeatedly that individual leukoencephalopathies present themselves with distinct patterns of MRI abnormalities, which are homogeneous among patients with the same disorder and different in patients with different disorders, indicating the high diagnostic value of MRI patterns.[2-4]

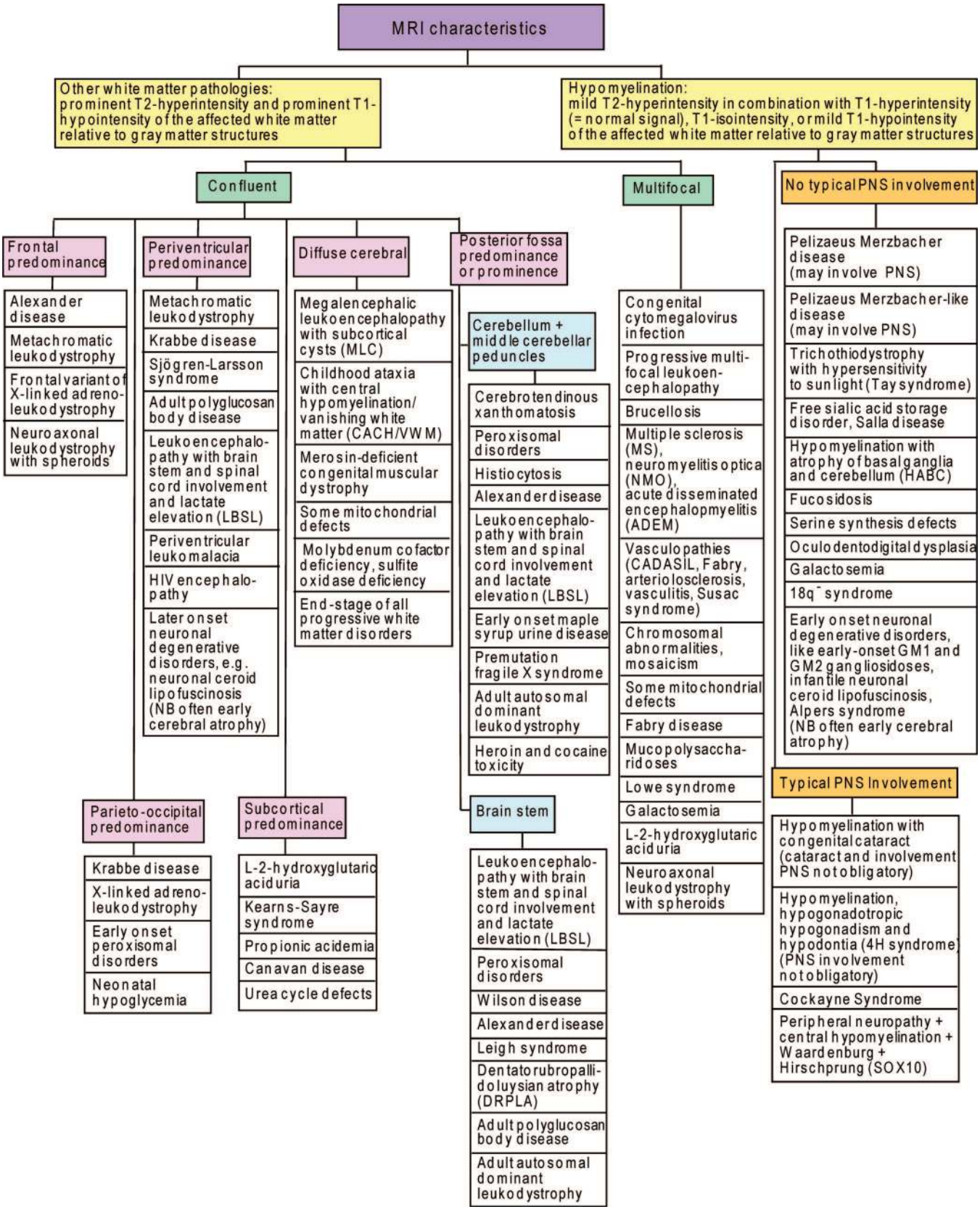
Supplemental data at www.neurology.org

From the Institute of Metabolic Disease (R.S.), Baylor Research Institute, Dallas, TX; and Department of Child Neurology (M.S.v.d.K.), VU University Medical Center, Amsterdam, The Netherlands.

M.S.v.d.K. received financial support from the Dutch Organization for Scientific Research (ZonMw, TOP grant 9120.6002) and the Optimix Foundation for Scientific Research. R.S. was supported by the Intramural Research Program of the National Institute of Neurological Disorders and Stroke (NIH).

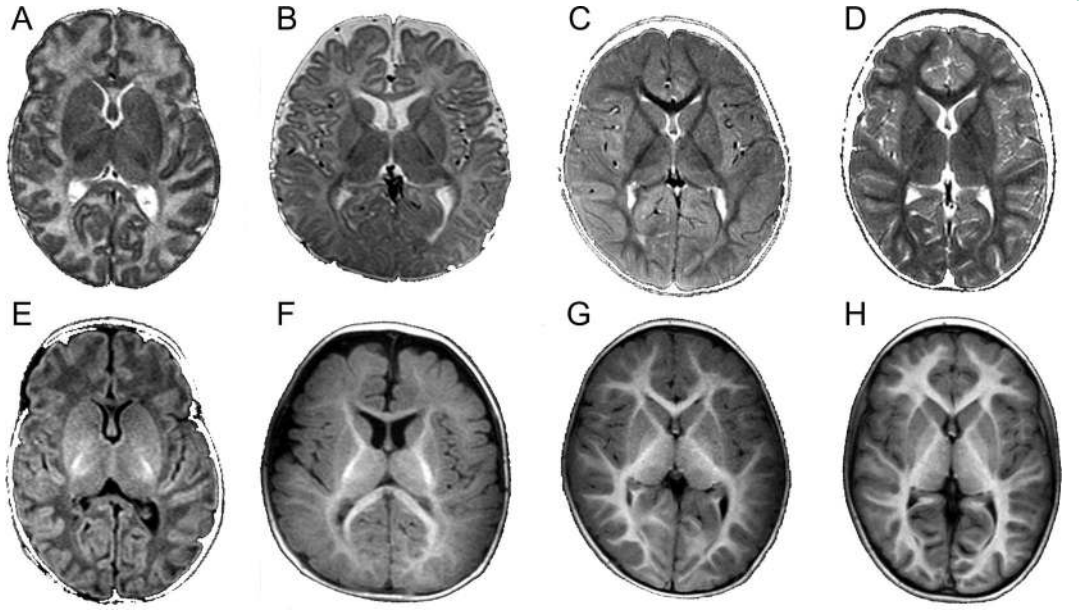
Disclosure: The authors report no disclosures.

Figure 1 MRI algorithm



MRI pattern recognition is a way to systematically analyze many details on MR images and integrate these into patterns per disease.[3,4] The scoring of MRI details is easy, but it is time consuming and not practical in routine practice. Systematic MRI pattern rec-

Figure 2 Normal myelination



Normal T2-weighted (A–D) and T1-weighted (E–H) images at term (A, E), and at the ages of 5 months (B, F), 1 year (C, G), and 5 years (D, H). Myelin deposition is represented by a low signal on T2-weighted images and high signal on T1-weighted images. Note that myelination consistently looks more advanced on T1-weighted images than on T2-weighted images.

ognition is important for research purposes, especially for the definition of novel disorders or description of phenotypic variation.[3,5-12] For routine practice, the main lines of MRI pattern recognition suffice. They help to establish a reasonably short differential diagnosis. We endeavored to provide a simple scheme to facilitate diagnostics, mainly based on MRI details (figure 1).

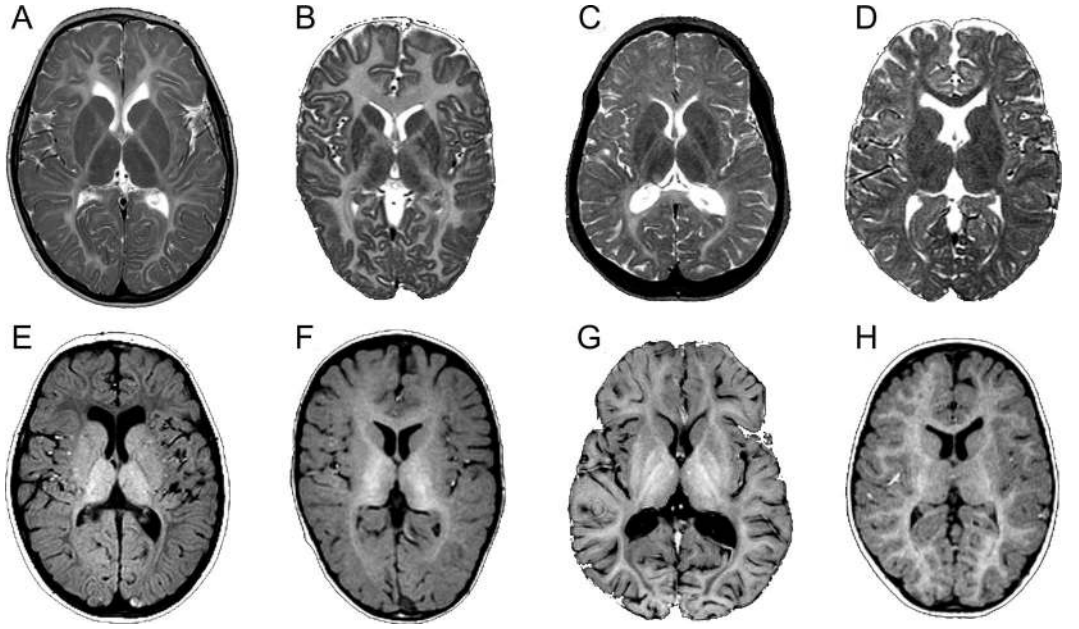
NORMAL MRI Normal, myelinated white matter structures have a shorter T1 and T2 than gray matter structures.[13,14] Hence, myelinated white matter structures have a higher signal than gray matter structures on T1-weighted (T1W) images and a lower signal on T2-weighted (T2W) images (figure 2, D and H).[13,14] Unmyelinated white matter structures have a longer T1 and T2 than gray matter structures. Consequently, the contrast is reversed: unmyelinated white matter structures have a lower signal than gray matter structures on T1W images and a higher signal on T2W images (figure 2, A and E).[13,14] With myelin deposition and its associated biochemical and structural changes, there is an earlier and more pronounced T1 shortening than T2 shortening (figure 2, B, C, F, and G).[13,14] Consequently, with deposition of a small amount of myelin, the white matter structure soon becomes isointense or hyperintense compared to gray matter on T1W images, whereas the signal of that structure is still high on T2W images (figure 2, B, C, F, and G).[13,14] The white matter becomes dark on T2W images only with more advanced stages of myelination (figure 2, D and H).[13,14]

The process of myelination of the brain mainly takes place in the first 2 years of life and follows a fixed plan.[13,14] There is a certain order in the structures to be myelinated sequentially and there is a certain time frame. The features and time scale of normal myelination on MRI are well known.[13,14]

THE FIRST MAJOR MRI DISCRIMINATOR It is abnormal for cerebral white matter to have a high signal on T2W images in a child over 1.5 years of age.[13,14] The first question to be addressed is whether the high signal is related to deficient myelination or whether something else is wrong with the white matter. So, the first major MRI discriminator concerns delayed myelination or permanent hypomyelination on the one hand vs all other forms of white matter pathology on the other hand (figure 1).

The first indication of delayed myelination and permanent hypomyelination is found in the signal behavior of the cerebral white matter. The signal of the cerebral white matter on T1W images depends on the amount of myelin deposited (figures 2 and 3 and figure e-1 on the *Neurology*® Web site at www.neurology.org).[8,14,15] If there is very little or no myelin, the signal of the cerebral white matter is lower than that of gray matter structures on T1W images (figure 3E). If there is some myelin, the white matter is isointense with gray matter structures (figure 3F). If there is more myelin, the white matter signal is

Figure 3 Variable degrees of hypomyelination



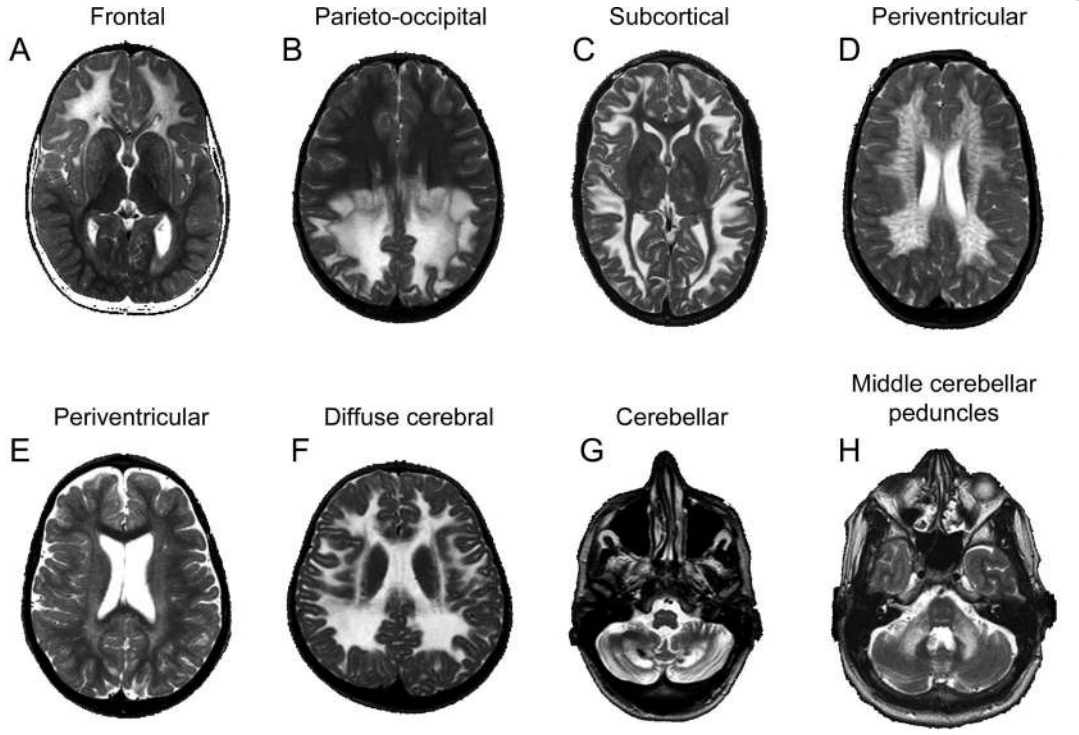
The first patient (A, E), 7 years old, has less myelin than a normal neonate; the cause is unknown. The cerebral white matter has a low signal intensity on T1-weighted images (E). The second patient (B, F), 6 years old, diagnosed with Pelizaeus-Merzbacher disease, has somewhat more myelin. The cerebral white matter is isointense with the cortex on T1-weighted images (F). The third patient (C, G), 11 years old, also diagnosed with Pelizaeus-Merzbacher disease, has more myelin. Large areas of the cerebral white matter have a higher signal intensity than the cortex on T1-weighted images (G). The fourth patient (D, H), 4 years old, diagnosed with the 18q$^-$ syndrome, has again more myelin. All cerebral white matter has a higher signal intensity than the cortex on T1-weighted images (H), but on the T2-weighted images (D) part of the cerebral white matter still has a slightly higher signal intensity than the cortex.

higher than that of gray matter structures on T1W images (figure 3, G and H). In all cases, the cerebral white matter has a moderately elevated signal on T2W images (figure 3, A–D).[8,14,15] Consequently, T1W images generally look better, suggesting more myelin, than T2W images in hypomyelination and delayed myelination. In all white matter pathologies other than deficient myelination, the signal changes are as a rule more prominent: the affected white matter has a much higher signal on T2W images and a much lower signal on T1W images than gray matter structures (figure 4 and figures e-2 and e-3). A second indicator of deficient myelination is that the T2-signal abnormalities are diffuse, without the presence of focal lesions (figure 3). It is also possible that there are lesions on a background of deficient myelination, but deficient myelination in itself is a widespread process. A third indicator of deficient myelination is that the MRI actually looks like a normal MRI of a young child (compare figures 2 and 3). As explained above, normal myelination involves brain structures in a certain sequence.[13,14] The brainstem acquires myelin before term birth. The cerebellar white matter is myelinated soon after birth. The internal capsule and corpus callosum acquire myelin in the first few months of postnatal life.[13,14] These structures most often have normal signal intensity in patients with deficient myelination, indicating their relatively high myelin content.

The differentiation between delayed myelination and permanent hypomyelination is important. Delayed myelination is a nonspecific feature observed in almost all children with a delayed development of any cause,[16] whereas permanent hypomyelination comes with a specific differential diagnosis, as explained in figure 1.[15] The differentiation between delayed myelination and permanent hypomyelination can be made by two MRIs with a significant time interval. Normal myelination occurs mainly in the first 2 years of life.[13,14] Within the first year of life, there is so little myelin in normal infants that it is not possible to diagnose permanent hypomyelination. So, permanent hypomyelination can be defined as an unchanged pattern of deficient myelination on two MRIs at least 6 months apart in a child older than 1 year. Experience has taught that if an MRI shows severely deficient myelination in a child older than 2 years, it is extremely unlikely that the child will ever acquire the myelin and permanent hypomyelination is highly likely.

The MRI features of different hypomyelinating disorders are similar (figure 3 and figure e-1), except for signal abnormalities of the thalami and basal ganglia in specific disorders. For instance, in hypom-

Figure 4 **Predominance of the white matter abnormalities**



Alexander disease (A) presents in many patients with predominantly frontal white matter abnormalities. Note the additional slight signal abnormalities in the basal ganglia. The most frequent presentation of the cerebral form of X-linked adrenoleukodystrophy (B) is with a lesion in the parieto-occipital white matter. Note that two zones can be distinguished within the lesion. Kearns-Sayre syndrome (C) is one of the disorders characterized by predominantly subcortical white matter abnormalities and relative sparing of the periventricular white matter. The disease also displays signal abnormalities in the thalamus (C). Metachromatic leukodystrophy (D) primarily affects the periventricular and deep cerebral white matter, whereas the U-fibers are relatively spared. The stripes with more normal signal within the abnormal white matter are typically seen in certain lysosomal storage disorders (D). Cortical neuronal degenerative disorders often have an ill-defined, broad, periventricular rim of mildly abnormal signal, as shown here in juvenile neuronal ceroid lipofuscinosis (E). Diffuse cerebral white matter abnormalities are seen in childhood ataxia with central hypomyelination/vanishing white matter (F). In cerebrotendinous xanthomatosis (G), the cerebellar white matter is usually more affected than the cerebral white matter. The cerebellum often also contains areas of low signal (G). In patients with autosomal dominant adult onset leukoencephalopathy related to a duplication of *LMNB1* (H), involvement of the middle cerebellar peduncles is frequently seen.

yelination with atrophy of the basal ganglia and cerebellum, the diagnosis is based on the fact that apart from diffuse hypomyelination, the MRI shows a very small or absent putamen, a small caudate nucleus, and atrophy of the cerebellum, especially the vermis (figure e-1, A and E).[8,15] Cerebellar atrophy in itself is a nonspecific finding in the context of hypomyelination.

In Cockayne syndrome, serine synthesis defects, oculodental digital dysplasia, and galactosemia, the hypomyelination may be incomplete and patchy.[17,18] The 18q$^-$ syndrome is commonly classified among the hypomyelinating disorders. It is correct that MRI shows that myelination is incomplete, also in older patients.[19] Myelination is, however, much more advanced than in the other hypomyelinating disorders mentioned. The myelin deficit as apparent on MRI is mild and patchy (figure 3, D and H).[19] The 18q$^-$ syndrome is associated with a particular clinical phenotype.[19]

It is important to realize that in early infantile onset degenerative brain disorders of any type, the process of myelination may be disturbed. Myelination requires close interaction among oligodendrocytes, astrocytes, and neurons. A defect in any of these cell types may interfere with the normal process of myelination. Early onset disorders affecting the function of oligodendrocytes, such as Krabbe disease, and disorders affecting the function of astrocytes, such as Alexander disease, are typical white matter disorders.[20,21] Although a component of hypomyelination may be seen in those disorders, the simultaneous or subsequent prominent signal abnormalities in the cerebral white matter make clear that the patients have a white matter disease, different from simple hypomyelination. Hypomyelination is also present in early onset neuronal degenerative disorders (figure e-1, B–D and F–H).[22-24] The hypomyelination may be more inhomogeneous and patchy than in most other hypomyelinating disorders. Early

and prominent cerebral atrophy is an indicator of the underlying neuronal disease (figure e-1, B and F).[22-24] Although slowly progressive cerebral atrophy, occurring in the course of years, is seen in several hypomyelinating disorders, including Pelizaeus-Merzbacher disease, Pelizaeus-Merzbacher-like disease, and Cockayne syndrome, the atrophy tends to be earlier and more severe in neuronal disorders. In the case of hypomyelination together with early severe cerebral atrophy, an underlying neuronal degenerative disorder is most likely; the differential diagnosis includes infantile neuronal ceroid lipofuscinosis,[22] Menkes disease,[23] and Alpers syndrome.[23] Signal abnormalities of the basal ganglia and thalami are another feature that may indicate an underlying neuronal degenerative disease (figure e-1, B–D and F–H).[2]

After MRI interpretation, the next step in the diagnostic workup of patients with hypomyelination should concern the possible involvement of the peripheral nerves. Peripheral nerve involvement is, however, not a perfect discriminator. In disorders typically associated with peripheral nerve involvement, such as hypomyelination with congenital cataract and hypomyelination with hypodontia and hypogonadotropic hypogonadism (4H syndrome), a peripheral neuropathy is inconstant or may be associated with normal nerve conduction velocity.[10,11,12] Peripheral nerve involvement may occasionally be observed in disorders not typically associated with a peripheral neuropathy, such as Pelizaeus-Merzbacher disease.[24] The DNA repair disorders trichothiodystrophy and Cockayne syndrome are invariably characterized by marked hypersensitivity of the skin to sunlight.[25] In 4H syndrome, delayed, deficient, and abnormal dentition is an early feature.[11,12] Hypogonadotropic hypogonadism leads to the absence of normal puberty at a later stage.[12]

Finally, it should be noted that the cause of hypomyelination presently remains unknown in many patients. Hypomyelination constitutes the largest single category among patients with a leukoencephalopathy of unknown origin.[3]

THE SECOND MRI DISCRIMINATOR The second MRI discriminator concerns the question whether the white matter abnormalities are confluent or isolated and multifocal (figure 1). Most genetic white matter disorders (leukodystrophies) present with confluent and bilateral, essentially symmetric, white matter abnormalities; multifocal isolated white matter abnormalities, often with an asymmetrical distribution, are most commonly related to acquired disorders (figure e-2, A–H). This rule, however, has many exceptions (figure 1 and figure e-2, I–N).[3] Several acquired disorders are typically characterized by bilaterally symmetric, confluent white matter abnormalities. Examples are toxic leukoencephalopathies, such as related to inhaled heroin ("chasing the dragon"), HIV encephalopathy, and delayed posthypoxic demyelination.[2] On the other hand, several genetic disorders are typically associated with multifocal white matter lesions (see below).

A few words should be said about genetic vs acquired disorders. Genetic disorders are those that have a Mendelian mode of inheritance (autosomal recessive, autosomal dominant, or X-linked) or maternal inheritance (for some mitochondrial disorders). Acquired disorders are those that are caused by an external influence or event. Undoubtedly, genetic factors play a role in determining the susceptibility for those external influences and, as such, the distinction between genetic and acquired is artificial. Still, the distinction is of practical value, because the types of tests that need to be performed are different for those two categories of disorders.

It is important to realize that multifocal lesions can only be seen up to a certain stage of the disease. In the far advanced stages of progressive diseases, when (almost) all white matter is affected, the white matter abnormalities will always be confluent. For instance, in far advanced stages of multiple sclerosis, the cerebral white matter abnormalities may become diffuse, simulating a leukodystrophy (figure e-2G). It is also important to note that some disorders that are not considered to be white matter disorders, such as tuberous sclerosis, may be misdiagnosed as a white matter disorder because of the prominent, multifocal white matter changes.

Multifocal white matter abnormalities come with a specific differential diagnosis, including infectious disorders, such as congenital cytomegalovirus infection[26] (figure e-2, A and B) and brucellosis; and inflammatory disorders, such as acute disseminated encephalomyelitis (figure e-2, C and D), neuromyelitis optica, and multiple sclerosis (figure e-2, E–H).[2] Vasculopathies also have multifocal white matter abnormalities in the early stages, but the abnormalities often become confluent in more advanced stages. Almost invariably, vascular leukoencephalopathies are characterized by the presence of additional multifocal lesions in the basal ganglia, thalami, and brainstem (figure e-2, I and K).[27,28] Vasculopathies can be either genetic or acquired and include those related to arterio(lo)sclerosis,[27] cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy,[27] amyloid angiopathy,[27] defects in collagen IV A1[28] (figure e-2, I and J), Fabry disease[29] (figure e-2, K and L), Susac syndrome, and vasculitis.[27] The presence of microbleeds on gradient echo images is a strong argu-

ment in favor of an underlying vasculopathy (figure e-2J).[30]

Several other genetic disorders are typically characterized by multifocal white matter abnormalities (figure 1).[2] They include some mitochondrial defects, L-2-hydroxyglutaric aciduria,[2] some cases of leukoencephalopathy with brainstem and spinal cord abnormalities (LBSL)[9] (figure e-2, M and N), the mucopolysaccharidoses,[2] and galactosemia.[2] Chromosomal abnormalities are, if accompanied by white matter abnormalities, usually associated with multifocal lesions. Examples are chromosomal mosaicism[2] and $6p^-$ syndrome (figure e-2, O and P).[31]

THE THIRD MRI DISCRIMINATOR If the white matter abnormalities are confluent, the most helpful third MRI discriminator concerns the predominant localization of the abnormalities. The major preferential localizations are frontal, parieto-occipital, periventricular, subcortical, diffuse cerebral, and posterior fossa (figure 1).

Frontal predominance is a feature of Alexander disease[21] (figure 4A and figure e-3, A and B), the frontal variant of X-linked adrenoleukodystrophy, and metachromatic leukodystrophy, especially the adult variant.[2] Parieto-occipital predominance is seen in the most common variant of cerebral X-linked adrenoleukodystrophy (figure 4B and figure e-3, C and D) and may also be seen in Krabbe disease.[2] If progressive demyelination occurs in early onset peroxisomal disorders, the abnormalities in the posterior fossa and parieto-occipital white matter predominate.[2] In brain damage related to neonatal hypoglycemia of any origin, both genetic and acquired, polycystic white matter degeneration with parieto-occipital predominance is commonly seen.[32]

Periventricular predominance with preservation of the U-fibers is seen in many disorders and has limited diagnostic utility (figure 4D and figure e-3E).[2] It is noteworthy that cortical degenerative disorders, such as the neuronal ceroid lipofuscinoses with onset after the infantile period, are often associated with an ill-defined, broad periventricular rim of mild signal alteration (figure 4E and figure e-3F).[33] Subcortical predominance is much more unusual and seen in specific disorders (figure 4C and figure e-3, G and H), mentioned in figure 1.[2]

Diffuse cerebral white matter signal abnormalities are a feature of hypomyelination. Hypomyelination has been discussed earlier. Diffuse cerebral white matter signal abnormalities (figure 4F and figure e-3, I and J) are also a feature from early in the course of the disease in several disorders, mentioned in figure 1. It should again be noted that the end stage of progressive cerebral white matter disorders is always characterized by diffuse abnormalities (figure e-2G).[2,3,5-7]

Signal abnormalities in the brainstem, cerebellar white matter, or both are often part of more extensive leukoencephalopathies.[2] They are rarely as prominent as the supratentorial abnormalities. If they are, they can affect the brainstem, the cerebellar white matter, or both. Striking cerebellar white matter abnormalities are often seen in cerebrotendinous xanthomatosis (figure 4G and figure e-3, K and L),[34] several peroxisomal disorders, Alexander disease (figure e-3N),[35] LBSL (figure e-2, M and N),[9] and early onset maple syrup urine disease.[2] They can also occur as a paramalignant syndrome in histiocytosis.[2] Prominent brainstem abnormalities are usually seen in the disorders mentioned in figure 1, including Alexander disease[35] (figure e-3, B, M, and N), LBSL[9] (figure e-2, M and N), and adult polyglucosan disease.[36] In premutation fragile X syndrome[37] and in autosomal dominant leukodystrophy related to a lamin B1 duplication[38] (figure 4H and figure e-3, O and P), the middle cerebellar peduncles are strikingly affected.

SPECIAL MRI CHARACTERISTICS Special MRI features that are typically seen in a number of specific disorders and have a high diagnostic value are 1) cystic white matter degeneration, 2) anterior temporal cysts, 3) megalencephaly, 4) enlarged perivascular spaces or small cysts, 5) additional gray matter lesions (cortical dysplasia, cortical lesions, basal ganglia lesions), 6) contrast enhancement, 7) calcium deposits, 8) microbleeds, 9) spinal cord involvement, and 10) evolution over time. Table e-1 lists the disorders in which these specific features are typically seen.

White matter rarefaction and cystic degeneration can be visualized best by fluid-attenuated inversion recovery (FLAIR) images. Abnormal white matter has a high signal on T2W images and a low signal on T1W images. If the abnormal white matter is rarefied, it has an intermediate signal on FLAIR images; if it is cystic, it has the same very low signal intensity as CSF. The white matter rarefaction and cystic degeneration in childhood ataxia with central hypomyelination/vanishing white matter occurs in a diffuse, melting-away fashion, leaving behind a cobweb of better preserved tissue stands.[6] There are usually no well-delineated isolated cysts. In mitochondrial defects the abnormal white matter may be partially cystic, but here the cysts are usually isolated and well delineated.[2] In Alexander disease, cysts may occur, especially in the frontal white matter.[21] In neonatal cerebral energy depletion, cystic cerebral white matter degeneration may occur. It may be diffuse in generalized hypoxia-ischemia, or focal in a middle cerebral artery infarction. In neonatal hypoglycemia,

the cystic white matter degeneration often affects the parieto-occipital white matter.[32]

Anterior temporal cysts, megalencephaly, and enlarged perivascular spaces each are a feature of specific white matter disorders, as detailed in table e-1.

In addition to the leukoencephalopathy, gray matter abnormalities may be present in the form of cortical dysplasia, cortical lesions, and basal ganglia lesions. Each of these is associated with a specific differential diagnosis, as summarized in table e-1.

Contrast enhancement comes with a specific differential diagnosis. It is worthwhile to obtain a contrast-enhanced MRI at least once in all patients with a leukoencephalopathy of unknown origin, because enhancement may be entirely unexpected.

MRI has a low sensitivity for the detection of calcium deposits. Gradient echo and susceptibility-weighted images are helpful to detect them. CT scan is often better. Gradient echo and susceptibility-weighted images are, however, superior when it comes to the detection of microbleeds, which provide strong evidence for an underlying vasculopathy (figure e-2J).[30]

The demonstration of spinal cord abnormalities has a high diagnostic value in several disorders. Focal or multifocal lesions are typically seen in acute disseminated encephalomyelitis, neuromyelitis optica, multiple sclerosis, brucellosis, vitamin B12 deficiency, Alexander disease, and mitochondrial defects.[2] In LBSL, the spinal cord contains signal abnormalities over its entire extent.[9]

DISCUSSION The present article describes a shortened version of a known MRI pattern recognition program,[2-4] which can be applied in routine neurology and neuroradiology. It involves 1) the differentiation of hypomyelination from other types of white matter pathology; 2) the distinction between confluent and multifocal, isolated white matter abnormalities; 3) the assessment of the predominant localization of confluent white matter abnormalities; and 4) the evaluation of special features as detailed in table e-1. In most cases, one cannot rely on the analysis of only one item in the MRI pattern recognition program. Combining features found in the different parts of the MRI pattern recognition program enhances the power of the MRI interpretation. Application of the algorithm does not take much time and helps in achieving a relatively short differential diagnosis. Clinical details should be used to further shorten the differential diagnosis. Rapid diagnosis in a white matter disease decreases patient and family anxiety and allows the rapid institution of appropriate therapy, if available.[39]

The imaging protocol in patients with a suspected leukoencephalopathy should be sufficient to answer the above four items. The minimum imaging protocol includes T1W, T2W, and FLAIR images of the brain. An accurate diagnosis can rarely be achieved without consideration of this imaging complement. It is worthwhile to obtain contrast-enhanced T1W images, gradient echo and susceptibility-weighted images, diffusion-weighted images, MR spectroscopy, and a spinal cord MRI at least once in all patients with a leukoencephalopathy of unknown origin.

This pattern recognition algorithm is based on the experience of the authors of this article. However, a study has been performed previously on a large group of patients with leukoencephalopathies of unknown origin, in which a statistical validation of the MRI pattern recognition approach is provided.[3] In addition, MRI pattern recognition has led to the description of several novel patterns, which have been associated with distinct clinical phenotypes.[5-12] The subsequent identification of associated disease genes again supports the validity of the MRI pattern recognition approach.[10,40-42]

With respect to the diagnostic workup, it is important that neurologists realize that leukoencephalopathies do not come with a standard differential diagnosis and a standard battery of tests to be performed. Most of the tests that are currently considered standard for leukoencephalopathies, such as metabolic screening of body fluids, assessment of lysosomal enzymes, and measurement of very long-chain fatty acids, are unnecessary in individual cases, but which tests are unnecessary depends on the specific MRI pattern. Some diagnoses are never achieved by these tests and require specific tests, outside the standard battery. Present practice may be characterized by a waste of time and money on tests for diagnoses that are incompatible with the MRI pattern, while the appropriate test may be unduly delayed. In a number of disorders the diagnosis can only be achieved on the basis of MRI characteristics. For instance, the diagnoses of megaloencephalic leukoencephalopathy with subcortical cysts and LBSL are solely based on MRI criteria.[40,41]

MRI pattern recognition does not lead to a specific diagnosis in all patients with white matter abnormalities. One reason is that the pattern of MRI abnormalities is not specific in all disorders. Second, the specificity of the pattern is disease stage-dependent. Minor lesions within the cerebral white matter in the early stages of a disease are usually nonspecific. The end stage of most progressive disorders is characterized by the involvement of all cerebral white matter, which may also result in a nonspecific MRI pattern. Third, the pattern, as observed in a patient, may not yet have been associated with a specific disorder. There is no study assessing the percentage of patients of all ages with white matter

abnormalities on MRI who presently remain without a specific diagnosis. Our estimate would be that the percentage is 30–40%. However, even though the MRI pattern does not lead to a specific diagnosis in all cases, it always helps to exclude many diagnoses, precluding undirected laboratory screening.

The disadvantage of shortened MRI pattern recognition is undoubtedly that no attention is paid to small details, variability of MRI patterns, and exceptions. Such exceptions would be important in a small but significant part of the patients. In those cases it might be preferable to ask for an expert opinion.

ACKNOWLEDGMENT

The authors thank the colleagues who sent MRIs for second opinion and kept the authors informed of the definite diagnosis. The authors also thank Dr. James M. Powers, University of Rochester, NY, for critical reading of the manuscript, and Han Poels for help in preparing the figures.

Received August 20, 2008. Accepted in final form November 18, 2008.

REFERENCES

1. van der Voorn JP, Pouwels PJ, Hart AA, et al. Childhood white matter disorders: quantitative MR imaging and spectroscopy. Radiology 2006;241:510–517.
2. Van der Knaap MS, Valk J. Magnetic Resonance of Myelination and Myelin Disorders, 3rd ed. Berlin: Springer; 2005.
3. van der Knaap MS, Breiter SN, Naidu S, Hart AA, Valk J. Defining and categorizing leukoencephalopathies of unknown origin: MR imaging approach. Radiology 1999; 213:121–133.
4. van der Knaap MS, Valk J, de Neeling N, Nauta JJ. Pattern recognition in magnetic resonance imaging of white matter disorders in children and young adults. Neuroradiol 1991;33:478–493.
5. Schiffmann R, Moller JR, Trapp BD, et al. Childhood ataxia with diffuse central nervous system hypomyelination. Ann Neurol 1994;35:331–340.
6. van der Knaap MS, Barth PG, Gabreels FJ, et al. A new leukoencephalopathy with vanishing white matter. Neurology 1997;48:845–855.
7. 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;37:324–334.
8. van der Knaap MS, Naidu S, Pouwels PJ, et al. New syndrome characterized by hypomyelination with atrophy of the basal ganglia and cerebellum. AJNR Am J Neuroradiol 2002;23:1466–1474.
9. van der Knaap MS, van der Voorn P, Barkhof F, et al. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. Ann Neurol 2003;53:252–258.
10. Zara F, Biancheri R, Bruno C, et al. Deficiency of hyccin, a newly identified membrane protein, causes hypomyelination and congenital cataract. Nat Genet 2006;38:1111–1113.
11. Wolf NI, Harting I, Boltshauser E, et al. Leukoencephalopathy with ataxia, hypodontia, and hypomyelination. Neurology 2005;64:1461–1464.
12. Timmons M, Tsokos M, Asab MA, et al. Peripheral and central hypomyelination with hypogonadotropic hypogonadism and hypodontia. Neurology 2006;67:2066–2069.
13. Barkovich AJ, Kjos BO, Jackson DE, Norman D. Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. Radiology 1988;166:173–180.
14. Barkovich AJ. Concepts of myelin and myelination in neuroradiology. AJNR Am J Neuroradiol 2000;21:1099–1109.
15. van der Knaap MS, Linnankivi T, Paetau A, et al. Hypomyelination with atrophy of the basal ganglia and cerebellum: follow-up and pathology. Neurology 2007;69: 166–171.
16. van der Knaap MS, Valk J, Bakker CJ, et al. Myelination as an expression of the functional maturity of the brain. Dev Med Child Neurol 1991;33:849–857.
17. Dabbagh O, Swaiman KF. Cockayne syndrome: MRI correlates of hypomyelination. Pediatr Neurol 1988;4:113–116.
18. De Koning TJ, Jaeken J, Pineda M, et al. Hypomyelination and reversible white matter attenuation in 3-phosphoglycerate dehydrogenase deficiency. Neuropediatrics 2000;31:287–292.
19. Loevner LA, Shapiro RM, Grossman RI, Overhauser J, Kamholz J. White matter changes associated with deletions of the long arm of chromosome 18 (18q− syndrome): a dysmyelinating disorder? AJNR Am J Neuroradiol 1996; 17:1843–1848.
20. Van der Voorn JP, Pouwels PJ, Kamphorst W, et al. Histopathologic correlates of radial stripes on MR images in lysosomal storage disorders. Am J Neuroradiol 2005;26: 442–446.
21. van der Knaap MS, Naidu S, Breiter SN, et al. Alexander disease: diagnosis with MR imaging. AJNR Am J Neuroradiol 2001;22:541–552.
22. Vanhanen SL, Raininko R, Autti T, Santavuori P. MRI evaluation of the brain in infantile neuronal ceroid-lipofuscinosis: part 2: MRI findings in 21 patients. J Child Neurol 1995;10:444–450.
23. Barkovich AJ, Good WV, Koch TK, Berg BO. Mitochondrial disorders: analysis of their clinical and imaging characteristics. AJNR Am J Neuroradiol 1993;14:1119–1137.
24. Vaurs-Barriere C, Wong K, Weibel TD, et al. Insertion of mutant proteolipid protein results in missorting of myelin proteins. Ann Neurol 2003;54:769–780.
25. Kraemer KH, Patronas NJ, Schiffmann R, Brooks BP, Tamura D, DiGiovanna JJ. Xeroderma pigmentosum, trichothiodystrophy and Cockayne syndrome: a complex genotype-phenotype relationship. Neuroscience 2007;145: 1388–1396.
26. Van der Knaap MS, Vermeulen G, Barkhof F, et al. Pattern of white matter abnormalities at MR imaging: use of polymerase chain reaction testing of Guthrie cards to link pattern with congenital cytomegalovirus infection. Radiology 2004;230:529–536.
27. Ringelstein EB, Nabavi DG. Cerebral small vessel diseases: cerebral microangiopathies. Curr Opin Neurol 2005;18: 179–188.
28. Van der Knaap MS, Smit LME, Barkhof F, et al. Neonatal porencephaly and adult stroke related to mutations in collagen IV A1. Ann Neurol 2006;59:504–511.
29. Moore DF, Ye F, Schiffmann R, Butman JA. Increased signal intensity in the pulvinar on T1-weighted images: a

pathognomonic MR imaging sign of Fabry disease. Am J Neuroradiol 2003;24:1096–1101.
30. Imaizumi T, Horita Y, Hashimoto Y, Niwa J. Dotlike hemosiderin spots on T2*-weighted magnetic resonance imaging as a predictor of stroke recurrence: a prospective study. J Neurosurg 2004;101:915–920.
31. van der Knaap MS, Kriek M, Overweg-Plandsoen WC, et al. Cerebral white matter abnormalities in 6p25 deletion syndrome. AJNR Am J Neuroradiol 2006;27:586–588.
32. Yalnizoglu D, Haliloglu G, Turanli G, Cila A, Topcu M. Neurologic outcome in patients with MRI pattern of damage typical for neonatal hypoglycemia. Brain Dev 2007;29: 285–292.
33. Autti T, Raininko R, Santavuori P, Vanhanen SL, Poutanen VP, Haltia M. MRI of neuronal ceroid lipofuscinosis: II: postmortem MRI and histopathological study of the brain in 16 cases of neuronal ceroid lipofuscinosis of juvenile or late infantile type. Neuroradiology 1997;39:371–377.
34. Dotti MT, Federico A, Signorini E, et al. Cerebrotendinous xanthomatosis (van Bogaert-Scherer-Epstein disease): CT and MR findings. AJNR Am J Neuroradiol 1994;15: 1721–1726.
35. van der Knaap MS, Ramesh V, Schiffmann R, et al. Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. Neurology 2006;66:494–498.
36. Berkhoff M, Weis J, Schroth G, Sturzenegger M. Extensive white-matter changes in case of adult polyglucosan body disease. Neuroradiology 2001;43:234–236.
37. Brunberg JA, Jacquemont S, Hagerman RJ, et al. Fragile X premutation carriers: characteristic MR imaging findings of adult male patients with progressive cerebellar and cognitive dysfunction. Am J Neuroradiol 2002;23: 1757–1766.
38. Melberg A, Hallberg L, Kalimo H, Raininko R. MR characteristics and neuropathology in adult-onset autosomal dominant leukodystrophy with autonomic symptoms. AJNR Am J Neuroradiol 2006;27:904–911.
39. Mahmood A, Raymond GV, Dubey P, Peters C, Moser HW. Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. Lancet Neurol 2007;6: 687–692.
40. Scheper GC, van der Klok T, van Andel2 RJ, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. Nat Genet 2007;39: 534–539.
41. Leegwater PAJ, Yuan BQ, van der Steen J, et al. Mutations of MLC1 (KIAA0027), encoding a putative membrane protein, cause megaloencephalic leukoencephalopathy with subcortical cysts. Am J Hum Genet 2001;68:831–838.
42. Leegwater PAJ, Vermeulen G, Könst AAM, et al. Subunits of the translation initiation factor eIF2B are mutated in leukoencephalopathy with vanishing white matter. Nature Genet 2001;29:383–388.