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The Reflection of Histology in MR Imaging of Pelizaeus-Merzbacher Disease

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Pelizaeus-Merzbacher disease is a rare disease of infants and young children in which there is an arrest of myelination of the CNS. The cause of the disorder is unknown. Three cases are reported, representing the connatal and classical forms of the disease. The MR images obtained of these children are compared with histologic findings as reported in the literature. In the connatal form a complete absence of myelin in the brain is demonstrated. In the classical form an arrest of myelination in an early stage of development is shown in combination with progressive abnormalities of the unmyelinated white matter and possibly a slow degradation of some myelin. MR imaging appears to be a unique diagnostic method for assessing the degree of hypomyelination, the core of Pelizaeus-Merzbacher disease, and for contributing to the understanding of the underlying pathology of this disorder.

Pelizaeus-Merzbacher disease (PMD) is a rare neurologic disorder affecting the myelination of the CNS in young children. The disease can be categorized into three types; classical, connatal, and transitional. These types differ in their time of onset and clinical severity [1].

The classical type [1, 2] has its onset during infancy or late infancy. Early symptoms are nystagmoid, dancing or trembling eye movements, and an inability to attain normal head control. The size of the head is small, in the low-normal or microcephalic range, and there may be a characteristic tremor or shaking movement of the head. Further evolution of the disease is variable. Spasticity, extrapyramidal features, and cerebellar ataxia are the rule, as well as severe psychomotor retardation. Seizures occur early in the course of the disease, and optic atrophy with blindness is common. The course of the disease is chronic. Usually, after the age of 5 or 6 years, there is a very slow progression of the neurologic signs and a decline in mental status. Death occurs in most patients in late adolescence or young adulthood.

The connatal, or Seitelberger, type [1, 3] is a rarer and more severe variant and is already clinically manifest in the neonatal period or early infancy. Abnormal, nystagmoid eye movements and extrapyramidal hyperkinesis occur early, followed by the development of spasticity and often optic atrophy. From birth onward there is a complete failure of psychomotor development or an early loss of attained milestones. Microcephaly is nearly always present and growth retardation and epilepsy develop early. Progression is relatively rapid with death occurring in the first decade, usually in early childhood.

The transitional form [1] shows a resemblance to the connatal type, but its course is not so rapid. The disease is noticed directly after birth or in early infancy. The average age at death is about 8 years.

The mode of inheritance of PMD is not completely understood [1–3]. The classical type has an X-linked recessive inheritance, but sometimes this type is seen in a female, so a dominant heredity cannot be excluded. Sporadic cases are also encountered. In connatal PMD the mode of inheritance is even less clear; and in

the transitional group only sporadic cases are known. Laboratory investigations, including CT scanning, are of little help in establishing a diagnosis of PMD. Until now, pathologic examination has always been necessary to confirm diagnosis [1]. In this article we demonstrate that MR is able to make a definite diagnosis of PMD during life. In addition, MR data appear to elucidate some of the controversies about the pathogenesis of this little known disorder.

Case Reports

Case 1

Patient 1 is a 9-year old boy who was the product of an uneventful pregnancy and birth. Nystagmoid eye movements were noted directly after birth; and during the first year of life he exhibited severe psychomotor retardation, spasticity, extrapyramidal hyperkinesis in absence of intentional movements, and poor vision. Epileptic seizures appeared during the second year of life. From the age of 5 years onward a slow deterioration was noted, and at the time of MR investigation the child was moribund.

The scans were obtained on a 0.6-T imaging system.* T2-weighted spin-echo (SE) images (Figs. 1A–1C and 1E) and T1-weighted inversion-recovery (IR) images (Figs. 1D and 1F) were obtained in the transverse plane and a T1-weighted SE image was obtained in the sagittal plane (Fig. 1G). The images confirmed the complete absence of myelin. A diagnosis of the connatal form of PMD was made.

Case 2

Patient 2 is a 7-month-old boy who appeared normal at birth. At 6 weeks of age, epileptic fits began to occur and continued with increasing frequency. Roving and nystagmoid eye movements were noted. The infant failed to develop normal head control, and spasticity of all four extremities was found on neurologic examination. After several months a gradual deterioration of his neurologic condition led to loss of contact with his surroundings and to a vegetative state.

The first series of MR images was made at the age of 3½ months (Figs. 2A, 2C, 2E, 2G, 2I, and 2K); the second series at the age of 6 months (Figs. 2B, 2D, 2F, 2H, 2J, and 2L). Again, T2-weighted SE images (Figs. 2A–2D) as well as T1-weighted IR images (Figs. 2E–2L) were obtained in the transverse plane on both occasions. The first series shows only some myelin in the central areas, leading to a suspicion of PMD. The T2-weighted images of the second series show the absence of any progress of myelination. The peripheral atrophy was increased owing to a further reduction in volume of unmyelinated white matter. The signals obtained from the white matter now had a coarse and less clearly delineated pattern. The T1-weighted images suggested some regression of myelination, with, especially, a loss of myelin in the subcortical regions. The diagnosis of classical PMD was made.

Case 3

Patient 3 is a 6-month-old boy whose mother's family has three males with known classical PMD. The mother's pregnancy was terminated at 8 months because of intrauterine growth retardation. Except for a low weight the child appeared normal after birth. At the age of 3 months a delay in psychomotor development was noted together with nystagmoid eye movements. Neurologic examination at the age of 4 months revealed an absence of normal head control, evidence of poor vision, and hyperreflexia. At the age of 1 year a severe psychomotor retardation was present, but there was no deterioration with loss of attained skills until the present examination at the age of 1½ years.

On MR imaging (Fig. 3) myelin was found in the deeper parts of the brain, excluding the cerebellum. Some myelin was also present in the subcortical white matter and the cortex of the pre- and postcentral gyri. The diagnosis of classical PMD was made.

In all three patients an infectious or metabolic cause of the disease was excluded by extensive laboratory investigations.

Discussion

Neuropathologic examination has always been of major importance in diagnosing PMD. Externally, there are signs of diffuse atrophy of the whole brain, and microscopic examination shows a lack of myelin in all parts of the CNS. However, there is a great variation in severity depending on the subtype of PMD.

In the connatal type the pathologic picture [1, 3–6] varies from a marked lack of myelin to a complete absence of myelin in all parts of the brain. The myelin that is present is usually found in the deeper parts of the brain: the diencephalon, the brainstem, and the central part of the cerebellum. Some residual myelin may also be present in the subcortical white matter. The gray matter is also affected. The intracortical myelin is completely or almost completely absent. There are no or hardly any signs of active myelin breakdown. Oligodendrocytes, the myelin-producing cells, may be reduced in number or completely absent, or they may show morphologic abnormalities. However, they may also be found with normal shape, number, and distribution. The severity of the concomitant fibrillary gliosis in the white matter varies from slight to dense. The axons are relatively well preserved, as is the normal cortical cytoarchitecture.

The abnormalities in the classical type [1, 2, 7] are less pronounced. Discontinuous parts of myelinated fiber groups are relatively well preserved in the myelin-lacking areas and stand out as myelin islets, predominantly located perivascularly. All parts of the CNS are affected in the same way, but the diencephalon, the brainstem, the cerebellum, and the subcortical white matter show a relatively good state of myelin preservation. Again, only small amounts of myelin-degeneration products are found, and the axons are spared. There may be few fibrillary astrocytes or an intense fibrillary gliosis in the affected areas. In the gray matter, myelin sheaths are reduced in number or absent, but the cortical cytoarchitecture and individual nerve cells are normal.

The transitional type of PMD [1] shows abnormalities between the connatal and classical type.

The MR images beautifully illustrate the histopathologic findings in PMD; that is, a lack or absence of myelin, which, if present, is predominantly localized in the deep parts of the brain and the subcortical white matter of the pre- and postcentral gyri. In addition, MR data contribute to the understanding of the pathogenesis of PMD. Theories about the pathogenesis have centered around either demyelination (i.e., loss of myelin) or a faulty myelination (i.e., an aplasia of myelin sheaths) [1, 2]. In our opinion PMD is caused by a genetically determined arrest of myelination at some stage of development.

Neuropathologic examination reveals no signs of active demyelination. Myelin-degradation products are inconspicuous or completely absent. Myelin breakdown, if present, is at best very slow and cannot account for the disease. There is
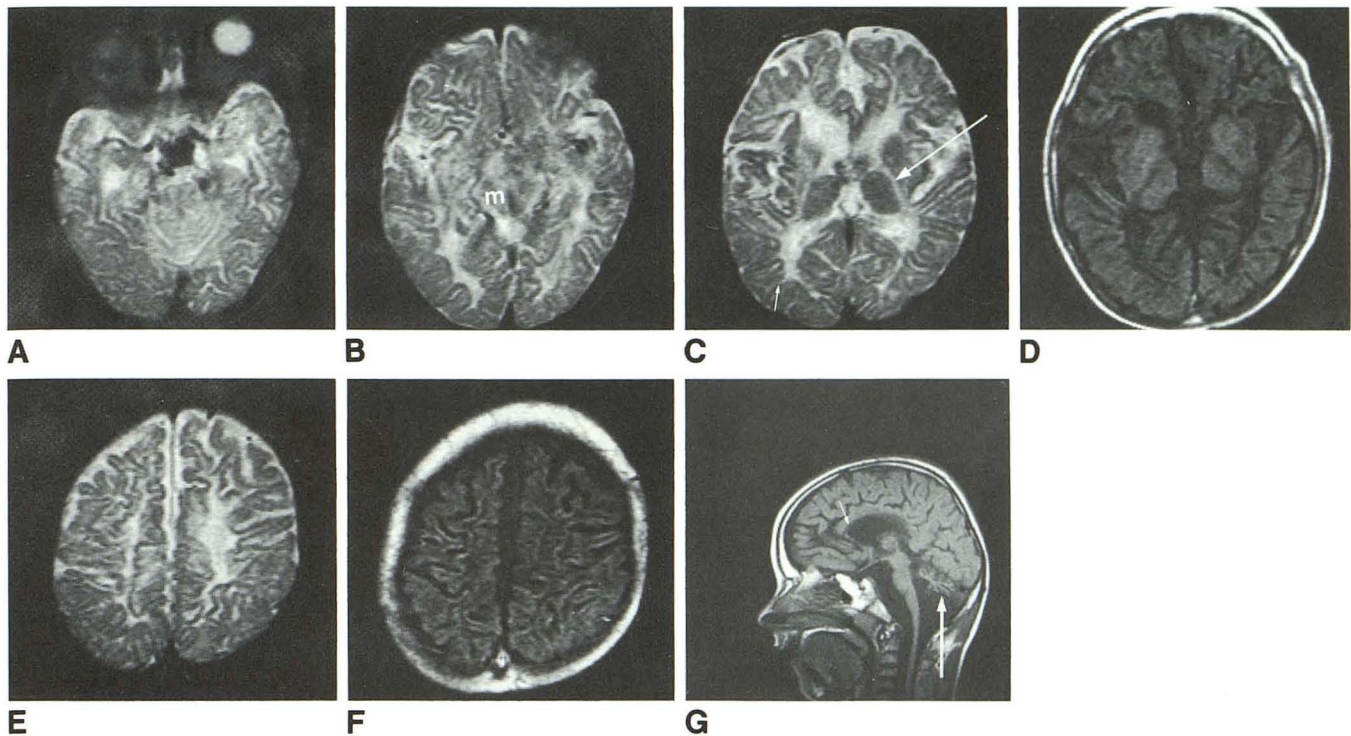
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Fig. 1.—Case 1.

A–C and *E* are T2-weighted spin-echo (SE) images, 3000/120/2, that reveal a complete absence of myelin, even in the brainstem (m = mesencephalon in *B*) and the internal capsule (*large arrow* in *C*). On T2-weighted images unmyelinated white matter has a higher signal intensity that gray matter, myelin appears dark. The unmyelinated white matter is severely reduced in volume (*small arrow* in *C*), and the cortical gray matter is collapsed in deep folds over it. As a consequence, the external appearance is extremely atrophic.

D and *F* are inversion recovery (IR) images, 2100/500/34/2, the T1-weighted counterparts of *C* and *E*.

G represents a midsagittal section on a T1-weighted SE image, 405/32/4, and shows that the atrophy also affects the cerebellum (*large arrow*) and the corpus callosum (*small arrow*).

also biochemical evidence: the chemical composition of the unmyelinated white matter with a normal concentration of cholesterol esters argues against active demyelination [4]. The chemical composition of the myelin that is present suggests an inhibition of myelin maturation, as the presence of glucolipids, small amounts of very long-chain fatty acids, hydroxy acids, and unsaturated fatty acids, as well as a reduction in basic protein and proteolipid protein with an increase in Wolfgram proteins are indicative of its immature state [8–12].

Our opinion is supported by MR findings. The MR images of our three PMD patients suggest an arrest of myelination. The precise developmental age at which further myelination is inhibited determines the localization and amount of myelin present [13–15]. In patient 1 no myelin is shown by MR, which is indicative of an inhibition of myelination from the beginning. This agrees with the diagnosis of a connatal form of PMD, in which the arrest of myelination occurs before birth. In patients 2 and 3 the topography of the myelin demonstrated on MR suggests an arrest of myelination soon after birth, which agrees with the diagnosis of classical or transitional PMD.

Of course, there may be an additional problem in the maintenance of myelin with a very slow breakdown of myelin

sheaths. As stated above, the chemical composition of myelin suggests an inhibition of myelin maturation and we do not exclude the possibility that this immature state makes it more liable to break down. In patient 2 the difference between two MR investigations (about 3 months apart) indeed points to a small loss of myelin. However, the changes in the unmyelinated white matter are more impressive. Its volume is progressively reduced in combination with an alteration of signal quality, probably due to increasing gliotic retraction. We do not exclude the possibility that in patient 1 a small amount of myelin had been present in earlier stages. However, the presence of definite neurologic abnormalities at birth, in contrast to patients 2 and 3, confirms the diagnosis of connatal PMD. So, in any case, the quantity of myelin that might have been present must have been smaller than shown in patients 2 and 3.

MR contributes to the understanding of the pathogenesis of PMD, but the underlying defect remains unknown. It is likely that the arrest of myelination and the inhibition of myelin maturation are associated with an abnormality of oligodendroglial function. The variation in developmental stage at which the defect becomes manifest has never been explained. An important question is whether the diagnosis of PMD can be made only by MR imaging. The images of patient 1, which
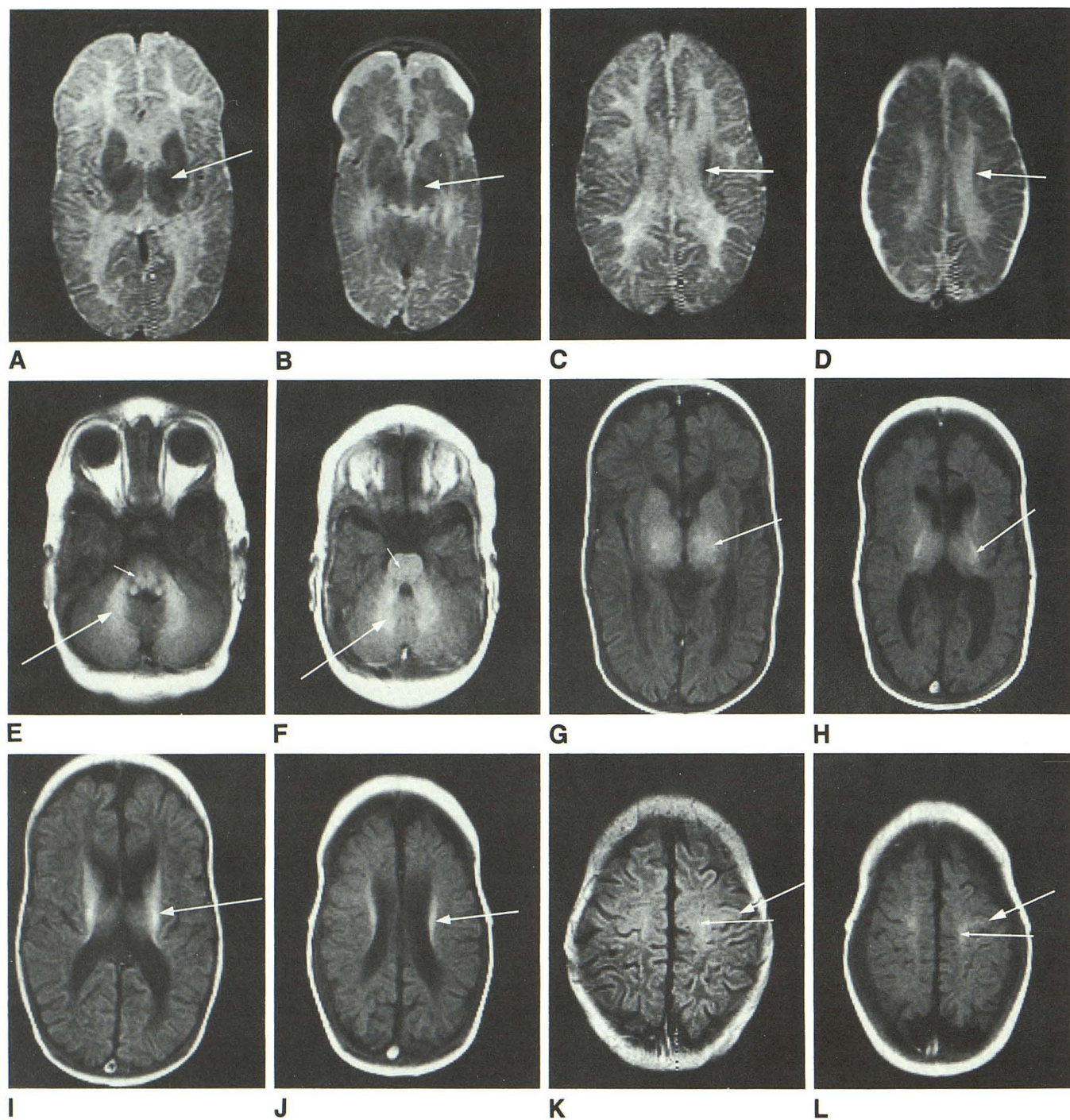
Fig. 2.—Case 2.
A–D are T2-weighted spin-echo (SE) images, 3000/128/2; E–L are inversion recovery (IR) images, 2400/600/32/2. A, C, E, G, I, and K were made at the age of 3½ months, their counterparts, B, D, F, H, J, and L, at the age of 6 months.
In A, myelin is present in the thalamus and basal ganglia, appearing dark (arrow). The unmyelinated white matter is hyperintense. In C, a small amount of myelin is present in the paraventricular region (arrow). In E, G, I, and K, myelin, appearing hyperintense on T1-weighted images, is found in the cerebellar white matter (large arrow in E), brainstem (small arrow in E), thalamus, basal ganglia, internal capsule (arrow in G), paraventricular region (arrow in I), and in the subcortical white matter (small arrow in K) and cortex (large arrow in K) of the pre- and postcentral gyri. In F, H, J, and L, a loss of volume of the unmyelinated white matter is seen with an increase in subarachnoid spaces on all sides of the brain. The unmyelinated white matter shows changes in signal quality. There is also some loss of myelin (compare the areas indicated by arrows in the images at 3½ months with those at 6 months).
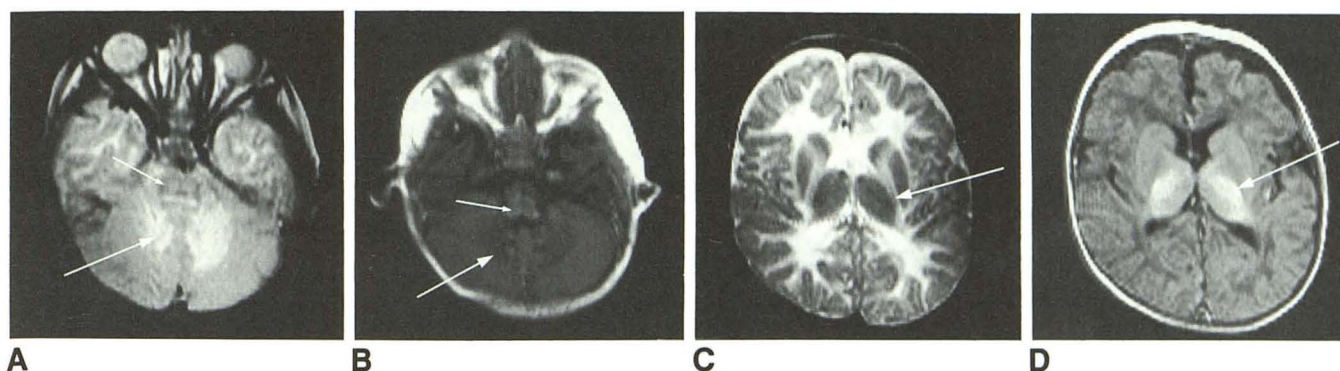
Fig. 3.—Case 3.
A and *C* are T2-weighted spin-echo (SE) images, 3000/90/2; *B* and *D* are inversion recovery (IR) images, 2400/600/30/2. The white matter is largely unmyelinated and appears hyperintense on the T2-weighted images and hypointense on the T1-weighted images. There is no myelin in the cerebellar white matter (*large arrow* in *A* and *B*) and hardly any in the brainstem (*small arrow* in *A* and *B*). Myelin is found in the thalamus and in the internal capsule (*arrow* in *C* and *D*).

show a complete absence of myelin, are strongly suggestive of PMD. In classical and transitional forms of PMD the differentiation from a retarded myelination is only possible with the help of repeated MR investigations. Of course, if definite PMD exists in the family, one MR investigation showing the characteristic pattern will suffice. An arrest of myelination may not only be caused by PMD, but also by external adverse factors. As a rule, the general appearance in these cases is quite different from PMD. So differentiation from an arrest of myelination due to other adverse factors is made by a combination of clinical history, clinical symptomatology, laboratory findings, and differences in MR patterns.

In conclusion, MR imaging allows an accurate assessment of the various conditions of white matter; thus, the progress or lack of progress of myelination in young children is easily followed. In this study the MR images of three PMD patients showed severe hypomyelination. The MR data are in conformity with the theory that PMD is due to an arrest of myelination in some stage of early development, possibly in combination with a very slow degradation of myelin. In addition, there is a progressive diminution of unmyelinated white matter with alterations of obtained MR signals suggestive of progressive gliotic retraction. The diagnosis of PMD is made on the basis of the clinical features, negative laboratory investigations, and characteristic MR patterns. Differentiation from retarded myelination is possible by means of follow-up MR scans. Differentiation from an arrest of myelination due to external adverse factors is made by the clinical history, laboratory findings, and the fact that the MR patterns are apt to be different.

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