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leukodystrophy.**

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AJNR Am J Neuroradiol 1997, 18 (4) 733-738

<http://www.ajnr.org/content/18/4/733>

This information is current as
of July 30, 2025.

MR of Childhood Metachromatic Leukodystrophy

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PURPOSE: To investigate the MR findings of childhood metachromatic leukodystrophy (MLD). **METHODS:** Nine MR imaging studies in seven children (five girls and two boys, 10 to 32 months old) with MLD were evaluated retrospectively for the extent and progression of white matter abnormalities and the presence of contrast enhancement. **RESULTS:** All seven cases showed symmetric, confluent high signal intensity on T2-weighted images in the periventricular white matter and centrum semiovale. A posterior predominance of white matter abnormalities was noted in all cases. Although initially spared from demyelination in all cases, in one case, the subcortical U fibers were later involved in demyelination on follow-up MR studies. Other sites of involvement were the genu (n = 5) and splenium (n = 6) of the corpus callosum, the posterior limbs of the internal capsule (n = 5), the descending pyramidal tracts (n = 4), the claustrum (n = 4), and the cerebellar white matter (n = 2); diffuse brain atrophy was seen in two cases. No enhancement of the lesion was seen on any of the five postcontrast examinations. A "tigroid" pattern, previously described in cases of Pelizaeus-Merzbacher disease, was noted in the centrum semiovale in six cases. **CONCLUSION:** In late-infantile MLD, demyelination is more prominent in the occipital region. In addition to demyelination of the periventricular white matter, common manifestations include a "tigroid" pattern and involvement of the corpus callosum, the internal capsule, and the corticospinal tract.

Index terms: Storage diseases; Children, diseases; Brain, magnetic resonance

AJNR Am J Neuroradiol 18:733-738, April 1997

Metachromatic leukodystrophy (MLD) is a lysosomal storage disease caused by a deficiency of the catabolic enzyme arylsulfatase A. Inheritance of the disease is autosomal recessive (1). It is known as the most common hereditary leukodystrophy, with a prevalence of one in 100 000 newborns (2). Deficiency of arylsulfatase A results in accumulation of a metachromatic lipid material, galactosylceramide sulfate, in the white matter of the peripheral and central nervous system (2), which undergoes symmetric demyelination with initial sparing of the subcortical U fibers (3). Many magnetic res-

onance (MR) imaging features of MLD have been described, including symmetric confluent demyelination of the periventricular white matter and centrum semiovale with sparing of the subcortical arcuate fibers, frontal predominance and frontooccipital progression of demyelination, subcortical white matter involvement with corticosubcortical atrophy in the later stage, low signal intensity in the thalami on T2-weighted images, involvement of the cerebellar white matter, and absence of contrast enhancement of the lesion (1-8).

Seven patients with biochemically proved MLD were treated at our institution during the past 7 years. A retrospective analysis of the nine MR imaging studies obtained in these patients disclosed several additional manifestations of MLD.

Materials and Methods

From May 1988 to December 1995, seven children (five girls and two boys, 10 to 32 months old; mean age, 24 months) with late-infantile MLD were examined with

Received June 19, 1996; accepted after revision October 31.

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AJNR 18:733-738, Apr 1997 0195-6108/97/1804-0733

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Seven patients with late-infantile metachromatic leukodystrophy

| | Case | | | | | | |
|---------------------------------------|-------|---------|-------|--------|---------|---------|------------|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Age, mo, at presentation/sex | 22/F | 24/F | 10/F | 29/F | 24/F | 27/M | 32/M |
| Age, mo, at symptom onset | 12 | 16 | 9 | 22 | 13 | 18 | 28 |
| Head circumference, percentile | 25-50 | 10 | 90-97 | 25-50 | 50-75 | ... | 50 |
| 24-hour urine arylsulfatase activity* | 0.023 | 0.06 | 0.03 | 0.019 | 0.380† | 0.003 | 0.01 |
| Sparing of subcortical U fibers | + | + | +→+ | + | + | + | +→- |
| Genu of corpus callosum | + | + | -→- | + | + | + | -→- |
| Splenium of corpus callosum | + | + | Eq→+ | + | + | + | -→- |
| Posterior limbs of internal capsules | - | + | +→+ | + | + | - | -→+ |
| Descending pyramidal tracts | - | - | +→+ | + | + | - | -→+ |
| Clastrum | - | - | +→+ | - | + | + | +→+ |
| Cerebellar deep white matter | - | - | Eq→+ | - | - | - | -→+ |
| "Tigroid" pattern | - | + | +→+ | + | + | - | Eq→+ |
| T2 low signal intensity in thalami | - | Diffuse | -→- | Patchy | Diffuse | Diffuse | -→- |
| Diffuse corticosubcortical atrophy | - | - | +→+ | - | - | - | -→+ |
| Contrast enhancement | ... | - | -→- | ... | - | - | Not done→- |

Note.—+ indicates present; -, absent; and Eq, equivocal.

* Normal range is 0.36 to 58.94 mg/mL per hour.

† Sural nerve biopsy was also done in this patient.

MR imaging at our institution. The diagnosis was confirmed with a decreased-activity 24-hour urine arylsulfatase test and, in one case, by results of a sural nerve biopsy, which showed metachromasia. Analysis of free amino acids and very long chain fatty acids was additionally performed in three of the children to rule out the possibility of amino acid disorders or adrenoleukodystrophy, all of which showed normal results.

MR examinations were done on a 2.0-T Spectro 20000 or a 1.5-T Magnetom imager. Axial T1-weighted (500-550/14-30/2 [repetition time/echo time/excitations]), axial proton density-weighted (3000-5000/19-30/1), and T2-weighted (3000-5000/80-112/1) spin-echo images were obtained. Contrast-enhanced T1-weighted (500-550/14-30/2) images were obtained in five patients. In two of seven children, follow-up MR studies were obtained 5 and 26 months, respectively, after the initial examinations, making a total of nine MR studies that were available for review.

MR images were evaluated for the extent, distribution, pattern, and progression of white matter degeneration that was shown as high signal intensity on T2-weighted images, and for the presence or absence of contrast enhancement.

Results

All seven of the children showed normal developmental progress until the onset of symptoms, which ranged from 9 to 28 months. Afterward, they experienced a regression of motor development, including loss of head control, inability to sit alone, gait disorders, speech disturbances, and quadriparesis. Head circumfer-

ences of these children were variable. The definitive diagnosis of MLD was made by documentation of a deficiency of arylsulfatase A in urine, peripheral leukocytes, fibroblasts, and tissue sample (6, 9, 10). All diagnoses included the assay of arylsulfatase A activity in 24-hour urine samples and, in one case, a sural nerve biopsy was also done. The results of the assay of 24-hour urine arylsulfatase A activity and the MR findings of the seven patients with late-infantile MLD are summarized in the Table.

In all seven cases, the major locations of white matter demyelination, shown as high signal intensity on T2-weighted MR images, were the periventricular deep white matter and centrum semiovale. In six cases, the splenium of the corpus callosum was involved; five of these also showed demyelination in the genu of the corpus callosum. The posterior limbs of the internal capsule were involved in five cases, and the demyelination had progressed into the descending pyramidal tracts in four, whereas the anterior limbs were spared in all cases. The claustra were also involved in four cases. High signal intensity was present in the cerebellar deep white matter in two advanced cases. In four cases, the thalami showed low signal intensity on T2-weighted images, which was diffuse (three cases) or patchy (one case).

Demyelination was bilateral, symmetric, and confluent in all cases (Fig 1). Characteristically, the subcortical arcuate fibers were spared from demyelination in all cases initially; however, in

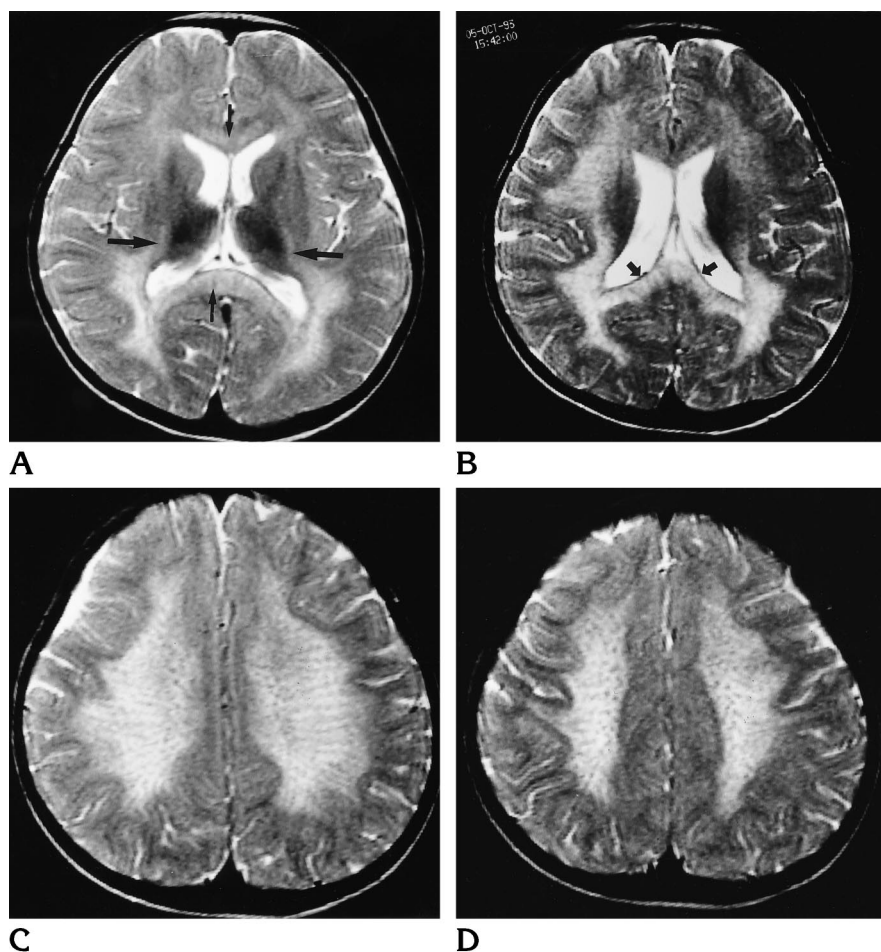


Fig 1. Case 2: T2-weighted axial MR images (3500/93/1) in a 24-month-old girl with MLD.

A, Diffuse, symmetric high signal intensity is shown in bilateral periventricular white matter, genu, and splenium of the corpus callosum (*small arrows*) and the posterior limbs of the internal capsules (*large arrows*). The subcortical arcuate fibers are spared from demyelination. Abnormal low signal intensity is noted in the thalami.

B, The immediate adjacent periventricular white matter, with a thickness of 1 to 3 mm, is spared from demyelination (*arrows*).

C, Within the demyelinated centrum semiovale, numerous linear tubular structures of low signal intensity are seen in a radiating (tigroid) pattern, suggesting spared perivascular white matter.

D, At higher convexity level, the linear structures seen in C have a punctate appearance (leopard-skin pattern).

case 7, the demyelinating process had progressed into the subcortical U fibers on the 26-month follow-up MR study (Fig 2).

In six cases, normal white matter signal intensity was seen within the background of demyelinated white matter as numerous radiating linear structures in the periventricular region or as a widespread punctate pattern at the higher level of the centrum semiovale (Fig 1C and D, Fig 3B). These linear or punctate structures showed enhancement on postcontrast MR images (Fig 3D).

The thin periventricular white matter (1 to 3 mm thick) immediately adjacent to the trigones of the lateral ventricles was spared from demyelination in all cases, which was seen as a linear band of normal white matter signal intensity wrapping around the lateral ventricles (Fig 1B). The degree of white matter degeneration seemed more prominent in the occipital lobes than in the frontal lobes in all cases.

Dorsoventral progression of demyelination was evident in one patient (case 7), in whom the

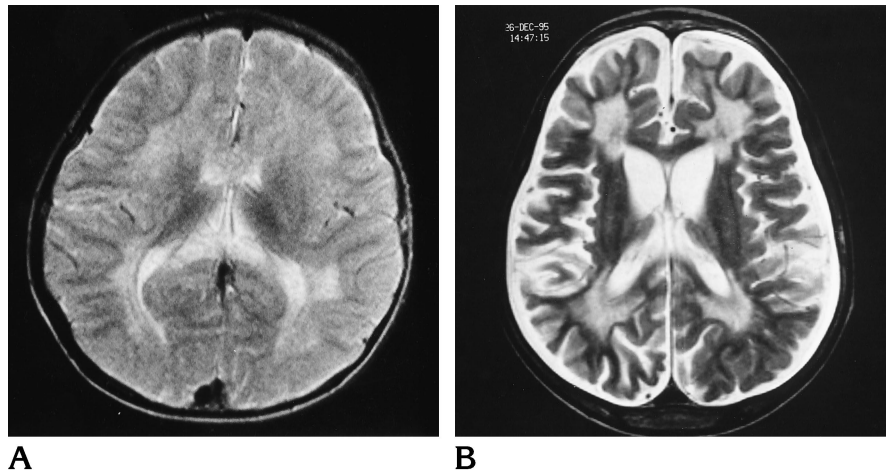
initial lesions appeared in the posterior white matter. The 26-month follow-up MR study showed anterior progression of demyelination onto the frontal white matter (Fig 2). However, in case 3, the initial demyelination was noted in the center of the periventricular white matter and centrum semiovale, and the lesions progressed centrifugally to involve the frontal and parietooccipital white matter on the follow-up study after 5 months (Fig 3A and B).

The sizes of the lateral ventricles were within normal range in four cases. In case 2, mild ventriculomegaly was evident without definite signs of cortical atrophy. In two patients (cases 3 and 7) in whom diffuse brain atrophy had developed, mild to moderate atrophic ventriculomegaly was noted on the follow-up MR images. Contrast-enhanced studies were obtained in five patients, but none showed enhancement of the lesion itself, although numerous enhancing linear or punctate structures were noted within the demyelinated white matter in four cases.

Fig 2. Case 7: 32-month-old boy with MLD.

A, T2-weighted image (3000/110/1) shows confluent, symmetric high signal intensity in the bilateral periventricular white matter. The subcortical U fibers are spared and demyelination is more prominent in the posterior lobes.

B, Follow-up T2-weighted image (3700/93/1) after 26 months shows that the high signal intensity of the frontal white matter has become more evident. The subcortical arcuate fibers are no longer spared from demyelination, and diffuse cortical atrophy has developed. The central portions of the periventricular white matter are relatively spared.



Discussion

MLD refers to several disorders caused by deficient lysosomal activity of arylsulfatase A, which results in an accumulation of sulfated lipids and in breakdown of the membrane of the myelin sheath in both the central and peripheral nervous systems (11, 12). MLD has been classified into three types according to the age at onset: late-infantile, juvenile, and adult forms. About 80% of cases are the late-infantile type, typically occurring between 1 and 2 years of age and manifesting as gait disorders, deterioration in coordination, speech disturbances, and quadriplegia (2, 13). Death occurs within 6 months to 4 years after the onset of symptoms (2).

As mentioned earlier, many MR features of MLD have already been described. Most of them—such as symmetric demyelination in the periventricular white matter and centrum semiovale with sparing of the subcortical white matter, corticosubcortical atrophy with subcortical arcuate fiber involvement in the later stage, hypointense thalami on T2-weighted images, involvement of the cerebellar white matter, and absence of contrast enhancement of the lesions—are consistent with our experience. However, in addition to these well-known findings, we also noted some additional or conflicting manifestations.

Concerning the prevalent location and progression of the lesions in MLD, it had been documented that the anterior white matter is more severely affected, and that the demyelinating process progresses anteriorly to posteriorly (2, 4, 7). Nevertheless, in all seven of our cases the demyelinating process was more prominent in

the occipital lobes than in the frontal lobes. A slight frontal preponderance of the demyelinating process, which is widely considered a manifestation of MLD, has been observed mainly in late-onset (juvenile and adult) MLD on computed tomographic (CT) scans (7), although little has been documented concerning the prevalent location of the demyelinating process on MR images in cases of late-infantile MLD, the most common variant of this disorder. The posterior preponderance of demyelination in all seven of our cases is a finding too constant to be just an atypical pattern. In case 7, the dorso-frontal extension of demyelination was evident, although the central portions of the periventricular white matter were relatively spared in the later stage (Fig 2). These findings suggest the possibility that the posterior white matter is affected initially and more severely, and that the direction of the demyelinating process is dorso-frontal in late-infantile MLD. The initial central lesions with subsequent centrifugal progression shown in case 3 are assumed to be an unusual manifestation of this disease.

One of the notable findings was the involvement of the corpus callosum (genu in five cases and splenium in six cases). Moreover, a posterior preponderance with dorsofrontal progression of demyelination was also highly suspected within the corpus callosum.

Involvement of the motor pathway is a well-known feature of adrenoleukodystrophy (14). However, there has been a case report of MLD involving the motor pathway (1). In our cases of late-infantile MLD, we noted frequent involvement of the posterior limbs of the internal capsules (five cases) and descending pyramidal

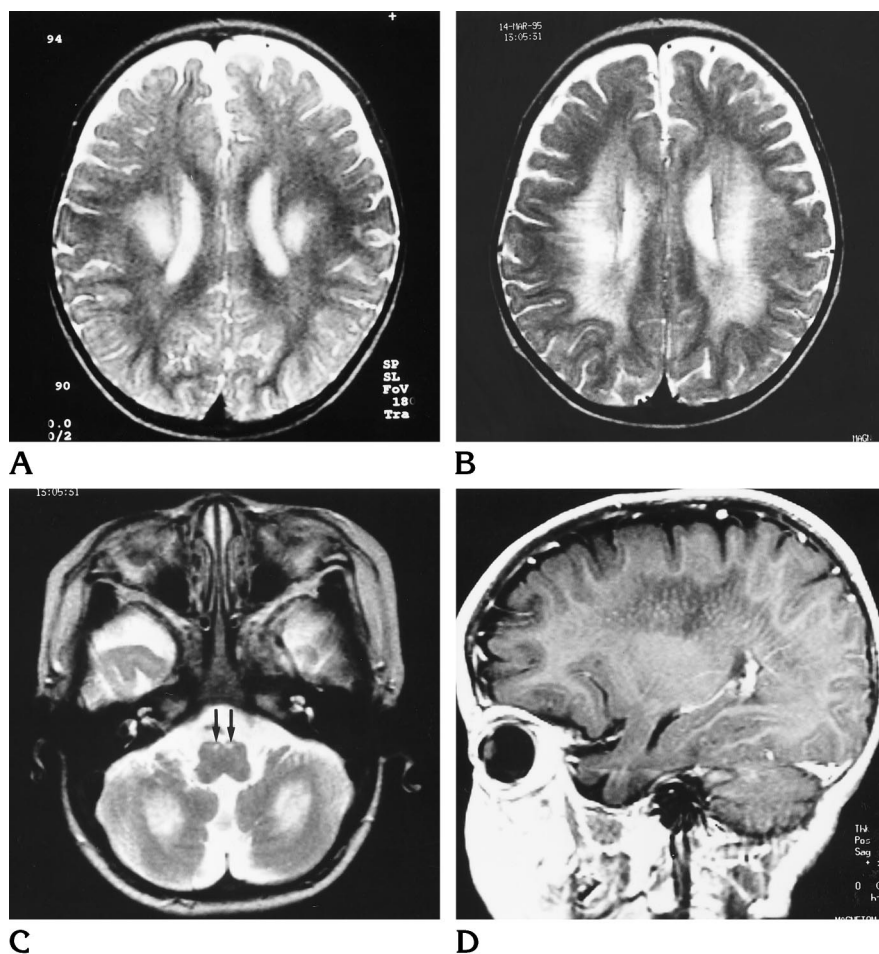


Fig 3. Case 3: 10-month-old girl with MLD.

A, T2-weighted image (5000/112/1) shows the initial demyelination in the center of the periventricular white matter.

B, Follow-up T2-weighted image (3500/93/1) after 5 months shows evidence of the centrifugal extension of demyelination. Tigroid pattern of demyelination is shown again.

C, At lower scan level (3500/93/1), descending pyramidal tracts of the medulla (arrows) and deep cerebellar white matter are also involved.

D, On contrast-enhanced T1-weighted sagittal image (550/14/2), tigroid pattern seen in B appears as numerous enhancing punctate foci in demyelinated deep white matter of nonenhancing low signal intensity (leopard-skin pattern).

tracts in the pons and medulla (four cases), suggesting that these features are not exclusive to adrenoleukodystrophy.

The numerous linear or punctate structures of about 1 mm thickness radiating in the demyelinated deep white matter were nearly identical with the finding described in some reports of Pelizaeus-Merzbacher disease (4, 13, 15, 16). The so-called tigroid or leopard-skin pattern of demyelination in Pelizaeus-Merzbacher disease, which is known to be most visible on T2-weighted images at the level of the convexities of the brain, is made by small scattered foci of more normal white matter signal intensity within the demyelinated white matter (16). The foci are known histopathologically to be residual islets of preserved myelin, especially around blood vessels (15). In our experience, these manifestations were equally or more prominent on contrast-enhanced T1-weighted images than on T2-weighted images by virtue of the well-enhancing nature of the foci (Fig 3D), and it is a plausible result in that the foci represent

the perivascular white matter spared from demyelination. Even though it has been said that this distinctive MR pattern of white matter might be a significant distinguishing feature by which to differentiate Pelizaeus-Merzbacher disease from other diffuse leukodystrophies (16), a similar pathophysiology may be applied to our cases of MLD, and these so-called tigroid or leopard-skin demyelination patterns may not be specific to Pelizaeus-Merzbacher disease. The significance of the thin white matter immediately adjacent to the lateral ventricles showing normal white matter signal intensity is uncertain.

In summary, in late-infantile MLD, the demyelination is more prominent in the occipital region and the direction of the demyelinating process seems dorsofrontal. Besides nonenhancing demyelination of the periventricular white matter with sparing of the subcortical U fibers, a tigroid or leopard-skin pattern of demyelination in the centrum semiovale and involvement of the corpus callosum, internal capsule, and corticospinal tract are frequent additional

manifestations. Further investigation, including pathologic correlation, is required to gain a complete picture of the prevalent location of the initial lesions, the direction of extension, the frequency of involvement of the internal capsule and descending pyramidal tract, and the tigroid pattern of demyelination in late-infantile MLD.

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