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Comparing Initial Magnetic Resonance Imaging Findings to Differentiate between Krabbe Disease and Metachromatic Leukodystrophy in Children

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Original Article

Purpose: To identify characteristic magnetic resonance imaging (MRI) features to differentiate between Krabbe disease and metachromatic leukodystrophy (MLD) in young children.

Materials and Methods: We collected all confirmed cases of Krabbe disease and MLD between October 2004 and September 2020 at Seoul National University Children's Hospital. Patients with initial MRI available were included. Their initial MRIs were retrospectively reviewed for the following: 1) presence of white matter signal abnormality involving the periventricular and deep white matter, subcortical white matter, internal capsule, brainstem, and cerebellum; 2) presence of volume decrease and signal alteration in the corpus callosum and thalamus; 3) presence of the tigroid sign; 4) presence of optic nerve hypertrophy; and 5) presence of enhancement or diffusion restriction.

Results: Eleven children with Krabbe disease and 12 children with MLD were included in this study. There was no significant difference in age or symptoms at onset. Periventricular and deep white matter signal alterations sparing the subcortical white matter were present in almost all patients of the two groups. More patients with Krabbe disease had T2 hyperintensities in the internal capsule and brainstem than patients with MLDs. In contrast, more patients with MLD had T2 hyperintensities in the splenium and genu of the corpus callosum. No patient with Krabbe disease showed T2 hyperintensity in the corpus callosal genu. A decrease in volume in the corpus callosum and thalamus was more frequently observed in patients with Krabbe disease than in those with MLD. Other MRI findings including the tigroid sign and optic nerve hypertrophy were not significantly different between the two groups.

Conclusion: Signal abnormalities in the internal capsule and brainstem, decreased thalamic volume, decreased splenial volume accompanied by signal changes, and absence of signal changes in the callosal genu portion were MRI findings suggestive of Krabbe disease rather than MLD based on initial MRI. Other MRI findings such as the tigroid sign could not help differentiate between these two diseases.

Keywords: Krabbe disease; Metachromatic leukodystrophy (MLD); Children; Leukodystrophy; Magnetic resonance imaging (MRI)

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INTRODUCTION

Leukodystrophy is a progressive white matter disease. It typically represents hereditary inborn errors of metabolism that can lead to abnormal formation, destruction, or turnover of myelin. This disease entity includes lysosomal, peroxisomal, and mitochondrial diseases. It is a group of over 30 heterogeneous genetic disorders. Lysosomal storage disorders are due to deficient activity of a specific lysosomal enzyme. They can be classified according to accumulated materials in the lysosomes (1, 2). Krabbe disease and metachromatic leukodystrophy (MLD) are two classic lysosomal storage diseases (3).

MLD is an autosomal recessive disorder that is caused by a deficiency of arylsufatase A or its cofactor involved in degradation of sulfatides. Abnormal accumulation of sulfatides within neurons and glial cells can cause problems in breakdown and reuse of myelin in central and peripheral nervous systems (1, 2). Bonkowsky et al. (4) have performed a retrospective study and estimated that the incidence of MLD is 1.4 to 1.8 per 100,000 live births, comprising 8.2% of identified inherited leukodystrophies. Krabbe disease is also an autosomal recessive disorder. It is caused by a deficiency of galactocerebrosidase (GALC), a lysosomal enzyme involved in the pathway of myelin breakdown and turnover (1, 2, 5). It affects approximately 1 in 100,000 individuals (6).

Both diseases can cause progressive demyelination with several neurological symptoms. Their primary magnetic resonance imaging (MRI) manifestation is abnormal signal change in the periventricular and deep white matter, relatively sparing the subcortical white matter (1, 2). They have similar clinical features, including age at onset. They even have similar imaging features. Sometimes, it can be challenging to differentiate between the two diseases before a genetic or enzymatic study. While there are still debates about the treatment of these diseases, the two diseases share common treatment methods including hematopoietic stem cell therapy (HSCT), bone marrow transplantation, and enzyme replacement therapy (ERT). However, there are some differences in treatment methods and responses between Krabbe disease and MLD. Patients with Krabbe disease can benefit from HSCT, especially those with asymptomatic infantile-onset forms (7, 8). Otherwise, there are still debates about the viability of transplants in some forms of MLD. For example, late-infantile onset forms of MLD with HSCT show poor motor skills and variable cognitive outcomes (7, 9). Thus, it is important to diagnose accurately as early as possible so that proper managements could be started. A deeper understanding of MR imaging findings of these diseases and their distinct imaging patterns may contribute to early diagnosis and appropriate management (10). Therefore, the objective of this study was to identify characteristic initial MRI features that could be used to differentiate between Krabbe disease and MLD in young children.

MATERIALS AND METHODS

This retrospective study was approved by our Institutional Review Board. The requirement for informed consent was waived due to its retrospective nature.

Study Population

We collected confirmed cases of Krabbe disease and MLD between October 2004 and September 2020 by searching electronic medical charts at Seoul National University Hospital. Patients were diagnosed based on gene sequencing and enzyme assay of arylsufatase A or GALC. Patients with available initial MRI in the picture archiving and communication system were included. We obtained age, sex, and presenting symptoms of patients from the electronic medical charts.

MRI Analysis

MRIs from initial presentation were retrospectively reviewed by two radiologists (Y.H.C. and S.Y.K. with 15 years and 2 years of experience, respectively) who reached a consensus regarding these images. The following variables were evaluated on T2-weighted image (T2WI): 1) presence of white matter signal abnormality involving periventricular and deep white matter, subcortical white matter, internal capsule, brainstem, cerebellum or corpus callosum; and 2) presence of the tigroid sign. Presence of volume decrease in the corpus callosum was evaluated on both T1WI and T2WI. Thalamic volume decrease and abnormal signal intensity were evaluated on T1WI. The presence of optic nerve hypertrophy was evaluated on T2WI or T1WI, whichever showed prechiasmatic optic nerve better. The presence of enhancement or diffusion restriction was evaluated respectively on contrast-enhanced T1WI and diffusion-weighted image (DWI) with apparent diffusion coefficient map (ADC map).

Corpus Callosum The presence of T2-hyperintensity of corpus callosal genu or splenium was evaluated on axial
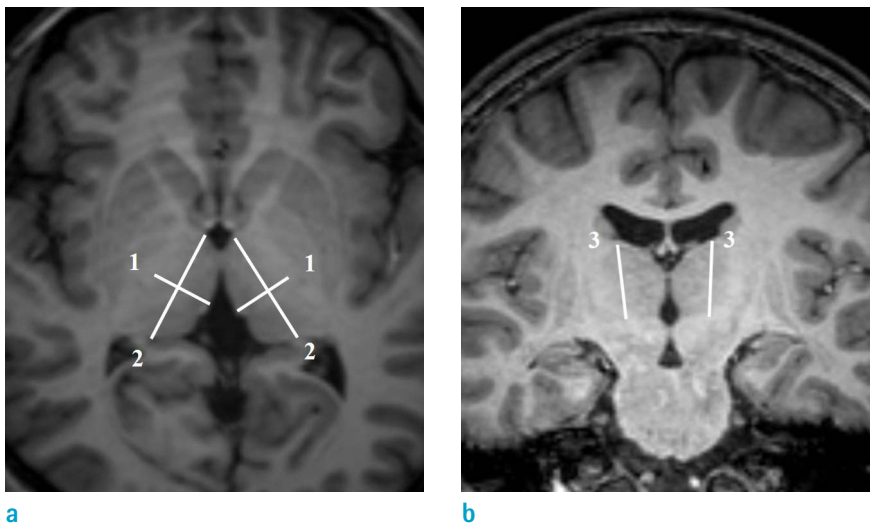
Fig. 1. (a) An axial T1-weighted image of a 13-year-old child with Krabbe disease. Line 1 refers to transverse length and line 2 refers to anterior-posterior length. (b) A coronal T1-weighted image in the same patient. Line 3 indicates cranio-caudal dimension.

T2WI. Volume decrease of corpus callosum was evaluated on T1, T2-weighted axial and sagittal images. Loss of volume in the corpus callosum was considered to exist only when both reviewers clearly agreed.

Thalamic Evaluation Three-dimensional measurements of thalamus were performed on T1WI that showed the longest anterior-posterior (AP) and transverse dimensions on the axial image (Fig. 1a) and cranio-caudal (CC) dimension on the coronal image (Fig. 1b). The volume of thalamus was calculated using the following equation: volume = $(\pi/6) \times$ AP $\times$ transverse $\times$ CC dimensions. A small thalamic volume was defined as < 25th percentile of thalamus size in healthy brains of a similar age group based on the previous study (11). Abnormal signal intensity of the thalamus was defined as T1 signal intensity higher than or similar to that of myelinated white matter.

Tigroid Sign The tigroid sign was defined on MRI as dark spots or stripes within T2 hyperintensity of demyelinated periventricular and deep white matter (1, 2).

Optic Nerve Hypertrophy Optic nerve hypertrophy was considered when the prechiasmatic optic nerve measured perpendicular to the long axis was more than 4 mm (5, 12) (Fig. 2).

Statistics

All statistical analyses were performed using a commercial software (SPSS ver. 25.0 for Windows, IBM Corp., Armonk, NY, USA). Mann-Whitney U test was used for a continuous variable. Fisher's exact test was used for categorical variables. P values < 0 .05 were considered to indicate statistical significance.
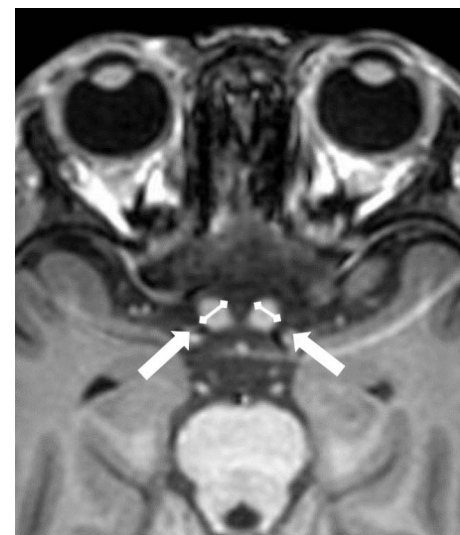

Fig. 2. An axial T1-weighted image of a 3-year-old child with MLD. The prechiasmatic optic nerve whit arrows was measured perpendicular to the long axis. Optic nerve hypertrophy was considered when the optic nerve was measured more than 4 mm.

RESULTS

Thirteen children were diagnosed with Krabbe disease or MLD. Among them, two children with Krabbe disease and one child with MLD without available initial MRI were excluded. As a result, a total of 23 children were enrolled, including 11 children with Krabbe disease (mean age, 3.94 years; range, 8 months to 13 years; nine boys and two girls) and 12 children with MLD (mean age: 2.50 years;

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range, 2 to 5 years; seven boys and five girls). Age, sex, and presenting symptoms were not significantly different between the two groups. Presenting symptoms included developmental delay or regression, seizure, ataxia, gait disturbance, paralysis, and irritability (Table 1).

When their initial MRI findings were compared (Table 2), periventricular and deep white matter signal alterations were present in almost all patients without involving the subcortical white matter (Figs. 3a, 4a). Signal change in the subcortical white matter was noted in only one patient with Krabbe disease. Patients with Krabbe disease had T2 hyperintensity in the internal capsule more frequently than patients with MLD (82% of patients with Krabbe disease vs. 33% of patients with MLD, P = 0.036). T2 hyperintensities in the brainstem were observed only in patients with Krabbe disease (Fig. 3b) (midbrain: 45% of patients with Krabbe disease vs. 0% of patients with MLD, P = 0.014; pons, 55% of patients with Krabbe disease vs. 0% of patients with MLD, P = 0.005). T2 hyperintensities in the splenium and genu of the corpus callosum were noted in 45% and 0% of patients with Krabbe disease (Fig. 3c) and 100% and 83% of patients with MLD (Fig. 4b), respectively (P = 0.005 and P < 0.001, respectively). A decreased volume of corpus callosum was more frequently observed in patients with Krabbe disease (Fig. 5) than in those with MLD (Fig. 6) (36% of patients with Krabbe disease vs. 0% of patients with MLD, P = 0.037). Corpus callosal volume loss was noted in the T2-

hyperintense splenium of Krabbe disease. Lower thalamic volume was also more frequently noted in patients with Krabbe disease (55% of patients with Krabbe disease vs. 8% of patients with MLD, P = 0.027) (Fig. 3d). Frequencies of the tigroid sign (Figs. 3a, 4a) and optic nerve hypertrophy were not significantly different between the two groups (tigroid sign: 45% of patients with Krabbe disease vs. 67% of patients with MLD, P = 0.414; optic nerve hypertrophy: 36% of patients with Krabbe disease vs. 8% of patients with MLD, P = 0.155). Only two children with MLD showed focal diffusion restriction in the corpus callosal splenium. However, none of them had contrast enhancement on their initial MRIs.

Table 1. Demographics of Patients with Krabbe Disease and MLD

Characteristics	Krabbe disease	MLD	P-value
Age at onset (year)[a]	3.94 ± 3.69	2.50 ± 1.00	0.402
Sex			
Male	9 (82)	7 (58)	0.371
Female	2 (18)	5 (42)	
Presenting symptoms			
Developmental delay/regression	6 (55)	10 (77)	0.390
Seizure	2 (18)	2 (15)	1.000
Ataxia/gait disturbance	5 (45)	4 (31)	0.675
Paralysis	2 (18)	1 (8)	0.576
Irritability	4 (36)	1 (8)	0.155

MLD = metachromatic leukodystrophy
Values are presented as mean±standard deviation and N (%).
Mann-Whitney test was used for a continuous variable[a] and Fisher's exact test was used for categorical variables (variables without superscript).
*Significance was confirmed by P-values < 0.05.

Table 2. Initial MRI Findings of Patients with Krabbe Disease or MLD

Characteristics	Krabbe disease	MLD	P-value
T2 hyperintensity			
Periventricular and deep white matter	10 (91)	12 (100)	0.478
Subcortical white matter	1 (9)	0 (0)	0.478
Internal capsule	9 (82)	4 (33)	0.036*
Midbrain	5 (45)	0 (0)	0.014*
Pons	6 (55)	0 (0)	0.005*
Cerebellum	2 (18)	0 (0)	0.217
Involvement of corpus callosum			
T2 hyperintensity of genu	0 (0)	10 (83)	< 0.001*
T2 hyperintensity of splenium	5 (45)	12 (100)	0.005*
Decreased volume of corpus callosum	4 (36)	0 (0)	0.037*
Involvement of thalamus			
Decreased volume of thalamus	6 (55)	1 (8)	0.027*
Abnormal signal intensity of thalamus on T1WI	0 (0)	2 (17)	0.478
Presence of the tigroid sign	5 (45)	8 (67)	0.414
Optic nerve hypertrophy	4 (36)	1 (8)	0.155
Diffusion restriction[1]	0 (0)	2 (17)	0.478
Contrast enhancement[1]	0 (0)	0 (0)	

MLD = metachromatic leukodystrophy; T1WI = T1-weighted imaging
Values are presented as N (%).
Fisher's exact test was used for statistical analysis and *significance was confirmed by P-values < 0.05.
[1]Diffusion-weighted and contrast enhancement images were available in six patients with Krabbe disease and MLD, respectively.
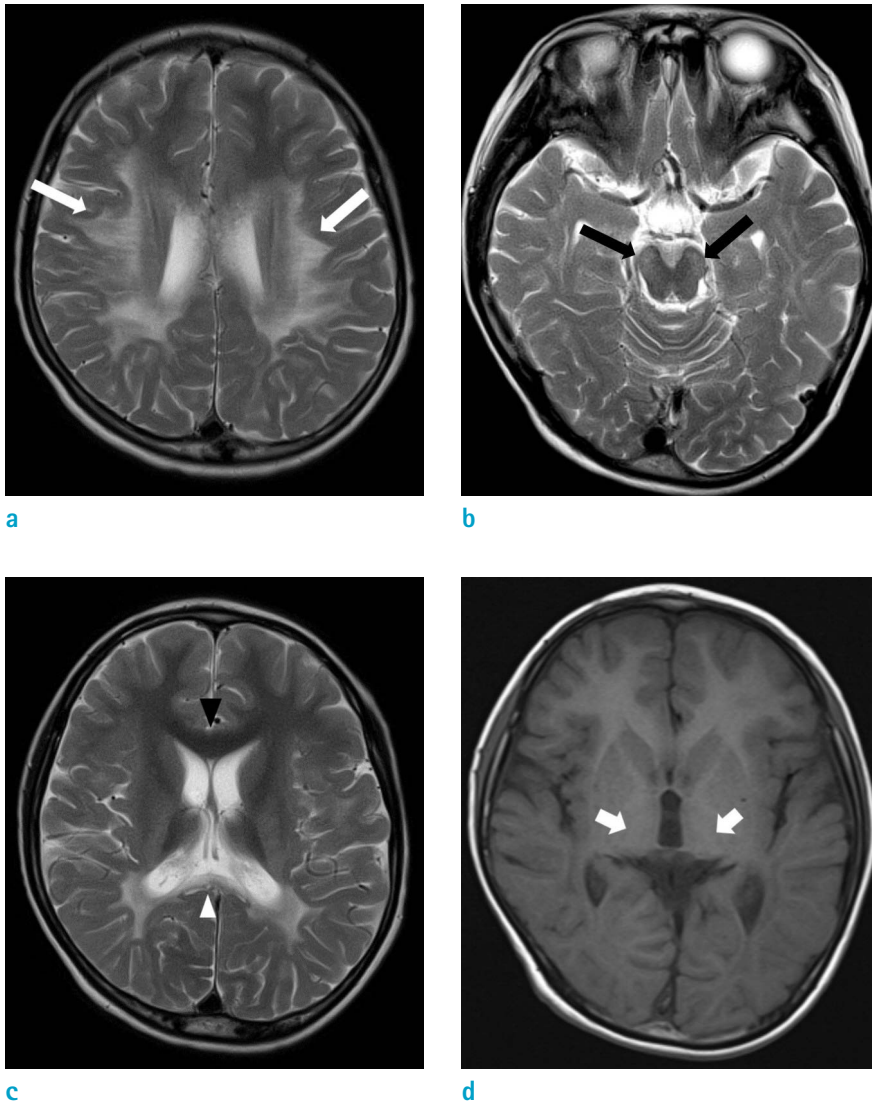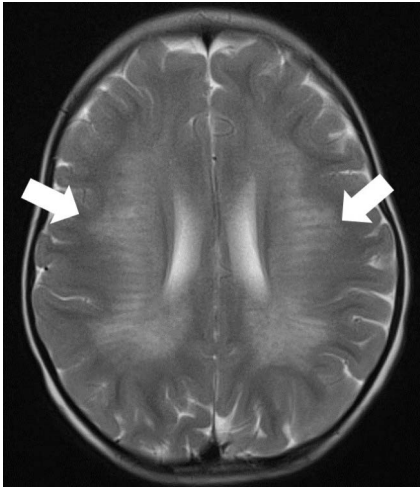
Fig. 3. A 5-year-old child with Krabbe disease. (a) A T2-weighted axial image showing hyperintensity of the periventricular and deep white matter with a tigroid sign (white arrows), which refers to multiple linear structures with low signal intensity within the demyelinated white matter. (b) This patient also shows T2-hyperintensity extending to the brainstem (black arrows). (c) T2-hyperintensity in the splenium of the corpus callosum (white arrowhead) is also noted, not involving the genu (black arrowhead). (d) A T1-weighted axial image showing volume decrease in bilateral thalami (short white arrows).

DISCUSSION

Krabbe disease and MLD have similar clinical and imaging features, making their differentiation challenging and leading to misdiagnosis sometimes following initial imaging studies. Krabbe disease can be classified as early infantile (age at onset < 6 months), late infantile (age at onset from 7 months to 3 years), juvenile (age at onset from 3 to 8 years), and adult (age at onset > 9 years) types (13). The early infantile form is the most common one. Its clinical manifestations include irritability, episodic fever, increased muscle tone, and developmental delay or regression. Cognitive decline, myoclonic seizure, and nystagmus can also develop as the disease progresses. MLD can also be classified as late-infantile (age at onset < 30 months),

juvenile (age at onset from 2.5 to 16 years), and adult (age at onset > 16 years) forms. Late infantile form of MLD is the most common one, followed by juvenile and adult types. Its clinical symptoms include strabismus, impaired speech, intellectual decline, and spasticity that can be similar to those of Krabbe disease (1, 2).

In addition to similarities in clinical presentations, Krabbe disease and MLD share common imaging features. Reported MRI findings for both diseases include confluent T2 hyperintensity in the periventricular and deep cerebral white matter sparing subcortical U fibers usually until late stages of the disease (1, 2). Likewise, in this study, we observed periventricular and deep white matter signal alterations sparing the subcortical white matter in almost all patients.
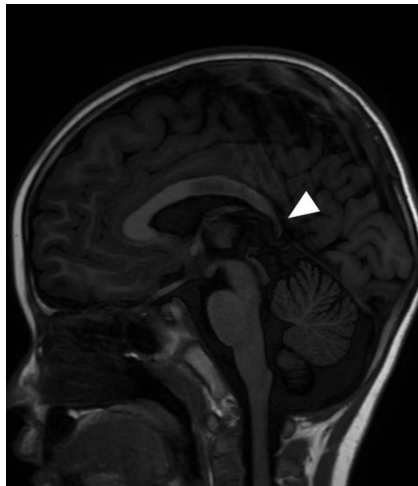
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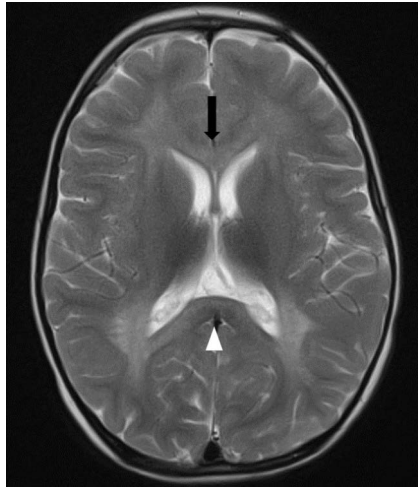
Fig. 4. A 3-year-old child with MLD. (a) A T2-weighted axial image showing hyperintensity of the periventricular and deep white matter with a tigroid sign (white arrows). (b) Another T2-weighted image showing hyperintensity in the genu (black arrow) and splenium (arrowhead) of the corpus callosum.
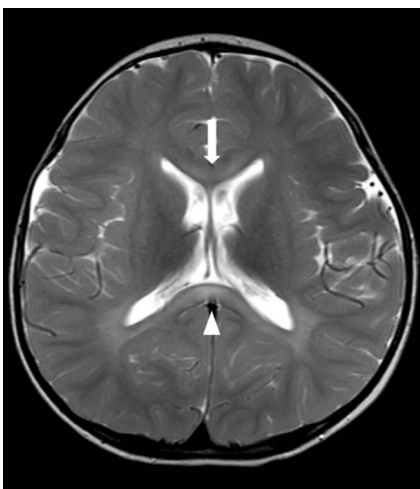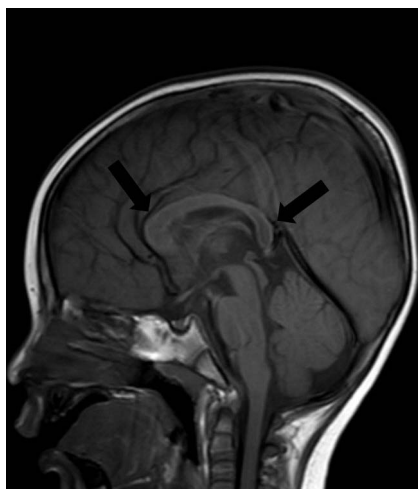

Fig. 5. A 3-year-old child with Krabbe disease. (a) A T2-weighted axial image showing hyperintensity in the splenium of the corpus callosum (black arrow) without involving the genu (black arrowhead). (b) Signal change in the corpus callosal splenium is accompanied by obvious volume decrease (white arrowhead) on a T1-weighted sagittal image.

Fig. 6. A 2-year-old patient with MLD. (a) A T2-weighted axial image showing hyperintensities in the corpus callosal genu (white arrow) as well as in the splenium (white arrowhead). (b) Corpus callosal volume is relatively preserved (black arrows) on a T1-weighted sagittal image.

We observed that Krabbe disease tended to extend vertically, involving the internal capsule or brainstem. Similarly, previous studies have shown T2 hyperintensity of the cerebellum and cortico-spinal tract along the internal capsule, brainstem, and cerebral white matter in early Krabbe disease (14-16). In MLD, however, involvement of cortical spinal tracts, cerebellar white matter, and basal ganglia is usually seen late in the disease course (17, 18). Another interesting finding in our study was that patients with MLD more frequently had corpus callosal signal change on initial MRI. T2 hyperintensities in the splenium of the corpus callosum were noted in 100% and 45% of patients with MLD and Krabbe disease, respectively. More interestingly, no patient with Krabbe disease had involvement of the corpus callosal genu on initial MRI, whereas 83% of patients with MLD demonstrated such involvement. This may indicate a rapid and early horizontal disease extension in MLD relative to that in Krabbe disease (19).

Another finding suggestive of Krabbe disease is volume loss of corpus callosum and thalamus at an early stage. Although signal change in the corpus callosum was observed only in five (45%) patients with Krabbe disease compared to 12 (100%) patients with MLD, four (80%) of those five showed decreased volume of the involved corpus callosum. In addition, thalamic volume loss was more frequently observed in patients with Krabbe disease. Although the cause of thalamic volume loss remains unknown, thalamic volume change might be related to white matter demyelination because thalamic axons are interconnected with cortical areas through the white matter. As a similar example, thalamic volume loss has been reported in patients with multiple sclerosis, where white matter sclerotic lesions, at least in part, are likely to lead to thalamic neuronal volume loss (20). Therefore, more frequent detection of thalamic volume loss in Krabbe disease might be caused by more aggressive destructive white matter changes than in MLD. According to previous histopathologic studies, psychosine, a very cytotoxic substrate, is known to accumulate in myelin-forming cells in Krabbe disease, resulting in more aggressive degeneration of oligodendrocytes and myelin degeneration than in MLD (3, 21).

van der Voorn et al. (22) have described the presence of a tigroid pattern in Krabbe disease, but not as consistently as in those with MLD. In our study, however, the frequency of the tigroid sign was not significantly different between the two groups. As many as 45% of patients with Krabbe disease had a tigroid sign, which was not helpful in differentiating it from MLD (67% of patients with MLD had a tigroid sign). This may be related to improved image quality with recent MRI scanners. With improved image resolution, small linear tubular and dot-like areas of spared white matter can be detected more frequently than before, even in patients with Krabbe disease.

Optic nerve hypertrophy has been considered a characteristic feature of Krabbe disease in previous studies (5, 23). However, frequency of optic nerve hypertrophy in Krabbe disease was not significantly different from that in MLD in the present study, although optic nerve hypertrophy tended to be more common in patients with Krabbe disease.

In conclusion, signal abnormalities in the internal capsule and brainstem, decreased thalamus volume, decreased splenial volume accompanied by signal changes, and absence of signal changes in the callosal genu portion were MRI findings more suggestive of Krabbe disease than MLD on initial MRI. Other MRI findings such as the tigroid sign failed to help differentiate between these two conditions.

Conflicts of Interest

The authors have no conflicts of interest relevant to this study to disclose.

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