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Use of Thalamus L-Sign to Differentiate Periventricular Leukomalacia From Neurometabolic Disorders

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Abstract

Purpose: To assess the diagnostic value of the thalamus L-sign on magnetic resonance imaging (MRI) in distinguishing between periventricular leukomalacia and neurometabolic disorders in pediatric patients.

Methods: In this retrospective study, clinical and imaging information was collected from 50 children with periventricular leukomalacia and 52 children with neurometabolic disorders. MRI was used to evaluate the L-sign of the thalamus (ie, injury to the posterolateral thalamus) and the lobar distribution of signal intensity changes. Age, sex, gestational age, and level of Gross Motor Function Classification System (only for periventricular leukomalacia) constituted the clinical parameters. Statistical evaluation of group differences for imaging and clinical variables were conducted using univariable statistical methods. The intra- and inter-observer agreement was evaluated using Cohen's kappa. Univariable or multivariable logistic regression was employed for selection of variables, determining independent predictors, and modeling.

Results: The thalamus L-sign was observed in 70% (35/50) of patients in the periventricular leukomalacia group, but in none of the patients with neurometabolic disorder ($P < .001$). The gestational age between groups varied significantly ($P < .001$). Involvement of frontal, parietal, and occipital lobes differed significantly between groups ($P < .001$). In the logistic regression, the best model included negative thalamus L-sign and gestational age, yielding an area under the curve, accuracy, sensitivity, specificity, and precision values of 0.995, 96.1%, 96%, 96.2%, and 96%, respectively. Both the lack of thalamus L-sign and gestational age were independent predictors ($P < .001$).

Conclusions: The thalamus L-sign and gestational age may be useful in distinguishing between periventricular leukomalacia and neurometabolic disorders.

Keywords

cerebral palsy, developmental delay, inborn errors of metabolism, magnetic resonance imaging, preterm

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Periventricular leukomalacia (PVL) is a term used to describe damage to the brain's white matter that primarily affects infants born before 37 weeks of gestation.[1] It is the most common cause of cognitive deficits and cerebral palsy in premature infants and occurs most frequently between 23 and 30 weeks of gestation.[1–4] Periventricular leukomalacia is primarily a disease of the periventricular white matter, and it initially manifests as periventricular structural changes with or without cystic transformation.[5] It is characterized histopathologically by necrosis of premyelinating oligodendroglia in the periventricular white matter, which are extremely vulnerable to death.[6–10]

The pattern of perinatal brain injury is highly dependent on gestational age. For example, in term infants, injuries primarily affect cerebral cortical parenchyma, especially posterior watershed regions or strokelike distributions.[11,12] On the other hand, in premature infants, periventricular white matter regions are primarily affected.[11,12] Thus, the suggested terminology for this process is

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"white matter injury of prematurity" or "cerebral white matter injury."[12] This study made use of the term *periventricular leukomalacia* because of its familiarity and widespread usage.

White matter damage in a premature brain can result in devastating neurologic complications.[13] The most prevalent long-term clinical manifestations of periventricular leukomalacia are cerebral palsy and developmental delay.[13,14] Spasticity, cortical blindness, vision loss, mental retardation, epilepsy, dystonia, behavioral, attentional, and social disorders are additional clinical manifestations.[15] Early and accurate diagnosis is particularly important because clinical confirmation of white matter injury is difficult in newborns and infants, who typically exhibit nonspecific clinical findings.[16] This has resulted in a significant reliance on diagnostic imaging for the evaluation of periventricular leukomalacia.

MRI is the optimal and gold standard imaging modality for detecting and quantifying periventricular leukomalacia–damaged brain regions.[16,17] It can identify the most subtle to the most obvious related changes. Using its advanced techniques such as diffusion tensor imaging, MRI can also provide valuable information about tract degenerations in addition to white matter injuries.[17,18]

Neurometabolic disorders are another common cause of cerebral white matter injury in children, and MRI is the preferred imaging modality for diagnosis.[19–22] MRI findings may aid in the diagnosis of a variety of neurometabolic disorders and can facilitate early treatment management prior to the arrival of time-consuming metabolic, biochemical, and genetic testing.[22,23] Numerous neurometabolic disorders and periventricular leukomalacia are characterized by periventricular white matter hyperintensities and may exhibit similar MRI findings. In uncertain cases, differential diagnosis can therefore be difficult.[16,19–21]

The purpose of this study was to investigate posterolateral thalamic injury (thalamus L-sign) in children with periventricular leukomalacia and neurometabolic disorders and to assess the possibility of using it as a biomarker to differentiate each group in MRI. On T2-weighted imaging and fluid-attenuated inversion recovery sequences, we noticed hyperintensity in the posterolateral margin of the thalami in patients with periventricular leukomalacia. We hypothesized that the "thalamus L-sign" on T2-weighted imaging / fluid-attenuated inversion recovery could be a useful diagnostic tool for distinguishing periventricular leukomalacia from neurometabolic disorders. Additionally, the age of the patients, their gestational ages, their lobar distributions, and level of Gross Motor Function Classification System (GMFCS; only for periventricular leukomalacia) were included in the analysis.

Materials and Methods

Study Design

Between January 2020 and July 2022, the current study was conducted in a tertiary academic hospital. All patients' medical records were analyzed for clinical diagnosis and eligibility to participate in this study. At the time of the MRI examination, the patient's age, gestational age, and gender were recorded.

Inclusion and Exclusion Criteria

Patients <18 years old who were referred to pediatric neurology and pediatric metabolic disorders clinics with a diagnosis of periventricular leukomalacia and neurometabolic disorder were included in the study. Exclusion criteria included children with current or past histories of postnatal ischemia, hemorrhagic stroke, hypoglycemia, malignancy, cranial surgery, birth trauma, or known systemic diseases.

MRI Protocol

All MRI studies were conducted using a 3.0-tesla (T) MRI scanner (Ingenia; Philips Healthcare), a 1.5-T MRI scanner (Echelon; Fujifilm Healthcare), and an open MRI scanner with a 1.2-T magnet (Oasis; Fujifilm Healthcare). All patients were scanned at random on the various MRI scanners. The scanning protocol for each patient consisted of axial and sagittal spin echo T1-weighted imaging, axial spin echo T2-weighted imaging, axial T2-weighted fluid-attenuated inversion recovery, and diffusion-weighted imaging with echo-planar imaging sequences. The MRI sequence parameters are listed in Supplementary Table 1.

Image Analysis

All anonymized MRI data were reviewed by 2 radiologists with at least 5 years of experience in neuroradiology, who were blinded to all clinical information pertaining to the patients. White matter injury in the frontal, parietal, occipital, and temporal lobes was used to categorize lobar distribution. Lobar distribution was evaluated by consensus of observers. The radiologists independently determined the presence or absence of the thalamus L-sign to evaluate interobserver concordance. MRI was considered positive or negative based on the presence or absence of the thalamus L-sign, respectively. A positive result for the thalamus L-sign necessitated a hyperintense signal on the posterolateral margin of the thalamus adjacent to the posterior limb of the internal capsule, indicating thalamic injury on T2-weighted imaging and fluid-attenuated inversion recovery.[24] A negative result for the thalamus L-sign necessitated the absence of thalamic injury on T2-weighted imaging and fluid-attenuated inversion recovery.

GMFCS Level Analysis for Periventricular Leukomalacia Cases

The GMFCS is a 5-level, ordinal grading system that classifies gross motor functions in children with cerebral palsy.[25] The GMFCS describes self-initiated movement and use of assistive devices (walkers, crutches, canes, wheelchairs) for mobility during an individual's usual activity. This classification system was initially designed to be used with children 2-12 years of age and later expanded and revised to include subclassifications according to age as 0-2 years, 2-4 years, 4-6 years, 6-12 years, and 12-18 years and patients were evaluated according to the developmental stages appropriate for their age groups.[26] A child in GMFCS level I is able to walk indoors and outdoors independently, climb stairs, and start to run and jump. A child classified in GMFCS II can walk with limitations including balance or endurance, use of a hand-held mobility device, use of a railing on stairs, or an inability to run or jump. A child classified in GMFCS III can often walk with a hand-held mobility device indoors but use wheeled mobility in the community and for longer distances. An individual classified in GMFCS IV can sit supported, but self-mobility is limited, often being transported in a manual wheelchair, or using powered mobility. Children classified in GMFCS V have more severe

limitations with head and trunk control and self-mobility is only possible using a power wheelchair. Adaptive equipment is required for sitting and standing, but function is still limited.[27] Ambulatory capacity of patients with periventricular leukomalacia were classified using GMFCS levels. The GMFCS levels of children with periventricular leukomalacia scored according to the examination by a pediatric neurologist or physical therapist were retrieved from patients' records.

Statistical Analysis

JASP v0.16.2 and Jamovi v2.2.5 were used to conduct the statistical analysis. Mean, median, standard deviation, and interquartile range are used to describe statistical data for continuous variables. The Shapiro Wilk test was used to determine normality. A parametric or nonparametric test was employed, depending on the group distributions, to evaluate statistical differences of continuous variables between groups. Depending on the number of cells in the contingency tables, the chi-square test or Fisher exact test (if any cell count <5) was used to compare the differences across categorical variables. Yates continuity correction was also applied to the chi-square test depending on the cell count (if any cell count <10). Phi-coefficient was used to assess the strength of correlation between categorical variables. With Cohen's kappa statistics, intra- and interobserver agreement for L-sign was evaluated. The interpretation scale for Cohen's kappa was as follows: poor agreement, ≤ 0.2; fair agreement, >0.2 and ≤ 0.4; moderate agreement, >0.4 and ≤ 0.6; good agreement, >0.6 and ≤ 0.8; and very good agreement, >0.8 and ≤ 1. The variables that met statistical threshold of $P < .05$ in the univariable logistic regression were included in multivariable logistic regression. Multivariable analysis was used to identify independent predictors if present, as well as to create a model. With the help of the Bayesian information criterion (BIC; ie, Schwarz information criterion), the best model was selected. Area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, and precision were utilized as diagnostic performance indicators. Statistics were considered significant for P values <.05. A Bonferroni correction was used for multiple comparisons.

Results

Baseline Characteristics

A total of 50 patients with periventricular leukomalacia and 52 patients with a diagnosis of neurometabolic disorder were included in this retrospective study. Regarding sex, there was no statistical difference between the periventricular leukomalacia and neurometabolic groups ($P = .112$). Additionally, there was no age difference between them ($P = .051$). The difference in gestational age between groups, however, was significant ($P < .001$) (Supplementary Figure 1). Cerebral palsy and prematurity were present in all periventricular leukomalacia cases. Descriptive statistics of patient age, gestational age, and sex between groups and subgroups of periventricular leukomalacia are presented in Table 1.

Metabolic, biochemical, imaging, and/or genetic analysis revealed that patients with neurometabolic disorder had a specific neurometabolic disease. Table 2 lists all patients diagnosed with neurometabolic disorder. This study excluded participants with both periventricular leukomalacia and neurometabolic disorder.

Imaging Features

In 70% (35/50) of the periventricular leukomalacia patient population, the thalamus L-sign was positive. It was observed bilaterally in 32 of 35 patients and unilaterally in 3 patients. In unilateral cases, injury to the ipsilateral cerebral white matter

Table 1. Group and Subgroup Differences for Patient Age, Gestational Age, Sex, and GMFCS Level.

Features	Group	Mean	Range	SD	Median	IQR	Count	Statistic	*P* value
Sex (boy/girl)	PVL	–	–	–	–	–	28/22	–	.112
	Neurometabolic	–	–	–	–	–	37/15		
Sex (boy/girl)	L-sign + (PVL)	–	–	–	–	–	23/12	3.251[a]	.071
	L-sign – (PVL)	–	–	–	–	–	5/10		
Patient age (y)	PVL	6.380	1-17	4.155	6.000	5.750	–	1009.000	.051
	Neurometabolic	4.942	1-15	3.913	3.000	6.000	–		
Patient age (y)	L-sign + (PVL)	6.200	1-17	4.192	6.000	5.500	–	290.500	.558
	L-sign – (PVL)	6.800	1-17	4.178	6.000	4.000	–		
Gestational age (wk)	PVL	31.300	24-36	3.164	32.000	5.000	–	14.632	<.001
	Neurometabolic	38.942	31-44	2.004	39.000	1.000	–		
Gestational age (wk)	L-sign + (PVL)	31.543	24-36	3.284	32.000	5.000	–	–0.826	.413
	L-sign – (PVL)	30.733	25-36	2.890	31.000	3.000	–		
GMFCS levels I and II	L-sign + (PVL)	18	–	–	–	–	–	–	.215
	L-sign – (PVL)	11	–	–	–	–	–	–	
GMFCS levels III, IV, V	L-sign + (PVL)	17	–	–	–	–	–	–	
	L-sign – (PVL)	4	–	–	–	–	–	–	

Abbreviations: PVL, periventricular leukomalacia; SD, standard deviation; IQR, interquartile range; GMFCS, Gross Motor Function Classification System.
[a]Obtained with Yates continuity correction.

Table 2. Neurometabolic Disorders With Profound Central Nervous System Manifestations.

Disorder	No. of Cases
Congenital disorders of glycosylation type I	6
β-Galactosidase deficiency	4
Leigh syndrome	4
Mitochondrial cytopathy	2
MELAS	2
Metachromatic leukodystrophy	2
Homocystinuria	2
Mucolipidosis type 2	2
Lowe syndrome	2
Pontocerebellar hypoplasia type I	2
Malonic aciduria	2
Fucosidosis	2
Fumaric aciduria	1
Riboflavin transporter deficiency	1
Glucose transporter type-I deficiency	1
Cerebral creatine deficiency	1
Lesch-Nyhan syndrome	1
Krabbe disease	1
Nonketotic hyperglycinemia	1
Mucopolysaccharidosis type-2 (Hunter syndrome)	1
Mucopolysaccharidosis type-3 (Sanfilippo syndrome)	1
GM2-Gangliosidosis (Sandhoff disease)	1
Mitochondrial neurogastrointestinal encephalomyopathy	1
Propionic acidemia	1
Methylmalonic acidemia	1
Complex-I deficiency	1
TORCH-like syndrome and 3-methylcrotonyl glycinuria	1
Zellweger syndrome	1
Phosphoglycerate kinase-I deficiency	1
Neurodegeneration with brain iron accumulation	1
Thiamine-responsive megaloblastic anemia	1
Oxidative phosphorylation deficiency-35	1

Abbreviation: MELAS, mitochondrial encephalomyopathy with lactic acidosis and strokelike episodes.

was more evident. None of the patients with neurometabolic disorder displayed an L-sign in the thalamus (Supplementary Figure 1). There was a statistically significant difference between the groups in terms of the thalamus L-sign ($P < .001$).

In the analysis of lobar distribution of white matter injury, frontal, parietal, and occipital lobes showed a significant difference between groups ($P < .001$). However, there was no statistical difference between groups for temporal lobes ($P = .731$).

Using Cohen's kappa statistics, the correlation between the 2 observers was strong, with a kappa of 0.824 (95% confidence interval, 0.707-0.905). The intraobserver correlation was very good, with a kappa of 0.934 (95% confidence interval, 0.861-1.000).

Logistic Regression for Distinguishing Periventricular Leukomalacia From Metabolic Diseases

In univariate logistic regression, 5 parameters (gestational age, thalamus L-sign, and frontal, parietal, and occipital lobes) with significant differences between groups were analyzed. The thalamus L-sign, occipital lobe involvement, and gestational age showed statistical significance in univariable logistic regression analyses (Table 3).

Table 3. Univariable Logistic Regression Analysis Results.

				Wald test		
Parameters[a]	Estimate	Standard error	z	Wald statistic	df	*P*
Thalamus L-sign (-)	−1.243	0.293	−4.242	17.993	1	<.001
Frontal lobe (+)	20.387	1963.405	0.010	1.078e−4	1	.992
Parietal lobe (+)	19.111	1360.064	0.014	1.974e-4	1	.989
Occipital lobe (−)	−2.068	0.467	−4.426	19.586	1	<.001
Gestational age	−0.975	0.201	−4.841	23.433	1	<.001

Abbreviation: df, degrees of freedom.
[a](+), presence; (−), absence.

The best model in multivariable logistic regression analysis included thalamus L-sign and gestational age. The chosen model achieved AUC, accuracy, sensitivity, specificity, and precision of 0.995, 96.1%, 96%, 96.2% and 96%, respectively. Gestational age and the negative thalamus L-sign were independent predictors in this analysis ($P < .001$) (Supplementary Figure 2). Table 4 and Supplementary Figure 3 show the outcomes of a multivariable logistic regression analysis.

Use of negative thalamus L-sign alone achieved AUC, accuracy, sensitivity, specificity, and precision of 0.850, 85%, 70%, 100%, and 100%, respectively. Use of gestational age alone achieved AUC, accuracy, sensitivity, specificity, and precision of 0.977, 91.2%, 86%, 96.2%, and 95.6%, respectively.

Example images of patients with periventricular leukomalacia and neurometabolic disorder are shown in Figures 1 and 2, respectively.

Periventricular Leukomalacia Subgroup Analysis

In the periventricular leukomalacia group, there was no significant difference between the patient's age and thalamus L-sign ($P = .558$) or gestational age and thalamus L-sign ($P = .413$). Also, there was no significant difference between the sex and thalamus L-sign ($P = .071$). These results show that the main issue for the thalamus L-sign positivity is the lobar distribution of the periventricular leukomalacia as described below.

The relationship between the lobar distribution of white matter injury and the L-sign in the thalamus was analyzed further in the periventricular leukomalacia group only. In every case of periventricular leukomalacia, the frontal and parietal lobes exhibited periventricular white matter involvement. In 34 of 35 thalamus L-sign-positive cases,

Table 4. Multivariable logistic regression analysis results.

Parameter[a]	Estimate	Odds ratio	z	Wald test			BIC
				Statistic	df	*P*	
Thalamus L-sign (–)	−25.961	1.882e + 11	4.007	16.056	1	<.001	34.3
Gestational age	−0.769	0.463	−4.122	16.995	1	<.001	

Abbreviations: df, degrees of freedom; BIC, Bayesian information criterion.
[a](–), absence.

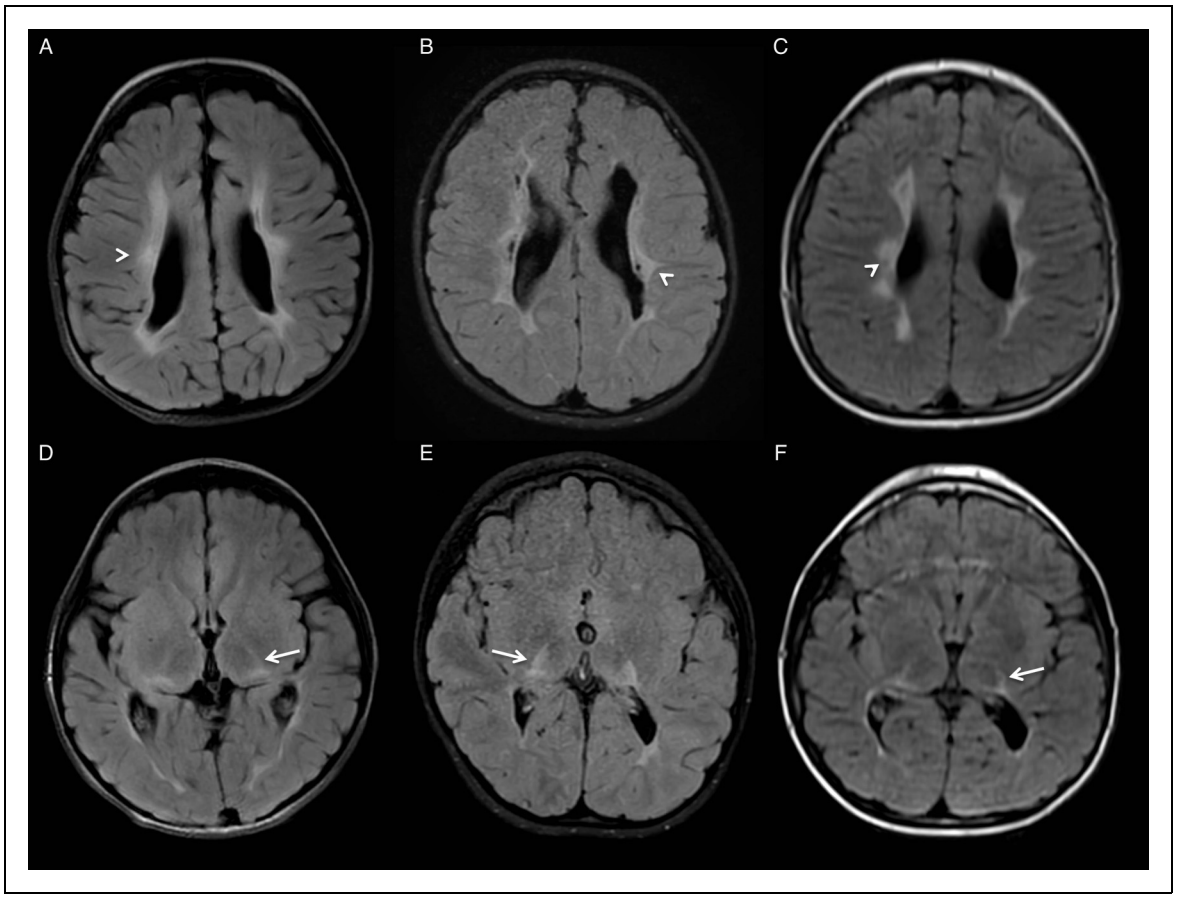

Figure 1. Cases of periventricular leukomalacia with the thalamus L-sign on various MRI scanners. (A, D) A 6-year-old girl with a history of prematurity (27 weeks) on a 3-T MRI; (B, E) a 6-year-old boy with a history of prematurity (36 weeks) on a 1.5-T MRI; (C, F) and an 8-year-old boy with a history of prematurity (28 weeks) on a 1.2-T open MRI system. Axial fluid-attenuated inversion recovery (FLAIR) images reveal the thalamus L-sign, a hyperintense signal in the posterolateral margin of thalami (arrows). In addition, all images display periventricular high-signal areas, wavy lateral ventricle borders, and white matter volume loss, which are all characteristics of periventricular leukomalacia (arrowheads).

periventricular occipital white matter involvement was identified. In addition, occipital lobes were involved with temporal periventricular white matter in 14 cases. Seven cases of occipital lobe involvement were identified among the 15 thalamus L-sign-negative patients. However, temporal lobes were not involved in any of these 15 cases. There was a statistically significant difference in occipital lobe involvement ($P < .001$) and temporal lobe involvement ($P = .004$) between L-sign positive and negative cases. No statistically significant difference was found in the involvement of the frontal or parietal lobes between the L-sign positive and negative cases ($P = .731$).

MRI Subgroup Analysis for L Sign

In the periventricular leukomalacia group, 28 patients were scanned in a 1.5-T MRI unit, 11 in a 3.0-T unit, and 11 in a 1.2-T (open) MRI unit. The rate of detection of an L-sign was higher on the 3.0-T MRI unit (82%, 9/11) compared with the 1.5-T (71%, 20/28) and 1.2-T MRI units (54%, 6/11). However, there was no

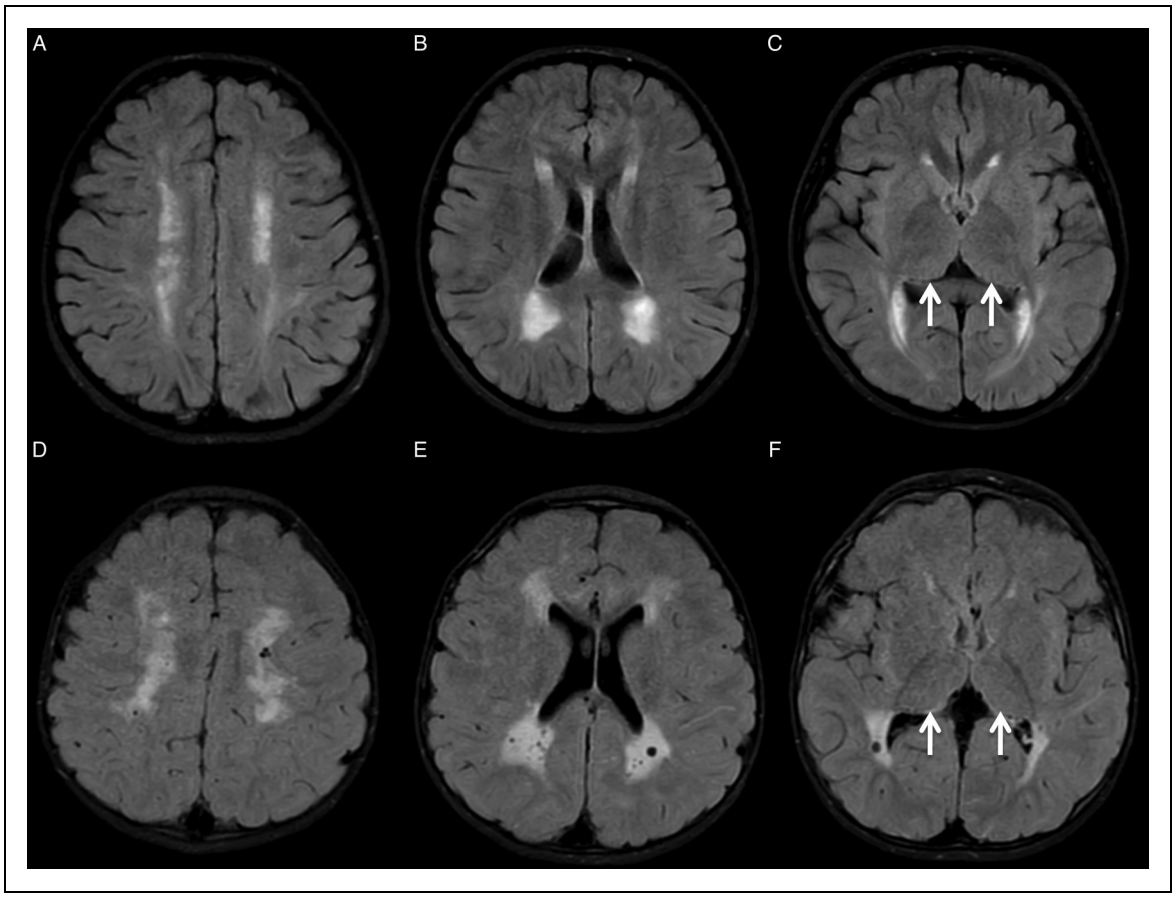

Figure 2. Cases with metabolic disorders. (A, B, C) A case of MNGIE syndrome in a 9-year-old and (D, E, F) a case of Lowe syndrome in a 3-year-old. Axial FLAIR (fluid-attenuated inversion recovery) images of both cases reveal hyperintense regions in the periventricular white matter and thalami with normal appearance (arrows). MNGIE, mitochondrial neurogastrointestinal encephalomyopathy.

statistical difference using Fisher exact test ($P = .411$), including all pairwise post hoc comparisons.

Relationship Between GMFCS Level and L Sign

GMFCS scores of 29 patients were evaluated as level I and II (level I: 4, level II: 25 patients) and they were able to walk unassisted, and for younger children, they were able to maintain their balance and posture without support. Twenty-one patients were found to be more affected and subgrouped as follows: 15 cases mildly impaired (level III), 4 cases moderately impaired (level IV), and 2 cases severely impaired (level V). In statistical analysis, there was no significant association and weak correlation for GMFCS level and L-sign positivity (Fisher exact test, $P = .215$; phi-coefficient, $P = .203$).

Discussion

In the present study, we examined posterolateral thalamic injury, also known as the thalamus L-sign, among patients with periventricular leukomalacia and neurometabolic disorders. In a model including thalamus L-sign and gestational age, we found excellent diagnostic performance characteristics to differentiate them. The L-sign in the thalamus was not observed in any of the neurometabolic disorder patients. In addition, we observed a strong positive correlation between the thalamus L-sign and the diagnosis of periventricular leukomalacia. By reducing the length of the diagnostic period, the findings of our study may facilitate an earlier and more timely administration of treatment.

An important differential diagnosis for white matter injury of periventricular leukomalacia in children is that of neurometabolic disorders (ie, leukodystrophies such as adrenoleukodystrophy, Lowe syndrome, and mucopolysaccharidoses such as Hurler syndrome), which are associated with periventricular white matter hyperintensities and sometimes cystic changes.[16,20,28]

Although other clinical findings, biochemical/metabolic screening, and advanced MRI techniques such as spectroscopy may help narrow the differential diagnosis and arrive at a definitive diagnosis, both conditions may be characterized by white matter injury along the periventricular region and may have similar MRI findings.[16] In uncertain situations, it can be difficult to distinguish between these 2 entities.[20,28] The sparse radiologic research literature on the comparison of periventricular leukomalacia with neurometabolic disorders causes diagnostic difficulty.[28] Therefore, we wanted to share our

knowledge to add new information about the unpublished aspects of these 2 entities that help to distinguish them.

Misser et al[24] have described the thalamus L-sign for the first time. Their research aimed to examine the diagnostic performance of the thalamus L-sign between hypoxic-ischemic injury, neonatal hypoglycemia, and both perinatal hypoxia-ischemia and confirmed hypoglycemia cases. The thalamus L-sign was observed in 86% (85/99) of cases of partial, prolonged hypoxia-ischemic brain injury. The thalamus L-sign was not observed in any of the pure hypoglycemic patients, whereas it was observed in all the hypoxic ischemia and hypoglycemic patients. The presence of the thalamus L-sign was 2.79 times greater when both the parietal and occipital lobes were involved. In their study, hypoxic-ischemic or hypoglycemic patients with a typical pattern of brain injury that is frequently observed in term cases with cortical destruction at the interarterial watershed zones, particularly in the parietooccipital lobes as opposed to the periventricular white matter, were evaluated. Three hundred twenty term newborns comprised the population of this study.

Because ischemic process is a predominant component in both the histopathology of periventricular leukomalacia and hypoxic-ischemic brain injury, it is not surprising that despite population and group differences, our study results were comparable. Like Misser et al, we believe that the L-sign in the thalamus may be caused by the contiguous injury of 2 structures. First, primary thalamic involvement in the pulvinar/lateral geniculate nucleus and, second, Wallerian degeneration of the posterior limb of the internal capsule (reticular formation nuclei) because of the white matter injury through which corticospinal tracts pass.[29,30]

The current study has several limitations, which can be summarized as follows: single center, small sample size, and retrospective nature. The fact that the neurometabolic disease group was heterogeneous and comprised various subtypes was another concern of the study.

Conclusion

In conclusion, our study demonstrates that the thalamus L-sign and gestational age have excellent performance characteristics, making them a potential discriminator between periventricular leukomalacia and neurometabolic disorders. In certain cases of periventricular leukomalacia in which a neurometabolic disorder is suspected, the results of this study can expedite the diagnosis and eliminate the need for costly and time-consuming biochemical, metabolic, or genetic tests. Additional research with larger samples is necessary to confirm our results.

Declaration of Conflicting Interests

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Author Contributions

SY drafted manuscript and contributed to conception and design. BK contributed to acquisition, analysis, and interpretation. MES, MB contributed to analysis. PC, IK contributed to interpretation. SY, MES, MB, PC, IK, BK critically revised manuscript, gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Institutional review board approval was granted by the medical Ethics Committee (no. 2022.09.300; 28/09/2022).

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Supplemental Material

Supplemental material for this article is available online.

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