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Phenylketonuria: A Scoring System for Brain Magnetic Resonance Imaging

Derya Bako[1], Kısmet Çıkı[2]

[1]Department of Pediatric Radiology, Van Regional Training and Research Hospital, Van, Turkey
[2]Department of Pediatric Metabolism, Van Regional Training and Research Hospital, Van, Turkey

What is already known on this topic?

- *Phenylketonuria (PKU) is a severe, autosomal recessive disorder, caused by the decreased function of the phenylalanine hydroxylase.*
- *If untreated, the accumulation of phenylalanine may lead to microcephaly, seizures, eczema, behavioral and psychiatric symptoms, autism, developmental delay, and severe intellectual disability.*
- *MRI enables observing abnormalities in patients with PKU.*
- *The typical brain MRI findings of PKU are T2-weighted hyperintense lesions, located in parietooccipital regions.*

What this study adds on this topic?

- *Building upon the widely used Loes and modified Loes scoring systems, we have developed a novel scoring system that can be readily implemented in clinical practice.*
- *Our study contributes to the long-forgotten and largely abandoned area-imaging findings in late diagnosed and untreated PKU patients.*

Corresponding author:
Derya Bako
✉ deryabakokeskin@gmail.com
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ABSTRACT

Objective: The purpose of our study was to devise a new brain Magnetic Resonance Imaging (MRI) scoring system based on the Loes and modified Loes scores in phenylketonuria (PKU) patients.

Materials and Methods: The brain MRI scans of patients with late diagnosed PKU were evaluated retrospectively. Patients' age at diagnosis, age at which diet started, age at MRI, and, blood phenylalanine (Phe) levels at the time point closest to the MRI were recorded.

Results: Eleven patients aged from 3 to 28 years were included in the study. The median MRI involvement score was 17 (interquartile range = 3). The most involved white matter areas were the parietooccipital areas. There was a significant ($P = .046$) correlation between the blood Phe level at the timepoint closest to the imaging and the MRI involvement score.

Conclusion: Our study provides insights into the MRI findings and scoring system in PKU patients. We have developed a scoring system based on the widely used Loes and modified Loes scoring systems that can be implemented in clinical practice. Also, our study contributes to the long-forgotten and largely abandoned area-imaging findings in late diagnosed and untreated PKU patients and set the stage for the future research in this field.

Keywords: Brain, MRI, phenylketonuria, scoring

INTRODUCTION

Phenylketonuria (PKU) is a severe, autosomal recessive disorder caused by the decreased function of the phenylalanine hydroxylase (PAH)—the enzyme that converts phenylalanine (Phe) to tyrosine.[1] If untreated, the accumulation of Phe may lead to microcephaly, seizures, eczema, behavioral and psychiatric symptoms, autism, developmental delay, and severe intellectual disability.[2] Neonatal screening programs for PKU have been implemented in numerous countries worldwide.

In Europe, the mean prevalence of PKU is approximately 1 : 10 000, while in Turkey and Ireland the reported prevalence higher.[2] Although the neonatal screening program was introduced in Turkey in 2006, we still encounter cases of late-diagnosed PKU patients, as well as recently diagnosed adolescents and adults. This is mostly due to challenges in diagnosis or management, such as inappropriate or early testing for PKU (the blood specimen for PKU screening must be obtained at least 24 hours after birth), improper storage of filter papers used for testing, the inability of physicians to reach or communicate with diagnosed patients, difficulties faced by diagnosed individuals in accessing health care due to financial constraints, failure to administer or delayed administration of screening tests due to home births, and migrations from underdeveloped countries or patients born before the introduction of the national screening program. Blood phenylalanine level is the only biomarker in the treatment

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management, and unfortunately, it may be insufficient in most patients in predicting the expected neurocognitive impairment score.[3,4]

Magnetic resonance imaging (MRI) enables observing abnormalities in patients with PKU. The typical brain MRI findings of PKU are T2-weighted hyperintense lesions, located in parieto-occipital regions.[5,6] In previous studies, it was stated that with early diagnosis and good dietary compliance, the development of white matter lesions could be prevented and even may resolve.[7-9] But recent studies based on diffusion tensor imaging (DTI) stated that even in early-diagnosed PKU patients with dietary compliance, the macroscopic and microscopic white matter damage process may persist.[10] Also, there are some PKU patients in whom no white matter changes were detected even with poor dietary compliance and late diagnosis. Therefore, there are contradictory results about the correlation between MRI findings and clinical and laboratory conditions.

For brain MRI scoring in PKU patients, Thompson[11] and modified Thompson scores[9] were developed. But they have not been well adopted and accepted in clinical practice. On the other hand, Loes[12] and modified Loes[13] scores, which were developed for the evaluation of brain involvement of adrenoleukodystrophy (ALD) and metachromatic leukodystrophy (MLD), have become fundamental in the follow-up of patients, mainly because they quantitatively indicate the level of disease involvement, are very well correlated with patient's clinical condition, and are easy to implement. Therefore, the main purpose of our study was to devise a new brain MRI scoring system based on the Loes and modified Loes scores in PKU patients.

MATERIALS AND METHODS

Settings

This study was conducted at Van Regional Training and Research Hospital, a large city in the eastern part of Turkey with a population of 1.1 million inhabitants. Our hospital served as a referral center for pediatric metabolism consultations. All patients requiring such consultations were referred to our hospital for further evaluation. Brain MRI examinations were performed on patients referred to the radiology department using our hospital's routine children's brain MRI protocol.

Study Design, Inclusion, and Exclusion Criteria

We retrospectively assessed brain MRI images of 13 patients with classical PKU who were late diagnosed. These patients were under the follow-up of our Department of Pediatric Metabolism from 2018 to 2023. The diagnosis of classical PKU was established based on blood Phe levels higher than 1200 μmol/L. Patients diagnosed between 3 months and 7 years of age are classified as late-diagnosed PKU cases, while patients diagnosed after 7 years of age are classified as untreated PKU patients. Brain MRI was performed in 5 patients to investigate the etiology of intellectual disability, in 2 patients after a loss of consciousness, and in 6 patients due to seizures or excessive aggressive behavior.

The only treatment used in our cases was phenylalanine-restricted diet therapy. As all cases were classical PKU patients, sapropterin dihydrochloride was not used. Large neutral amino acid treatment, which was recommended in suitable cases, was either declined by the families or discontinued shortly after starting due to its challenging use in cases with severe intellectual disability. Enzyme substitution therapy using phenylalanine ammonia-lyase was not used as it was not licensed in our country.

We recorded the patient's age at the time of PKU diagnosis, the age at which the diet was started, the age at MRI, and the blood Phe levels closest to the time of the MRI (the blood Phe level determined within the 2-week period before or after the MRI). Cognitive status was assessed through clinical evaluation.

Magnetic Resonance Imaging and Magnetic Resonance Imaging Scoring Protocol

All examinations were carried out using our hospital's routine brain MRI protocol on a 1.5-T MRI scanner (SIGNA Explorer, GE Healthcare, USA). Axial T2, axial T1, axial fluid-attenuated inversion recovery (FLAIR); coronal FS T2; sagittal T1-weighted images; and axial DWI sequences (b0 and b1000) were evaluated.

The PKU brain MRI evaluation score (Table 1) was designed similarly to the MRI scoring system for ALD and MLD. Normal areas were scored as 0, unilateral involvement as 1, and bilateral involvement as 2. If the T2 and FLAIR hyperintensities in the affected areas are faint, 1 point is added to the score of the affected area. If any of the hyperintensities were observed as hypointense on the T1W image, the involvement was considered severe, and 2 points were added. Since it would be difficult to distinguish unilateral or bilateral involvement of the corpus callosum and brainstem, the presence of any finding in favor of involvement was scored as 1, and the hyperintensity was scored as previously stated. The presence of cerebral and cerebellar atrophy was evaluated separately. Mild atrophy was scored as 1 and moderate atrophy was scored as 2. In the presence of an area with diffusion restriction, 2 points were added to the total score since it could be considered an active process.

Magnetic resonance imaging scans were evaluated and scored at different times by a pediatric radiologist and a metabolic diseases specialist experienced in brain MRI.

The relationship between the PKU brain MRI score and the patient's age at diagnosis, the age at which the diet was started, the age at MRI, blood Phe levels at the time point closest to the MRI, and the clinical status of the patient was evaluated.

Ethics Committee Approval

The study was performed in accordance with the ethics guidelines of the Helsinki Declaration and was approved by the Ethics Committee of Van Regional Training and Research Hospital on March 16, 2023 (Approval number: 2023/06-03).

Statistical Analysis

Data were evaluated with the IBM Statistical Package for the Social Sciences Statistics version 23.0 program (IBM Corp.; Armonk, NY, USA). Our sample size was very small, and upon examining the distribution curves, we decided that nonparametric tests would be more appropriate to apply. While evaluating the study data, descriptive statistics (mean, SD, median) were presented for numerical variables. Spearman's correlation test was used to test the relationship between numerical variables. $P < .05$ was considered for statistical significance.

Table 1. Brain MRI Scoring System for PKU (Maximum 63 Points)

Parieto-occipital WM involvement (maximum 8 points)
- Periventricular
- Central
- Subcortical
- Hyperintensity (faint/dense)

Frontal WM involvement (maximum 8 points)
- Periventricular
- Central
- Subcortical
- Hyperintensity (faint/dense)

Temporal WM involvement (maximum 8 points)
- Periventricular
- Central
- Subcortical
- Hyperintensity (faint/dense)

Corpus callosum involvement (maximum 4 points)
- Genu
- Splenium
- Hyperintensity (faint/dense)

Projection fiber involvement (maximum 6 points)
- Internal capsule posterior limb
- Internal capsule anterior limb
- Hyperintensity (faint/dense)

Thalamus involvement (maximum 4 points)
- Thalamus
- Hyperintensity (faint/dense)

Basal ganglia involvement (maximum 4 points)
- Basal ganglia
- Hyperintensity (faint/dense)

Auditory pathways involvement (maximum 4 points)
- Auditory pathways
- Hyperintensity (faint/dense)

Visual pathway involvement (maximum 4 points)
- Visual pathways
- Hyperintensity (faint/dense)

Brainstem involvement (maximum 3 points)
- Brainstem
- Hyperintensity (faint/dense)

Cerebellum involvement (maximum 4 points)
- Cerebellum
- Hyperintensity (faint/dense)

Atrophy (mild/moderate) (maximum 4 points)
- Cerebral atrophy
- Cerebellar atrophy

Diffusion restriction (maximum 2 points)

RESULTS

Patient Characteristics and Clinical Findings

Two patients were excluded from the study due to excessive movement artifacts that hindered the evaluation of brain MRIs. Eleven patients whose images were suitable for evaluation were included in the study. Four of the patients were male, and 7 of them were female. The age of the patients ranged from 3 to 28, with a median of 16 years and IQR = 11.5. All patients were late diagnosed (after the third month) PKU patients. All our patients required close supervision and assistance with self-care activities. They exhibited very limited communication abilities and had difficulty understanding even simple commands, consistent with severe intellectual disability.

At the MRI time point, 8 patients were under treatment (diet), while 3 patients were not receiving any treatment due to treatment incompatibility or newly diagnosis (untreated). The patients who were on dietary treatment had started the treatment between the ages of 9 months and 6 years. The mean blood Phe level at the time point closest to the imaging was 1303 μmol/L (240-3060 ± 486), with a median of 1320 μmol/L. Demographics, clinical, and laboratory characteristics of patients are presented in Table 2.

Magnetic Resonance Imaging Findings

The mean MRI involvement score of the patients was 11.9. The highest score was 33, while the lowest was 0 (patient no. 3). The most commonly involved white matter areas were the parie to-occipital—which were involved in 9 of 11 (81%)—and frontal (63%) areas. Temporal white matter involvement was less common (54%). There was diffusion restriction in the images of 7 (63%) patients. Mild cerebral atrophy was observed in 4 (36%) patients. Cerebellar involvement was present in 3 (27%) patients. Corpus callosum and brain stem involvement were observed in 2 (18%) patients. Basal ganglia involvement was present in 1 patient (9%). The thalamus and projection fibers were not involved in our patients. The detailed MRI scores of the patients are presented in Table 3.

Correlation Analysis

There was a significant and moderate–strong correlation between the blood phenylalanine level at the time point closest to the MRI and the MRI involvement score (rho = .611, $P = .046$). A graph illustrating the MRI involvement scores plotted against Blood Phe levels at the time point closest to the MRI was presented as Figure 1. However, there was no significant correlation between the age at the MRI, the age at which the treatment was begun, and MRI involvement scores. An analysis showing

Table 2. Demographics, Clinical, and Laboratory Characteristics of Patients

Patient No.	Gender	Age at Which the Diet Was Started (years)	Age at MRI (years)	Blood Phe Levels at the Time Point Closest to the MRI (μmol/L)	Neurological Findings*
1	M	1	13	960	None
2	F	2	4	1620	Seizure, ataxia
3	F	4	17	1380	Seizure, ataxia
4	M	0.75	15	1320	None
5	F	6	28	480	Seizure
6	F	2	24	240	Ataxia
7	F	4	22	1020	Ataxia
8	M	Untreated	19	3060	Seizure, aggressive behavior
9	F	Untreated	3	1320	Ataxia
10	M	0.75	10	1140	Tremor
11	F	Untreated	16	1800	Seizure, ataxia, aggressive behavior

F, female; M, male; MRI, magnetic resonance imaging.
*All patients had severe intellectual disabilities.

the correlation between MRI scoring and the severity of intellectual disability could not be performed due to the presence of severe intellectual disability in all patients; they were all in a similar status.

DISCUSSION

Although some studies have suggested limited clinical contributions of brain imaging in PKU patients, the physiopathology and mechanisms underlying white matter damage and the MRI involvement pattern have not been fully elucidated. Therefore, neuroimaging remains an area of interest that requires further investigation. Our aim was to develop a scoring system that could be integrated into the standard MRI protocol and utilized by both radiologists and clinicians for PKU patients. We think that our scoring system, based on the Loes and modified Loes scores and adapted to PKU, will be useful in clinical practice.

The previously developed Thompson[11] and modified Thompson scores for PKU patients have certain limitations. The main limitation of the Thompson scoring system is that it assumes that lesions associated with PKU involvement mostly exhibit a parieto-occipital distribution. Additionally, the system employs a scoring method based on visual percentages, which can introduce errors due to its subjectivity, unless actual volume measurements are conducted. Furthermore, studies have indicated that the corpus callosum and other parts of cerebrum can be affected at different disease stages, including the early ones. These factors pose challenges to the practical implementation of the scoring system. Although the modified Thompson scoring system incorporates the involvement of other lobes and diffusion restrictions in its classification, it only assigns scores for the severity of involvement in the periventricular areas, relying once again on a highly subjective evaluation method using percentages. Additionally, despite studies frequently reporting the involvement of basal ganglia, brainstem, and visual pathways in the disease, both classification systems have overlooked these aspects. Therefore, to surpass the limitations of these 2 scoring systems, all lobes of the brain, as well as visual and auditory pathways, brainstem, and basal ganglia, are included in the involvement score. Additionally, the involvement of white matter is not limited to the periventricular area alone; the central white matter and subcortical U fibers' involvement is also evaluated. Furthermore, the presence of cerebral and cerebellar atrophy, which could serve as an indicator of long-term treatment compliance, is also incorporated into the scoring system.

Although the size of our study population was small, our MRI involvement score showed a significant correlation with the blood Phe level of the patients at the time of MRI. We think that this correlation may be an indicator that our scoring system may be valid, since blood Phe levels are the best biomarker we currently have for Phe monitoring. A similar correlation between Phe level at the time of MRI and the severity of white matter involvement has been reported in many studies as well as in the study by Thompson et al[11] in 1993, and it is another indicator of the applicability of our scoring system to the clinical practice.[7,9,14,15] We detected diffusion restriction in 7 out of 11 patients, indicating that there is an active metabolic process in these areas and supporting the findings of previous studies.[5,7,9,16-18] On the other hand, the presence of signal changes in T2 and FLAIR sequences despite the absence of restriction in the diffusion sequence in 4 patients reveals the importance of evaluating the MRI scans of the patients together with other conventional sequences. Therefore, we think that conventional sequences and diffusion sequences should be considered together in the scoring or evaluation process.

In our patients, the parieto-occipital regions were the most affected areas, and the frontal and temporal regions were less involved, supporting the findings of previous studies.[5,6,17,18] In all patients in whom frontal and temporal areas were involved, parieto-occipital areas were more severely affected. Since parieto-occipital areas were affected in most of the patients, we thought that those areas might be the early involved areas. Although it was mentioned in the literature, basal ganglia and projection fibers were not involved in our patients, which may be related to the low number of our patients.

On the other hand, despite the severe cognitive impairment in all patients, the involvement of the areas corresponding to the superior longitudinal fasciculus, which plays an important role in verbal, cognitive, and cognitive functions, was present in only a few of the patients, contrary to what we expected. The corpus callosum, which plays an important role in the transmission of

Table 3. Detailed Brain MRI Scores of the Patients

		Patients										
		Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**	**Patient 7**	**Patient 8**	**Patient 9**	**Patient 10**	**Patient 11**
Parieto-occipital WM	PV	2	2		2	2		2	2	2	2	2
	Central		2		2			2	2		2	2
	U fibers											2
	Hyperintensity: faint /dense	1	2		2	1		2	2	1	2	2
Frontal WM	PV		2		2			2	2	2	2	2
	Central		2								2	2
	U fibers											2
	Hyperintensity: faint /dense		2		2			1	2	1	2	2
Temporal WM	PV		2		2			2	2		2	2
	Central											
	U fibers											2
	Hyperintensity: faint /dense		2		2			1	2		1	2
Corpus callosum	Genu											1
	Splenium										1	1
	Hyperintensity: faint /dense										2	2
Projection fibers	İnternal capsule posterior limb											
	İnternal capsule anterior limb											
	Hyperintensity: faint /dense											
Thalamus	Thalamus											
	Hyperintensity: faint /dense											
Basal ganglia	Basal ganglia									2		
	Hyperintensity: faint /dense									2		
Brainstem involvement	Brainstem involvement		1							1		
	Hyperintensity: faint /Dense		1							1		
Cerebellar involvement	Cerebellar involvement		1							2		2
	Hyperintensity: faint /dense		1							1		1
Auditory pathways	Auditory pathways											
	Hyperintensity: faint /dense											
Visual pathways	Visual involvement											
	Hyperintensity: faint /dense											
Atrophy	Cerebral atrophy						1	1	1			1
	Cerebellar atrophy											1
Diffusion restriction			2		2			2	2	2	2	2
Total score		3	22	0	16	3	1	15	17	17	20	33

PV, periventricular; WM, white matter.

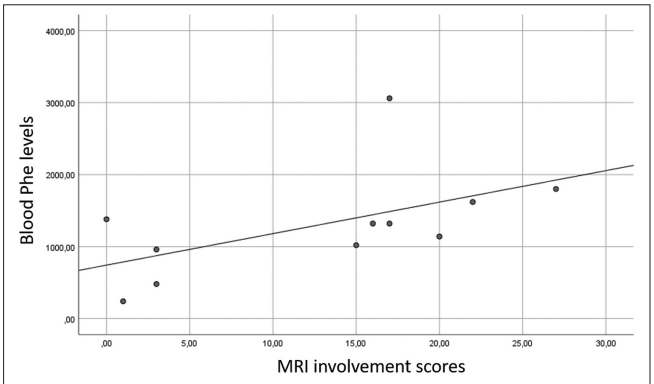

Figure 1. A graph plotting the MRI involvement scores against blood Phe levels at the time point closest to the MRI (μmol/L).

interhemispheric information such as reading and calculation, was involved in only 2 patients.

It is very interesting that 17-year-old patient no. 3, who was diagnosed late and started the diet at the age of 4 years, with poor dietary compliance and high blood Phe levels at the time of MRI (1380 μmol/L), had completely normal brain MRI. It is obvious that this finding cannot be explained by the high dietary compliance or low blood Phe levels as suggested in previous studies. Literature also contains several untreated cases with normal cranial MRI findings, and a comprehensive investigation of this phenomenon is warranted.[19-21] There are studies claiming that the relationship between blood Phe level and brain Phe level is not always linear, and changes in the interpersonal permeability of the LAT1 (large neutral amino acid transporter type 1) protein, which plays an important role in the transfer of Phe to the brain, may be another reason for the absence of any findings in MRI.[3,11,22] Undoubtedly, differences in genetic mutations may also contribute to the explanation of this situation.

Also, we noticed that there is an inconsistency between dietary compliance, the age at diagnosis, neurocognitive skills, and lesion loads in MRI in general (Figures 2 and 3). For example, patient no. 5 and patient no. 6 were 28 and 24 years old, respectively, were diagnosed late, and had severe intellectual disabilities; they had lower blood Phe levels at the time point closest to the MRI, and the MRI involvement score was also low (3 and 1, respectively). This finding can be explained by studies indicating that MRI lesions may be reversible with treatment management; however, although lesions detected in MRI may be reversible, it is clinically obvious that the neurocognitive effect is permanent. Also, data from many studies are unfortunately inconsistent and support that the brain involvement process of the disease in question is multicomponent and complex.

There are some important limitations to our study. The first limitation is the relatively small number of patients. However, considering that most studies nowadays focus on patients with an early diagnosis of PKU, we found it appropriate to share the data of a relatively homogeneous group of patients with late diagnosis and no treatment. Moreover, since the main purpose of our study is to create a new scoring system, we think that we have correctly defined the expected involvement areas considering existing literature data. The second limitation of our study is that we could not apply advanced MRI examination methods such as MRI spectroscopy or DTI. We think that these techniques may provide additional contributions to the process of understanding the brain disease of PKU in the future. Another limitation of our study is that lifetime median Phe levels were not included. Long-term Phe levels are undoubtedly crucial indicators for cognitive and other systemic impairments

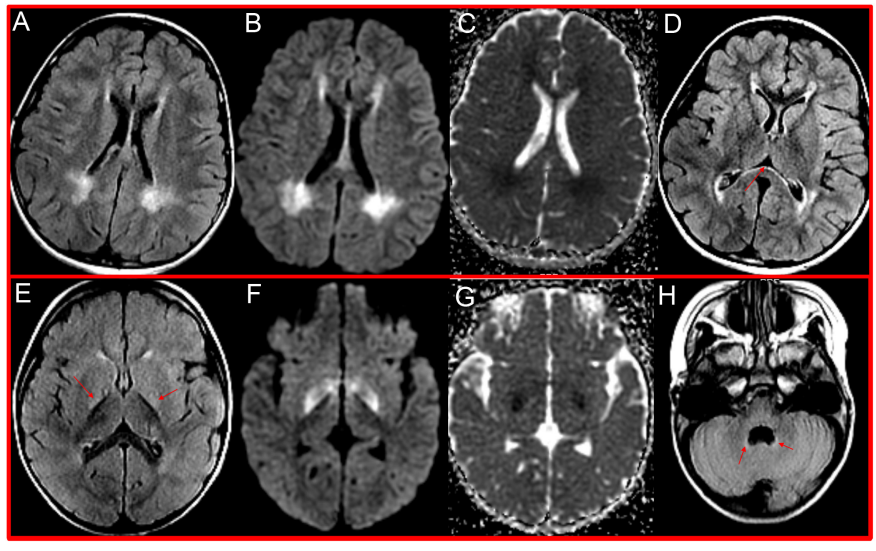

Figure 2. Upper row: 10-year-old, late-diagnosed, intellectually disabled patient with PKU, under treatment (patient number 10). Axial FLAIR (A) and matching DWI (B) and ADC (C) images show increased signal intensity in bilateral parieto-occipital and frontal regions, along with corresponding diffusion restriction. Additionally, a thin linear signal intensity (red arrow) is observed in the splenium of the corpus callosum on D. Lower row: 3-year-old, late-diagnosed, untreated intellectually disabled patient with PKU (patient number 9). Axial FLAIR (E) and matching DWI (F) and ADC (G) images reveal increased signal intensity and restricted diffusion in both globus pallidus. Increased signal intensities near the fourth ventricle are indicated by the red arrows in H. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; PKU, phenylketonuria.

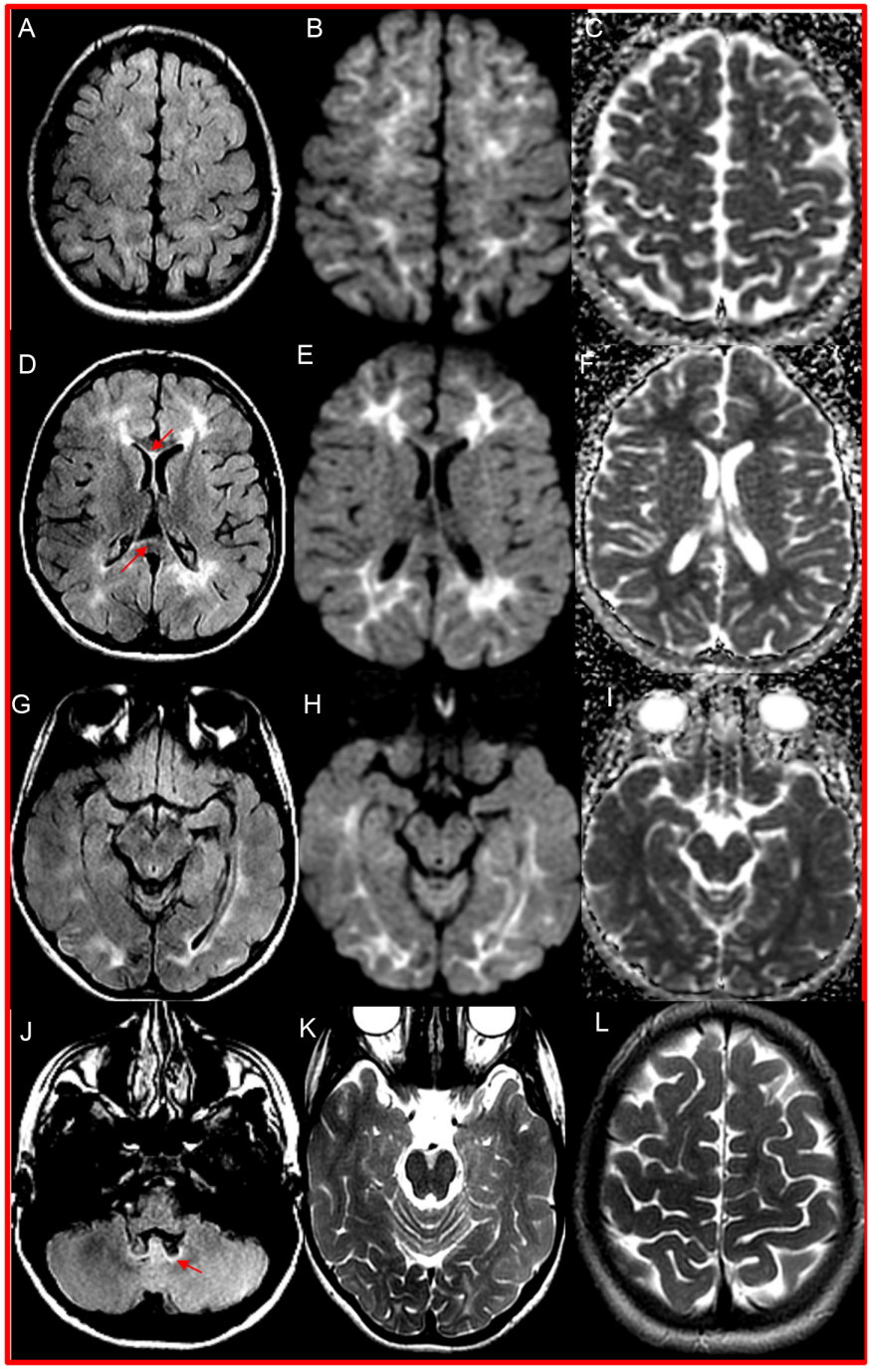

Figure 3. Magnetic resonance imaging of 16-year-old, late-diagnosed, untreated, and intellectually disabled patient with PKU (patient no. 11). Axial FLAIR (A D, G) MRI shows increased signal intensity in the frontal, parietal, occipital, and temporal white matter, also genu and splenium of the corpus callosum (D, red arrows). Matching axial plane DWI (B, E, H) and ADC (C, F, I) maps show restricted diffusion in the corresponding areas. Increased signal intensity on the axial plane FLAIR image (J) is seen in the cerebellum near the fourth ventricle (red arrow). Axial T2W images from the posterior fossa (K) and vertex (L) show slightly enlarged cerebellar folia and cerebral sulci and fissures due to mild cerebellar and cerebral atrophy. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; PKU, phenylketonuria; T2W, T2-weighted.

in PKU patients. Additionally, the atrophy assessment included in the scoring system is also associated with long-term Phe control. Unfortunately, all the included cases in the study were individuals who received late diagnosis or were untreated and living in low socioeconomic areas, remote villages, and districts far from the city. Regular follow-up for these individuals with severe cognitive impairment could not be conducted, and some of them made only 2 or 3 visits to the hospital. Therefore, long-term Phe levels, which could have significant clinical relevance, could not be included in the study. The lack of interobserver and intraobserver agreement could be another limitation. Due to the very small number of patients and our ability to remember the cases even with a time interval of up to 6 months, we did not assess intraobserver agreement. Since the study was

designed retrospectively, the clinical evaluation of the involvement of auditory and visual systems could not performed. However, it would have been useful to assess whether there was any clinical impact, considering that none of the pathways in question showed any signs of involvement on MRI. The last limitation of our study is that the patients were examined only once. Since it was stated in some studies that the lesions might be reversible, imaging could be beneficial after adopting an appropriate treatment approach in patients that can adapt. However, since all patients had severe intellectual disability and MRIs were performed under sedation, we think that this is a reasonable limitation.

CONCLUSION

In conclusion, our study provides insights into MRI findings and scoring systems in PKU patients. We have developed a scoring system based on the widely used Loes and modified Loes scoring systems that can be implemented in clinical practice. Also, our study contributes to the long-forgotten and largely abandoned area-imaging findings in late diagnosed and untreated PKU patients and sets the stage for future research in this field.

Ethics Committee Approval: The study was performed in accordance with the ethics guidelines of the Helsinki Declaration and was approved by the Van Regional Training and Research Hospital's Ethics Committee on March 16, 2023 (Approval no.: 2023/06-03).

Informed Consent: Informed written consent was obtained from all subjects' legal guardians.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – D.B., K.Ç.; Design – K.Ç., D.B.; Data Collection and Processing – D.B., K.Ç.; Analysis and Interpretation – K.Ç., D.B.; Literature Search – D.B., K.Ç.; Writing – K.Ç., D.B.

Declaration of Interests: The authors have no conflict of interest to declare.

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