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The Role of Diffusion Tensor Magnetic Resonance Imaging in Understanding Neurological and Ocular Outcomes in Preterm Infants with Periventricular Leukomalacia

Periventriküler Lökomalazili Prematüre İnfantlarda Nörolojik ve Oküler Sonuçların Değerlendirilmesinde Difüzyon Tensor Manyetik Rezonans Görüntülemenin Rolü

Yıldız EKEMEN KELEŞ[1], Elif DEMİRKILINÇ BİLER[2], Filiz AFRASHİ[2], Mehmet Cem ÇALLI[3], Mehmet YALAZ[4], Sema TANRIVERDİ[5], Sanem YILMAZ[6], Gül AKTAN[6], Sarenur GÖKBEN[6]

[1]Çiğli Training and Research Hospital, Clinic of Pediatric Infectious Diseases, İzmir, Türkiye
[2]Ege University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
[3]Ege University Faculty of Medicine, Department of Radiology, İzmir, Türkiye
[4]Ege University Faculty of Medicine, Department of Neonatology, İzmir, Türkiye
[5]Manisa Celal Bayar University Faculty of Medicine, Department of Neonatology, Manisa, Türkiye
[6]Ege University Faculty of Medicine, Department of Pediatric Neurology, İzmir, Türkiye

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ABSTRACT

Objective: This study aimed to compare neurological and ophthalmological findings with diffusion tensor magnetic resonance imaging (DTMRI) results in patients with periventricular leukomalacia (PVL).

Methods: This prospective study included 24 premature infants with PVL diagnosed by cranial ultrasonography (USG) or magnetic resonance imaging (MRI). Neurological and comprehensive ophthalmological evaluations were conducted at 3, 6, and 12 months of corrected age. MRI was performed on a 3-Tesla scanner, and DTMRI data were analyzed for fractional anisotropy (FA) and other diffusion parameters. Statistical analyses were performed using SPSS software, with $p<0.05$ considered significant.

Results: Our study included 11 preterm patients with PVL, of whom 72.7% developed cerebral palsy (CP) by 6 months' corrected age. Cranial USG detected PVL in 63.3% of patients, whereas MRI identified PVL of varying severity: mild (54.5%), moderate (18.2%), and severe (27.3%). Neurological examinations revealed increased muscle tone and brisk deep tendon reflexes (DTRs), findings consistent with early indicators of CP. Ophthalmologic assessments indicated normal light fixation and tracking in most patients, though visual evoked potentials (VEPs) revealed abnormalities in 63.6% of patients. In the DTMRI results, right optic tract, FA values were found to be significantly lower in the patient group compared to the control group ($p=0.010$).

Conclusion: Early neurological signs, such as increased muscle tone and brisk DTRs, are predictive of subsequent CP. Despite improvements in visual tracking, VEP abnormalities highlight the need for comprehensive neuro-ophthalmological evaluations in preterm infants. DTMRI provides valuable insights into white matter microstructure and may help predict neurological and ophthalmological outcomes in infants with PVL.

Keywords: Periventricular leukomalacia, premature, cerebral visual impairment, visual evoked potentials, diffusion tensor magnetic resonance imaging

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Corresponding Author/ Sorumlu Yazar:
Yıldız EKEMEN KELEŞ, MD,
Çiğli Training and Research Hospital, Clinic of Pediatric Infectious Diseases, İzmir, Türkiye
✉ kutupylz@hotmail.com
ORCID: 0000-0002-6122-1726

ÖZ

Amaç: Bu çalışma, periventriküler lökomalazili (PVL) hastalarda nörolojik ve oftalmolojik bulguların difüzyon tensor manyetik rezonans görüntüleme (DTMRG) sonuçlarıyla karşılaştırılmasını amaçlamıştır.

Yöntem: Prospektif olarak yürütülen bu çalışmaya, kranial ultrasonografi (USG) veya manyetik rezonans görüntüleme (MRG) ile PVL tanısı konulan 24 prematüre bebek dahil edilmiştir. Nörolojik ve kapsamlı oftalmolojik değerlendirmeler düzeltilmiş yaşın 3., 6. ve 12. aylarında yapılmıştır. Görüntülemeler 3 Tesla cihazla gerçekleştirilmiş, DTMRG verileri fraksiyonel anizotropi (FA) ve diğer difüzyon parametreleri açısından analiz edilmiştir. İstatistiksel analizler SPSS yazılımı kullanılarak yapılmış, p<0,05 değeri anlamlı kabul edilmiştir.

Bulgular: Çalışmaya dahil edilen 11 prematüre PVL tanılı hastanın %72,7'sinde düzeltilmiş altıncı ayda serebral palsi (SP) gelişmiştir. Kranial USG ile PVL olgularının %63,3'ünde saptanırken, MRG bulgularına göre hastaların %54,5'i hafif, %18,2'si orta, %27,3'ü ağır düzeyde PVL saptanmıştır. Nörolojik muayenelerde artmış kas tonusu ve canlı derin tendon refleksleri (DTR) erken SP göstergeleriyle uyumlu bulunmuştur. Oftalmolojik değerlendirmelerde çoğu olguda ışık fiksasyonu ve takibi normal olmasına rağmen, görsel uyarılmış potansiyellerin (VEPs) %63,6'sında anormallikler saptanmıştır. DTMRG analizinde hasta grubunda sağ optik trakt FA değerleri kontrol grubuna göre anlamlı derecede düşük bulunmuştur (p=0,010).

Sonuç: Erken dönemde saptanan artmış kas tonusu ve canlı DTR gibi nörolojik bulgular ileride gelişebilecek SP için öngörücü olabilir. Oftalmolojik anormal bulgular izlemde düzelmesine rağmen devam eden VEP anormallikleri, prematüre bebeklerde kapsamlı nöro-oftalmolojik değerlendirmenin gerekliliğini vurgulamaktadır. Difüzyon tensor MRG görüntüleme, PVL'ye eşlik eden motor ve duysal bozuklukların patofizyolojisini anlamada değerli bilgiler sunmaktadır.

Anahtar Kelimeler: Periventriküler lökomalazi, prematüre, serebral görme bozukluğu, görsel uyarılmış potansiyeller, difüzyon tensor manyetik rezonans görüntüleme

INTRODUCTION

Periventricular leukomalacia (PVL) is a condition characterized by ischemic injury to the white matter, especially in premature infants. It is the leading cause of cerebral palsy (CP) in preterm infants.[1] Today, the incidence of PVL is increasing in parallel with the survival rates of premature infants.[2] With the development of more sensitive imaging techniques, such as magnetic resonance imaging (MRI), the detection rate of PVL has increased. Despite these advances, not all cases can be detected by conventional radiological examinations. Some cases can be diagnosed at school age, when they cause neurocognitive and behavioral problems.[3] The pathogenesis of PVL remains unclear, though ischemia, hypoperfusion, and hypoxia are considered key initiating factors leading to oligodendrocyte precursor cell damage, axonal injury, and necrosis. Damage occurs in areas reperfused after ischemia. Destruction of oligodendrocyte precursor cells in the periventricular area leads to axonal damage and necrosis.[4]

The consequences of PVL can vary significantly; ocular problems are frequently encountered in affected infants because the periventricular area is adjacent to the optic nerve fibers.[5] The consequences of PVL may range from severe cerebral visual impairment (CVI) accompanied by CP to milder conditions such as strabismus and learning disabilities.[5,6] Visual acuity in patients with CVI due to damage to the periventricular areas or to generalized hypoxic encephalopathy can vary widely. This condition has become the leading non-ocular cause of visual impairment in the developed world.[7] Although visual acuity is often reduced, it can range from no light perception to 20/20 vision, with some individuals exhibiting symptoms solely attributable to CVI.[6]

In the past, early-stage PVL was diagnosed based on repeated neurological evaluations. Today, MRI can still be used to diagnose PVL before clinical findings are fully developed.[8,9] It can provide information about PVL stage and neuromotor status by assessing lateral ventricular volume, white matter volume loss, and myelination status. However, the fact that clinical findings in affected patients do not always correspond to imaging results constitutes a limitation of this technique.[8,9]

Diffusion tensor imaging (DTI) is a recently developed technique that reveals the microstructural integrity of the brain by imaging the motion of water molecules.[10,11] In white matter, the movement of water molecules varies with axonal structure and myelination status.[10] Water molecules move along the axon. Thus, the localization and spread of tracts can be visualized. Objective data from DTI can be obtained as the apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial diffusion [(AD), parallel to white matter fibers], and radial diffusion [(RD), perpendicular to white matter fibers].[12] The FA value varies with axonal myelination, orientation, number, density, and other cellular components.[13] In studies of newborns, increased FA and decreased ADC and RD values are observed with increasing age, myelination, and axonal growth. Increased myelin production reduces water diffusion and ADC values. In addition, increased axon diameter and greater longitudinal movement of water molecules along the axon will increase FA.[12] Decreased FA values and increased ADC values are observed in white matter damage.[12,14] This technique has recently been used, especially in cases of PVL, and has provided more detailed information about the extent of brain damage.[8,11,15,16]

This study aimed to compare neurological and ophthalmological findings with DTI findings in patients

with PVL and to investigate whether DTI findings contribute to these patients' neurological and ophthalmological prognoses.

METHODS

In this prospective study, patients with a diagnosis of PVL who were evaluated at three months of age or younger were enrolled. The study was conducted at Ege University Hospital. Demographic data, gestational age, gender, birth weight, history of birth asphyxia or chorioamnionitis, the need for and duration of mechanical ventilation, history of sepsis, and maternal age were collected from all participants.

Inclusion criteria encompassed the detection of PVL via cranial ultrasonography (USG) and/or cranial MRI; the presence or absence of Grade 1 intraventricular hemorrhage (IVH); and stage 1 premature retinopathy (ROP). Exclusion criteria included Grade 2 or higher IVH, stages 2-3 ROP, optic nerve atrophy, severe refractive errors, significant genetic or cardiac anomalies, neurometabolic disorders, hydrocephalus, and a ventriculoperitoneal shunt.

A total of 24 patients with a corrected age of 3 months or less and PVL detected on cranial USG and/or cranial MRI were included in the study. Five patients were excluded from the study because stages 2-3 ROP was detected. Four patients who did not return for follow-up and two who relocated to other cities were excluded from the study. Two patients with PVL detected on USG were excluded from the study because their cranial MRI and neurological examinations were normal. The study included eleven patients.

The study received ethical approval from the Ege University Clinical Research Ethics Committee (decision number: 12-11.1/9, date: 27.12.2012). Participation was contingent on obtaining informed consent from the patients' parents.

Neurological Evaluation

The same physicians conducted neurological examinations at three and six months of corrected age. Evaluations included assessments of newborn reflexes, cranial nerve function, light and sound responses (opticofacial reflex and acoustic facial reflexes), gross motor function, and psychomotor development.

Ophthalmological Examination

The same physician performed a thorough ophthalmological evaluation at the third, fifth, and sixth months of corrected age. In four patients (patient nos. 1, 3, 4, 5), eye examinations were repeated at the twelfth month. The evaluations included cycloplegic refractive error assessment, oculomotor status (strabismus assessment), anterior segment and fundus examinations, and flash VEP recordings. Flash VEP responses were analyzed for amplitude, latency, and configuration, with interpretation based on our institution's typical values for the same age group. Given that the development of visual fixation and object tracking typically occurs by six months of age, examinations were targeted for this time frame.[17]

Radiological Techniques

Cranial USG was performed on all participants during the neonatal period. Cranial MRI was performed if USG detected PVL or if any suspicious findings appeared before three months of corrected age. Only one patient, a twin whose sibling had a PVL diagnosis, did not undergo an MRI. In addition to early MRI, a second cranial MRI was performed as part of the study protocol at 6 months corrected age, and DTI acquisition, allowing both structural PVL grading and microstructural diffusion assessment at the same time point. All 6-month MRI and DTI scans were acquired with a 3 Tesla MRI scanner (Siemens Magnetom Verio 3 Tesla MRI and 16-channel head coil), 30 minutes post-sedation. The radiological images were assessed by a single neuroradiologist blinded to patient identities, using the Flodmark criteria for grading PVL.[18] DTI data were evaluated on diffusion-weighted images using FSL software and eddy-current correction. Color-coded maps were prepared using twenty-four directions. FA was performed semi-automatically with the tract-based spatial statistics (TBSS) method by the same operator, blinded to the patients. FA values of all vectors of the determined neuronal fibers were evaluated for both hemispheres. Images containing FA values were arranged until they reached a standard space of 1 x 1 x 1 mm^3. The average FA value and its skeleton were created. All images containing the arranged FA value were transferred to the skeleton. The average threshold value was 0.2. In this way, the results were purified from the diversity in the peripheral neuronal fibers in the cases and the partial effect of the gray matter. A voxel-based statistical analysis was conducted to compare FA, AD, RD, and ADC values between the patient and control groups.

The DTI free-hand region-of-interest (ROI) method was used to determine the patients' FA values from the images, and a single radiologist, blinded to clinical information, manually delineated the ROIs for each patient. FA values were measured in the genu and splenium of the corpus callosum, the right and left internal capsules, the right optic tract, and multiple regions of the left optic tract. They were calculated by averaging the values.

Control Group Imaging Protocol

Seven infants were included in the control group. All control patients underwent cranial MRI, diffusion MRI, and DTI at a corrected age of 6 months for clinical indications (including

nystagmus, macrocephaly, microcephaly, epilepsy, or widespread cutaneous hemangiomas); therefore, no healthy infants were imaged solely for research purposes. MRI and DTI acquisitions in both the PVL and control groups were performed on the same scanner (Siemens Magnetom Verio 3T), using identical parameters (b-value =1000 s/mm², 24 diffusion directions, voxel size of 1 × 1 × 1 mm³, standard EPI sequence, identical scan duration) and the same sedation protocol. Imaging was evaluated by the same neuroradiologist, who was blinded to group allocation. Gestational age and corrected age at the time of imaging were matched between groups.

Statistical Analysis

Descriptive statistics for continuous variables were reported as means or medians, depending on the data distribution. Categorical variables were presented as counts and percentages. Depending on sample size and variable distribution, the chi-square test or Fisher's exact test was applied to compare categorical variables. A p value of less than 0.05 was deemed statistically significant. Statistical analyses were conducted using SPSS version 15.

RESULTS

Patient's Demographics

The gestational ages of the 11 patients with PVL ranged from 26 to 34 weeks, with a mean gestational age of 30.9±3.0 weeks; seven were boys (63.6%). The mean birth weight of the patients was 1727±718 g (range, 830-2790 g). When the patients were evaluated according to their gestational weeks, three patients were detected between 26 and 28 weeks, three cases were detected between 28 and 32 weeks, and five cases were detected between 32 and 34 weeks (Table 1).

Cranial USG was performed on each patient during their intensive care stay. PVL was detected on cranial USG in seven patients (63.3%). Cranial MRI was performed on all patients, except one, before their corrected age of 3 months. The only case without cranial MRI (patient no. 4) was the twin of case no. 3, and since case no. 3 had PVL confirmed by MRI, only cranial USG was performed on this patient.

Neurological Examination

Neurological and developmental assessments of the patients were performed at corrected ages of 3 and 6 months (Table 2). All patients exhibited social smiles; only patients 5 and 8 lacked head control. Increased muscle tone was detected in the third month, except for two patients (patient nos. 10 and 11), and brisk deep-tendon reflexes (DTRs) were detected in the lower extremities, except for three patients (patient nos. 1, 2, and 7).

At a corrected age of six months, neurological examinations revealed spastic CP in eight patients (72.7%) (Table 2). In addition, five of the patients with CP (62.5%) had spastic diparesis, while three (37.5%) had spastic tetraparesis. Regarding psychomotor development, eight patients rolled over. However, they were not acquired in two patients (patients nos. 8 and 10) and were partially acquired in one patient (patient no. 3). Supported sitting was acquired by all but five patients by the sixth month.

Radiological Examination

Cranial MRI revealed mild PVL in six patients (54.5%), moderate PVL in two patients (18.1%), and severe PVL in three patients (27.2%) (Table 2, Figure 1). The DTI results

Table 1. Perinatal and postnatal characteristics of the patients

Patient number	Gender	Birth week	Birth weight*	Perinatal asphyxia	Chorioamnionitis	Need for MV	Number of days of ICU stay	History of septicemia
1	Boy	32	830	-	-	+	64	+
2	Girl	33	1850	-	-	+	17	-
3	Boy	33	2140	+	-	+	18	-
4	Boy	33	2240	-	-	-	10	-
5	Boy	33	2500	+	-	+	8	-
6	Boy	26	900	-	-	+	72	+
7	Boy	27	1160	+	-	+	90	+
8	Girl	32	1320	-	-	+	21	+
9	Girl	34	2790	-	-	-	9	-
10	Boy	26	930	-	+	+	38	+
11	Girl	31	2340	-	-	+	42	-

*Gram
MV: Mechanical ventilation, ICU: Intensive care unit

Table 2. Comparison of psychomotor development at three and six months and cranial magnetic resonance imaging results at six months of patients

Patient no	Third month				Sixth month			
	Head control	Social smile	Muscle tone	DTR	Rolling over	Supported sitting	Neurological examination	PVL grade on cranial MRI
1	+	+	Inc (LE)	Normal	+	-	Spastic diparesis with right Achilles contracture	Moderate
2	+	+	Inc (LE)	Normal	+	+	Normal	Mild
3	± (5. mo)	+ (5. mo)	Spastic tetraparesis		±	-	Spastic tetraparesis	Severe
4	+ (5. mo)	+ (5. mo)	Inc	Brisk (LE)	+	+	Spastic diparesis	Mild
5	-	+	Inc	Brisk (LE)	+	-	Spastic diparesis, right extremity was more affected	Moderate
6	+	+	Inc	Brisk (LE)	+	+	Spastik diparesis	Mild
7	+	+	Inc	Normal	+	+	Normal	Mild
8	-	+	Inc	Brisk (right LE)	-	-	Spastic tetraparesis, right extremity was more affected	Severe
9	+	+	Inc	Brisk (LE)	+	+	Spastic diparesis	Mild
10	+	+	Normal	Brisk (LE)	-	-	Spastic tetraparesis, left extremity more affected	Severe
11	+	+	Normal	Brisk (LE)	+	+	Normal	Mild

DTR: Deep tendon reflex, PVL: Periventricular leukomalacia, MRI: Magnetic resonance imaging, Inc: Increase, LE: Lower extremity, mo: Month

of the patients at six months were evaluated using TBSS and freehand ROI methods. The TBSS method found no statistically significant differences between the FA, AD, RD, and ADC values in the whole white matter between the patient and control groups (p>0.05), as shown in Figure 2. The average FA values of the patients, calculated using the free-hand ROI method, are given in Table 3 (shown in Figure 3). Right optic tract FA values were significantly lower in the patient group compared with the control group (p=0.010). Mean right optic tract FA was 0.244±0.98 in patients and 0.42±0.32 in controls. No statistically significant differences were found in FA values of the genu and splenium of the corpus callosum, right internal capsule, left internal capsule, and left optic tracts between the two groups (p>0.05).

Ophthalmologic Examination

Ophthalmologic evaluation was performed in seven cases at the corrected age of three months. One patient had no fixation to light. Only three patients were able to track objects. At the corrected age of 6 months, all patients demonstrated light fixation, light tracking, and object tracking, except patient 3, who showed none of these (Table 4). The optic discs were pale, and the patient had cortical blindness. Flash VEP results were normal in four patients; prolonged latencies were detected in five patients, decreased amplitude in one patient, and wave pattern disorder in four patients.

DISCUSSION

Normal cerebral blood flow is crucial for brain development, and even minor stress during the prenatal and perinatal periods can disrupt this flow, leading to cerebral ischemia and the formation of free oxygen radicals.[19] Consequently, many infants who survive hypoxic-ischemic encephalopathy develop sequelae; with approximately 90% experience spasticity and minor neurological impairments (4). In our study, we found CP in 72.7% of preterm infants. The literature reports CP rates resulting from PVL ranging from 60% to 100%.[20,21] While CP may not be clinically evident in patients with PVL, perceptual and behavioral issues can emerge during the school-age years.[22]

Although a combination of clinical history, standardized neuromotor assessment, and MRI findings can identify, at an early age, infants with CP and those at risk of developing CP, in clinical practice CP is diagnosed more accurately by age 2.[23]

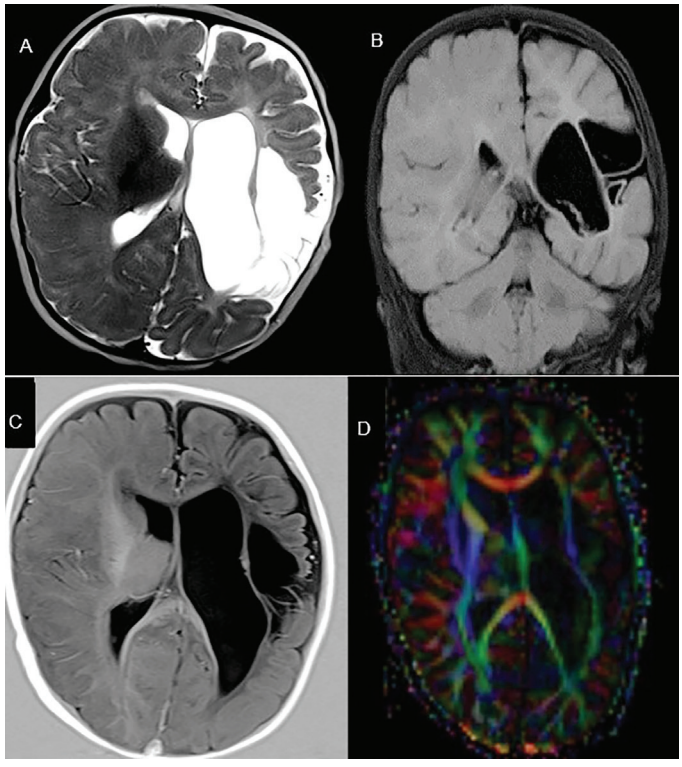

Figure 1. Magnetic resonance imaging of patient number eight. A) Severe periventricular leukomalacia on the left in T2 axial imaging. Retraction and dilatation in the same ventricle. Marked tissue loss in the cortex and white matter. Encephalomalacia area and porencephalic cyst. B) Coronal FLAIR C) T1 axial image. D) Color-code fractional anisotropy map. Red indicates transverse (x-axis), green indicates anterior-posterior (y-axis), and blue indicates superior-inferior (z-axis) direction

In newborns with CP, only brisk DTRs and increased muscle tone are detected on neurological examination.[24] In our study, neurological evaluations of patients at the corrected age of three months revealed increased muscle tone in 81% of patients and brisk DTR in 72%. Additionally, 27% of patients exhibited changes in muscle tone or DTR at three months, which resolved by six months; mild PVL was observed on MRI. At 3 months, 75% of those with CP showed increased muscle tone and brisk DTRs. These clinical findings are significant for early CP development.

Serial cranial USG provides essential information about the preterm infant's overt brain injury and how it changes over time.[25] Cranial USG is safe, relatively inexpensive, and readily available at the bedside for serial imaging of brain injury and its evolution.[15,25] In our study, cranial USG detected PVL in 63.3% of patients during their stay in the intensive care unit. Among the eight infants who developed CP, PVL was detected on cranial USG in five (62.5%). The positive predictive value of USG for detecting CP was 71.4%,

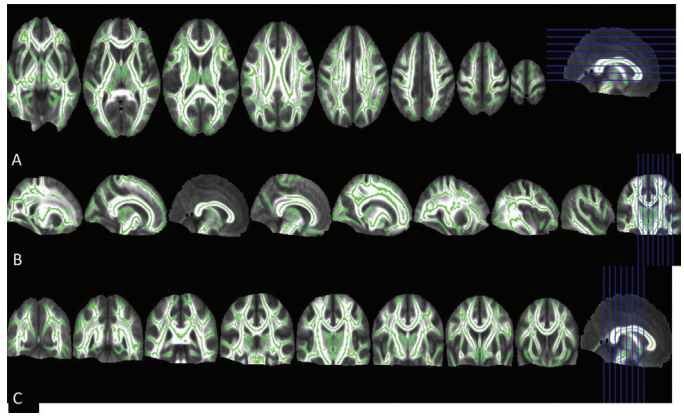

Figure 2. Fractional anisotropy (FA) skeleton. A) Axial B) Sagittal C) Coronal sections. Comparison of mean FA values in the white matter of the patient and control groups using the Tract-Based Spatial Statistics method was performed at each voxel level on the FA skeleton (green color)

while the negative predictive value was only 25%. Previous studies indicate that USG can diagnose severe PVL and cystic changes in only about one-third of patients, making it less effective at detecting diffuse PVL.[16,26] In our study, cranial MRI was performed in all cases except one before their corrected age reached 3 months. PVL was observed on cranial MRI in all patients except one. On neurological examination at three months, DTR vitality was noted in the lower extremities, whereas the examination at six months was normal. Mild PVL was detected on the six-month MRI. In our study, the positive predictive value of cranial MRI for diagnosing PVL was 77.8%, while the negative predictive value was 100%. As expected, MRI is both more sensitive and more specific than USG in identifying PVL. Numerous studies have directly compared MRI and cranial USG in predicting neurodevelopmental outcomes within the same population, including a recent systematic review of preterm infants.[9,26] MRI was found to detect more abnormalities and offer more detailed insights into the severity and extent of brain injuries related to prematurity, especially concerning white matter injury and cerebellar hemorrhage. While MRI demonstrated a high negative predictive value for outcomes, it showed a relatively low positive predictive value for the same outcomes. The prognostic value of MRI varied across studies, primarily influenced by the evaluation tools used and the comprehensiveness of brain abnormality assessments.[9] Based on MRI results at six months, we found mild PVL in 54.5% of cases, moderate PVL in 18.2%, and severe PVL in 27.3%. Neuromotor functions corresponded with MRI findings: normal neurological examinations correlated with mild PVL, whereas all patients with tetraparesis had severe PVL.

Table 3. The mean fractional anisotropy values of the patients with the diffusion tensor imaging results with the free-hand region of interest method

FA values	Genu	Splenium	Right internal capsule	Left internal capsule	Right optic tract	Left optic tract
PVL group (n=11)	0.375±0.93	0.435±0.16	0.378±0.10	0.558±0.87	0.244±0.98	0.306±0.21
Control group (n=7)	0.391±0.79	0.543±0.11	0.388±0.95	0.587±0.69	0.420±0.32	0.318±0.44
p value	0.710	0.140	0.860	0.510	0.010	0.770
FA depreciation	5%	20%	2.6%	5%	42%	3.2%

FA: Fractional anisotropy, PVL: Periventricular leukomalacia

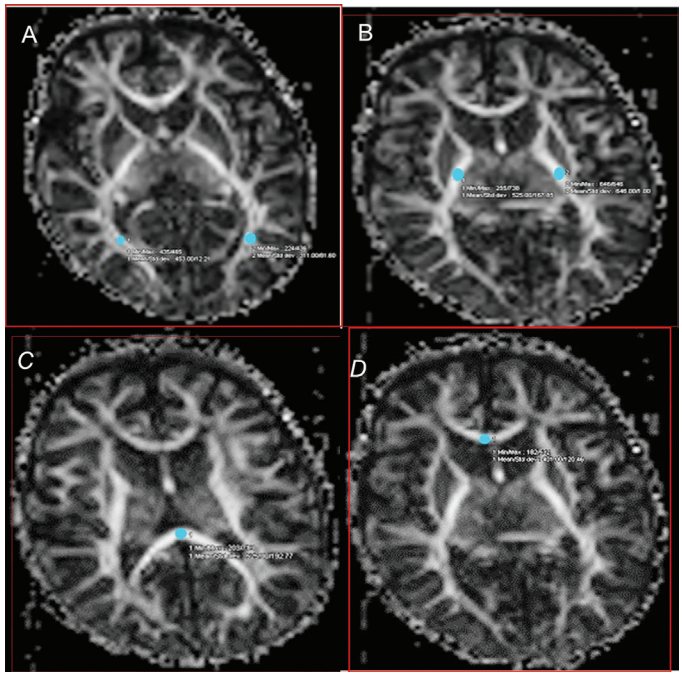

Figure 3. Fractional anisotropy calculation with free-hand region of interest method. The diffusion tensor imaging of the 6-month-old patient was appeared normal. A) Right and left optic tracts. B) Right and left internal capsule. C) Genu section of the corpus callosum. D) Splenium section of the corpus callosum

Inspection, assessment of optokinetic nystagmus, light-response testing, object tracking, and forced preferential gaze can be used in the ophthalmologic evaluation of newborn patients. Eye tracking shows promise for visual assessment in clinical and research settings because it is objective, quantitative, and capable of assessing diverse visual parameters.[27] For ophthalmologic evaluations, we assessed object fixation and tracking. Six of seven patients with a corrected age of three months showed light fixation and tracking, but only three were able to track objects. By six months, all but one case achieved normal light fixation and tracking. This development aligns with the maturation of the optic nerve and visual cortex, which continues until approximately two years of age.[28]

Visual evoked potentials (VEPs) are used in patients unable or unwilling to consistently complete subjective or behavioral tests, as well as in individuals with difficulties in perception and recognition, to assist in localizing visual defects. VEPs can also be used to measure thresholds as a proxy for visual acuity; this technique has been used for many years.[29,30] In our study, VEPs revealed abnormalities in 63.6% of the patients, all of whom developed spastic diplegia or tetraplegia by six months. Six of 10 cases with good vision showed a VEP abnormality (60%). No significant correlation was observed between neuromotor development and VEP responses. This may be due to the small sample size in the normal group. In one study, visual impairment was identified in 357 of 383 (93.2%) patients with CP who had abnormal VEP waveforms.[31] Howes et al.[32] investigated whether pattern reversal VEPs could predict future visual acuity in infants with CVI. VEPs may help predict future visual acuity in young children with CVI.

MRI has revolutionized the early diagnosis of PVL and enabled the assessment of neuromotor status. While traditional imaging techniques have limitations, advancements such as DTI enable the measurement of brain microstructure and connectivity. In our study, we used DTI at a corrected age of 6 months to compare diffusion parameters between 11 PVL patients and 7 controls. FA values were measured multiple locations within the genu and splenium of the corpus callosum, in the right and left internal capsules, and in the right and left optic tracts using the free-hand ROI method; mean values were obtained. FA values in all tracts were lower in the patient group than in the control group. The FA values were lower in the patient group, with statistical significance noted only in the right optic tract. While FA values measured via TBSS did not reveal significant differences, a higher frequency of mild PVL may have influenced the results. In the study conducted by Murakami et al.,[8] DTI was used to evaluate sensorimotor fibers in patients with PVL. The analysis included ROI measurements and TBSS in a cohort of 10 patients with a mean age of 19±9.5 months. The results showed that the mean FA values of the motor tract were

Table 4. Ophthalmological evaluations and visual evoked potential results at corrected age of three and six months of the patients

	Third month			Sixth month				
Patient no	**Light fixation**	**Light tracking**	**Object tracking**	**Light fixation**	**Light tracking**	**Object tracking**	**Additional**	**VEP**
1	+	+	+	+	+	+	Retina diffuses thin	Prolongation of latency
2	+	+	-	+	+	+	None	Normal
3	None			-	-	-	The optic discs are very pale, and exotropia in one eye	The wave pattern is disrupted.
4	None			+	+	+	None	Prolongation of latency
5	-	-	-	+	+	+	Intermittent exotropia	Prolongation of latency breaks the wave pattern.
6	+	+	+	+	+	+	None	Prolongation of latency, the wave pattern is broken
7	+	-/+	-	+	+	+	Intermittent exotropia, optic disc tilt, peripapillary atrophy	Normal
8	None			+	+	+	High astigmatism	Prolongation of latency, the wave pattern is broken
9	+	+	-	+	+	+	None	Amplitude low
10	+	+	±	+	+	+	None	Normal
11	None			+	+	+	Optic disc tilt and slight pallor	Normal

VEP: Visual evoked potential

significantly higher in patients with mild PVL than in patients with severe PVL. Additionally, ROI measurements were less sensitive than tractography-based measurements.[32] In their study, Fan et al.[10] examined 12 patients of PVL, with patients aged between 3 and 10 years and a mean age of 6.5 years. The researchers found a significant reduction in mean FA across several brain structures compared to those in the ipsilateral regions of healthy controls. Specifically, the affected areas included the posterior limb of the internal capsule, arcuate fasciculus, posterior thalamic radiation, corona radiata, cingulum, superior longitudinal fasciculus, and both the splenium and genu of the corpus callosum. Similarly, Madhavan et al.[33] showed that reduced white matter integrity (i.e., greater white matter damage), as reflected by the decreased FA values, in the middle third of the posterior limb of the internal capsule was the most descending; white matter motor pathways converged, which was highly indicative of poor motor function and the diagnosis of CP at 12 months. These advanced imaging methods can now investigate how brain connectivity networks are altered by white matter injury and other influencing factors.

Study Limitations

There are several limitations to our study. Firstly, the application of DTI MRI in young children can be challenging, particularly because sedation is often required.[11] Additionally, the small size of brain structures in this age group, together with a high prevalence of artifacts and rapid myelination, complicates interpretation of results.[11] Diffusion parameters are known to vary significantly during the first two years of life, especially within the first six months, due to ongoing myelination processes, which may influence the comparability of measurements across patients.

Furthermore, as noted by Plaisier et al.,[34] structural brain abnormalities identified on MRI were strongly associated with long-term neurodevelopmental outcomes, suggesting that imaging at a term-equivalent age may yield more stable and interpretable findings. However, early MRI scans hold significant promise, as they can inform early intervention strategies and advance research on preterm brain injuries. Differences in FA values at an early age in patients with PVL have been reported to correlate with motor function loss in later years.[32,33]

In addition to these methodological considerations, our study is limited by its relatively small sample size, short follow-up duration, and incomplete ophthalmic assessments in a subset of patients. These constraints reflect the inherent challenges of conducting longitudinal, multimodal evaluations in premature infants, they but

should be considered when interpreting the generalizability of the findings. Larger, multicenter studies with extended follow-up are needed to elucidate long-term neuro-ophthalmologic and diffusion-based outcomes in this population.

CONCLUSION

In conclusion, DTI is a powerful tool for assessing the microstructural integrity of neural tissues. Our study demonstrates that DTI provides critical insights into the orientation and integrity of white matter tracts; these insights are essential for understanding various neurological conditions in patients with PVL at a corrected age of six months. Moreover, developmental assessments indicated that early neurological signs, such as increased muscle tone and brisk DTRs, predicted subsequent CP outcomes. While ophthalmologic evaluations showed promising improvement in visual tracking, VEP abnormalities were prevalent, underscoring the need for comprehensive assessments beyond conventional methods.

Ethics

Ethics Committee Approval: The study received ethical approval from the Ege University Clinical Research Ethics Committee (decision number: 12-11.1/9, date: 27.12.2012).

Informed Consent: Participation was contingent on obtaining informed consent from the patients' parents.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Y.E.K., E.D.B., F.A., M.C.Ç., M.Y., S.T., S.Y., G.A., S.G., Concept: Y.E.K., F.A., M.Y., S.Y., G.A., S.G., Design: Y.E.K., E.D.B., F.A., M.Y., S.Y., G.A., S.G., Data Collection or Processing: Y.E.K., E.D.B., M.C.Ç., S.T., S.Y., G.A., S.G., Analysis or Interpretation: Y.E.K., M.C.Ç., M.Y., S.T., S.G., Literature Search: Y.E.K., E.D.B., S.G., Writing: Y.E.K., F.A., S.G.

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