

Diffusion Tensor Imaging and Fiber Tractography Analysis in Patients with Pelizaeus-Merzbacher Disease

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ABSTRACT

Introduction: Pelizaeus-Merzbacher Disease (PMD) is a hypomyelinating disorder with X-linked recessive inheritance caused by mutations in the proteolipid protein 1 (PLP1) gene on chromosome Xq22. In the early stages of PMD, head tremor and pendular nystagmus are observed, while in the later stages, psychomotor developmental delay, choreoathetosis, ataxia, and spasticity are added to the clinical presentation. This study aimed to investigate the relationship between diffusion tensor imaging-fiber tractography (DTI-FT) findings, the clinical and pathogenetic features in PMD patients.

Methods: Nineteen patients diagnosed with PMD between 1995-2006 and 19 healthy controls were included in our study. Both patient and control groups underwent 3 Tesla Magnetic Resonance Imaging (MRI), DTI, and FT examinations. By using DTI regions of interest (ROI) were drawn in the corticospinal tract, right inferior occipitofrontal fasciculus (RIOFF), middle cerebellar peduncle, and right cingulum. The mean fractional anisotropy (FA) values of the tractographies which obtained

from the ROIs were calculated. Clinical and genetic features were compared with mean FA values.

Results: Significant differences were found between the PMD and control groups in the FA values of the corticospinal tract (CST), corpus callosum, right inferior occipitofrontal fasciculus, middle cerebellar peduncle and right cingulum. This patient group had significantly higher FA values. Patients with severe disabilities showed marked reductions in anisotropy at the corticospinal tract level.

Conclusion: The significantly reduced FA values in the white matter regions in the patient group are sufficient to suggest predominantly white matter involvement in PMD. The markedly lower CST FA values in patients with severe disabilities indicate that CST may serve as an important localization for determining disease severity. Studies using DTI-FT in similar patient groups will non-invasively enhance our understanding of structural differences.

Keywords: Diffusion tensor imaging-fiber tractography, fractional anisotropy, Pelizaeus-Merzbacher Disease

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INTRODUCTION

Pelizaeus-Merzbacher Disease (PMD) is a dysmyelinating disorder of the central nervous system (CNS) caused by mutations in the PLP1 gene located on the Xq22 chromosome (1). It predominantly exhibits X-linked recessive inheritance. However, some cases with autosomal recessive (AR) inheritance and clinically resembling PMD have also been reported. These cases are classified as Pelizaeus-Merzbacher-Like Disease (PMLD) and associated with mutations in the “gap junction” protein gene (GJA12) located on chromosome 1q41-42 (2–4). Gene duplication is the most common mutation observed, although missense mutations, insertions, and deletions have also been reported in PMD. The disease is classified into classic, connatal, and transitional forms. The classic form is clinically mild and typically results from gene duplication, whereas the connatal form is severe and is often associated with point mutations (5,6). In early infancy, head tremors and pendular nystagmus are observed. As the disease progresses, psychomotor developmental arrest, choreoathetosis, ataxia, and

spasticity become part of the clinical presentation. Optic atrophy and seizures appear in the later stages (7). Diffusion Tensor Imaging (DTI) is a non-invasive imaging method that enables the detection of white matter content and brain abnormalities at early stages. DTI allows for the measurement of mean water diffusion and fractional anisotropy (FA) in an orientational manner (8). Tractography is the visualization of specific white matter pathways and their three-dimensional representation by using specialized graphical techniques (9–12). The spatial resolution of Diffusion Tensor Imaging-Fiber Tractography (DTI-FT) is approximately 1–2 mm, making it an anatomical imaging method capable of displaying overall fiber structure but not functional or synaptic connections (10). For this reason, congenital and postnatal developmental CNS disorders affecting major fiber bundles such as the corticospinal tract or corpus callosum have become the primary application areas of DTI.

Highlights

- DTI-FT revealed significantly reduced FA values in white matter regions of PMD patients.
- Lower CST FA values correlated with severe disability in PMD patients.
- DTI-FT can non-invasively detect structural differences in PMD.

In our study, the aim was to identify clinical and DTI-FT differences in a group of PMD patients with X-linked and autosomal recessive inheritance and to determine whether a genetic-clinical-DTI-FT correlation exists by comparing the findings with a control group.

METHODS

Participants

The study included 19 patients (3 females and 16 males, aged 2–27 years) evaluated at our clinic between 1995–2006 and diagnosed with PMD-PMLD through molecular, genetic, and conventional brain MRI, and also 19 age-matched healthy controls were included. Individuals with congenital, metabolic, developmental, or chronic brain diseases other than PMD-PMLD were excluded. Patients were grouped based on their demographic and clinical characteristics. Clinical severity was graded according to the presence of Achilles contracture, axial hypotonia and cerebellar findings. Disability levels were classified using the Gross Motor Function Classification System (GMFCS). Patients with GMFCS levels 1, 2, or 3 were grouped as mild-to-moderate, while those with levels 4 or 5 were categorized as severe.

This study was approved by the Ethics Committee of İstanbul University, İstanbul Faculty of Medicine (Decision No. 2007/1735). Informed consent forms were obtained from all patients relatives.

DTI Fiber Tractography

A 3T Siemens Trio MR scanner (Erlangen, Germany) was used for cranial imaging in both the patient and control groups (Figure 1). The examination was performed using an eight-channel cranial coil. Diffusion tractography imaging was conducted using the ssEPI sequence (single-shot echoplanar imaging). The data were processed on the LEONARDO VD10B syngo VX49B workstation using DTI software (The General Hospital Corporation, 2001–2004). FA and color FA maps were obtained through the eigenvalues and eigenvectors extracted using mathematical methods. Using DTI, a color FA map at the level of the posterior limb of the internal capsule was used to draw the corticospinal ROI, and tractography was generated from the drawn ROI using the single ROI technique with an 45° angle threshold and FA threshold of 0.2 (Figures 2–4). The average FA value of the resulting tracts was calculated. Using a similar technique, ROIs were drawn for different areas, such as the right inferior occipitofrontal fasciculus (RIOFF), middle cerebellar peduncle, and right cingulum, in the coronal plane, with color FA maps, and the average FA values of the tracts obtained from the drawn ROIs were calculated.

Statistical Analysis

Statistical analysis and data evaluation were performed using the IBM Statistical Package for Social Sciences (SPSS) program version for Windows 10.0 statistical software package, and comparisons were made using the Mann-Whitney U test. A p-value of <0.05 was considered statistically significant, <0.01 was considered highly significant, and <0.001 was considered very highly significant.

RESULTS

A total of 19 patients were included, three of whom were female (mean age 9.0 ± 3.4 years) and 16 were male (mean age 12.3 ± 8.2 years), with an overall mean age of 11.7 ± 7.0 years. In the control group there were 6 females (mean age 9.8 ± 6.4) and 13 males. Molecular genetic testing revealed X-linked inheritance in 13 patients and autosomal recessive (AR) inheritance in 6 patients. All patients with X-linked inheritance had PLP 1 gene mutations (2 point mutations and 11 duplications). Among the AR inheritance group there was 1 point mutation, 3 deletions, and

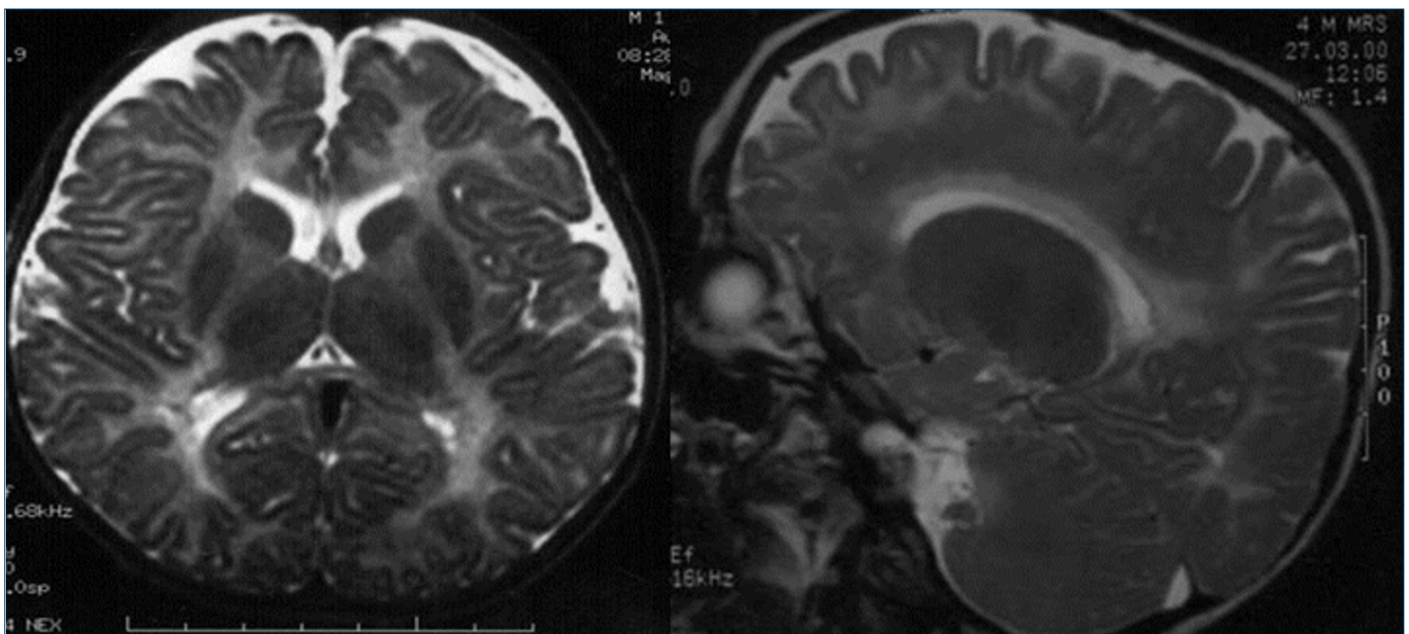


Figure 1. Axial and sagittal T2 cranial MRI of a PMD patient.

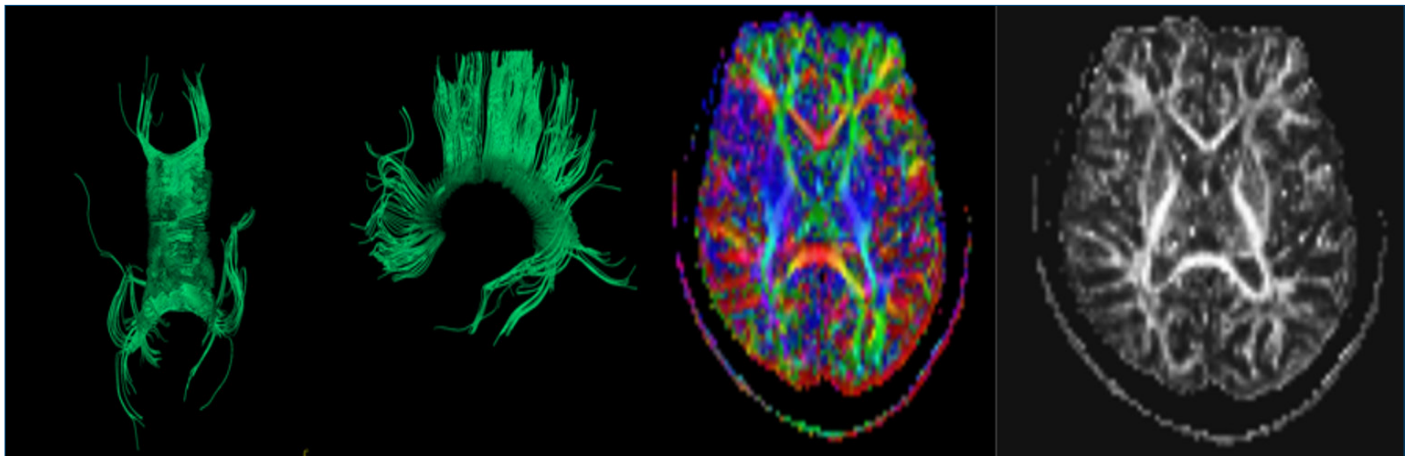


Figure 2. Patient number 7 in table 1 (CC Tract FA: 0.401 ± 0.175) superior and sagittal views of the corpus callosum tract, and axial FA mapping image (colors indicate tract direction: red: left to right, green: anterior-posterior, blue: superior-inferior).

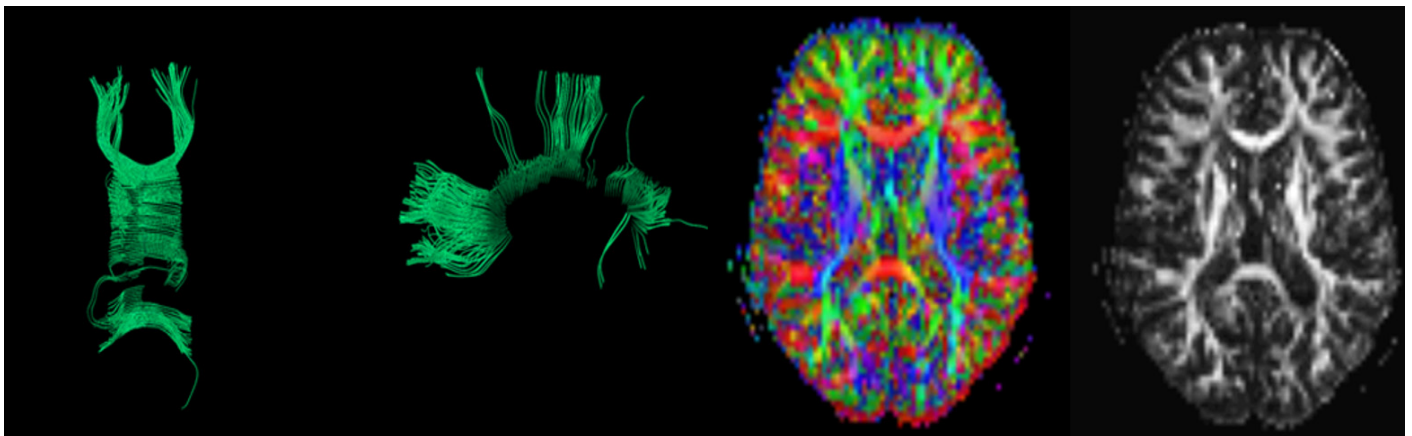


Figure 3. Patient number 3 in table 2 (CC Trakt FA: 0.392 ± 0.174) superior and sagittal views of the corpus callosum tract, and axial FA mapping image (colors indicate tract direction: red: left to right, green: anterior-posterior, blue: superior-inferior).

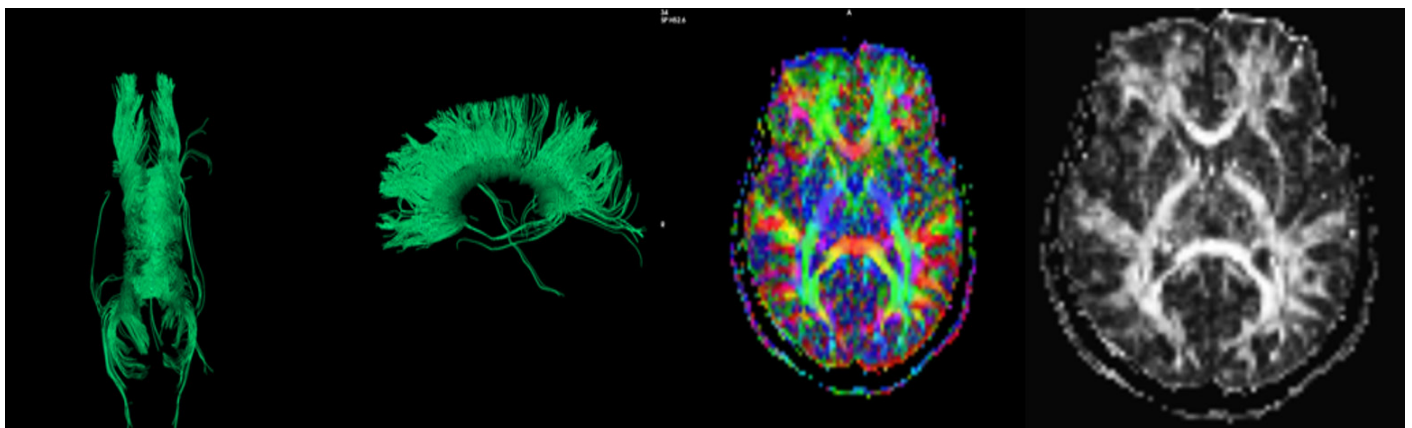


Figure 4. Control group, 11 years old female (CC Tract FA: 0.448 ± 0.212) superior and sagittal views of the corpus callosum tract, and axial FA mapping image (colors indicate tract direction: red: left to right, green: anterior-posterior, blue: superior-inferior).

2 duplications all of which had GJA12 mutations (Table 1 and Table 2). For patients with mild to moderate disability, there was no significant difference in FA values between the right and left corticospinal tracts, right cingulum, corpus callosum body and splenium ROIs compared to the control group. However, for patients with severe disability, the FA values in the same regions were significantly lower than those in the control group (Table 3 and Table 4). The general tract FA values of patients with mild to moderate disability were significantly lower than those of the control group ($p < 0.05$). On the other hand, patients with

severe disability had significantly lower FA values in the same regions when compared to the control group (Table 3 and Table 4, Fig. 1 and Fig. 2). Except for the right and left corticospinal tract ROI FA there was a significant relationship in FA values of all regions between the patient (with and without Achilles contracture) and the control group. Fractional anisotropy values of the right and left corticospinal tract, genu ROI, and corpus callosum tract were significantly lower in patient with axial hypotonia compared to the control group ($p < 0.05$).

In patients with cerebellar involvement, FA values for regions other than the splenium ROI were significantly lower compared to the control group, both in severe and mild-to-moderate involvement ($p < 0.05$).

DISCUSSION

PPMD-PMLD is a rare leukodystrophy that presented with hypodysmyelination. With the clinical use of magnetic resonance imaging (MRI), significant insights into brain myelin structure and myelination

have begun to emerge. Due to brain maturation or myelination, conventional MRI shows shortening of T1 and T2 relaxation times, decreased water diffusion, anisotropy, and increased magnetization transfer. In PMD MRI shows diffuse or patchy (tigroid) hyperintensities in the cerebellum, brainstem, and supratentorial white matter on T2 sequences (13,14). Various studies on MRI and proton magnetic resonance spectroscopy (MRS) findings in PMD have reported different results regarding the relationship between disease severity and MRI findings. Despite different clinical severity among patients, hyperintense lesions

Table 1. Clinical and demographic features of PMD patients with X-linked inheritance

| P | C | G | Mut. type | Inh | Gene | Age at the end of follow up | Disability at the end of follow-up | Nystagmus onset age | Nystagmus prognosis |
|----|---|---|-----------|----------|------|-----------------------------|------------------------------------|---------------------|---------------------|
| 1 | - | M | Mis | X-linked | PLP1 | 4 | Standing with support can't walk | Congenital | Reduced |
| 2 | - | M | Dup | X-linked | PLP1 | 14 | Standing with support can't walk | 3 months | Unchanged |
| 3 | - | M | Dup | X-linked | PLP1 | 16 | Stand and walk with support | Congenital | Reduced |
| 4 | - | M | Dup | X-linked | PLP1 | 14 | Stand and walk with support | Congenital | Unchanged |
| 5 | - | M | Dup | X-linked | PLP1 | 5 | Can't stand and walk with support | 2 months | Reduced |
| 6 | - | M | Dup | X-linked | PLP1 | 25 | Stand and walk without support | Unknown | Reduced |
| 7 | - | M | Dup | X-linked | PLP1 | 26 | Stand and walk without support | Unknown | Reduced |
| 8 | - | M | Dup | X-linked | PLP1 | 11 | Stand and walk with support | 1 year | Reduced |
| 9 | - | M | Dup | X-linked | PLP1 | 4 | Standing with support can't walk | 2.5 months | Unchanged |
| 10 | - | M | Dup | X-linked | PLP1 | 14 | Stand and walk with support | Congenital | Unchanged |
| 11 | - | M | Dup | X-linked | PLP1 | 5 | Stand and walk with support | Congenital | Unchanged |
| 12 | - | M | Dup | X-linked | PLP1 | 15 | Can't stand and walk with support | Congenital | Reduced |
| 13 | - | M | Dup | X-linked | PLP1 | 27 | Can't stand and walk with support | Absent | Absent |

P: patient; C: consanguinity; G: gender; Mut: mutation; Inh: inheritance; M: male; Dup: duplication; Mis: missense; Del: deletion

Table 2. Clinical and demographic features of PMLD patients with autosomal recessive inheritance

| P | C | G | Mut. type | Inh | Gene | Age at the end of follow up | Disability at the end of follow-up | Nystagmus onset age | Nystagmus prognosis |
|---|---|---|-----------|-----|-------|-----------------------------|--|---------------------|---------------------|
| 1 | + | M | Del | AR | GJA12 | 11 | Sits unsupported, stands and walks with support | Congenital | Unchanged |
| 2 | + | M | Del | AR | GJA12 | 2 | Sits unsupported, stands and walks with support | 20 days | Unchanged |
| 3 | + | F | Del | AR | GJA12 | 11 | Can't sit, stand and walk | 2 months | Unchanged |
| 4 | - | F | Mis | AR | GJA12 | 11 | Sits unsupported, stands with support and can't walk | 3 months | Unchanged |
| 5 | - | F | Dup | AR | GJA12 | 5 | Can't sit, stand and walk | 1 month | Reduced |
| 6 | + | M | Dup | AR | GJA12 | 4 | Sits unsupported, stands and walks with support | 1 month | Unchanged |

P: patient; C: consanguinity; G: gender; Mut: mutation; Inh: inheritance; M: male; Dup: duplication; Mis: missense; Del: deletion

Table 3. Comparison of the patient group with mild-to-moderate disability and the control group

| Localization | Control group | | Disability (GMFCS 1–2–3) mild-moderate | | P |
|--------------------|---------------|--|--|--|--------|
| | Mean | | Mean | | |
| R CST ROI FA | 0.43±0.06 | | 0.37±0.11 | | >0.05 |
| L CST ROI FA | 0.45±0.08 | | 0.4±0.13 | | >0.05 |
| R CST tract FA | 0.43±0.03 | | 0.39±0.04 | | <0.05 |
| L CST tract FA | 0.48±0.02 | | 0.43±0.04 | | <0.01 |
| Cgenu ROI FA | 0.9±0.09 | | 0.72±0.12 | | <0.01 |
| Ccorpus ROI FA | 0.73±0.07 | | 0.65±0.11 | | >0.05 |
| Csplenium ROI FA | 0.82±0.13 | | 0.68±0.17 | | >0.05 |
| Cc tract FA | 0.46±0.03 | | 0.4±0.02 | | <0.001 |
| RIOFF ROI FA | 0.44±0.08 | | 0.34±0.07 | | <0.05 |
| RIOFF tract FA | 0.42±0.03 | | 0.34±0.03 | | <0.001 |
| Rcingulum ROI FA | 0.45±0.10 | | 0.39±0.06 | | >0.05 |
| Rcingulum tract FA | 0.44±0.04 | | 0.38±0.04 | | <0.01 |
| Mcrblped ROI FA | 0.6±0.06 | | 0.47±0.05 | | <0.001 |
| Mcrblped tract FA | 0.44±0.03 | | 0.38±0.03 | | <0.01 |

CST: corticospinal tract; FA: fractional anisotropy; R: right; L: left; ROI: region of interest; Tract: tractography; Cgenu: corpus callosum genu; Ccorpus: corpus callosum body; Csplenium: corpus callosum splenium; Cc: corpus callosum; RIOFF: right inferior occipitofrontal fasciculus; Rcingulum: right cingulum; Mcrblped: middle cerebellar peduncle.

Table 4. Comparison of the patient group with severe disability and the control group

| Localization | Control group | Disability (GMFCS 4–5) severe | P |
|--------------------|---------------|-------------------------------|--------|
| | Mean | Mean | |
| R CST ROI FA | 0.43±0.06 | 0.35±0.06 | <0.001 |
| L CST ROI FA | 0.45±0.08 | 0.37±0.07 | <0.05 |
| R CST tract FA | 0.43±0.03 | 0.35±0.04 | <0.001 |
| L CST tract FA | 0.48±0.02 | 0.40±0.04 | <0.001 |
| Cgenu ROI FA | 0.90±0.09 | 0.70±0.14 | <0.001 |
| Ccorpus ROI FA | 0.73±0.07 | 0.63±0.10 | <0.05 |
| Csplenium ROI FA | 0.82±0.13 | 0.69±0.17 | <0.05 |
| Cc tract FA | 0.46±0.03 | 0.38±0.03 | <0.001 |
| RIOFF ROI FA | 0.44±0.08 | 0.30±0.06 | <0.001 |
| RIOFF tract FA | 0.42±0.03 | 0.32±0.04 | <0.001 |
| Rcingulum ROI FA | 0.45±0.10 | 0.32±0.05 | <0.001 |
| Rcingulum tract FA | 0.44±0.04 | 0.35±0.04 | <0.001 |
| Mcrblped ROI FA | 0.60±0.06 | 0.49±0.07 | <0.001 |
| Mcrblped tract FA | 0.44±0.03 | 0.36±0.03 | <0.001 |

CST: corticospinal tract; FA: fractional anisotropy; R: right; L: left; ROI: region of interest; Tract: tractography; Cgenu: corpus callosum genu; Ccorpus: corpus callosum body; Csplenium: corpus callosum splenium; Cc: corpus callosum; RIOFF: right inferior occipitofrontal fasciculus; Rcingulum: right cingulum; Mcrblped: middle cerebellar peduncle.

in the white matter showed similarities and clinical correlation with hyperintensity could not be established even with disease progression (13–17). In our study, the MRI findings in all patients supported the diagnosis of PMD without correlation with mutation differences and clinical features (Fig. 1). Unlike conventional MRI, diffusion tensor imaging (DTI) allows us for the detection of microstructural changes in cerebral white matter by quantitatively measuring mean water diffusion and fractional anisotropy (FA) (10). Studies have shown that DTI-FT is superior to conventional MRI in detecting myelin loss, axonal damage, and abnormal white matter connections in demyelinating diseases, epilepsy, developmental malformations, trauma, stroke, cerebral palsy and neurodegenerative diseases such as Alzheimer's disease (18–23). Consistent with the literature, our study found a decrease in FA in all selected regions of the DTI-FT in the patient group compared to the control group. Additionally, unlike conventional MRI, the fractional anisotropy values varied according to the degree of myelin loss and clinical involvement (Table 3 and Table 4, Fig. 2 and Fig. 3). In studies on patients diagnosed with adrenoleukodystrophy (ALD) and other leukodystrophies, an increase in diffusion and a reduction in FA were detected in affected areas (18,24). In our patient group, FA values were similar to those reported in ALD studies, reflecting myelin breakdown and axonal loss, with decreased FA observed in the corticospinal tract (CST). In multiple sclerosis (MS), a demyelinating disease, studies have reported increased mean diffusion and decreased FA in lesion areas visible on T2-weighted images, with the lowest anisotropy observed in acute lesions and black holes on T1-weighted images (12). Similarly, in patients with chronic epilepsy and hippocampal sclerosis, increased diffusivity and decreased anisotropy were found in the sclerotic hippocampus (25). In our study, compared to the control group, all regions in the patient group showed FA reduction, but the decrease in FA was more pronounced in patients with severe clinical involvement and disability particularly in the CST.

According to the limited number of studies on DTI-FT in PMD patients in the literature, it has been observed that as clinical involvement, disability and hypomyelination increase, the degree of FA decreases and diffusion increases become more pronounced (26,27). In our study, FA measurements in all regions clearly and significantly reflected the disease when compared to healthy individuals. When comparing mild and severe disability cases, the reduction in FA in the bilateral CST is more pronounced in severe cases than mild ones. This semi-quantitative correlation suggests that CST-FA measurements may reflect clinical disability and

making CST a useful localization. According to the literature, patients with PLP1 duplication show the best clinical outcomes, while those with point mutations display the most severe clinical course. Clinical heterogeneity is more commonly observed in patients with autosomal recessive inheritance (6–9). In our study there was clinical heterogeneity even among patients with the same GJA12 deletion. Consistent with previous studies, the best clinical outcomes in our patient group were observed in X-linked inheritance patients with PLP1 duplication. Patient number 7 had the best clinical outcome, with higher FA values compared to the others (Table 1). As similarly with previous studies, the most severe clinical cases in our study were found in patients with PLP1 point mutations. Also visually there was meaningful correlation between the clinical features of the patients and their tractographies (Fig. 2–4).

While the number of patients in our study was sufficient for a rare disease like PMD, a limitation of the study was the insufficient subgroup sizes for statistical comparison of different mutations. Another limitation was the comparison of the patient group only with healthy controls.

The selection of the control group from different disease groups, particularly other leukodystrophies and demyelinating diseases, could have allowed us to comment on which anatomical regions are more specifically affected in PMD. A comparison with different disease groups, particularly other leukodystrophies and demyelinating diseases, could have provided new insights and interpretations.

As a result although clinical, genetic and cranial MRI are sufficient for diagnosing hypomyelinating disorders such as PMD and PMLD, DTI-FT can provide valuable insights into diagnosis and prognosis. Furthermore, in countries like ours, where consanguineous marriages are common, genetic counseling plays a critical role, particularly in the diagnosis and follow-up of patients with autosomal recessive inheritance.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul University, İstanbul Faculty of Medicine (Decision No. 2007/1735).

Informed Consent: Informed consent forms were obtained from all patient's relatives.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- ZY; Design- ZY, HAE; Supervision- ZY; Materials- AD; Data Collection and/or Processing- PT; Analysis and/or Interpretation- HAE; Literature Search- İA; Writing- HAE; Critical Reviews- AD.

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