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Turkish Running Head: Pelizaeus Merzbacher Genotip ve Fenotipi

Title: Genotype-Phenotype Correlation in Pelizaeus Merzbacher Disease and Pelizaeus Merzbacher-Like Disease

Running Head: Genotype-Phenotype in Pelizaeus Merzbacher

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Öz

Amaç: Çocukluk çağı hipomiyelinizan hastalıklarından Pelizaeus Merzbacher Hastalığı (PMH), X'e bağlı proteolipid protein (PLP) gen mutasyonu ile oluşmaktadır. PLP mutasyonu bulunmayan ve Pelizaeus Merzbacher Benzeri Hastalık (PMBH) olarak adlandırılan hastalarda ise otozomal resesif geçiş gösteren gap junction protein $\alpha 12$ (GJA12 /GJC2) gen mutasyonu bulunabilmektedir. Bu çalışmada amaç, PLP mutasyonuna bağlı PMH ve GJA12 /GJC2 mutasyonuna bağlı PMBH hastalarında klinik tutulum şiddeti ve progresyon patternlerini incelemektir.

Yöntemler: Hastaların motor gelişim basamakları öğrenilerek hastalık şiddeti, başarabildikleri yürüme kabiliyetlerine göre sınıflandırıldı. Progresyon patternleri çalışma zamanında ve takip vizitlerindeki nörolojik bulguları karşılaştırılarak yapıldı. PMH ve PMBH hastaları hastalık şiddeti ve progresyon patternleri açısından karşılaştırıldı. Ayrıca tüm hastalardaki farklı mutasyon tipleri kendi aralarında incelendi.

Bulgular: Çalışmaya 9 PMH (ortalama yaş 15.2±3.1) ve 11 PMBH (ortalama yaş 12.4±1.9) hastası alındı. PMH hastalarında şiddetli hastalık tutulumu PMBH'e göre daha fazlaydı. PMH hastaları içinde, yanlış bağlanma (missens) mutasyonu olanlar en şiddetli hastalık ve en hızlı progresyonu gösterirken, delesyon mutasyonu olanlarda hastalık şiddeti daha hafif, progresyon daha yavaş izlendi. PMBH'a neden olan farklı mutasyonların hastalık şiddeti ve progresyon patterni açısından heterojen olduğu görüldü.

Tartışma: PMBH, PMH ile kıyaslandığında daha hafif bir hastalık fenotipi gösteriyor olsa da PMBH'ina neden olan farklı mutasyonlar birbirinden farklı fenotiplere neden olabilir.

Anahtar Kelimeler: Pelizaeus-Merzbacher Hastalığı, pelizaeus-merzbacher-benzeri hastalık, gap junction protein $\alpha 12$, genotip, fenotip

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Abstract

Aim: Among the hypomyelinating diseases of childhood, Pelizaeus Merzbacher Disease (PMD) is caused by X-linked proteolipid protein (PLP) gene mutations, whereas patients without mutations of PLP gene -called Pelizaeus Merzbacher-like Disease (PMLD)- includes patients with autosomal recessive gap junction protein α 12 (GJA12 /GJC2) gene mutations. The aim of this study was to evaluate clinical severity and progression in time between PMD and PMLD patients.

Methods: The motor developmental stages of the patients were reviewed; disease severity was classified according to the walking ability they were able to achieve. Progression pattern was determined according to comparison of neurological findings at the time of the study and at follow-up visits. PMD and PMLD patients were compared in terms of disease severity and progression rates as well as patient groups with a unique causative mutation were analyzed individually.

Results: There were 9 PMD patients (mean age 15.2 ± 3.1) and 11 PMLD patients (mean age 12.4 ± 1.9). The presence of severe disease was more common in PMD patients when compared to PMLD. In X-linked PMD, missense mutations had the most severe disease and rapid progression, while deletion mutations had mild disease severity and slow progression. Disease severity and progression patterns seemed to be heterogenous in different causative mutations of PMLD.

Conclusion: Although PMLD might have milder disease phenotype when compared to PMD, certain causative mutations in different genetic traits may cause different disease severity and progression patterns.

Keywords: Pelizaeus-Merzbacher Disease, pelizaeus-merzbacher-like disease, gap junction protein α 12, genotype, phenotype

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Introduction

Pelizaeus-Merzbacher disease (PMD) is the prototype of hypomyelinating diseases of childhood which has been firstly described as an X-linked disorder caused by mutations or rearrangements in the proteolipid protein 1 (PLP1) gene. Causative mutations of the PLP1 gene are -in declining order of frequency-duplications, point mutations, insertions, and deletions (1). Clinical features include nystagmus (typically occurs in the first months of life and resolves within 2-5 years of age), dysarthria, ataxia, hypotonia and developmental delay evolving into spastic quadriplegia in the first years of life (2). The clinical severity and rate of progression vary widely, probably depending on the variability of the causative mutation(1). Although, it has firstly described as a X-linked disorder, patients with PMD phenotype but without mutations of PLP1 gene have been shown to have an autosomal recessive (OR) trait. One of the causative mutations in these patients -called Pelizaeus-Merzbacher-like disease (PMLD)- is in gap junction protein α 12 gene (GJA12 /GJC2) coding for Connexin 47(3). Although GJA12/GJC12 mutations have been found in a minority of PMLD, its frequency is higher in Turkish patients(4). The data about which phenotypical differences occur in these different types of genetic traits is limited. In this study, we aimed to compare the age of onset, clinical severity and progression rates in PMD and PMLD.

Methods

The data of this study was obtained from 20 patients who had been followed between 1995- 2013 in the XXXXXXXXXXXXXXXXXXXX. All genetic analysis of patients and families were performed in the XXXXXXXXXXXXXXXXXXXX. Only patients who had a causative mutation were included into the study. Screening tests for metabolic diseases were performed. All patients underwent brain magnetic resonance imaging (MRI). Exclusion criteria were as following: a) the presence of any other congenital, metabolic or developmental brain diseases b) the absence of follow-up visits c) rejection to give written informed consent for the study.

The history of birth and motor developmental stages of the patients were learned from parents as well as from clinical charts. Detailed neurological examination was performed in all patients and compared with the clinical findings at follow-up visits. Moreover, Functional Independence Measurement (FIM/weeFIM), Scale for the assessment and rating of ataxia (SARA) and Modified Achworth Spasticity Scale (MAS) were also evaluated in all patients. FIM is an 18-item of motor and cognitive function that is used to assess a patient's level of functionality(5). weeFIM is, on the other hand, is used to assess this functional independence in children(6). The total score for the FIM/weeFIM instrument (the sum of the motor and cognition subscale scores) will be a

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value between 18 and 126. The higher the score, the more independent the patient is according to the FIM/weeFIM scores. SARA is a clinical scale to assess ataxia (7). It has 8 categories with accumulative score ranging from 0 (no ataxia) to 40 (most severe ataxia). The Modified Ashworth Scale (MAS) is the most widely used clinical scale to measure the increase of muscle tone (8). It has 5 categories ranging between 0 (no increase in muscle tone) and 4 (affected parts rigid in extension of flexion). In the study, The MAS score was scored according to the tone of lower extremities.

According to the obtained data, the patients were grouped according to the development of walking ability as follows: a) Group 1 (severe disease) includes patients who never had the ability to walk b) Group 2 (moderate disease) includes patients who had the ability to walk with assistance c) Group 3 (mild disease) includes patients who had the ability to walk without assistance during the developmental stages. Groups were compared in terms of age, sex, clinical scores and genetic traits and causative mutations.

Progression -which was accepted if the patient lost the major activities that he/she was able to (walking, sitting and speech) during the follow-up was evaluated in every patient. Categorical variables were presented as percentage (%) and continuous variables as mean± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Categorical variables were analyzed using Pearson Chi-Square or Fisher 's Exact Test, and continuous variables using the Independent-Sample T-test (for normal distributions) and Kruskal–Wallis Test (for non-normal distributions). Statistical assessments were performed using SPSS software pack (Statistical Package for Social Sciences for Windows Version 23 software). A p value of less than 0.05 was considered statistically significant.

The study approved by local ethical committee. Written informed consent was obtained from all participants and/or their parents.

Results

A total of 20 patients (14 female, 6 male) with a mean age of 13.7 ± 7.84 (min-max:4-30) were included in the study. Follow-up period was between 3-12 years. According to the genetic analysis, 9 patients had X-linked PMD and the remaining 11 patients had OR PMLD trait. The mean of age between X-linked and OR patients was not different (15.2 ± 3.1 vs 12.4 ± 1.9 , $p = 0.448$). Detailed information about demographics, causative mutation and developmental stages according to the walking ability are given in Table 1.

There was no difference between 3 groups in terms of age ($p = 0.905$), FIM/weeFIM score ($p = 0.085$), SARA score ($p = 0.313$) and MAS ($p = 0.305$). Of X-linked PMD patients, 33.3% were in the severe, 33.3% in moderate and the

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remaining 33.3% were in mild disease group. Of PMLD, 18.2% were in the severe, 45.2 % in moderate and the remaining 36.4 % were in mild disease group.

In 5 patients with a duplication in PLP1 gene, 3 patients never had the ability to walk, 2 patients, other hand, had at once the ability to walk with assistance. Of these patients, case 5 (29 years of age) was still able to walk with assistance and he had only mild ataxia. When compared with the neurological examination performed 5 years before, he had a very slow progression. The other patient in moderate disease group was Patient 1 who was 7 years of age. According to the follow-up visits, this patient had lost the walking ability with a progression in ataxia. The 2 patients with comparative genomic hybridization (CGH) duplication had also apparently progressed during follow-up period. The 2 patients with GJA12 /GJC2 duplications had the ability to walk with assistance, but both lost this ability during the 8-year follow-up period. Patient 7 (17 years of age) with a deletion in PLP1 gene had the ability to walk but it was late according to normal motor developmental stages of childhood. Progression of the disease was slow in early follow-up period, but he was not able to walk at the time of study. Of 4 patients with a deletion in GJA12/GJC2 gene, two patients had never have the ability to walk, the other two patients, on the other hand, had the ability to walk with assistance, one of whom (6 years of age) was still able to be walking at the time of study. The patient 6 (7 years of age) with a missense mutation in PLP1 gene had the ability to walk with assistance however he lost this ability in a short time period. All of 4 patients with missense mutation in GJA12/GJC2 gene had the ability to walk with assistance. Of these, 2 patients who were in the age of 18 and 21 lost this ability during the recent 5 -year follow-up period. The only patient with an insertion in GJA12/GJC2 gene (patient 12; 7 years of age) had completed motor developmental stages in time. He was able to walk without assistance at the time of the study.

Regarding to clinical scales, there were no difference in terms of FIM/weeFIM, SARA and MAS scores between PMD and PMLD (Table 2). Age was correlated neither of these scales.

Discussion

To our knowledge, this study has the largest Turkish patient series available that evaluates the association of phenotypic characteristics with the PMD and PMLD patients. Both PMD and PMLD are hypomyelinating disorders with similar clinical and neuroradiological phenotypes. The patients present in infancy with nystagmus, jerky head movements, hypotonia, ataxia and developmental delay evolving into spastic paraplegia(9).

There have been numerous genetical and molecular studies that investigates the nature of the PMD and other hypomyelinating disorders(10-12). However, data about the clinical features and prognosis of the patients with

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genetically confirmed PMD and PMLD is limited. In a study investigated the clinical types in patients having point mutations in PLP1 gene, clinical severity was found to be correlated with the nature of the mutation such that single amino-acid mutations in highly-conserved region of PLP caused the most severe forms of PMD (13). Another study that investigated the phenotype-genotype correlation in 5 PMD patients with duplication mutation, did not find any correlation with the extent of the duplicated genomic segments and the clinical severity(14). In a previous report in our patient population carrying duplication mutation (4), the severity of the disease did not show any correlation with the duplication size in contrary to previously reported studies (15, 16). Our study did not focus on genetic basis of the disease, but to compare clinical features and prognosis in two different traits and mutations in PMD and PMLD. Although PMD is known as the prototype of hypomyelinating diseases, PMLD caused by OR genetic trait has been reported to be seen in high frequency in Turkey as well as in other Eastern countries, probably depend on high rate of consanguineous marriages (4, 17, 18).

In a study that investigated clinical features of 16 PMLD patients according to developmental scores, the majority of the patients were found to have ambulation capacities, speech and good cognitive functions (3). Our results also support that PMLD has better clinical severity and prognosis when compared to X-linked PMD. When we analyzed different types of causative mutations in all patients, X-linked duplications was the most heterogeneous patient group in terms of clinical severity and progression, while OR duplications had a moderate clinical severity and progression rates of these patients were not severe such that they had milder ataxia and hypotonia even in late stages of the disease. In patients with X-linked deletion mutation, clinical findings were milder and progression rate was slower relative to other causative mutations, similar to previous publications (19). Clinical findings both in early and late stages of the disease were severe in patients with X-linked missense mutations, as previously reported (13). On the other hand, OR missense mutations had moderate severity and the progression was slower. The only patient with insertion in GJA12/CJG2 had moderate severity and slow progression rate. We did not find any differences in terms of clinical scores between PMD and PMLD, probable due to the fact that the small size of the cohort as well as the absence of age-matching PMD and PMLD patient groups. Although the mean of age between PMD and PMLD was not different and we used two different scale formats according to the age (FIM vs weeFIM) for functional independency ataxia rating scales has been reported to be age-dependent even in healthy children (20). Nevertheless, clinical scales enhance the communication between health professionals and they increase the objectivity when used to compare the patients with similar clinical findings.

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There are limitations of the study. In spite of we performed detailed neurological examinations and interviews with the families to identify the severity of the disease, the evaluation of progression was based on the retrospective review of clinical charts. Moreover, clinical scales we used at the time of present study were not be performed at the previous follow-up visits. Previous studies reported similar neuroradiological findings in patients with PMD and PMLD (21). We did not report MRI findings in patient groups, however MRI results were very similar in our patient series based on an unpublished data. In a study comparing neurophysiologic findings between PMD and PMLD reported a clear difference in brain stem evoked potentials (BAEP) (22). However, BAEP studies were not performed in our patients.

With the increase in the use of MRI as well as the availability of genetical analysis, the number of patients receiving a diagnosis of PMD and PMLD have been increasing. However, the similarities in clinical features between them may complicate the decision of the appropriate genetic testing particularly if there is no evidence of genetic transformation pattern based on patient's pedigree. It might be helpful to know that X-linked PMD patients may have more severe disease when compared to OR PMLD patients. Certain causative mutations in different genetic traits differ in terms of clinical severity and progression rates. These data can be used when informing the family members about the possible course of the disease according to the existing causative mutation. Further prospective studies are needed in larger patient series.

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Table 1. Demographics, genetic characteristics and motor development stages of all patients

Patient	Age	Sex	Genetic mutation	Causative mutation	Development of sitting ability	Development of speech ability	Development of walking ability	Groups according to walking ability
1	7	E	PLP1 gene	Duplication	6 months of age	2 years of age	2 years of age With assistance	Moderate disease
2	8	E	PLP1 gene	Duplication	2 years of age	1 years of age	-	Severe disease
3	5	E	PLP1 gene	Duplication	-	2 years of age	-	Severe disease
4	17	E	PLP1 gene	Duplication	-	1,5 years of age	-	Severe disease
5	29	E	PLP1 gene	Duplication	8 months of age	1 years of age	3 years of age	Mild disease
6	7	E	PLP1 gene	Missense	8 months of age with assistance	3 years of age	3 years of age with assistance	Moderate disease
7	17	E	PLP1 gene	Deletion	6 months of age	2 years of age	3 years of age	Mild disease
8	17	E	PLP1 gene	CGH duplica	6 months of age	2 years of age	3 years of age with assistance	Moderate disease

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9	30	E	PLP1 gene	CGH duplica	6 months of age	1 years of age	1.5 years of age	Mild disease
10	9	K	GJA12 /GJC	Duplication	5 years of age With assistance	3 years of age	5 years of age with assistance	Moderate disease
11	21	K	GJA12 /GJC	Duplication	8 months of age	2 years of age	2 years of age with assistance	Moderate disease
12	7	E	GJA12 /GJC	Insertion	1 years of age	1 years of age	2 years of age	Mild disease
13	5	K	GJA12 /GJC	Missense	6 months of age	1 years of age	2 years of age	Mild disease
14	18	K	GJA12 /GJC	Missense	6 months of age	1 years of age	2 years of age with assistance	Moderate disease
15	4	K	GJA12 /GJC	Missense	1 years of age	1 years of age	1.5 years of age	Mild disease
16	21	E	GJA12 /GJC	Missense	1 years of age	1 years of age	4 years of age	Mild disease
17	14	E	GJA12 /GJC	Deletion	1 years of age	1 years of age	1 years of age with assistance	Moderate disease
18	6	E	GJA12 /GJC	Deletion	8 months of age	1 years of age	2 years of age with assistance	Moderate disease
19	18	E	GJA12 /GJC	Deletion	1 years of age	1 years of age	-	Severe disease
20	14	E	GJA12 /GJC	Deletion	-	1 years of age	-	Severe disease

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Table 2. Comparison of clinical scales between PMD and PMLD patients

Clinical Scales	PMD	PMLD	p
SARA, median (IQR)	35 (29.5-39)	37 (15-40)	0.788
FIM/weeFIM, median (IQR)	46 (36-57.5)	45 (36-83)	0.592
Ashworth Spasticity Score, (IQR)	2 (1.5-3.5)	3 (0-4)	0.816

PMD: Pelizaeus Merzbacher Disease, PMLD: Pelizaeus Merzbacher Disease, SARA: Scale for the assessment and rating of ataxia FIM: Functional Independence Measurement, IQR: Interquartile range

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