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Clinical and Molecular Features of Our Pompe Patients: Single-Center Experience

Pompe Tanısı Alan Hastalarımızın Klinik ve Moleküler Özellikleri: Tek Merkez Deneyimi

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ABSTRACT

Introduction: *Pompe disease (PD), glycogen storage disease Type II (GSD II), is an autosomal recessive inherited lysosomal storage disease caused by pathogenic variants in the GAA gene that encodes lysosomal acid α-glucosidadase (GAA) enzyme. The incidence of the disease varies from country to country. PD is mainly presents as two groups of phenotypes as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease.*
Objective: *The aim of this study is to discuss the molecular and clinical characteristics of infantile-onset Pompe disease (IOPD) and late-onset pompe disease (LOPD) followed-up in our center.*
Method: *A total of 10 patients diagnosed with IOPD and 4 patients diagnosed with LOPD in Izmir Dr. Behcet Uz Pediatric Health and Diseases and Surgery Training and Research Hospital Pediatric Metabolism Unit between 06.01.2015 and 06.01. 2019 were included in the study. The patients' demographic characteristics, clinical findings at the time of diagnosis and during the folllow-up period, biochemical findings, muscle biopsy data, results of enzymatic analyses and molecular-genetic characteristics were recorded retrospectively.*
Results: *A total of 10 patients were included in the study. 7 patients were diagnosed with IOPD and 3 patients with LOPD. The median follow-up period of all patients was 26 months (range: 6-42 months). The c.896 C> T (8/32, 25%) is detected as the most common variant. 1237G>T (p.Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p.Asn140Tyr) variants were detected for the first time.*
Conclusion: *Pompe disease is one of the most important congenital metabolic diseases in which early diagnosis and treatment are of great importance. Despite the significant improvement in disease prognosis with the introduction of enzyme replacement therapy, there are still patients with poor prognosis despite early diagnosis. Phenotype-genotype studies are crucial in this respect.*

Keywords: *Pompe disease, hypertrophic cardiomyopathy, hypotonicity*

ÖZ

Giriş: *Pompe hastalığı (PD), glikojen depo hastalığı Tip II (GSD II), lizozomal acida-glucosidadase (GAA) enzimini kodlayan GAA genindeki patojenik varyantlar sonucu ortaya çıkan otozomal resesif kalıtımlı lizozomal depo hastalığıdır. Hastalığın sıklığı ülkeden ülkeye değişmektedir. Temel olarak erken başlangıçlı pompe hastalığı (IOPD) ve geç başlangıçlı pompe hastalığı (LOPD) olmak üzere iki gruba ayrılır.*
Amaç: *Çalışmamız, merkezimizde izlenen LOPD hem IOPD hastalarının moleküler ve klinik özelliklerinin tartışılmasını amaçlamaktadır.*
Yöntem: *Çalışmamıza 01.06.2015-01.06.2019 tarihleri arasında İzmir Dr.Behçet Uz Çocuk Sağlığı ve Hastalıkları ve Cerrahisi Eğitim Araştırma Hastanesi Çocuk Metabolizma Ünitesi'nde IOPD hastalığı tanısı alan toplam 10 hasta ve LOPD tanısı alan 4 hasta dahil edilmiştir. Hastaların retrospektif olarak demografik özellikleri, tanı anındaki ve izlem sırasındaki klinik bulguları, biyokimyasal bulguları, kas biyopsisi verileri, enzimatik analiz sonuçları ve moleküler-genetik özellikleri kayıt altına alındı.*
Bulgular: *Çalışmamıza toplam 10 hasta dahil edilmiştir. 7 hasta IOPD, 3 hasta LOPD tanısı almıştır. Tüm hastaların izlem süresi median 26 ay (range: 6-42 ay) olarak saptanmıştır. En sık görülen varyant c.896 C>T (8/32, %25) olarak saptanmıştır. 1237G>T (p.Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p.Asn140Tyr) varyantları ilk kez saptanmıştır.*
Sonuç: *Pompe hastalığı erken tanı ve sonuç olarak tedavinin büyük önem taşıdığı doğumsal metabolik hastalıkların başında gelmektedir. Enzim replasman tedavisinin kullanıma girmesi ile hastalık prognozunda belirgin düzelme olmakla birlikte erken tanıya rağmen halen prognozu kötü giden hastalar bulunmaktadır. Fenotip-genotip çalışmaları bu açıdan önem taşımaktadır.*

Anahtar kelimeler: *Pompe hastalığı, hipertrofik kardiyomyopati, hipotonisite*

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INTRODUCTION

Pompe disease (PD), or glycogen storage disease Type II (GSD II), is an autosomal recessive inherited lysosomal storage disease caused by pathogenic variants in the GAA gene that encodes llysosomal acidα-glucosidadase (GAA) enzyme [1]. The GAA gene is a typical housekeeping gene expressed in all cell types. Pathogenic variants in the GAA gene are present in all cell types, but some organs and functions are affected more strongly. Skeletal muscle and heart muscle are the primarily affected tissues [2].

The prevalence of PD varies in different ethnic groups according to clinical forms. The incidence of rapidly progressive infantile-onset pompe disease (IOPD) was 1/138000 in Caucasian race and 1/30000 in Taiwan [3]. The clinical classification of PD is based on the age and progression of the disease. PD is presented in two main groups as infantile-onset Pompe disease (IOPD) and late-onset Pompe disease (LOPD). Classical IOPD or rapidly progressive IOPD is a progressive disease presenting within the first few days to several weeks of life with severe cardiomyopathy, respiratory failure and death in the first few years of life. Non-classical IOPD occurs in the first year of life and cardiomyopathy is milder compared to classical IOPD. However, muscle weakness is significant and in untreated cases respiratory failure occurs in early childhood [3,4]. The 28% of PD cases were IOPD and 85% of them were shown to be classical IOPD [5]. Clinical findings of Pompe disease develops due to GAA activity decreasing to less than 30% [1]. Classical IOPD occurs when enzyme activity is less than 1% of normal [6]. LOPD occurs after infantile period; while onset of the clinical findings may vary from the first to the sixth decades of life [7]. Clinical presentation in LOPD can be seen as limb-girdle muscular dystrophy or severe respiratory muscle weakness that require treatment with mechanical ventilation. Heart muscle is rarely affected in this group [8].

In 2006, enzyme replacement therapy (ERT) with recombinant human acid α-glucosidase (rhGAA; alglucosidase alfa©; Myozyme©, Lumizyme©, Genzyme Corporation, Cambridge, MA) was introduced. Although the natural course of the disease changes with ERT; 51% of patients become ventilator dependent before age 3 [9]. The effective dose of ERT remains controversial. There is information in the literature on the use and efficacy of doses ranging from 20 mg / kg / every other week (eow) to 40 mg / kg / week [9,10]. There are many conditions that influence the efficacy of ERT other than its dosage, but one of them is undoubtedly the cross-reacting immunologic material (CRIM). It is known that CRIM-negative patients demonstrate much weaker response to ERT compared to CRIM-positive patients [11-14].However, the fact that CRIM is not available in all centers and that the results come from overseas centers pose significant difficulties in the decision-making process.

The aim of this study is to discuss clinical follow-up, molecular genetic characteristics and phenotype-genotype relationships of 10 patients with IOPD and LOPD.

MATERIALS and METHODS

Patient Selection

A total of 7 patients diagnosed with IOPD and 3 patients with LOPD in Izmir Dr. Behcet Uz Pediatric Health and Diseases and Surgery Training and Research Hospital Pediatric Metabolism Unit between 06.01.2015 and 06.01. 2019 were included in the study. The patients' demographic characteristics, clinical findings at the time of diagnosis and over the folllow-up period, biochemical findings, results of enzymatic and molecular-genetic analysis were recorded retrospectively.

Lysosomal acid α-glucosidadase (GAA) measurement

Lysosomal acidα-glucosidadase activity was measured with UHPLC MS/MS method (Orsini JJ) in dry blood and leukocytes (Waters Acquity ™ UPLC I-Class system). The substrate was provided by CDC [15].

GAA mutation analysis

GAA mutation analyses were performed in 10 patients with highly suspected PD. DNA was extracted from 2 ml EDTA containing peripheral blood samples using QIAamp DNA Mini Kit in accordance with the manifacturer's instructions. The full coding sequen-

ces of the GAA gene (NCBI: NT024871) were amplified and sequenced. The most likely disease-causing variants, identified by data analysis, were confirmed using Sanger sequencing method. Segregation analysis was then performed.

RESULTS

Demographic Findings and Clinical Features

The clinical characteristics of our patients are summarized in Table 1. A total of 10 patients were included in the study. Seven patients were diagnosed with IOPD and 3 patients with LOPD. The median follow-up period of all patients was 26 months (range: 6-42 months). Clinical, laboratory and genotypic features of our patients are summarized in Table 1. Most (80%) of the patients were male (8/10) and 20% of them were female (2/10). The median age of onset of symptoms was 3.6 months (range: 0-12 months) in IOPD patients. Hypotonicity was the most common symptom (5/7; 83%), followed by respiratory distress (5/7, 83%). Cardiomyopathy (6/7; 85%) and hypotonicity (6/7; 85%) were the most common findings at presentation. Arrhythmia was seen in 66% of our patients (4/7). Two IOPD patients were diagnosed during the postnatal evaluation due to sibling history; one IOPD patient was diagnosed incidentally after detection of hypertrophic cardiomyopathy (HCM) and elevated muscle enzymes in the evaluation for congenital metabolic diseases during his admission with hemolytic anemia. Five of our 7 IOPD patients had been investigated for spinal muscular atrophy (SMA) before investigation for Pompe disease.

The median age of onset of LOPD patients was 8 years (1-23 years). The most common initial symptom was muscle weakness (4/4; 100%) followed by fatigue (3/4; 75%). None of our LOPD patients required the use of wheelchairs or invasive or noninvasive mechanical ventilators during follow-up. During the follow-up of our LOPD patients in different clinics, 3 patients were seen to have been followed up with a preliminary diagnosis of limb-girdle muscular dystrophy.

GAA activity measurement and Creatine Kinase values

GAA activites, analyzed from the dry blood samples of patients diagnosed with IOPD and LOPD, were determined as 0.12± 0.16 nmol/ml/hour (N: 1.1-4.02) and 0.51± 0.93 nmol/ml/hour, respectively. A statistically significant difference was found between the GAA activities of LOPD and IOPD patients (Table 2).

Serum creatine kinase (CK) levels were found to be high in all of our patients. Mean serum CK levels were 463± 45.6 in IOPD and 521± 59.3 IU/l (N: <175) in LOPD patients. No statistically significant difference was found between LOPD and IOPD patients.

GAA mutations

Pathogenic GAA variants detected in our patients were studied as 20 alleles in total from 10 patients listed in Table 3. In 80% (8/10) of our patients, kinship was found between parents. Patient 2-3, and patient 5-6 were siblings. Homozygous pathogenic variant was detected in 8 patients and compound

Table 1. Clinical feaures of patients.

Patient	Gender	Age at onset	Age at diagnosis	Cardiomyopathy		Dysrithmia	Hypotonicity	Muscle weakness	Disease classification	Survival Time	Current Age
				Hypertrophic	Dilated						
1	Male	0 months	3 months	+	-	+	+	-	IOPD	8 months	-
2	Male	4 months	12 months	+	-	-	+	-	IOPD	12 months	-
3	Male	0 months	0 months	+	-	-	+	-	IOPD	-	4 years
4	Male	2 months	2 months	+	-	+	-	-	IOPD	-	3.5 years
5	Male	0 months	6 months	+	-	+	+	-	IOPD	9 months	-
6	Male	2 months	6 months	-	-	-	-	-	IOPD	-	13 months
7	Female	0 months	1 month	-	+	+	+	-	IOPD	-	8 months
8	Male	5 years	9 years	+	-	+	-	+	LOPD	-	13 years
9	Female	23 years	24years	-	-	-	-	+	LOPD	-	26 years
10	Male	8 years	17 years	-	-	-	-	+	LOPD	-	19 years

Table 2. Molecular genetic findings of patients .

Patient	Allele 1	Location	Allele 2	Location	Variant classification	CPK at diagnosis (IU/L) (N:<175)	GAA enzyme activity (nmol/ml/saat) (N:1.-4.02)
1	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	345	0,24
2	c.258dup p.(Asn87GlnfsX9)	Exon 2	c.258dup p.(Asn87GlnfsX9)	Exon 2	A (very severe)	521	0,11
3	c.258dup p.(Asn87GlnfsX9)	Exon 2	c.258dup p.(Asn87GlnfsX9)	Exon 2	A (very severe)	672	0,12
4	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	456	0,26
5	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	389	0,21
6	c.896 T>C p.(Leu299Arg)	Exon 5	c.896 T>C p.(Leu299Arg)	Exon 5	B (Potentially less severe)	474	0,1
7	c.2019C>A p.(Asn673Lys)	Exon 14	c.2019C>A p.(Asn673Lys)	Exon 14	Unknown	567	0.1
8	c.1237 G>T p.(Asp413Tyr)	Exon 8	c.-32-13T>G	Intron 1	Unknown/ D (potentially mild)	651	0,42
9	c.418 A>T	Exon 2	c.-32-13T>G	Intron 1	Unknown/ D (potentially mild)	497	0,36
10	c.-32-13T>G	Intron 1	c.-32-13T>G	Intron 1	D (potentially mild)	532	0,28

heterozygous variant in 2 patients.

Of the 20 alleles studied, 12 were identified as missense (12/20, 60%), 4 as splice-sites (4/20; 20%), and 4 as frameshift (4/20, 20%). The most common variant was c.896 T> C (8/14, 57.1%) and the second most common mutation was c.258dup (4/20, 20%). Of the 6 variants we identified, 3 had already been described in the literature; while c.1237G> T (p. Asp413Tyr), c.2019 C> A(P.asn673lys) , c.418A> T (p.Asn140Tyr) variants were detected for the first time. Variants C.1237 G>T and c.418 A>T were classified as variant of uncertain significance (VOUS) according to the ACMG classification; and c.2019 C>A variant was classified as 'likely pathogenic', but all 3 variants were considered as pathogenic because of their location in a highly conserved region among species and interpretation by in-silico prediction programs as damaging.

Enzyme Replacement Therapy

Three of our IOPD patients received ERT at a dose of 20 mg/kg/2 weeks and 4 patients at a dose of 20 mg/kg/week. One patient died without receiving ERT. CRIM status could not be evaluated in our patients. Desensitization was performed in one patient due to anaphylaxis developed during ERT.

DISCUSSION

The phenotype and genotype relationship of Pompe disease in different ethnic groups has been discussed.(16-19) There are no studies investigating phenotype-genotype characteristics of IOPD patients in our country.

- When the initial symptoms were evaluated in two different groups, hypotonicity was the most and respiratory distress was the second most frequently seen disorders in IOPD patients. The first symptom was most frequently muscle weakness in LOPD patients. When the initial symptoms are compared, hypotonicity is seen in IOPD and muscle weakness in LOPD. While noninvasive mechanical ventilator support was required in 3 IOPD patients (3/7; 45%), respiratory support was not required in LOPD patients during follow-up. Most (90%) of our IOPD patients whereas 33% (1/3) of LOPD patients had HCM at the time of diagnosis,. Arrhythmia, which is an important part of cardiac involvement in Pompe disease, was seen in 57% (4/7) of IOPD and in 33% (1/3) of LOPD patients. Our initial symptoms were evaluated to be consistent with the literature. However, wheelchair use was not seen in our LOPD group. The lack of need for wheelchair and respiratory support in our patients can be explained by the early initiation of ERT. In the literature, in the natural course studies performed before ERT, wheelchairs was used in 38% and respiratory support in 31% of the patients with LOPD. All of our LOPD patients had muscle weakness at the time of diagnosis. All 3 patients received initial diagnosis of LGMD and long-term follow-up. Pompe disease should be considered in patients followed up with a preliminary diagnosis of LGMD who have not been definitely diagnosed by molecular genetic methods.

When the diagnostic process of the patients was evaluated, two patients (patient 4 and patient 6) were diagnosed based on sibling history, and one

patient (patient 4) was diagnosed after incidental detection of HCM during the investigation of the etiology of hemolytic anemia. All three of these patients were diagnosed early in life and enzyme replacement therapy was started in the early period. During the follow-up with ERT of all three patients, HCM regressed completely. When the literature is examined, it is observed that HCM can completely return to normal in 46% of patients started on ERT during the early stage of the disease [20].

To date, around 600 pathogenic variants have been detected in the GAA gene (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ga to). GAA pathogenic variants, namely, exon 2 with start codon, exon 10 and 11 with enzyme catalytic domain and exon 14 with a highly conserved region among species are seen in three critical regions.(21) Six different variants detected in our patients were distributed in intron 1, exon 2, exon 5, exon 8 and exon 14. c.1237G>T (p.Asp413Tyr), c.2019 C>A (p.Asn673Lys), c.418A>T (p.Asn140Tyr), variants were detected for the first time in our study. The variant c.2019 C>A (p.Asn673Lys) was detected only in exon 14 in the region highly conserved among species. All of these variants are missense variants (Tables 1, 2).

When the variant types of patients were evaluated out of 20 alleles, 12 missense (12/20, 60%), 4 splice-site (4/20; 20%), and 4 frameshift (4/20, 20%) variants were detected While missense variants are commonly thought to have a better course than nonsense and frameshift variants that lead to premature stop codon; it is difficult to make clear comments on other than c.-32-13T>G variant. In their study towards resolving the confusion in this regard, Kroos et al. divided the detected variants in 6 groups.(17,22-24) The most severe variants are CRIM negative (class A, very severe), followed by classes ending in class F according to severity. c.258dup variant class A, c.896T>C variant class B (potentially less severe), c.da-32-13T>Gclass D (potentially mild) were detected in our patients. The classification of the newly identified 3 variants is not yet known. CRIM status is not known in our patients due to the fact that CRIM status is needed to be determined before ERT for technical reasons, because of the necessity of waiting for sample transport material to become available and necessity of urgent ERT initiation to the patients. For this reason, classification could not be made especially in newly identified variants, since CRIM status, which is the first condition in the classification of Kroos et al., could not have been checked. Sibling patients 2 and 3, who carried c.258dup variant, a class A variant, homozygously, showed very different clinical courses. When the patient 2 was brought to the hospital at the age of 12 months due to hypotonicity that started at 4 months of age, HCM was detected and the diagnosis of Pompe disease was made very quickly. However, due to immigrant status of the patient, ERT could not be provided with health insurance and the patient died very quickly before ERT could be started. Patient 3 was diagnosed with Pompe disease in the first month of its life and ERT could be started immediately. At present 4-year-old patient's HCM findings completely regressed and neuromotor development is close to normal. It is clear that the clinical difference between the two siblings is due to the early start of ERT.

The phenotype-genotype correlation of Pompe disease varies considerably. Clinics of siblings are very important in determining phenotype- genotype correlation. While sibling concordance in late-onset Pompe disease has been investigated, sibling concordance in early-onset Pompe disease has not been addressed much. In our patient group, 4 patients (2 families) were siblings. In the concordance study conducted by Smith et al., it was demonstrated that clinics of the siblings were very similar [25]. When the prognosis and clinical features of our patients were compared among siblings, it was found that the sibling after the proband had better clinical progression due to index case being diagnosed late and treatment being started in the newborn period with siblings detected in the family screening. When patients 1, 4, 5 and 6, who had class B c.896 C> A variant which was the most common in our series, were evaluated among themselves, there was no significant difference in the initial symptoms of the disease, age at onset, enzyme activity and ERT start time; though differences were observed in clinical findings and prognosis. This suggests that there may be other factors or other modifying genes in the same gene, other than the GAA gene variant in Pompe disease. Filippi et al. suggested that polymorphisms in the ACE gene affect the prognosis of the disease [22].

CONCLUSION

Pompe disease is the first metabolic myopathy in which corrective treatment is started. Since the start of the active use of ERT, there has been an improvement in the course of the disease and a significant increase in the number of surviving patients. Therefore, it is one of the diseases where early diagnosis is vital. While the phenotype-genotype is not known to be well correlated, it is of great importance in predicting prognosis and response to treatment as in all congenital metabolic diseases. Although the molecular genetic features of LOPD patients have been presented in the literature, there are limited studies about the molecular genetic features of IOPD patients Our study is one of the first studies in our country to discuss the molecular and clinical features of both LOPD and IOPD patients.

Ethics Committee Approval: Approval was obtained from the İzmir Katip Çelebi University Non-Interventional Clinical Research Ethics Committee (01/12/2018, 31829978-050.01.04-E.1700086095).

Conflict of Interest:

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Informed Consent: Informed consent was obtained from the patients' parents.

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