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ARAŞTIRMA / RESEARCH

GM2 gangliosidoses: evaluation of clinical, biochemical and genetic findings of patients with three novel mutations

GM2 gangliosidozis: üç yeni mutasyonlu hastaların klinik, biyokimyasal ve genetik bulgularının değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate the diagnosis characteristics, clinic findings, phenotypical and genotypical features of children with GM2 gangliosidoses.
Materials and Methods: The file records of 14 patients diagnosed with GM2 gangliosidoses in our clinic were retrospectively reviewed. The GM2 gangliosidoses diagnosis was confirmed by determining the levels of serum total hexosaminidase and β-hexosaminidase activity with genetic analysis.
Results: We identified a total of seven different mutations, three of which were novel (one in the HEXA gene and two in the HEXB gene) in 14 patients. We found a high frequency of c.1100_1111del (p.Gly367_Tyr370del) mutation in HEXA affected patients. The mean age at diagnosis was 13.4±6.3 months and 14.2±4.2 months for patients with Tay–Sachs disease (TSD) and Sandhoff disease (SD) respectively. Neuroregression was present in 92.9% of our patients. Of the 14 patients, 11 had epilepsy, 10 had developmental delay, 6 had hyperacusis, 6 had cherry-red spots and 6 had macrocephaly, but none of the patients had organomegaly.
Conclusion: GM2 gangliosidoses disease should be considered for children with developmental regression and/or delay. For early diagnosis, enzyme analysis and gene detection should be performed in children with suspected GM2 gangliosidoses in the presence of clinical findings.

Keywords: Lysosomal storage disorders, GM2 gangliosidoses, hexosaminidase, Tay-Sachs disease, Sandhoff disease

Öz

Amaç: Bu çalışmanın amacı, GM2 gangliosidozlu çocukların tanı özelliklerini, klinik bulgularını, fenotipik ve genotipik özelliklerini değerlendirmektir.
Gereç ve Yöntem: Kliniğimizde GM2 gangliosidoz tanısı alan 14 hastanın dosya kayıtları retrospektif olarak incelendi. GM2 gangliosidoz tanısı; serum total heksosaminidaz ile β-heksosaminidaz aktivitesi düzeyleri ve genetik analiz ile doğrulandı.
Bulgular: On dört hastada üçü novel (biri HEXA geninde ve ikisi HEXB geninde) olmak üzere toplam yedi farklı mutasyon saptandı. HEXA mutasyonu olan hastalarda c.1100_1111del (p.Gly367_Tyr370del) mutasyonu yüksek sıklıkta bulundu. Tay-Sachs (TSD) ve Sandhoff (SD) tanılı hastaların ortalama tanı yaşı sırasıyla 13,4±6,3 ay ve 14,2±4,2 aydı. Hastaların %92.9'unda nöroregresyon mevcuttu. On dört hastanın 11'inde epilepsi, 10'unda gelişim geriliği, 6'sında hiperakuzi, 6'sında cherry-red spot ve 6'sında makrosefali saptanırken, hiçbir hastada organomegali görülmedi.
Sonuç: Gelişim geriliği ve/veya gecikmesi olan çocuklarda GM2 gangliosidoz hastalığı akla gelmelidir. GM2 gangliosidoz şüphesi olan çocuklarda klinik bulgular varlığında erken tanı için enzim analizi ve gen tespiti yapılmalıdır.

Anahtar kelimeler: Lizozomal depo hastalıkları, GM2 gangliosidoz, hekzosaminidaz, Tay-Sachs hastalığı; Sandhoff hastalığı

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INTRODUCTION

GM2 gangliosidoses are autosomal recessive lysosomal storage diseases with variable clinical phenotypes characterized by GM2 ganglioside accumulation into the lysosome, caused by deficiency of the β-hexosaminidase enzyme. This enzyme comprises two polypeptide chains as α (encodes by *HEXA* gene) and β subunits (encodes by *HEXB* gene)[1]. The Tay–Sachs disease (TSD) is caused by mutations in the *HEXA* gene and has deficient HEXA enzyme activity and normal HEXB activity. On the other hand, Sandhoff disease (SD) develops due to mutations in the *HEXB* gene and is associated with deficiencies in both HEXA and HEXB enzyme activity[2-4]. Furthermore, mutations in the GM2 activator protein (encodes by *GM2* gene) cause to GM2 activator protein deficiency (OMIM 272750)[2]. So far, 108 different mutations in the *HEXA* gene, 103 different mutations in the *HEXB* gene and 9 different mutations in the *GM2A* gene have been identified, including missense/nonsense, splicing, small and large deletions[1,5].

As a result of the accumulation of GM2 ganglioside in neurons, various cytotoxic effects occur to progressive neurological impairment, including motor deficits, weakness, hypotonia, seizures and visual impairment[6,7]. At the onset of the classical disease, accumulation in the retinal ganglion cells cause to a cherry-red spots can be determined in patients[8]. Patients with SD may have systemic symptoms such as organomegaly, unlike TSD patients[9,10]. There are acute (infantile), subacute (juvenile) and chronic (adult) forms according to the onset time[2,11].

Diagnosis of the disease is confirmed by measurement the enzymatic activity and mutation analysis in patients suspected by clinical features[12]. The diagnosis may also be supported by neuroimaging, which is characterized by hyperdensity of the basal ganglia, accompanied by other changes in the white matter and sometimes marked but nonspecific cerebellar atrophy[12].

Several therapeutic strategies have been tried as enzyme replacement therapy, chaperones, substrate reduction, stem cell transplantation and gene therapy, but there is no approved therapy for these patients yet[1,3,13]. In this study, the clinical, biochemical, radiological and genetic results of 14 patients referred to our clinic with neurological complaints such as development delay, neuroregression, and epilepsy within two years and diagnosed with GM2 gangliosidoses were evaluated. Furthermore, three novel mutations have been detected in these rare diseases, and different clinical features of the patients are indicated.

MATERIALS AND METHODS

Ethical approval for this descriptive cross-sectional type study was obtained from University of Health Science, Adana Training and Research Hospital, Clinical Research Ethics Committee (Decision number: 1236).

Sample

From the file records of 14 patients who were diagnosed with GM2 gangliosidoses between December 2018 and December 2020 at the pediatric metabolism clinic of Health Sciences University Adana City Training and Research Hospital. The pediatric clinic which has a total bed capacity of 193 and 30 outpatient clinics, has two pediatric metabolism polyclinics.

Diagnosis of GM patients was made as a result of low serum Hexosaminidase A and/or Serum Total Hexosaminidase enzyme levels and molecular analyzes of HEXA and HEXB genes from patients suspected by pediatric metabolism specialists due to their clinical findings. Neuroregression of the patients was evaluated by pediatric neurologists. The age of admission, gender, complaints and complaints onset, age of diagnosis, systemic and neurological findings, radiological images, enzyme levels, molecular genetic results and prognosis were reviewed retrospectively. The patients' data retrieved from the hospital's electronic patient registry and patient files.

Molecular analysis

Molecular analysis was performed for *HEXA* genes in nine patients whose clinical findings and enzyme levels were compatible with TSD, and for *HEXB* genes in five patients who were compatible with SD. DNA was obtained from peripheral blood after obtaining informed consent from the parents of the patients. All exons and exon-intron junctions of *HEXA* and *HEXB* genes were evaluated by next-generation sequencing method by the manufacturer's protocol. Molecular analysis results were evaluated by medical geneticists. The pathogenicity of the detected

variants was evaluated according to the 'American College of Medical Genetics' (ACMG) 2015 criteria[14]. Each pathogenic criterion is weighted as very strong (PVS1), strong (PS1–4); moderate (PM1–6), or supporting (PP1–5) and each benign criterion is weighted as stand-alone (BA1), strong (BS1–4) or supporting (BP1–6)[14].

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) (SPSS for Windows, Version 25.0, Chicago, IC, USA) program was used for statistical analysis. Results were presented as mean and standard deviation for numerical variables, and frequency and percentage for categorical data.

Table 1. Clinical characteristics and findings of the patients

Patient no	Gender	Diagnosis	Clinic form	Age at diagnosis (months)	Macrocephaly	Cherry red spots	Development delay	Neuroregression	Epilepsy	Hyperacusis
1	M	TSD	I	23	+	+	+	+	+	+
2	M	TSD	I	10	-	+	+	+	+	+
3	M	TSD	I	21	-	-	-	+	-	+
4	M	TSD	I*	2	-	-	+	*	+	-
5	M	TSD	I	15	+	-	-	+	+	-
6	M	TSD	I	14	+	-	+	+	+	+
7	F	TSD	I	9	-	+	-	+	-	-
8	M	TSD	I	12	-	+	-	+	+	+
9	F	TSD	I	15	-	+	+	+	+	-
10	M	SD	I	13	+	-	+	+	+	-
11	F	SD	I	12	-	+	+	+	+	-
12	M	SD	I	18	+	-	+	+	+	-
13	M	SD	I	9	-	-	+	+	-	-
14	F	SD	I	19	+	-	+	+	+	+

M; male, F; female, *; patient diagnosed before the symptoms started because of positive family history; I : Infantile

Table 2. Enzyme levels and genetic analyzes of the patients

Patient no	Serum Total Hexosaminidase enzyme level (µmol/L.hour) (range: 600-3500)	Serum HEXA enzyme level (µmol/L.hour) (range: 50-250)	Gene	Genetic analyses result
1	893	<0.1	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
2	1049	<2	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
3	950	<2	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
4	-	-	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
5	867	<2	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
6	965	1.88	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
7	1264	<2	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
8	973	<2	*HEXA*	c.1100_1111del (p.Gly367_Tyr370del) (homozygous)*
9	890	<0.1	*HEXA*	c.409C>T (p.Arg137Ter) (homozygous)
10	50.5	15.7	*HEXB*	c.1417+5G>A (homozygous)
11	53.4	5	*HEXB*	c.1417+5G>A (homozygous)
12	147	<2	*HEXB*	c.185T>A (p.Leu62Ter) (homozygous)*
13	135	12.9	*HEXB*	c.988T>G (p.Tyr330Asp)* / c.1597C>T (compound heterozygous)
14	156	5.5	*HEXB*	c.1613+15_1613+18dupAAGT (homozygous)

*; novel mutation, Patients 1,2,4, and 7 are from the same family, patients 5 and 8 are from the same family.
Transcripts number of *HEXA*: NM_000520.6, transcripts number of *HEXB*: NM_000521.4

Table 3. Characteristics of detected genetic mutations

Gene	*HEXA*	*HEXA*	*HEXB*	*HEXB*	*HEXB*	*HEXB*	*HEXB*
Position (hg19)	3:0791	15:72647903	5:74014801	5:73981270	5:74011421	5:74016556	5:74016586
Transcript number	NM_000520.6	NM_000520.6	NM_000521.4	NM_000521.4	NM_000521.4	NM_000521.4	NM_000521.4
Nucleotide exchange	c.1100_1111del*	c.409C>T	c.1417+5G>A	c.185T>A*	c.988T>G*	c.1597C>T	c.1613+15_1613+18dupAAGT
Amino acid exchange	p.Gly367_Tyr370del*	p.Arg137Ter		p.Leu62Ter*	p.Tyr330Asp*	p.Arg533Cys	
Mutation type	In-frame deletion	Nonsense	Splice site	Nonsense	Missense	Missense	Intronic
Region	Exon 10	Exon 3	Intron 11	Exon 1	Exon 8	Exon 13	Intron 13
Zygosity	Homozygous	Homozygous	Homozygous	Homozygous	Compound heterozygous	Compound heterozygous	Homozygous
SIFT Score	-	-	-	-	0	0	-
SIFT Prediction	-	-	-	-	Damaging	Damaging	-
PolyPhen2 Score	-	-	-	-	-	1	-
PolyPhen2 Prediction	-	-	-	-	-	Probably Damaging	-
Mutation Taster Score	-	1	-	1	0,99	1	-
Mutation Taster Prediction	-	Disease causing	-	Disease causing	Disease causing	Disease causing	-
GERP Score	3,0791	3	2,5199	3,99	5,78	6,0799	0.2263
Frequency of gnomAD	0%	% 0.00028	0.000015	0%	0%	0.000031	0%
Pathogenicity (ACMG)	Likely Pathogenic PP4, PM2, PM4, PP3	Pathogenic PVS1, PP5, PM2, PP3	Uncertain Significance PM2, BP4	Pathogenic PVS1, PM2, PP4	Likely Pathogenic PM2, PP2, PP3, PP4, PP5	Pathogenic PM2, PP2, PP3, PS1, PP5	Likely Pathogenic PM2, PP4, PS3
dbSNP ID	-	rs121907962	rs763517499	-	-	rs764552042	rs779273534
Reference	-	PMID:9851891	-	-	-	PMID:21567908	PMID:23158871

*; novel mutation

RESULTS

In our study, 14 patients (4 female and 10 male) from 10 different families diagnosed with GM2 gangliosidoses [9 (64,3%) with TSD, 5 (35,7%) with SD] were included. There was consanguinity between the parents of 13 (92.9%) patients. In addition, there was a family history of GM2 gangliosidoses in 7 (50%) patients. While 11 of the patients (78.6%) were of Turkish origin, 3 patients (21.4%) were refugees.

The first symptoms of GM2 diseases were detected at the mean age of 9.23±2.31 months for 13 of total 14 patients (one patient was diagnosed before the symptoms started because of positive family history). On physical examination, macrocephaly was found in six patients (42.9%), microcephaly was found in two patients (14.3%), and head circumference was normal in six patients (42.9%). The mean weight of the patients was -1.28 SD (minimum: -2.5 and maximum: -0.12), while the mean height was -1.25 SD (minimum: -2.7 and maximum: -0.10).

Six patients had cherry-red spots (5 TSD, 1 SD). It was also determined that 10 (71.4%) of 14 patients had developmental delay and 6 patients (42.9%) had hyperacusis (Table 1). Neuroregression was present in 13 (92.9%) of a total of 14 patients, the mean age of developmental regression was 10±2.32 months and 8±1.87 months (range 8-22 months) for patients with TSD and SD, respectively.

None of our patients had organomegaly. Also, 11 patients (78.6%) were found to have epilepsy; 7 had generalized tonic-clonic, 2 had seizures triggered by fever, and 2 had status epilepticus (Table 1). All of our patients presented with the infantile form of the disease. Age of diagnosis of the cases between 2 months and 23 months. Only seven patients (50%) had cranial MR images; all of these patients had T2 thalamic hypointensity, while four patients had periventricular and subcortical involvement, and 4 patients had delayed myelination. The mean age at diagnosis was 13.4±6.3 months and 14.2±4.2 months for patients with TSD and SD, respectively. The β-hexosaminidase A enzyme activity, the total β-hexosaminidase enzyme activity and mutation analysis for *HEXA* and *HEXB* gene in Tay-Sachs and Sandhoff patients, and genetic characteristics of mutation results are shown in Table 2,3. Three of the 14 patients were died due to pneumonia.

Mutation analysis

A homozygous novel mutation c.1100_1111del (p.Gly367_Tyr370del) was detected in the *HEXA* gene in 8 of 14 patients, while a previously described c.409C>T (p.Arg137Ter) homozygous mutation was detected in one patient. In addition, for the *HEXB* gene, a previously defined c.1417+5G>A homozygous mutation in two patients, c.185T>A (p.Leu62Ter) homozygous novel mutation in one patient, c.988T>G (p.Tyr330Asp)/c.1597C>T compound heterozygous mutation in one patient, and c.1613+15_1613+18dupAAGT homozygous mutation in one patient was detected (Table 2, 3).

DISCUSSION

The GM2 gangliosidoses are lysosomal storage diseases caused by a deficiency of the β-hexosaminidase enzyme[2]. While mutations in *HEXA* gene are reason of the TSD by loss of β-hexosaminidase A enzyme, mutations in *HEXB* gene are causative of SD because of loss of both the β-hexosaminidase A and β-hexosaminidase B enzyme[2,4,15]. In this article, a total of 14 patients with GM2 gangliosidoses, nine TSD with *HEXA* gene mutation and five SD with *HEXB* gene mutation were presented.

In our study, although the number of male patients is 2.5 times higher than female patients, there were no significant difference by gender. Er et al.[4] reported no significant gender-related differences. Similarly, in our study, we found that TSD was more common in males, but there was no difference in SD by gender.

Infantile type SD is characterized with early onset of clinical symptoms and usually consist at 6 months old. These patients death about before 5 years old[15]. Tavasoli et al.[16] noticed that the average age of SD patients at the onset of clinical manifestations and diagnosis was 6.4 months and 14 months, respectively. Furthermore, reported eleven patients died of intractable seizures and aspiration pneumonia[16]. Er et al.[4] reported the mean age at diagnosis was 14.5 months (8-36 months) and 18.2 months (4-48 months) for patients with TSD and SD, respectively, and the mean age at death in 10 of the 14 GM2 gangliosidoses cases was 29.4 months (19-45 months) by pneumonia. Smith et al.[17] reported that the mean age at death was 36.3 months by pneumonia in GM2 gangliosidoses.

In our study, all of our five patients with SD were infantile form, the mean age of onset of clinical symptoms was 8.0±1.87 months, and only one patient (patient 10) died at the age of 3. In addition, the mean age of onset of clinical symptoms was 10.0±2.32 months in our TSD patients, and two patients (patient 1 and 4) died at the age of 2 years, 6 months and 2 years and 2 months, respectively (Table 1).

Gort et al.[2] reported that the age at diagnosis for thirty-four TSD and fourteen SD patients were between 7-36 months and 7-21 months, respectively. Similar to this study, Er et al.[4] noticed the mean age at diagnosis was 14.5 months (8-36 months) and 18.2 months (4-48 months) for patients with TSD and SD, respectively[4]. Tavasoli et al.[16] reported infantile SD 25 patients with the average age of patients was 15.8 months, ranging from 9 to 24 months. Our study determined the mean age at diagnosis was 13.4±6.3 months and 14.2±4.2 months for patients with TSD and SD, respectively.

SD is characterized by progressive neurological impairment, low muscle tone, hyperacusis, cherry-red

spots and epileptic seizures. Cherry-red spots are a characteristic ocular sign of infantile SD caused by the accumulation of sphingolipid in retinal ganglion cells[15]. In a study, the detected cherry-red spots rate was 88%[8], similar to a study in Turkey by Er et al.[4]. Tavasoli et al.[16] found that the cherry-red spots was present 17 of 25 (68%) patients with SD. A few cases may have mucopolysaccharide-like manifestations, such as the coarse face, giant tongue, hepatosplenomegaly, and spinal bone damage[15]. We determined epilepsy and cherry-red spots but no organomegaly of the patients diagnosed with SD in our study. Likewise, Er et al[4] and Barness et al.[18] reported no organomegaly for any individuals diagnosed with SD. In addition, only one of the 5 SD patients had hyperacusis in our study. We also found cherry-red spots, epilepsy, and hyperacusis in some of our patients with TSD (Table 1).

In GM2 gangliosidoses, multiple seizures types were noted[1]. Gort et al.[2] reported that seizures occurred in patients with infantile disease at an average age of 15.1 months (4-30 months). Similar to this study, Er et al.[4] reported seizures in 64% with mean age of 14 months (4-28 months) patients with GM2 gangliosidoses. In our study, 78.6% of the cases had epilepsy, and the seizure types were generalized tonic-clonic, seizures triggered by fever, and status epilepticus.

Karimzadeh et al.[8] reported, 18 patients with GM2 gangliosidoses from Iran and noticed that 66% of patients presented with developmental delay at the mean age of 15 months. Also, Er et al.[8] reported that 71% of GM2 patients showed developmental regression, and the mean age of developmental regression was 12.3 months. In our study, 71.4% of the patients were mental retardation (Table 1). Neuroregression was present in 92.9% of our patients, and the mean age of developmental regression was 10±2.32 months and 8±1.87 months for with TSD and SD patients, respectively. In cranial MRI with GM2 gangliosidoses patients, presence of a symmetrical abnormal signals in the thalamus can be detected[15]. T2-weighted cranial MRI shows a low signal for the thalamus and a high signal for the cerebral white matter. Additionally, atrophy of the cerebral cortex, thinning of the corpus callosum, abnormal signals of the caudate nucleus, cerebellum, globus pallidus, and brainstem may also be determined[19]. In Er et al. study[4], 55% of GM2 patients had T2 hyperintensity of the posterior thalami and 9% of the patients had myelination delay. In our study, only 7 of 14 patients had cranial MR images, and we found that all of them had T2 thalamic hypointensity, 4 had periventricular and subcortical involvement, and 4 had myelination delay.

Gort et. al.[2] presented the molecular analysis of 34 patients with TSD and 28 patients with SD. They identified 27 different mutations for TSD, including 14 that were reported for the first time, and 14 different mutations for SD, 8 of which were described for the first time[2]. Er et al.[4] reported the results of molecular analysis in 6 (4 TSD and 2 SD) of 14 patients and identified a novel mutation in one TSD patient. In our study, we presented the molecular genetic analysis of a total of 14 patients, 9 TSD and 5 SD. Furthermore, we reported three different novel mutations (one for TSD, two for SD) (Table 2,3). Since the c.1100_1111del (p.Gly367_Tyr370del) mutation was detected especially among patients with number 1-8. These patients were from four different families in a certain geographical region. We thought that this mutation site could be due to a founder effect for TSD (Table 2). Furthermore, c.1613+15_1613+18dupAAGT is an interesting mutation (Table 3). It is intronic, but is not located in a splice site (nucleotides +15,16,17,18 are not typically involved in splicing). Pierson et al.[20] have concluded that this alteration produces a cryptic splice donor site. Er et al.[4] reported that two different patients had deletions, including the area close to this region we detected.

The limitation of this study is the small sample size. Another limitgation is that only seven of the 14 patients had cranial MRI results.

In conclusion, we present fourteen GM2 gangliosidoses patients with clinical findings and molecular analysis in this study. Specific enzyme analysis and gene detection should be performed early in children with suspected GM2 gangliosidoses in the presence of clinical findings. Early intervention may be crucial for disease prevention through genetic counseling and prenatal diagnosis.

Yazar Katkıları: Çalışma konsepti/Tasarımı: BBG, FDB, ÖÖY; Veri toplama: BBG, ES, BS, HKU; Veri analizi ve yorumlama: BBG, ÖÖY, FDB, HKU; Yazı taslağı: BBG, FDB, HKU, ES, BS, FDB; İçeriğin eleştirel incelenmesi: BBG, FDB; Son onay ve sorumluluk: BBG, FDB, HKU, ES, BS, ÖÖY; Teknik ve malzeme desteği:BBG; Süpervizyon: BBG, BS; Fon sağlama (mevcut ise): yok.
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