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CASE REPORT

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The Effects of 6q26-q27 Terminal Deletion on Intellectual Disability & Brain Malformations and the Genotype/Phenotype Relationship: A Case Report

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ABSTRACT

Terminal microdeletion of chromosome 6q is a rare syndrome that can result in a spectrum of phenotypes varying from normal intelligence-minimal clinical symptoms to severe neurological defects and developmental delays. The most frequent clinical characteristics include developmental delays prior to and following birth as well as intellectual disability, brain malformations, and facial dysmorphism. These clinical characteristics may not be correlated with the size of the deletion; as many cases have been identified with either minor or major deletions, the genotype-phenotype correlation should be better investigated.

To our knowledge, this is the first report of 6q26-q27 chromosome microdeletion in Turkey. In this article, we determine the clinical and genomic characteristics of a 2-year-old female case of 6q26-q27 chromosome microdeletion by investigating the level of development of the patient, brain malformations and dysmorphic characteristics, and ultimately comparing them to other cases reported in literature. Our patient was diagnosed with severe Global Developmental Delays (GDD). Although our case had similar clinical characteristics to corresponding cases in literature, there is a difference in the variety and group of symptoms exhibited.

Keywords: 6q26-q27 microdeletion, intellectual disability, global developmental delay

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INTRODUCTION

Determining the etiology of brain malformations (BM) and intellectual disability (ID) usually proves to be difficult. Global developmental delay (GDD) is a term applicable in children below the age of 5. On the other hand, intellectual disability (ID) is a more appropriate term for older children as they can undergo valid and reliable Quality of Intelligence (IQ) tests. GDD/ID may be used interchangeably depending on age (1).

GDD/ID has an estimated prevalence of 1-3%. The etiological distribution of GDD/ID cases are 50% due to genetics, 10% due to prenatal exposure, due to gestational and perinatal complications by 10%, 5% due acquired disorders, and 25% with an unknown cause (2).

The etiology of BM and ID can be due to various genetic reasons; one reason is believed to be terminal deletion of the 6q chromosome. This is a rare chromosomal anomaly characterized by a diverse phenotype spectrum. Studies have shown that the genes in this area may have a significant role in normal brain development (3, 4). This syndrome has been reported to be characterized by intellectual insufficiency, facial dysmorphism, seizures, hypotonia, multiple malformations and brain abnormalities (hydrocephalus, cerebellar agenesis, corpus callosum agenesis) (5).

6q27 microdeletion is a complex syndrome involving various phenotypes that lead to brain malformations and neurodevelopmental disorders. The phenotypes may vary from normal intelligence-minimal clinical symptoms to severe neurological damage and serious developmental delays.

The most common clinical features of 6q terminal deletion include developmental delays before/after birth, intellectual disability, microcephaly and/or hydrocephalus, and facial dysmorphism (6).

Highlights

- **Effect of 6q26 deletion on neurodevelopmental and neurological disorders in children**
- **The first isolated case of 6q26 terminal deletion reported from Turkey**
- **6q26.27 deletion and genotype/phenotype correlation in a mentally retarded patient**
- **Congenital disorders and developmental delay in a case with 6q terminal deletion**

This article presents the genotype-phenotype correlation in the case of a 2-year-old female with 6q26-27 microdeletion and GDD. To the best of our knowledge, our case is the first case with 6q26-27 microdeletion syndrome in Turkey.

CASE

This case report presents a 24-month-old female patient delivered by C-section at 40 weeks with a height of 51 cm, weight of 3650 g, and a head circumference of 38 cm. At the time of birth, the mother was 26 years old and the father was 30, no consanguineous marriage was reported. The family history revealed an autism diagnosis in the mother's cousin. The mother did not have any illnesses or medication use throughout the pregnancy.

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The patient presented to our clinic with delayed speech. Ventriculomegaly was observed in the prenatal 20th week. The patient exhibited post-partum tongue-tie (ankyloglossia) and a weak sucking reflex, and magnetic resonance imaging (MRI) showed severe dilation of the third ventricle; a shunt was placed at 3 months of age. An arachnoid cyst became apparent following shunt placement. The patient also exhibited asymmetric crying and a closing anomaly of the left eye. Cranial MRI at 11 months showed fusion of the thalami, mesencephalothalamic synechia, elongated tectal plate, mild hypoplasia of the pons, brachium pontis hypoplasia, and mild hypoplasia in the cerebellar hemisphere. The patient was diagnosed with congenital hydrocephalus. The 5th sacral segment and coccyx could not be observed on spinal MRI. Caudal regression was observed. In our clinical evaluation, the 24-month-old female patient weighed 10.5 kg, 85 cm tall and with a head circumference of 46 cm. She had a high forehead and wide hairline. The position and shape of her nose were both normal. There was mild esotropia present in the right eye. She had evident facial asymmetry on the right side while crying, mild ptosis on the right eye, noticeable facial grooves, thin and long lips, broad philtrum, low-set and posteriorly rotated ears, and mild hypotonia accompanied by a diagnosis of epilepsy. No hearing problems were detected.

In terms of speech, the patient could only babble from 8 months of age. She had severe linguistic delay, especially in expressive and receptive terms. She could sit without support, hold her head up, and perform give-take interactions. She could not walk or crawl. The patient could point at objects she was interested in. She could follow objects with her eyes, but had limited eye contact, and could not recognize colors or body parts. She could not wave goodbye or perform a 'peek-a-boo.' The patient was evaluated with the Denver Developmental Screening Test; with a calendar age of 24 months, the patient had a general development level of a 6-7-month-old baby, social skill and gross motor levels of a 7 month-old, , fine motor level of a 10month-old, and language-cognitive development level of 7 months. She was diagnosed with moderate-severe GDD.

Genetic Analysis

Our patient had a 46, xx karyotype. Molecular karyotype analysis was conducted using the Affymetrix cytoscan 750k Array system; a 9515kbp deletion was detected on area q26q27 of the 6th chromosome, encompassing 30 OMIM genes (OMIM Genes: MAP3K4, AGPAT4, PARK2, PACRG, CAHM, QKI, PDE10A, T, MPCI, RPS6KA2, RNASET2, FGFRIOP, CCR6, GPR31, UNC93A, TCP10, MLLT4, KIF25, DACT2, SMOC2, THBS2, C6orf120, PHF10, TCTE3, ERMARD, DLL1, FAM120B, PSMB1, TBP, PDCD2). It contained the FRA6E fragile site.

Result: arr (GRCh37)6q26q27(161399393_170914297)*1 Size: 9514.904 kbp deletion

DISCUSSION

Because of its widespread use in patients with neurodevelopmental disorders, chromosome microarray analysis enabled the discovery of novel microdeletion/microduplication syndromes and the candidate genes responsible for certain clinical phenotypes (7).

In this study, we used microarray to identify the patient's 6q26-q27 deletion, determined the clinical and genomic features, and revealed the associated developmental state, brain malformations, and dysmorphic characteristics.

In this patient, we identified a 9515 kbp sized deletion on areas q26-q27 of the 6th chromosome, encompassing 30 OMIM genes. The 'FRA6E' fragile site was present. FRA6E is widely known as a genomic hotspot susceptible to chromosomal deletions. FRA6E is recognized as the third most fragile site that is susceptible to mutations in the human genome (8). The 'PARK2' gene is found at the center of this genomic area. PARK2 gene loss has been reported in Autism Spectrum Disorder and in intellectual developmental delay (9). Defects associated with the TBP gene have been found in patients with intellectual developmental delay. RNASET2, CCR6, DACT2, SMOC2, DLL1 were part of the deleted genes that are specific to the brain. These are all significant candidate genes that have the potential to affect functions of the brain and lead to clinical manifestations of terminal deletion syndrome (5).

Previous studies have shown that 6q terminal deletion can lead to highly variable clinical symptoms, regardless of the deletion extent (4, 10). This is because activation of the genes near the deleted or duplicated area may get affected and subsequently alter clinical results. This 'position effect' may explain the complexity and heterogeneity of the phenotype associated with terminal 6q deletion (11).

Global Developmental Delays (GDD)/Intellectual disability (ID) are common neurodevelopmental disorders in patients with 6q terminal deletion; the clinical extent of these conditions may vary among patients (5, 12). Our case exhibited a severe case of Global Developmental Delay (GDD). Our patient's clinical and neurological imaging features were presented and compared with other cases described in literature. (Table 1)

Patients with the microdeletion may face several problems such as brain malformations, cerebellar anomalies, corpus callosum anomalies, polymicrogyria, periventricular nodular hypertrophy (PNH) and hydrocephalus (13, 14). Similarly, our case exhibited cerebellar hypoplasia, arachnoid cyst, fusion of the thalami, mesencephalothalamic synechia, brachium pontis hypoplasia and hydrocephalus. Our patient with 6q microdeletion had an anomaly of the corpus callosum, PNH and polymicrogyria. The 6q27 terminal area contains 4 genes, THBS2, PHF10, DLL1, and C6orf70, which play critical roles in the morphogenesis of the nervous system during embryogenesis. In this context, the proximity of these genes may result in the development of many different brain malformations. The low-resolution MRI may have failed to detect small brain malformations (4, 5, 8, 10).

Structural brain abnormalities and developmental delays were not correlated with the size of the deletion and were identified in most cases with small or large deletions. There is no typical face figure in 6q terminal deletions. Common features include ear shape deformities, lip anomalies, and hypertelorism (5, 15). Our patient had low-set and posteriorly rotated ears, long-thin lips and broad philtrum deformities. Most cases do not exhibit a broad philtrum gap. Our patient was also diagnosed with epilepsy, which is observed in nearly half of 6q deletion cases. In addition, hypotonia is one of the most common clinical findings in 6q deletion patients (16). Brain malformations may be the reason for the development of hypotonia. Hypotonia can be regarded as a cause delays in gross and fine motor skills. Fewer cases have reported spinal cord malformations in the vertebrae; our patient's 5th sacral segment and coccyx bone were absent, and caudal regression was present, whichmay be associated with the delayed motor development and hypotonia of the patient.

In conclusion; 6q26-q27 microdeletion is a complex syndrome characterized by differing expressivity and genotype-phenotype manifestations (17). Our study described the clinical and genetic components of a case which the literature describes as 6q terminal deletion, and compared them to previous 6q26-q27 microdeletion cases with an emphasis on clinical features, including our contributions to better understand the clinical picture. In literature, clinical manifestation shows discrepancies among patients, and it is not clear which symptoms and findings present together. The only set of symptoms which may be considered typical and similar are developmental delays and structural brain anomalies (3, 5). Further studies are required to comprehensively evaluate the clinical manifestations of 6q26-q27 microdeletion.

Table 1. Anomalies seen in 6q terminal microdeletion syndromes

Reference	Hanna et al. (12) 2019	Thakur et al. (13) 2018	Peddibhotla et al. (5) 2015		Zhou et al. (10) 2014	Conti et al. (14) 2013	Dupe et al. (15) 2011	Mosca et al. (16) 2010	Eash et al. (3) 2005	Rooms et al. (17) 2006	Striano et al. (6) 2006	This study
Patient No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Deletion size Mb	0.3	0.3–0.6	1.5	5.39	1.3	~1.9	2.2	5.7	0.4	0.9–1.1	3–13	0.9
Age at diagnosis	11 yrs	fetus	30 mo	8 mo	27 yrs	18 yrs	New-born	8 yrs	8 yrs	18 yrs	4 yrs	24 mo
Sex	F	F	F	F	F	M	F	F	M	M	F	F
Facial Dysmorphism												
Hypertelorism	–	NA	+	+	+	+	NA	–	–	NA	+	+
Broad nasal bridge	+	NA	+	+	+	-	NA	-	-	NA	-	-
Ear anomalies	+	NA	+	+	-	-	NA	+	+	NA	+	+
Midface hypoplasia	NA	NA	-	-	-	NA	NA	NA	-	NA	-	-
Long philtrum	NA	NA	-	-	-	NA	NA	NA	-	NA	-	+
Thin upper lip	-	NA	-	-	-	-	NA	+	-	+	-	+
Palatal abnormality	+	NA	-	-	-	-	NA	-	-	+	-	-
Neurodevelopmental Anomalies												
Developmental Delay	+	NA	+	+	+	+	NA	+	+	+	+	+
Epilepsy	-	NA	-	+	-	+	NA	-	+	+	+	+
Structural brain anomalies/ abnormalities	+	+	+	+	+	+	+	-	+	+	+	+
Periventricular nodular heterotopia	+	-	-	+	-	+	NA	-	-	-	-	-
Polymicrogyria	NA	–	NA	NA	–	NA	NA	NA	+	NA	NA	–
Corpus callosum anomalies	–	-	+	-	+	-	NA	-	+	-	-	-
Hydrocephalus	+	-	-	+	-	-	+	-	+	-	-	+
Vertebral or spinal cord malformation	NA	-	-	-	+	+	NA	+	+	NA	-	+
Hypotonia	–	NA	+	+	+	+	NA	+	+	-	-	+

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Informed Consent: We have received written informed consent from the family to publish the patient's clinical information and medical images.

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