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OLGU SUNUMU / CASE REPORT

Constitutional chromosome 16q mosaicism: inheritance and phenotypic effects

16. kromozomun q kolunda gözlenen kalıtımsal mozaisizm ve fenotipik etkileri

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Abstract
Partial monosomies of chromosome 16q are rare. Here, we report a boy showed various aberrations in the q22.1→qter region of chromosome 16 and some important clinical features. The patient presented low IQ, delayed speech, delayed psychomotor development, late walking, clapping hands in case of excitement, deficiency in social adjustment and incompatibility with peers. Standard cytogenetic analysis was performed to patient and his family. Cytogenetic analysis results showed deletions, breaks and fragilities in the q22.1 region in one of chromosome 16. Analyzed cells of patient and his father showed 38% and 26% structural aberrations, respectively. Aberrations were inherited from an apparently normal father. The comparison of the present case to other 16q22.1→qter monosomies contributed to narrow down the critical region for delayed speech and full undeveloped fine motor skills in the 16q22.1→qter deletion syndrome. We showed that 16q deletions are confined to the phenotypic features such as delayed speech, full undeveloped fine motor skills.
Key words: Delayed speech, Full undeveloped fine motor skills, Monosomy 16q22→qter

Öz
16q parsiyel monozomilerine ender olarak rastlanmaktadır. Bu çalışmada, 16. kromozomun q22.1→qter bölgesinde değişik düzensizlikler gösteren ve bunlarla birlikte önemli klinik bulguları bulunan bir erkek çocuğu olgusu sunulmaktadır. Hastada; düşük IQ, konuşma güçlüğü, geç psikomotor gelişme ve yürüme, heyecan durumunda el çırpma, sosyal uyumda eksiklik ve akranlarıyla uyumlu olamama gibi klinik bulgulara rastlandı. Hastaya ve ailesine standart sitogenetik kromozom analizi yapıldı. Sitogenetik analiz sonucunda, 16. kromozomun q22.1 bölgesinde delesyonlara, kırıklara ve frajilitelere rastlandı. Hasta ve babasının analiz edilen hücrelerinde, sırasıyla %38 ve %26 oranlarında 16q22.1 bölgesinde yapısal hasarlara rastlandı. Kromozom hasarlarının fenotipik olarak normal görünümlü babadan aktarıldığı anlaşıldı. Bu vakadan elde edilen sonuçlar, diğer q22.1→qter monozomisi vakaları ile karşılaştırmalı olarak değerlendirildiğinde, q22.1→qter delesyon sendromunda geç konuşma ve motor yeteneklerin gelişememesi ile ilişkili kritik kromozom bölgesi daha da spesifik olarak ortaya çıkmıştır.
Anahtar kelimeler: Geç konuşma, gelişmemiş motor yetenekler, 16q22→qter monozomisi

INTRODUCTION

The chromosome 16 deletions are genetic conditions in which part of the genetic material that makes up chromosome 16 are missing[1]. Mosaicism as the presence of genetically distinct populations of somatic cells in an organism can result in major phenotypic changes and reveal the expression of otherwise lethal genetic mutations. Mosaicism can be caused by DNA mutations, epigenetic alterations of DNA, CAs and the spontaneous reversion of inherited mutations[1].

Partial monosomy for an autosomal chromosome is often associated with a specific pattern of recognizable malformations. Although such autosomal monosomy may involve large regions of DNA which would contain many genes, it is apparent that monosomy syndromes can originate from the effects of abnormal dosage of relatively few genes. Partial monosomies often originating

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from meiotic segregation of parental balanced translocations, can be viable and be associated with a specific recognizable pattern of malformations[1].

Published reports of chromosome 16 abnormalities have been described as rare events. A patient reported as a del(16q22) was subsequently shown to be a balanced t(5;16) translocation[1]. A malformed newborn with a karyotype 46,XX,del(16q21) was reported in 1977[2]. There have been confirmed partial monosomies for the distal segment of the long arm of chromosome 16. The deletions vary in size with the distal breakpoint between 16q22.1 and 16q24[2]. Generally, the more distal the deletion, the patients have been less severely affected[3,4]. Some of the patients with deleted 16q have similar patterns of malformations and this has resulted in the concept of a deletion syndrome involving the long arm of chromosome 16. It has been suggested that there are critical regions within 16q22[5] which produce a pattern of features including growth retardation, intellectual disability, physical anomalies, renal and musculoskeletal malformations and congenital heart defects. In addition, deletion of chromosome 16q is frequently associated with diverse tumors. Numerous studies strongly suggest the presence of one or more tumor suppressor genes on chromosome 16q22 to 16qter including the widely studied cadherin gene family. However, the specific tumor suppressor genes residing in this region need better definition and characterization.

Here, we report a boy showed some important clinical features and various paternally inherited CAs in the q22.1→qter region of chromosome 16. We have compared clinical and the various aberrations in the q22.1→qter region of chromosome 16 in this case with those described in the literature to gain more accurate genotype-phenotype correlations.

CASE

The patient is the first child of healthy parents (non-consanguineous). He was born preterm at 39 weeks of gestation with a weight of 3.700 kg, now was 4.5 years old. He applied to the clinic because he was delayed in speaking and his fine motor skills were not good. Perinatal anoxia was not observed. Patient started to walk at 18 months. He could compose simple sentences but showed difficulties in understanding. Social adaptation was not good and he was not inclinable to play with his peers. Results of physical and neurological examinations were normal. Eye contact, interest to his surroundings and speaking about individuals and events in his near surroundings were present. When he gets excited he shoots one of his hands. IQ was scored as 72 (Stanford Binet test). Tyroid functions, blood levels of glucose, vitamin B12 and folate were also recorded as normal. In cerebral MRI scanning, a small arachnoid cyst which developed in the posterior aspect of the vermis and did not have any pressing effect was found. EEG test result showed biphasic and triphasic sharp waves in the mid-temporal region. Waves sometimes took generalized form.

Cytogenetic analysis

Firstly, patient has been seen and diagnosed by the Departments of Pediatrics and then they were referred to Department of Medical Biology and Genetics, Faculty of Medicine, Çukurova University for cytogenetic analyses. Peripheral blood was taken from the patient and her parents for culture studies. A 0.3 ml sample of blood was incubated at 37°C for 72 h in 2 media (RPMI-1640). For eliminating ethical concerns, informed consent document has been obtained from patient's parents. Standard techniques used for the cultivation of lymphocytes from peripheral blood. Metaphase spread preparations and GTG-banding was performed according to standard method. A total of 50 metaphase cells were analysed. Evaluation of karyotypes was done according to the International System for Human Cytogenetic Nomenclature (ISCN, 2005).

A total of 3 individuals from the same family members were analyzed (the patient and his parents). The patient showed structural aberrations in 38% (19 cells) of 50 cells analyzed but the karyotype results were normal in 62% (31 cells). These CAs were very serious and very important genetic instabilities; 4 deletions (21.1% of CAs), 3 chromosome breaks (15.8%), 5 chromatid breaks (26.3%) and 7 gaps (36.8%) in q22.1 region of chromosome 16 (Figure). Chromosome breaks were also evaluated as deletion. So the ratio of all deletions proportion was 18% (4 del, + 5 chrbr) (Table). In the father, the distal deletion on chromosome 16q was found in 28% (14 cells) of 50 cells analyzed. These CAs included 4 deletions (8%), 5 chromosome breaks (10%), 4 chromatid breaks (8%) and 1 gap (2%). The proportion of all deletions was 18% (4 del, 5 chrbr) (Table). The

mother showed normal karyotype. Structural chromosome 16 abnormalities in the boy inherited from an apparently normal father.

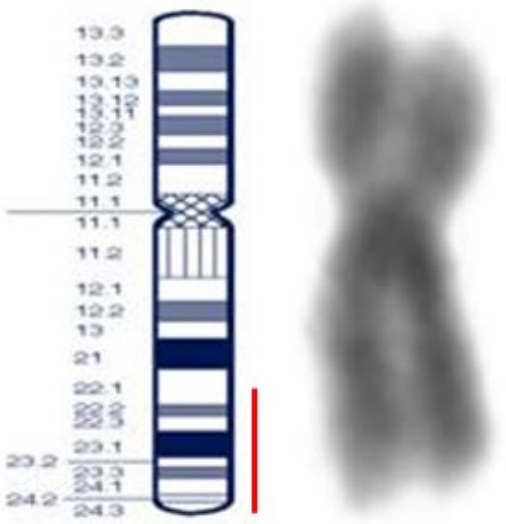

Figure 1. The damaged region on q22.1→qter region of chromosome 16.

DISCUSSION

Partial monosomies of chromosome 16q are rare. To our knowledge, there have been no confirmed partial monosomies for the very distal segment of the long arm of chromosome 16. In this study, we describe deletions, breaks and frajilities on the distal region of 16q22.1→qter sub-band in 38% of cells in a boy. Those CAs were inherited from an apparently normal father. Nevertheless, we have compared clinical and cytogenetic findings of this case with those described in the literature to gain more accurate genotype-phenotype correlations. The proband showed the low IQ, delayed speech, delayed psychomotor development, late walking, clapping hands in case of excitement, deficiency in social adjustment and incompatibility with peers. These findings suggested that the critical region responsible for the low IQ and psychomotor retardation might span about the distal region of 16q22.1 to the 16qter sub-band.

The literature on 16q deletions, though relatively sparse, describes an array of serious medical and developmental consequences. There are no published cases with the deletion 16q22→qter mosaicism. However, 16q22 deletion is a recognized OMIM[6] syndrome, associated with the deletion of the whole 16q22 band, presenting failure to thrive in infancy, poor growth, delayed psychomotor development, hypotonia, and dysmorphic features, including large anterior fontanelle, high forehead, diastasis of the cranial sutures, broad nasal bridge, hypertelorism, low-set abnormal ears, and short neck. The phenotypic features and deletion sizes of the affected patients are variable, but deletion of 16q22 appears to be critical for manifestations of the syndrome[5].

Our case had lost only part of this chromosome material and showed significant impairments. Our case did not show the typical symptoms of 16q22 deletion syndrome, such as low birth weight, global developmental delay, short stature, microcephaly, low set dysmorphic ears and mild facial dysmorphisms, but shows only delayed psychomotor development. This phenotypic variability should depend on mosaicism rate and deletion size, but deletion of 16q22→qter appears to be critical for manifestations of the syndrome.

Establishing a clear picture of the developmental consequences of chromosome 16q deletions is difficult because of the small number of published reports, the limited developmental data that are usually provided, the lack of data at more than one point in time, and the fact that the cases vary considerably in relation to the exact breakpoints and size of deleted segments[1]. It reported a Japanese boy with an approximately 1.2-Mb deletion of chromosome 16q22[7]. The proband showed mild psychomotor retardation and dysmorphic features, including midface hypoplasia, upslanting palpebral fissures, epicanthal folds, prominent earlobes, broad nasal tip, and pointed chin. We have attempted to clarify the role of distal deletions, breaks and fragilities on chromosome 16q22.1→qter mosaicism in the development of psychomotor retardation. The 16(q22.1→qter) deletion in 38% of the proband's cells might be responsible for the phenotypic features, but it was noteworthy that father did not show clinical manifestations which patient showed. He was normal healthy man. It was also important that the father's mosaicism rate is 10% lower than the child; indicating that the rate of chromosomal damage increases, the clinical picture also increases. How those aberrations were initially constituted, what caused them. First possible

explanation is that the father inherited those aberrations from his parents (grandparents of patient) and this ratio of aberrations (28%) did not lead to any clinical consequence. The second explanation and the more possible one was that those chromosomal aberrations were constituted during development of father, affecting his somatic and gonad tissues.

Extrinsic or intrinsic factor/factors might have led to above-mentioned chromosome 16 related damages which passed on to child with an increased ratio of 10%. Complete or partial aneuploidy may involve large regions of DNA which would contain many genes, it is apparent that aneuploidy syndromes can originate from the effects of abnormal dosage of relatively few genes. Autosomal chromosome monosomies are lethal. However, partial monosomies, often originating from meiotic segregation of parental balanced alterations, can be viable and be associated with a specific recognizable pattern of malformations. As for partial and full trisomies, it is likely that one or a few genes are involved in producing the abnormal phenotype. Aneuploidy for the entire chromosome 16 is lethal. Trisomy 16 is found in approximately 5% of spontaneous abortuses[8].

Monosomy for this chromosome has not been reported in studies of abortion material, although karyotyping of sperm shows that this aneuploidy probably occurs[9]. 16q22.1→qter mosomies are rare cases, but a number of patients with interstitial long arm deletions of chromosome 16 have been reported. Some of these patients have similar patterns of malformations and this has resulted in the concept of a deletion syndrome involving the long arm of chromosome 16.

Table 1. The structural aberrations on chromosome 16.

Chromosome 16 images	**Karyotypes**	**The patient**		**The father**	
		Cell #s	%	Cell #s	%
	Normal chromosome 16	31	62.0	36	72.0
	Chromosome 16 aberrations	19	38.0	14	28.0
	Total	50		50	
	Structural chromosome 16 abnormalities				
	del(16)(q22.1→qter)	4	8.0	4	8.0
	chrbr(16)(q22.1)	5	10.0	5	10.0
	total	9	18.0	9	18.0
	chtbr(16)(q22.1)	3	6.0	4	8.0
	gap(16)(q22.1)	7	14.0	1	2.0
	total	19	38.0	14	28.0

The presented case is a young boy with a rare chromosome disorder involving a distal deletion on chromosome 16 (q22.1→qter) in mosaic form. The present case provided evidence that a larger deletion possibly caused delayed speech and full undeveloped fine motor skills might be hidden behind a classical phenotype that is specific for a syndrome. However, more cases, well characterized both for phenotypic signs and genomic details, are needed to further restrict candidate regions for phenotypic features in 16q deletions. It is evident that the genes located on 6q22.1→qter region are important in

psychomotor development. Therefore, chromosome analysis should be performed to family members of 16q deletions carriers and a clinical geneticist or genetic counsellor should give guidance to those families.

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