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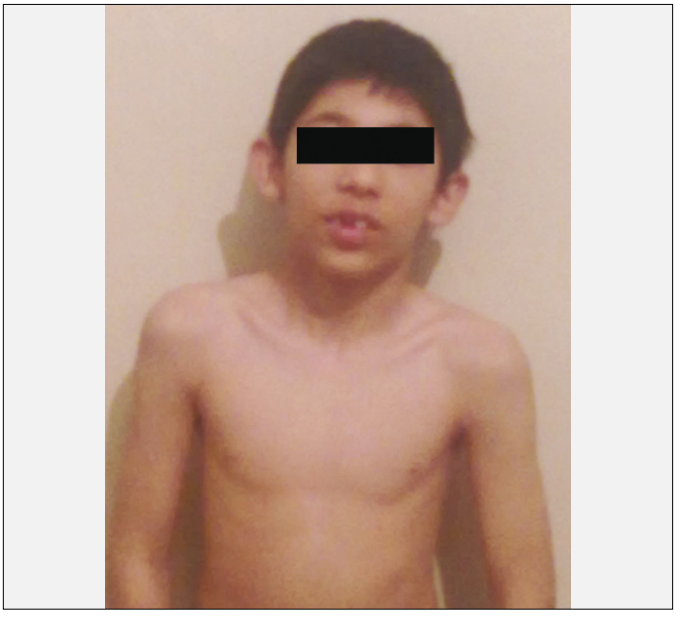
Mosaic ring chromosome 6 and clinical significance in resistant epilepsy

To the Editor,

Epilepsy is a neurologic disease occuring as a result of sudden, abnormal and synchronized discharges of a group of neurons in the central nervous system (CNS) characterized with convulsions (1). Genetic diseases with monogenic, chormosomal and multi-factorial inheritance are involved in the etiology in 40% of the patients with epilepsy (2). Very significant dysmorphic characteristics are present in most chromosamal disorders associated with epilepsy (3). We presented a 7-year old male patient who was referred to our clinic because of resistant epilepsy and whose chromosomal analysis on peripheral blood revealed mos 47,XY,+r(6)[3]/ 46,XY, r(6)[40]/ 45,XY,-6[7]. Based on this case we aimed to discuss the significance of use of cytogenetic techniques and multidiciplinary study in understanding clinical and basic mechanisms of epilepsy.

Familial history of our patient who had mental retardation revealed no consanginuous marriage or recurrent abortus. He was born from healthy parents from the second pregnancy and his perinatal history was normal. On physical examination, his body weight was found to be 20 kg (10-25th percentile), his height was found to be 104 cm (<3rd percentile) and his head circumference was found to be 36 cm (<3rd percentile). The patient had dysmorphic characteristics including bilateral wide and borderline low-set ears, brachycephaly, low frontal hair line, wide and prominent nose, micrognatia and microcephaly. In addition, he had high-arched palate and irregular and overcrowded teeth (Picture 1). Our patient had retardation in neuromotor development. It was reported that he started to walk without support in the last one year with physiotherapy education. The patient was receiving speech therapy. In spite of this, he could not make a long sentence composed of 3-4 words and talked indeterminedly. Abdominal ultrasonography (USG), brain magnetic resonance imaging (MRI) and metabolic screening tests were found to be normal. The intelligence quotient was measured to be 43 by WISC-R. Sleep electroencephalography (EEG) revealed diffuse epileptic changes. The mother stated that the patient was diagnosed as epilepsy when he was 6 months old, but he had generalized seizures 2 times a week despite all antiepileptic drugs used with different combinations. Chromosomal analysis on peripheral blood was planned because of the dysmorphic characteristics, epilepsy and mental retardation. For karyotype analysis peripheral blood lymphocytes stimulated by phytohemaglutinine (FHE) were cultured for 72 hours. Metaphase preparations obtained from the culture were stained using trypsin-giemsa banding method (GTG). Cytogenetic examination of prometaphases revealed a chromosomal organization of mos 47,XY,+r(6)[3]/ 46,XY,r(6)[40]/ 45,XY,-6[7] (Picture 2). Ring chromosome was observed to have a single centromer in CBG banding. The karyotypes of the mother and the father were found to be 46,XX and 46, XY, respectively.



Picture 1. Dysmorphic characteristics including bilateral wide and borderline low set ears, wide and prominent nose, micrognatia and microcephaly are observed

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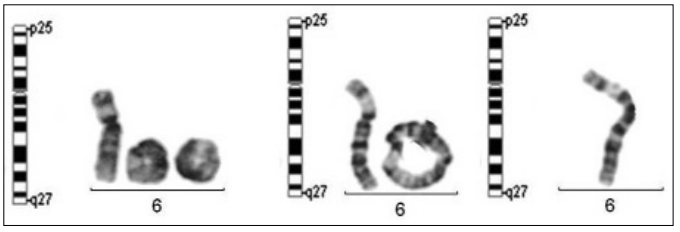

Picture 2. The appearance of ring chromosome 6 belonging to mos 47,XY,+r(6)[3]/ 46,XY, r(6)[40]/ 45,XY,-6[7] karyotype determined by G banding in the chromosome analysis

Ring chromosome is defined as a structural chromosomal change occuring by adherence of the two ends of a normal chromosome forming a ring. Ring chromosomes are observed rarely and are generally de novo (3). More than 90% of the patients with ring chromosome have been observed to be rare. Phenotype and genotype may show difference, since the amount of substance deleted at the ends varies from patient to patient. (3,4). Ring chromosome 6 was defined by Moore et la.(4) for the first time in a child with growth retardation. Afterwards, cases from different areas have been reported occasionally. These diseases reported have generally been diagnosed postnatally, but there are also patients who have been diagnosed prenatally (3,4,5,6). Chilren with ring chromosome 6 who have been reported until the present time in the literature have been observed to display a wide clinical spectrum ranging from normal intelligence level to neurologic and dysmorphic findings including epilepsy, hydrocephaly, microcephaly and mental retardation (5,6). Similarly, our patient had dysmorphic characteristics including microcephaly and low-set ears. However, the main significant findings in our patient included epilepsy and mental retardation. Jajal et al. (7) reported that the phenotypic properties caused by chromosome 6p deletion may be similar to the phenotype caused by ring chromosome 6 (7,8). However, Kara et al. (3) showed that de novo mosaic ring chromosome 6 and deletions occuring at the end of chromosome 6q caused different clinical pictures. This was thought to be related to the unstable state of ring chromosome in mitosis, mosaicism of cells and variance of the regions where deletion occurs. In the literature, a relation has been shown between some chromosome regions and epilepsy by "linkage" analyses. 6p22,32 and 6q23-25 which are among these regions were deleted in our patient explaining epilepsy. Proteins coded by EPM2A, EPM2B, NHLRC1 genes defined in these regions have been shown to remove polysaccharides from the cell by tyrosine phosphatase activity (9,10). In patients in whome these genes are not functioning, understanding complex genetic mechanisms is important in terms of defining neurotransmitters and ion channels determining the course of treatment.

Understanding genetic base in patients diagnosed with epileptic syndromes is the most significant step in determining treatment. In addition to genetic counselling for the family, understanding the physiopathology of the disease and development of new therapeutic methods will be only possible by displaying the profile of the genetics of epilepsy. Development of more specific treatments with studies directed to determine known genes and chromosome anomalies and potential prevention of the etiopathogenetic process will pioneer applicable treatment methods in the future.

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