

Jacobsen syndrome without thrombocytopenia: a case report and review of the literature

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Jacobsen syndrome (JS), a rare disorder with multiple dysmorphic features, is caused by the terminal deletion of chromosome 11q. Typical features include mild to moderate psychomotor retardation, trigonocephaly, facial dysmorphism, cardiac defects, and thrombocytopenia, though none of these features are invariably present. The estimated occurrence of JS is about 1/100,000 births. The female/male ratio is 2:1. The patient admitted to our clinic at 3.5 years of age with a cardiac murmur and facial anomalies. Facial anomalies included trigonocephaly with bulging forehead, hypertelorism, telecanthus, downward-slanting palpebral fissures, and a carp-shaped mouth. The patient also had strabismus. An echocardiogram demonstrated perimembranous aneurysmatic ventricular septal defect and a secundum atrial defect. The patient was <3rd percentile for height and weight and showed some developmental delay. Magnetic resonance imaging (MRI) showed hyperintensive gliotic signal changes in periventricular cerebral white matter, and leukodystrophy was suspected. Chromosomal analysis of the patient showed terminal deletion of chromosome 11. The karyotype was designated 46, XX, del(11) (q24.1). A review of published reports shows that the severity of the observed clinical abnormalities in patients with JS is not clearly correlated with the extent of the deletion. Most of the patients with JS had short stature, and some of them had documented growth hormone deficiency, or central or primary hypothyroidism. In patients with the classical phenotype, the diagnosis is suspected on the basis of clinical findings: intellectual disability, facial dysmorphic features and thrombocytopenia. The diagnosis must be confirmed by cytogenetic analysis. For patients who survive the neonatal period and infancy, the life expectancy remains unknown. In this report, we describe a patient with the clinical features of JS without thrombocytopenia. To our knowledge, this is the first case reported from Turkey.

Key words: Jacobsen syndrome, thrombocytopenia, 11q deletion.

Jacobsen syndrome (JS) is a contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11. The condition was first described by Jacobsen in 1973 in a family with multiple members that inherited an unbalanced 11;21 translocation derived from a balanced translocation carrier parent¹. The most common clinical features of JS include: pre- and postnatal physical growth retardation, psychomotor retardation, characteristic facial dysmorphism, and thrombocytopenia or pancytopenia. A subset of patients have malformations of the

heart, kidney, gastrointestinal tract, genitalia, central nervous system, and/or skeleton. Ocular, hearing, immunological, and hormonal problems may be also present^{2,3}. More than 200 cases of JS have been reported so far in the literature^{3,4}. The estimated occurrence of JS is about 1/100,000 births²⁻⁴. The female/male ratio is 2:1. In most cases, de novo isolated terminal deletions of 11q have been found, while in the remainder, one of the parents has been a carrier of a balanced chromosome translocation involving 11q⁵. Familial cases of



Fig. 1. Facial dysmorphism of the patient.

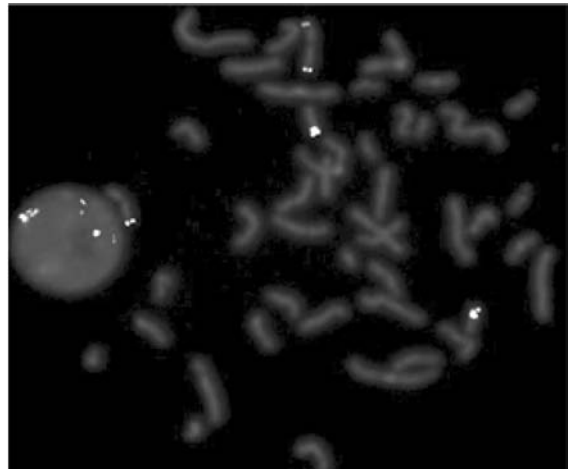


Fig. 3. Chromosome analysis of the patient.

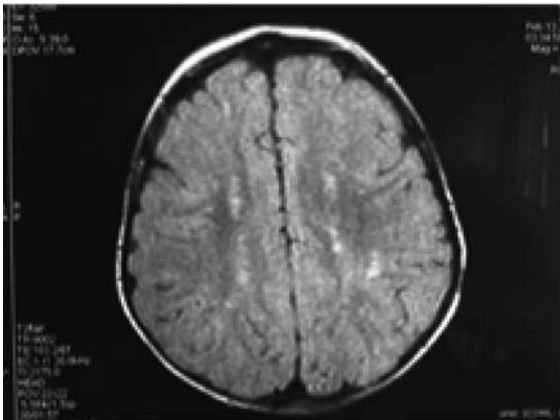


Fig. 2. MRI of the patient.

JS are very rare. Almost all JS patients present with thrombocytopenia (Paris-Trousseau type), abnormal platelet function, dysmegakaryocytes in bone marrow, and abnormally appearing “giant” platelets in the peripheral blood⁶.

In this report, we describe a patient with the clinical features of JS without thrombocytopenia. To our knowledge, this is the first case reported from Turkey.

Case Report

A female from the first pregnancy of non-consanguineous parents was born at 38 weeks gestation to a 29-year-old female, delivered by cesarean secondary to placental abruption. The pregnancy was uneventful. The patient admitted to our clinic at 3.5 years of age with a cardiac murmur and facial anomalies. Facial anomalies included trigonocephaly with bulging forehead, hypertelorism, telecanthus, downward-



Fig. 4. FISH analysis of the patient.

slanting palpebral fissures, and a carp-shaped mouth. The patient also had strabismus. An echocardiogram demonstrated perimembranous aneurysmatic ventricular septal defect and a secundum atrial defect. The patient was <3rd percentile for height and weight and showed some developmental delay. She was referred to us from another clinic with a suspected diagnosis of hypochondroplasia. Complete blood count, including platelets, and urea, creatinine, glucose, alanine aminotransferase, aspartate aminotransferase, calcium, phosphate, sodium, and potassium levels were normal. Thyroid function tests were appropriate for her age. Insulin-like growth factor (IGF-1)

and IGF binding protein-3 (IGFBP-3) levels were normal. FGFR3 gene mutation test was normal. Magnetic resonance imaging (MRI) showed hyperintensive gliotic signal changes in periventricular cerebral white matter, and leukodystrophy was suspected.

Chromosomal analysis of the patient showed terminal deletion of chromosome 11. The karyotype was designated 46, XX, del(11)(q24.1). Chromosomal analysis in both parents was normal. Using fluorescence in situ hybridization (FISH), a deletion of the terminal part of chromosome 11q was identified in the patient. The chromosome breakpoint was mapped to 11q24.1 qter. The patient was accepted as JS according to these findings, and followed in our clinic.

Discussion

Jacobsen syndrome (JS) is a rare cytogenetic disorder that has a well-characterized phenotype. The deletions are variable in size, ranging from as small as 7 Mb to greater than 20 Mb². A review of published reports shows that the severity of the observed clinical abnormalities in patients with JS is not clearly correlated with the extent of the deletion. Thus, there is no clear phenotype-karyotype correlation in patients with JS⁷. However, Penny et al.² suggested that there was a general relationship between the degree of psychomotor impairment and extent of deletion. Patients with larger deletions extending into 11q23 or q24.1 tended to have moderate psychomotor retardation with significant speech impairment, while the patients with small terminal deletions had mild or no psychomotor retardation. Many possible explanations have been suggested for the apparent lack of phenotype-karyotype correlation in JS patients. These explanations range from undetected mosaicism to redundant gene loci⁴. The published cases show a wide range of phenotypic variability, which could be related either to differences in the size of the deleted region at the molecular level, the different ages of the patients (stillborn to 21 years), or a non-homogeneous criterion of classification. Most of the patients with JS had short stature, and some of them had documented growth hormone deficiency or central or primary hypothyroidism. Our patient had a short stature but had neither growth hormone deficiency nor

hypothyroidism. Another defect, other than endocrine abnormalities, might cause growth retardation in these patients.

There has been an apparent abnormal sex ratio deviating towards females in patients with JS. Approximately 70% of the patients with 11q deletion were female, including the present case. In order to explain the preponderance of female patients with JS, it is hypothesized that the expression of 11q terminal deletion is somehow determined by the sex chromosome complement and that it contributes to a differential survival depending on the sex of the patient⁸.

Paris-Trousseau syndrome is characterized by thrombocytopenia, abnormal platelet function, abnormal megakaryocytes (from bone marrow), and abnormally appearing giant platelets in the peripheral blood. This phenotype is highly penetrant, affecting at least 92% of patients with JS. Our patient was found to have none of the features of Paris-Trousseau. FISH analysis revealed terminal deletion of chromosome 11. The chromosome 11 breakpoint was localized to 11q24.1 qter. The *FLI-1* gene (Friend leukemia virus integration 1) maps to chromosome subband 11q24, in the region deleted in JS patients. It is a proto-oncogene belonging to the ETS family and interacting with a number of genes involved in vasculogenesis, hematopoiesis and intercellular adhesion. There is *in vivo* and *in vitro* evidence that *FLI-1* plays a fundamental role in megakaryocytic differentiation and that heterozygous loss of the *FLI-1* gene is associated with dysmegakaryocytopoiesis and the Paris-Trousseau thrombocytopenia in JS⁷. However, given the normal platelet number in our patient, we suggest other genes proximal to 11q24.1 may contribute to the Paris-Trousseau syndrome. In a recently published report, Trkova et al.⁹ also suggested that the deletion of the seemingly causal *FLI-1* gene might lead only to the predisposition to thrombocytopenia, and a second unknown hit may be required.

In patients with the classical phenotype, the diagnosis is suspected on the basis of clinical findings: intellectual disability, facial dysmorphic features and thrombocytopenia. The diagnosis must be confirmed by cytogenetic analysis. The clinical diagnosis may be difficult in patients with less characteristic clinical aspects, borderline mental development,

and with no thrombocytopenia. Children with JS share some clinical features (short stature, short, wide, sometimes webbed neck, downslanting palpebral fissures, ptosis, and aortic or pulmonary stenosis) with Turner and Noonan syndromes. Prenatal diagnosis is possible by amniocentesis or chorionic villus sampling and cytogenetic analysis. Management is multi-disciplinary and requires evaluation by a general pediatrician, pediatric cardiologist, neurologist, and ophthalmologist. About 20% of children die during the first two years of life, most commonly related to complications from congenital heart disease, and less commonly from bleeding. For patients who survive the neonatal period and infancy, the life expectancy remains unknown. An important limitation of this report is the absence of SNP or CGH analysis, which cannot be done because of the high cost and ethical issues. However, we think that this report contributes to the current literature as the first case reported from our country and because no thrombocytopenia was seen despite the large size of the deletion. Thus, in the future reports, new genes or secondary trigger mechanisms must be researched to better define thrombocytopenia.

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