

## Morphological and genetic abnormalities in a Jacobsen syndrome

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### Abstract

Jacobsen syndrome (JS) is a contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11. The syndrome is rare and there are very few observations regarding the pubertal period of the affected individuals. We report the case of a 22-year-old female, with JS, monitored since the age of three months. She presented intrauterine growth retardation, failure to thrive and feeding difficulties from the first year of the life, and she learned to walk at the age of four years. Phenotypically, the case is characterized by distinctive facial and limb abnormalities. She shows spasticity and profound delay in gross and fine motor skills. Additionally, she has severe learning difficulties, non-verbally communicates, and displays hetero-aggressive and auto-aggressive behavior. The evolution of puberty was characterized by hypogonadism and primary amenorrhea. Thrombocytopenia and IgM deficiency became apparent also at puberty. Array comparative genomic hybridization (aCGH) analysis confirmed a deletion of 16.3 Mb on 11q23.3-q23.4. We report this case as the first documented case of JS in Romania, as well as for clinical particularities (long period of survival and late appearance of hematological and immunological disorders).

**Keywords:** Jacobsen syndrome, mental retardation, thrombocytopenia, puberty, aCGH.

### Introduction

Jacobsen syndrome (JS) is a contiguous gene deletion syndrome caused by partial deletion of the long arm of chromosome 11. It was first described by Jacobsen, in 1973 [1]. The key features of the syndrome are prenatal and postnatal growth failure, mental retardation, craniofacial dysmorphism, and thrombocytopenia.

It is a rare syndrome, there have been reported over 200 cases. Females are more prone to develop the disease. From genetic point of view, most of JS cases are the result of a *de novo* deletion and a smaller number of cases are due to balanced translocations [2]. JS is typically not inherited, but an affected person can pass the deletion to his children [3]. According with the published data, JS can be associated with attention deficit-hyperactivity disorder (ADHD) and with an increase in autism spectrum disorders [4]. There is no data in the literature about the life expectancy. A quarter of children with JS die in infancy. The most common cause of death is congenital heart diseases followed by hematological disorders. The patients that survive need a long-term special care. The oldest patient with JS is around 50 years old.

The aim of this case report is to contribute to a better knowledge of the phenotype and genotype of this rare syndrome.

### Case presentation

The patient P.O., female, was referred to Department

of Genetics, "Dr. Gavril Curteanu" Municipal Clinical Hospital, Oradea, Romania, on the third month of life, in July 1993, by the family doctor for craniofacial dysmorphism. The patient was the second child in the family, born prematurely at 32 weeks (1850 g), Apgar score was 4 at one minute and 5 at five minutes. Family history was unremarkable, being the child of young, healthy, non-consanguineous parents.

### Clinical signs and symptoms

Clinical signs and symptoms revealed:

- growth retardation (weight and height below the 5<sup>th</sup> percentile);
- craniofacial dysmorphism: trigonocephaly, high prominent forehead, flat occiput, thin and brittle hair, downslanting palpebral fissures, palpebral ptosis, epicanthal folds, iris coloboma, arched eyebrows, hypertelorism, small and low set ears, short nose with large and depressed nasal bridge, anteverted nostrils, downturned corners of the mouth, large mouth, high palate, dental anomalies, micrognathia (Figure 1);
- limbs and toraco-abdominal anomalies (Figures 2 and 3): brachydactyly, clinodactyly, camptodactyly; bilateral simian creases; club feet; muscular atrophy; stiff joints, pectus excavatum; dorsal scoliosis, lumbar lordosis;
- neuromotor and psychiatric disabilities: delayed stands and walk, profound language learning difficulties, compulsive, hetero-aggressive and auto-aggressive behavior;

▪ additional signs and symptoms appeared at puberty: primary amenorrhea, genital infantilism (Tanner stage I), repeated episodes of sinusitis.



**Figure 1** – Cranio-facial dysmorphism at 11 years (a) and 22 years (b); note iris coloboma (a and b), self harm and injury of the perioronasal region (b).



**Figure 2** – Brachydactyly, clinodactyly and camptodactyly at hands.

### Genetic analysis

Karyotype was performed by blood sample (lymphocytes) analysis. The cells were stained by Giemsa (G), 500 bands resolution in 20 metaphases analyzed. We used an Olympus BX51 light microscope with white and black camera and software provided by CytoVision. The karyotype result was 46,XX,del(11)(q23.3-qter).

Genetic assessment through array comparative genomic hybridization (aCGH) analysis was performed. DNA isolated and purified from peripheral blood was examined for copy number variations (CNVs) using Agilent CGH + SNParray 4x180K ISCA design oligonucleotide microarray (Agilent Technologies, Inc., USA). Copy number data was analyzed with Agilent Cyto-genomics 4.0 software. aCGH analysis revealed an interstitial deletion on chromosome 11q23.3-q23.4 of about 16.3 Mb (Figure 4). The deleted region encompasses several protein-coding genes, such as: *SORL1*, *TIRAP*, *ACAD8*, *ROBO3*, *KIRELL3*, *HYLS1*, *SCL37A4*, *MFRP*, *KCNJ1*, *CIQTNF5*, *PVRL1*, *TECTA* and *FEZ1*.

### Laboratory investigations

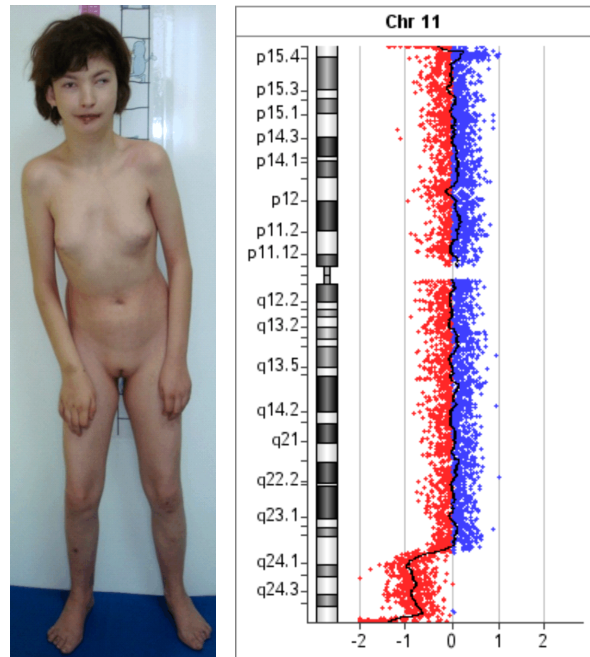
Laboratory investigations exhibited:

- hematological analysis: peripheral blood was normal on red and white cells; thrombocytopenia ( $62\ 000/\text{mm}^3$ ); bone marrow cellularity with normal appearance;
- immunological analysis: low value of IgM 42 mg/dL (reference range 56–352 mg/dL);
- biochemical and endocrinological analyses were normal.

### Imagistic investigations

The bone age (wrist radiography) at 16 years old was delayed (Greulich–Pyle atlas), corresponding to age of 14 years. Abdominal and genital ultrasound showed splenomegaly 14.2 cm (reference value 11 cm), ptosis

of right kidney. Brain magnetic resonance imaging (MRI) shows cerebral atrophy and sphenoidal sinusitis.



**Figure 3** – Stature and posture anomalies; limb joint contractures at 22 years.

**Figure 4** – Array-based comparative hybridization revealed an interstitial deletion on chromosome 11q23.3-q23.4 of about 16.3 Mb.

### Interdisciplinary checkups

Ophthalmologic exam showed bilateral iris coloboma, strabismus. Cardiac exam and electrocardiogram (EKG) were normal. Gynecologic exam show primary amenorrhea, genital infantilism. Neurological exam revealed chronic encephalopathy, cerebral palsy, right hemiparesis, severe psychomotor retardation and electroencephalography (EEG) generalized diffuse irritative activity with synchronous discharge. Psychological exam revealed a severe mental retardation, intelligence quotient (IQ) <25, behavioral problems, aggression, psychomotor agitation.

### Discussion

Jacobsen syndrome is a very rare chromosomal anomaly involving partial deletion of chromosome 11. It was first described in 1973, by Jacobsen, in a family where many members have inherited an unbalanced translocation t(11, 21) from one parent. Concerning the etiology of this syndrome, 85% of cases presented *de novo* terminal deletions, 15% of cases presented unbalanced translocations; a few cases have been reported in mosaic form [1, 2, 5, 6]. The breakpoint was at a fragile site, *FRA11B*, in a small number of cases. The deletion size ranges from 7 Mb to 20 Mb, with the proximal breakpoint within or telomeric to sub-band 11q23.3 and the deletion extending usually to the telomere [7]. Ji *et al.* (2010) noted that the incidence of distal 11q deletions in the population is difficult to estimate, but JS occurs in about one in 100 000 births, and the female:male ratio is 2:1 [8, 9]. Our case is isolated, there were no other affected family members and parents have normal karyotype; the anomaly is considered a *de novo* deletion. The implementation of

array technology in the clinics has permitted precise characterization of the deletions and detailed genotype–phenotype correlation in cases with JS.

The diagnosis is suspected based on clinical findings: mental retardation, cranio-facial dysmorphism and thrombocytopenia and confirmed by cytogenetic analysis. Differential diagnosis was made with Turner syndrome and Noonan syndrome: short stature, short, wide, sometimes webbed neck, downslanting palpebral fissures, ptosis, aortic or pulmonary stenosis. Occasionally, JS children have had a clinical diagnosis of Kabuki syndrome (mental retardation, unusual palpebral fissures, short stature, finger pads). All these syndromes were excluded by cytogenetic and/or molecular testing [2].

Concerning the genotype/phenotype correlation, usually, a large deletion shows a severe phenotype because the involved region (11q23–qter) is one very rich in genes (more than 300 genes). Genes in this region are playing a critical role in the normal development of brain, heart and craniofacial development. In our case, without sequencing, only by clinical bases we can appreciate that the most probably it is a large deletion [10]. According with Afifi *et al.* (2008), almost all patients with JS have a bleeding disorder called Paris–Trousseau syndrome, caused by low platelets number [11]. Usually, hematological anomalies (thrombocytopenia or pancytopenia) occur at birth, often being the first sign of disease; in our case, thrombocytopenia appeared only at pubertal age, with no associated obvious clinical manifestations [12]. Paris–Trousseau syndrome is a syndrome caused by the deletion of the 11q23.3, characterized by thrombocytopenia due to dysmegakaryopoiesis. Losos *et al.* considered that Paris–Trousseau syndrome is a variant of JS manifested by a mild lifelong bleeding tendency [13]. In patients with JS that have deletions which do not involve 11q23.3, thrombocytopenia exists but is mild and resolves spontaneously in the first year of life.

Immunodeficiency is another feature characteristic of JS manifested by repeated respiratory infections including sinusitis [14, 15]. JS leads to IgG, IgM deficiencies along with B-, T- and natural killer (NK)-cell abnormalities and should therefore be considered a syndromic primary immunodeficiency. Our patient has had repeated episodes of sinusitis, and also IgM deficiency. Dalm *et al.* concluded that early detection of immunodeficiency may reduce the frequency and severity of infections. All JS patients should therefore undergo immunological evaluation. Future studies in a larger cohort of patients will more precisely define the pathophysiology of the immunodeficiency in JS [16].

Regarding the cerebral anomalies, 65% of patients with JS, had structural abnormality observed on imagistic examination of the brain: enlarged ventricles with or without spina bifida, cerebral atrophy, agenesis of corpus callosum, pachygyria, no Dandy–Walker malformation [17, 18]. In our case, MRI described only the cerebral atrophy.

Prenatal diagnosis can be made through amniocentesis or chorionic villus sampling and cytogenetic analysis in case there is a known risk for familial balanced translocation or mosaicism [19, 20].

## Conclusions

Jacobsen syndrome is a very rare genetic anomaly. There are suggestive clinical signs and symptoms but for diagnosis, the cytogenetic testing is mandatory. Blood tests, endocrine and immunological assessment, medical imaging and follow-up should be offered to all patients. Management of patients with JS is multi-disciplinary and requires evaluation by geneticist, pediatrician, pediatric cardiologist, hematologist, neurologist, nephrologist and ophthalmologist. Our case report is the first documented case of JS in Romania. As particularity, we notice the long period of survival and the late appearance of hematological and immunological disorders.

## Conflict of interests

The authors declare that they have no conflict of interests.

## Consent

Written informed consent was obtained from the patient's parents for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this Journal.

## References

- [1] Grossfeld PD, Mattina T, Lai Z, Favier R, Jones KL, Cotter F, Jones C. The 11q terminal deletion disorder: a prospective study of 110 cases. *Am J Med Genet A*, 2004, 129A(1):51–61.
- [2] Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. *Orphanet J Rare Dis*, 2009, 4:9.
- [3] Favier R, Akshoomoff N, Mattson S, Grossfeld P. Jacobsen syndrome: advances in our knowledge of phenotype and genotype. *Am J Med Genet C Semin Med Genet*, 2015, 169(3):239–250.
- [4] Maruani A, Huguet G, Beggiato A, ElMaleh M, Toro R, Leblond CS, Mathieu A, Amsellem F, Lemièrre N, Verloes A, Leboyer M, Gillberg C, Bourgeron T, Delorme R. 11q24.2-25 micro-rearrangements in autism spectrum disorders: relation to brain structures. *Am J Med Genet A*, 2015, 167A(12):3019–3030.
- [5] Taillemite JL, Morlier BG, Roux C. [Interstitial deletion of the long arm of one 11 chromosome]. *Ann Genet*, 1975, 18(1):61–63.
- [6] Horelli-Kuitunen N, Gahmberg N, Eeva M, Palotie A, Järvelä I. Interstitial deletion of bands 11q21–22.3 in a three-year-old girl defined using fluorescence *in situ* hybridization on metaphase chromosomes. *Am J Med Genet A*, 1999, 86(5):416–419.
- [7] Jacobsen P, Hauge M, Henningsen K, Hobolth N, Mikkelsen M, Philip J. An (11;21) translocation in four generations with chromosome 11 abnormalities in the offspring. A clinical, cytogenetical, and gene marker study. *Hum Hered*, 1973, 23(6):568–585.
- [8] Ji T, Wu Y, Wang H, Wang J, Jiang Y. Diagnosis and fine mapping of a deletion in distal 11q in two Chinese patients with developmental delay. *J Hum Genet*, 2010, 55(8):486–489.
- [9] Sutherland GR, Baker E. The clinical significance of fragile sites on human chromosomes. *Clin Genet*, 2000, 58(3):157–161.
- [10] Dirsé V, Cimbalistienė L, Kasnauskienė J, Kučinskis V. Report of Jacobsen syndrome with a mild facial dysmorphism, severe hearing impairment and thrombocytopenia. *Acta Med Litu*, 2012, 19(1):1–6.
- [11] Afifi HH, Zaki MS, El-Gerzawy AM, Kayed HF. Distal 11q monosomy syndrome: a report of two Egyptian sibs with normal parental karyotypes confirmed by molecular cytogenetics. *Genet Couns*, 2008, 19(1):47–58.
- [12] Sirvent N, Monpoux F, Pedeutour F, Fraye M, Philip P, Ticchioni M, Turc-Carel C, Mariani R. [Jacobsen's syndrome,

- thrombopenia and humoral immunodeficiency]. *Arch Pediatr*, 1998, 5(12):1338–1340.
- [13] Losos M, Kahwash BM, Conces M, Thompson J, Kumar R, Kahwash SB. Jacobsen/Paris–Trousseau syndrome: report of a case with emphasis on platelet's light microscopic and ultrastructure findings. *Open J Pathol*, 2016, 6(1):8–13.
- [14] Blazina Š, Ihan A, Lovrečić L, Hovnik T. 11q terminal deletion and combined immunodeficiency (Jacobsen syndrome): case report and literature review on immunodeficiency in Jacobsen syndrome. *Am J Med Genet A*, 2016, 170(12):3237–3240.
- [15] Seppänen M, Koillinen H, Mustjoki S, Tomi M, Sullivan KE. Terminal deletion of 11q with significant late-onset combined immune deficiency. *J Clin Immunol*, 2014, 34(1):114–118.
- [16] Dalm VA, Driessen G, Barendregt BH, van Hagen PM, van der Burg M. The 11q terminal deletion disorder Jacobsen syndrome is a syndromic primary immunodeficiency. *J Clin Immunol*, 2015, 35(8):761–768.
- [17] Lin JH, Hou JW, Teng RJ, Tien HF, Lin KH. Jacobsen distal 11q deletion syndrome with myelodysplastic change of hemopoietic cells. *Am J Med Genet*, 1998, 75(4):341–344.
- [18] Jurcă MC, Kozma K, Petchesi CD, Bembea M, Pop OL, Muțiu G, Coroi MC, Jurcă AD, Dobjanschi L. Anatomic variants in Dandy–Walker complex. *Rom J Morphol Embryol*, 2017, 58(3):1051–1055.
- [19] Lo JO, Feist CD, Hashima J, Shaffer BL. Jacobsen syndrome detected by noninvasive prenatal testing. *Obstet Gynecol*, 2015, 125(2):387–389.
- [20] Wax JR, Smith JF, Floyd RC, Eggleston MK. Prenatal ultrasonographic findings associated with Jacobsen syndrome. *J Ultrasound Med*, 1995, 14(3):256–258.

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