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Report of Jacobsen syndrome with a mild facial dysmorphism, severe hearing impairment and trombocytopenia

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Background. Jacobsen syndrome is a rare syndrome with variable phenotypic expression depending on the breakpoints and the size of 11q deletion. There is presented a wide range of phenotypes of varying severity. Detailed molecular cytogenetic analysis leads to better knowledge of genetic causes of this syndrome.

Materials and methods. Molecular cytogenetic analysis using subtelomeric FISH and array CGH was performed for a patient with Jacobsen syndrome.

Results. Subtelomeric FISH detected an unbalanced translocation 46,XY,der(11)t(11;13)(q24.2;p11.2) of our patient. Array CGH analysis revealed a 13.95 Mb terminal deletion of the 11q23.3 region (breakpoint positions 120, 505, 418–134, 452, 384, NCBI build 36). FISH and GTG banding analysis identified a balanced translocation 46,XX,t(11;13)(q24.2;p11.2) of patient's mother.

Conclusions. The results of this case report suggest the need of combining both molecular cytogenetic methods: array CGH and FISH for precise analysis of patients with Jacobsen syndrome.

Key words: Jacobsen syndrome, array CGH, subtelomeric FISH

INTRODUCTION

Jacobsen syndrome (11q deletion disorder, JBS OMIM 147791) was one of the first recognized cytogenetic syndromes, resulting from a terminal deletion of the long arm of chromosome 11 (1, 2). JBS is a rare syndrome with variable phenotypic expression depending on the breakpoints and the size of 11q deletion. There is presented a wide range of phenotypes of varying severity. The typical clinical findings include a short stature, facial dysmorphism (ocular hypertelorism, broad nasal bridge, down slanting palpebral fissures, v-shaped mouth, thin upper lip, low set malformed ears). Serious cardiac defects present in 56% of cases, malformations of kidneys in 13%, gastrointestinal tract problems in 18%, abnormal genitalia in 36%, central nervous system in 65% and skeletal dysplasias in 14% of cases. Nearly all patients (94%)

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have Paris-Trousseau thrombocytopenia and platelet dysfunction. Ocular, hearing, immunological and hormonal problems may be also present. Cognitive function ranged from normal or borderline (3%) to moderate mental retardation (97%) (3, 4). To date, over 200 cases of JBS have been described, with an estimated prevalence of 1:100,000 births (4). The majority of genetic causes are terminal deletions of 11q, size ranges from 7 to 20 Mb. The breakpoints occur within distal to subband 11q23.3 and the deletion usually extends to the telomere (3). The deletion occurs to be *de novo* in 85% of reported cases, and in 15% of cases it results from an unbalanced segregation of a familial balanced translocation or from other chromosome rearrangements. Only several translocations between chromosome 11q and chromosomes 6, 16, 22, Y have been described (5–9). Detection of 11q chromosomal rearrangements using routine karyotyping and subtelomeric FISH, precise identification of breakpoints using microarrays and detailed analysis of affected genes lead to clear, exact genotype-phenotype correlation and clinical determination of the patients with Jacobsen syndrome. We report a previously unreported unbalanced translocation 46,XY,der(11)t(11;13)(q24.2;p11.2) detected in a patient with typical features of Jacobsen syndrome.

MATERIALS AND METHODS

Clinical presentation

The proband, 11 months old boy, was referred to our department due to suspected genetic disorder. This male patient was the first child of healthy unrelated parents. His mother was 29 years old and his father was 26 at the time of delivery. The pregnancy was uncomplicated, except for allergy, which developed around 6 weeks of gestation. He was born by the Cesarean section because of abnormal fetal presentation after a full term of pregnancy. His Apgar score was 10–10, birth weight 3 000 g (3–10th percentile), height 50 cm (10–25th percentile), and head circumference 35 cm (50 percentile). At the age of 2 months he was hospitalized due to atopic dermatitis and severe folliculitis on the face. Laboratory investigations revealed mild anemia with Hb of 109 g/l, a low platelet count (78×10^9/l, ref. 180–320) and giant platelets (2.5%). Over next 6 months his platelet count remains at $86–101 \times 10^9$/l, without any transfusions. There was no history of excessive bleeding. The serum level of IgM, IgA, IgG was normal. Clinical examination at 24 months of age revealed a short stature of 84 cm (3–10th percentile), weight 12,3 kg (25–50th percentile), macrocephaly (OFD 50.5 cm, 90 percentile), short neck, ocular hypertelorism, strabismus, epicanthal folds, broad nasal bridge, prominent glabella, down slanting palpebral fissures, v-shaped mouth, thin upper lip, low set malformed ears, slight retrognathia, abnormal palmar creases, brachydactyly, stubby feet, mild cutaneous syndactyly of 2nd and 3rd toes, malformed scrotum. Sonography of the abdominal organs including kidneys was normal. There were no cardiac, genitourinary and renal anomalies. Thyroid function was also normal. Cerebral CT scans have shown evidence of an abnormal white matter lesion, which was thought to be due to delayed myelination. Ophthalmological evaluation revealed optical nerve subatrophy. Audiological examination showed a severe bilateral selective high frequency hearing loss. Slight delay in psychomotor development was noted (Fig. 1–3). The consent for publication of the clinical pictures has been obtained.

Subtelomeric fluorescence *in situ* hybridization (FISH) method

Subtelomeric FISH analysis for all long and short arms of chromosomes has been performed. The set of subtelomeric FISH probes was used for hybridization (ToTelVysion™). The ToTelVysion™ Multi-color DNA FISH Probe Mixture consists of a total of 62 DNA FISH probes. The mixtures include various combinations of TelVysion™, CEP® and LSI® probes. The TelVysion™ probes are homologous to DNA sequences specific to the p and q arm telomeric regions of each of the chromosome (except for the p arm of chromosomes 13, 14, 15, 21 and 22) and are mixed with blocking DNA. The TelVysion™ probe contains a locus estimated to be within 300 kb of the end of the chromosome. In addition, several of the multi-color mixtures contain unique sequence LSI® probes or alpha satellite CEP® probe for purposes of identifying certain chromosomes within mixtures. The ToTelVysion™ probes are directly labeled with either SpectrumOrange™ and / or SpectrumGreen™ fluorophores. The LSI® and CEP® probes are labeled with SpectrumAqua™ fluorophore. FISH analysis was

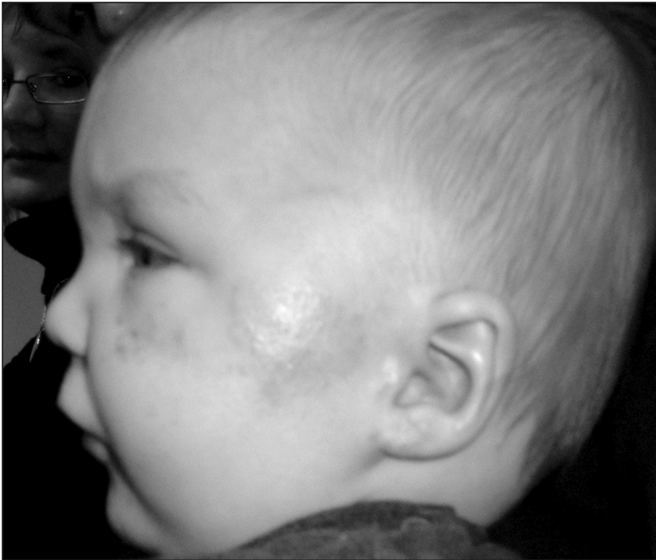

Fig. 1. The proband aged 11 months

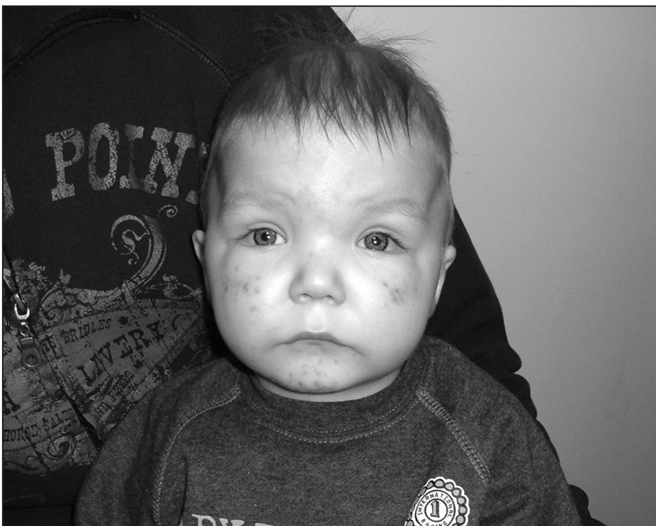

Fig. 2. The proband aged 11 months

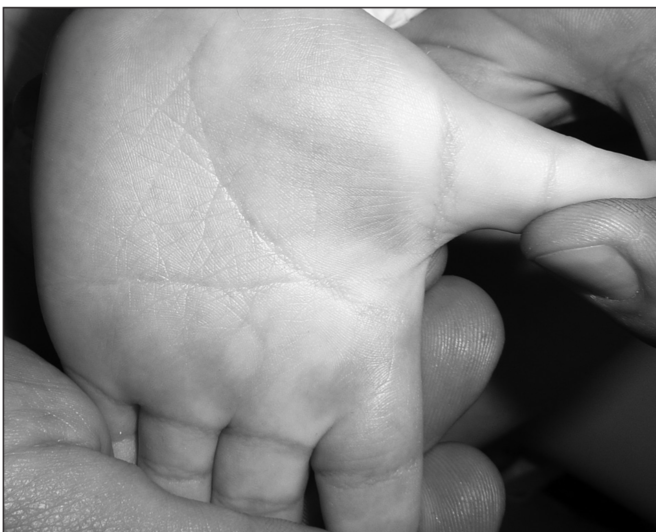

Fig. 3. Abnormal palmar creases

performed according to standard protocols. A minimum of five metaphases and 10 interphase nuclei is required to analyze each chromosome.

Array comparative genomic hybridization (aCGH) method

DNA from the patient, his father and mother were isolated using the phenol-chlorophorm extraction method. A 400K oligo-array (Agilent Technologies, Santa Clara, CA, USA) was used for array CGH analysis. Array-CGH was carried out according to the recommendations of the manufacturer. DNAs were labeled by random priming using a BioPrime labeling kit (Invitrogen, Paisley, UK) with cyanine 3 and cyanine 5 (Amersham Biosciences, Buckinghamshire, UK) fluorescent dyes. Microarrays were scanned using an Agilent G2565B scanner, data were extracted using Feature Extraction software (Agilent Technologies, Santa Clara, CA, USA) and analyzed with Nexus copy number software (BioDiscovery, Inc, CA, USA).

RESULTS

Subtelomeric FISH analysis

FISH analysis using subtelomeric specific probes (ToTelVysion) for all long and short arms of chromosomes has been performed. It has detected submicroscopic deletion at 11q25. For specification of the results, subtelomeric FISH analysis for patient's parents has been performed. Father's chromosomes analysis showed no abnormalities, while the mother revealed to be a balanced translocation carrier. Subsequently we analysed mother's karyotype (GTG banding) to determine the breakpoints of the translocation which appeared to be 46,XX,t(11;13)(q24.2;p11.2). We postulate that the patient has an unbalanced translocation 46,XY,der(11)t(11;13)(q24.2;p11.2). FISH analysis indicated only terminal deletion on chromosome 11q (one green signal on 11q) because the ToTelVysion^{TM} probe set does not include a probe for the chromosome 13p terminal region.

Array CGH analysis

Array-CGH with a 400K oligo chip (Agilent Technologies, Santa Clara, CA, USA) was used for array-CGH analysis, which revealed a 13.95 Mb terminal deletion of the 11q23.3 region (positions 120, 505, 418–134, 452, 384, NCBI build 36).

DISCUSSION

Our patient with the previously described clinical features has an unbalanced translocation 46,XY,der(11)t(11;13)(q24.2;p11.2). The main chromosomal abnormality causing Jacobsen syndrome is usually *de novo* pure terminal deletion (85% of cases). The deletions are variable in size, ranging from as small as 7 Mb to greater than 20 Mb (3). Less frequent cases are unbalanced translocations, which are the result from segregation of a familial balanced translocation (4). There are proposed five critical regions which are mostly mentioned in association with clinical features in patients with Jacobsen syndrome: 11q23, 11q24.1, 11q24.2, 11q23.3q24.2, 11q24.3 (10). The clinical phenotype in 11q- is variable. The patients with the deletion involving the 11q23 region have severe developmental delay, marked growth retardation, hypotonia, trigonocephaly, hypertelorism, moderate bilateral hearing loss, congenital heart defects (11, 12). Hematological abnormalities are common in patients with Jacobsen's syndrome who share the genetic defect of 11q23 deletion observed in patients with Paris-Trousseau syndrome (13). The patients with the deletion starting from 11q24 region have these clinical features: thrombocytopenia, developmental delay, ptosis, hypertelorism, micrognathia. Although patients with larger deletions extending into 11q23 usually have a larger number of dysmorphic facial features, the region of 11q24 is most likely to be associated with Jacobsen syndrome. It is suggested that the deletion of subband 11q24.1 is crucial for the full clinical expression of the syndrome (14).

It is widely accepted that the chromosome breakage characteristic of Jacobsen syndrome is associated with folate-sensitive fragile site FRA11B, which is located at chromosome band 11q23.3. This fragile site is caused by extensive expansion of CCG trinucleotide repeats (15, 16). Detection of 11q23.3 breakage of our patient using array CGH approves this hypothesis of fragile FRA11B site as the main genetic cause for chromosomal abnormalities in Jacobsen syndrome cases. Furthermore, it explains localization of the deleted part of 11q which is attached on chromosome 13 satellite. Both fragile FRA11B site of 11q and satellite part of 13p are full of various CG repeats which could have influence on the formation of an unbalanced translocation of the patient and a balanced translocation of patient's mother.

Only several translocations are described in patients with Jacobsen syndrome. *De novo* translocation (Y;11)(q11.2;q24) was detected in the patient with clinical features which all are characteristic of Jacobsen syndrome – trigonocephaly, ptosis, deep-set short nose and carp-shaped mouth (9). Translocation between 11q and 22q was detected in the patient with Jacobsen syndrome. Analysis of breakpoints of this translocation indicated the breakpoints to be at 11q23 and 22q11. Both regions are spanned with LCR which could have influence on the formation of translocation (7). In two cases monosomy of 11q24.2-qter and partial trisomy of 16q24.1-qter were detected. Patients have characteristic clinical features for Jacobsen syndrome including thrombocytopenia, hearing deficiencies, foot anomalies, renal malformations as well as some dysmorphic features. However, patients also have muscular hypotonia, bitemporal narrowing which could be the cause of partial trisomy of 16q24.1-qter (6).

CONCLUSIONS

The variation of breakpoints in Jacobsen syndrome cases leads us to detailed and discussed analysis for searching breakpoints and genes which may be responsible for Jacobsen syndrome. The case described above emphasizes the need of combining both molecular cytogenetic methods: array CGH and FISH for precise analysis of patients with Jacobsen syndrome.

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ATVEJO PRISTATYMAS: JAKOBSENO SINDROMAS SU NEDIDELIU VEIDO DISMORFIZMU, SUNKIU KLAUSOS SUTRIKIMU IR TROMBOCITOPENIJA

Santrauka

Įvadas. Jakobseno sindromas yra retas. Jis pasižymi fenotipinės raiškos įvairove, kuri priklauso nuo 11 chromosomos ilgajame petyje esančio trūkio vietos ir dydžio. Išsami molekulinės citogenetikos analizė padeda tiksliau išaiškinti šio sindromo genetines priežastis ir susieti jas su fenotipu.

Metodai. Pacientui su Jakobseno sindromu buvo atlikta genetinė analizė subtelomerų fluorescencinės *in situ* hibridizacijos (FISH) bei vektorinės lyginamosios genominės hibridizacijos (vLGH) metodais.

Rezultatai. Taikant subtelomerų FISH pacientui buvo nustatyta nesubalansuota translokacija 46,XY,der(11) t(11;13)(q24.2;p11.2). vLGH analize buvo patikslintas šios chromosominės aberacijos trūkio taškas, kuris yra ties 11q23.3 (koordinatės nukleotidais 120505418-13445238436), bei dydis (13,95 Mb). G dažymo ir subtelomerų FISH metodais nustatyta subalansuota translokacija 46,XX,t(11;13)(q24.2;p11.2) paciento motinai.

Išvada. Molekulinės citogenetikos FISH ir vLGH metodų taikymas padeda nustatyti bei patikslinti pacientų su Jakobseno sindromu genetines priežastis.

Raktažodžiai: Jakobseno sindromas, vektorinės lyginamosios genominės hibridizacijos (vLGH) metodas, subtelomerų fluorescencinės *in situ* hibridizacijos (FISH) metodas