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Case Report

Jacobsen syndrome associated with cleft lip: A patient report and review☆☆

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ABSTRACT

Background: Jacobsen syndrome is a rare chromosomal disorder causing multiple physical and mental impairments. This syndrome is due to a partial deletion of the long arm of chromosome 11. The prevalence has been estimated at 1 in 100,000 births. To date, more than 200 cases have been reported worldwide. Jacobsen syndrome associated with cleft lip is rare. We report the case of a female infant with Jacobsen syndrome who had a cleft lip and alveolus.

Case: The patient was born at 38 weeks' gestation (weight, 2282 g). She had a bilateral cleft lip with thrombocytopenia and an ear ossicle anomaly. Growth disturbance, anemia, spina bifida, pulmonary regurgitation, and limb myotonia became apparent with time. G-banding revealed that the chromosome anomalies were caused by a terminal deletion (partial monosomy; deleted at the long arm of the chromosome [11q24-qter]). All subtelomeric regions were analyzed using fluorescence in situ hybridization analysis. Cheiloplasty was performed under general anesthesia when she was 1 year old and again at 1 year 6 months old, with uneventful postoperative courses. Further follow-up is necessary to monitor her development, including maxillofacial growth.

Conclusions: Jacobsen syndrome is a contiguous gene syndrome causing multiple abnormalities with mental retardation. Patients with this syndrome have various clinical features. Array comparative genomic hybridization was performed, and a literature review about the relation between a gene in a deleted location and clinical signs was conducted. The patient's development will be followed carefully, and specialists in other departments will be consulted about her progress as needed.

1. Introduction

Jacobsen syndrome (JS) is a contiguous gene syndrome causing multiple congenital abnormalities with intellectual disabilities. It is due to a partial deletion of the long arm of chromosome 11 [1]. JS is a rare disease, with an estimated incidence of 1 in 100,000 babies [2–4]. Since Jacobsen et al. [5] first described the syndrome, only approximately 200 cases have been reported [2,3]. As only a few cases of JS associated with cleft lip and/or cleft palate have been reported, no cases could be found in the OMIM (Online Mendelian Inheritance in Man) database (MIM number: 147791). We here describe the case of a patient with bilateral cleft lip and alveolus associated with JS. The deleted region of the chromosome was examined in detail with array comparative genomic hybridization (array CGH), and the literature was reviewed.

2. Case report

The patient was the first child of a 33-year-old mother and a 34-year-old father. Because the fetus developed intrauterine growth

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retardation at the 27th week of gestation, fetal progress was followed. Ultrasonography at the 29th week of gestation revealed that the fetus had a cleft lip. Cytogenetic analysis of the cultured amniotic fluid cells was performed. Staining of G-banded chromosomes in amniotic suspension cells revealed that the long arm of chromosome 11 was deleted from q24 to the end. In November 2009, the patient was born on the 4th day of the 38th gestational week by cesarean section (full-term birth). The birth weight was 2282 g, and the Apgar score was 8/9. In November 2010, the patient was brought to our center for the first time for a detailed examination and for cleft lip treatment.

Shortly after birth, the patient was hospitalized in the department of neonatology of the hospital where she was born because the obstetrician suspected the presence of multiple abnormalities. Therefore, the patient underwent a comprehensive, whole-body examination. The G-band chromosomal analysis of peripheral blood showed a terminal deletion of the long arm of chromosome 11 (46,XX, del (11) (q24)). Echocardiography, echopyelography, and brain magnetic resonance imaging did not show any abnormalities. Computed tomography (CT) of the auditory apparatus identified an ear ossicle anomaly. Because the baby developed severe neonatal jaundice, she underwent phototherapy postnatally and recovered well. Laboratory tests during her hospitalization showed that the platelet count in blood had decreased to $7.3 \times 10^4/mm^3$. Her thrombocytopenia was considered to be a sign of 11q (-) syndrome; thus, her progress needed to be followed. The blood test on the 32nd postnatal day on hospital discharge showed that the platelets had increased to $11.8 \times 10^4/mm^3$.

On the patient's first visit to our hospital, her weight was 3074 g, height was 49.3 cm, and head circumference was 36.2 cm, which are near the average measurements for her age. She was also found to have hydronephrosis, spina bifida, and limb dystonia. Although she had a bilateral cleft lip and alveolus, she did not have a cleft palate (Fig. 1).

The infant had a protruded premaxilla, which was taped to narrow the clefts and to pull the protruded premaxilla inward. She was observed monthly until cheiloplasty to determine whether her weight increased and her general condition was adequate. Cheiloplasty under general anesthesia was scheduled for late May 2010. Preoperative blood tests gave the following results: red blood cells (RBC), $381 \times 10^4/\mu L$; hemoglobin (Hb), 9.2 g/dL; platelets, $22.4 \times 10^4/\mu L$; hematocrit (Hct), 29.4%; mean cell volume (MCV), 77.2 fL; mean corpuscular Hb concentration (MCHC), 31.3 fL; and creatinine kinase (CK), 555 IU/L. Despite the increase in the number of platelets, anemia and a high CK value were found. Therefore, the operation was postponed to ensure recovery of the anemia and improvement of the CK. She was started on an oral iron preparation because her anemia was found to be an iron-deficiency anemia. At her regular examination at the end of June, her heart murmur had become worse, and grade II/VI murmur was diagnosed. She was referred for cardiological consultation. Her electrocardiogram was normal; however, mild aortic valve insufficiency was found on echocardiography. At the end of October 2010, blood tests were repeated in the department of pediatric cardiovascular medicine. Although she still had mild anemia (RBC, $407 \times 10^4/\mu L$; Hb, 10.7 g/dL; Hct, 32.7%; MCV, 80.4 fL; MCHC, 32.8 fL; Fe, 66 μg/dL; ferritin, 32.8 IU/L), her status had improved. Preoperative blood tests were performed at the end of November 2010. Her anemia further improved, and the CK value decreased (CK, 423 IU/L; Hb, 12.2 g/dL; white blood cells, $8.1 \times 10^2/\mu L$; RBC, $459 \times 10^4/\mu L$; platelets, $19.4 \times 10^4/\mu L$; Hct, 37.5%). Cheiloplasty under general anesthesia was performed on the left-sided cleft, as the first stage of a 2-stage cheiloplasty. Her postoperative course was good, and she was discharged on postoperative day 9. In the middle of May 2011, the second cheiloplasty procedure was performed also under general anesthesia. She again showed a good postoperative course and was discharged on postoperative day 11. Her condition remains good (Table 1).

Chromosome analysis: G-banding revealed that the chromosome anomalies were caused by a terminal deletion (partial monosomy; deleted at the long arm of the chromosome [11q24-qter]). All subtelomeric regions were analyzed using fluorescence in situ hybridization (FISH) analysis with ToTelVysion Multi-Color FISH Probe Panel VYS-33-270000. No imbalanced translocations were observed, including subtelomeric regions. Furthermore, chromosomes were analyzed using an oligonucleotide array (AgilentSurePrintG3 60K; Genome hg19) to accurately identify the deleted region. The breakpoints of the deletion were found to be Arr 11q24.2-q25 (124,488,292–134,868,407) x1 11q24.2-q25, and

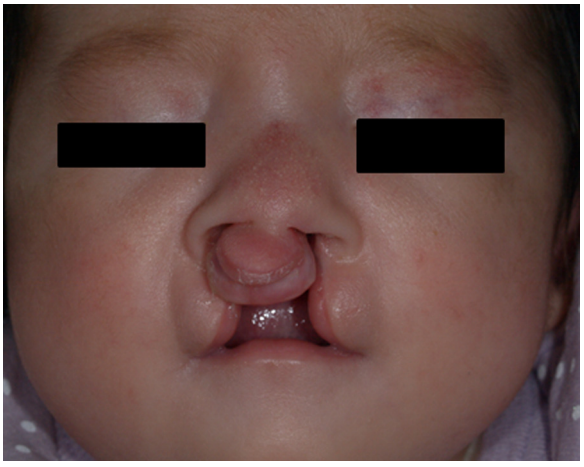

Fig. 1. Facial features of the patient in this report.

Table 1
Common dysmorphic features in Jacobsen syndrome.

Phenotype	Percentage [3] (%)	Present case
Ears		
Low set, malformed earsears	81	+
Nose		
Broad nasal bridge	91	+
Short nose	69	+
Anteverted nares	64	+
Mouth		
Thin upper lip	84	–
V-shape mouth	67	–
High-arched palate	64	+
Long philtrum	58	–
Eyes		
Ocular hypertelorism	92	+
Down slanting palpebral fissues	83	–
Strabismus	67	–
Ptosis	58	–
Spares eyebrows	50	–
Feet		
Toe anomaly	83	+
2–3 syndactyly	58	–
Hands		
Syndactyly	72	–
Finger pad anomalies	56	–
Low-set thumb	56	–
Hand anomalies	53	–
5th finger clinodactyly	53	–
Dermatoglyphic anomalies	53	–
Others		
Prominent forhead	62	+
Short neck	50	+