Case Report

Hypoimmunoglobulinemia and Protein C Deficiency in a Girl with Jacobsen Syndrome: A Case Report

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Jacobsen syndrome is a rare contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11. The typical clinical manifestations include physical growth retardation, mental retardation, facial dysmorphisms, congenital heart disease, thrombocytopenia, or pancytopenia.

A Thai-Australian girl was born with multiple abnormalities. Typical features and her karyotype, 46, XX, del(11)(q23-qter), confirmed Jacobson syndrome. She had many uncommon findings including upslanting palpebral fissures, tortuousity of retinal vessels and hypogammaglobulinemia. In addition, this case also presented with protein C deficiency, which has not been reported previously in Jacobsen syndrome. The patient was treated with phototherapy, intravenous antibiotic injection, and platelet transfusion in neonatal period. Cranioplasty was performed for prevention of the increased intracranial pressure at three months of age. Surgical correction for strabismus was in the treatment plan.

Keywords: *Jacobsen syndrome, Deletion 11q, 11q deletion syndrome, Hypoimmunoglobulinemia, Immunodeficiency, Immune deficiency*

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Jacobsen syndrome (JS) was first described in 1973[1]. This rare contiguous genetic disorder with variable expression is caused by partial deletion of the long arm of chromosome 11. The clinical features depend on the size of the 11-qter deletion, which usually varies between 7 and 20 Mb. The typical clinical manifestations include physical growth retardation, mental retardation, characteristic facial dysmorphism, congenital heart disease, thrombocytopenia, or pancytopenia. About 20% of patients die within the first two years of life due to congenital heart disease, bleeding tendency, and sepsis, respectively[2]. Patients who could survive through infancy would require life-long treatment. Life expectancy in such cases, however, remains unknown.

Case Report

A Thai-Australian girl was born at 41 weeks after an uncomplicated pregnancy and delivery. She was the first child of healthy non-consanguineous parents. Measurements at birth were weight 2,620 g (just above tenth percentile), length 46 cm (below tenth percentile) and head circumference 33 cm (thirty-fifth percentile). Multiple dysmorphic features were detected. Skull deformities including trigonocephaly (Fig. 1) and high prominent forehead were demonstrated. Characteristic facial dysmorphism included ocular

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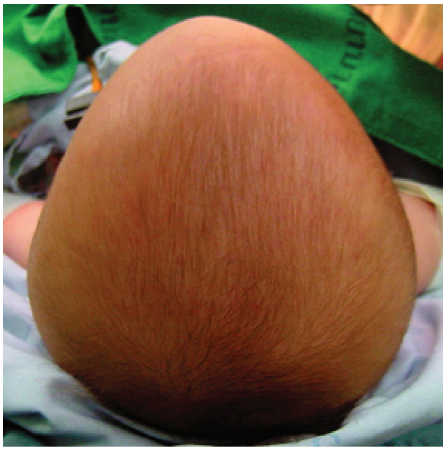

Fig. 1 Trigonocephaly.

hypertelorism, epicanthal folds, upslanting palpebral fissures, flat and broad nasal bridge, anteverted nares, posterior rotated low-set ears, long and flat philtrum and thin upper lip, and high arched palate (Fig. 2). Her neck was short. Hands also showed abnormal palmar creases (simian crease), clinodactyly, clenched hand, and hypoplasia of both fifth fingers. Both feet were flat and stubby. At only one day after birth, generalized petichiae and ecchymosis were found. Blood count analysis demonstrated bicytopenia, leukopenia (6,140/ul) and thrombocytopenia (48,000/ul). The patient developed jaundice without blood group incompatibility. Hemolysis was evident on peripheral blood smear. Further investigations revealed very low serum immunoglobulin (IgM <16.8 mg/dl) and protein C deficiency (17.7 IU/dl). No other visceral malformations or hormonal deficiencies were detected. No hydrocephalus or gross anomalies demonstrated on cranial ultrasound. The cranial CT scan revealed small old cerebral infarction at left caudate nucleus. The patient was treated with phototherapy, intravenous antibiotic injection, and platelet transfusion. Since multiple system disorders were found in this patient, chromosomal analysis was investigated. Her karyotype was described as 46, XX, del(11) (q23-qter), which confirmed Jacobson syndrome.

At 3 months of age, the patient underwent cranioplasty for prevention the increased intracranial pressure that usually occurred following premature closure of the metopic suture. The upslanting palpebral fissures could be disappeared after the surgery (Fig. 3). During the first year of life, moderate global delayed development was detected. The patient also had recurrent mild respiratory tract infection and otitis media.

The patient was referred to the ophthalmologist after parental concerns over her left eye, which appeared to "drift out". Ocular examination at 4 years of age revealed good fixation on both eyes. Mild palpebral ptosis was observed on the left eye. An alternating exotropia was determined by Krimsky test. Fundoscopic examination showed the tortuosity of retinal vessels (Fig. 4). She developed strabismic amblyopia and left head tilt that improved with part-time occlusion of the right eye, and then we planned to correct exotropia surgically. Institutional Review Board Number: IR00001189. Ethical Reference Number: HE500505.

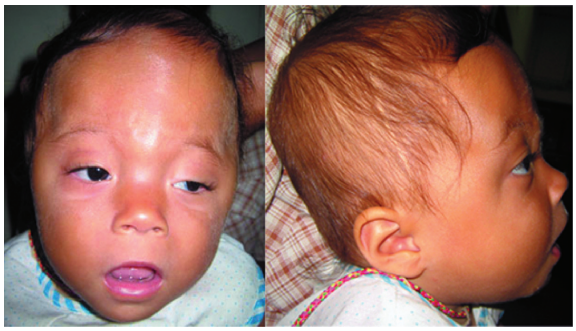

Fig. 2 Characteristic facial dysmorphisms.

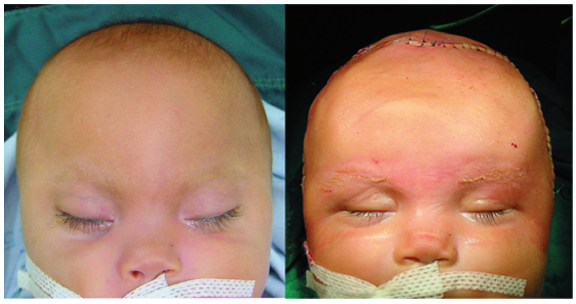

Fig. 3 The upslanting palpebral fissures were disappeared after the cranioplasty.

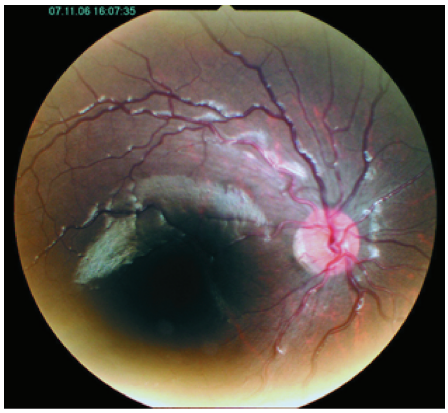

Fig. 4 Tortuosity of retinal vessels.

Discussion

Trigonocephaly is an abnormality of the skull shape characterized by a triangular appearance of the forehead when the head is viewed from above. Twenty-eight point five percent of children with trigonocephaly were JS patients and the prevalence of trigonocephaly in JS patients was about 30%, therefore the presence of this skull deformity may raise the possibility of diagnosis[2,3]. Downslanting palpebral fissures are one of the characteristic facial dysmorphisms. To the best of our knowledge, this is the second report describing the upslanting palpebral fissures in patient with JS that could be corrected by cranioplasty. Common ocular features were ptosis

and strabismus. Fundus picture showed uncommon finding, tortuousity of retinal vessels.

Thrombocytopenia or pancytopenia is one of the typical characteristic of JS. Patients usually present at birth with bleeding tendency due to the storage pool deficit that may resolve over time. However, protein C deficiency has not been reported before and it may be the cause of cerebral infarction revealed in CT brain of this case.

Many genetic syndromes are associated with immunodeficiency, which could result from several mechanisms such as a mutation of a gene involved in immune system, alteration of activity or structure of such proteins could cause dysfunction in immune system, etc. Immune deficiency, humoral immunity and/or cellular immunity, associated with JS are uncommon and poorly identified[4-7]. There is a report describing the treatment of immune deficiency in a 12-year-old boy with JS and who suffered from persistent hypoimmunoglobulinemia and recurrent infection. He required multiple hospitalizations and intravenous antibiotic therapy. The patient was treated with regular intravenous immunoglobulin (IVIG) administration starting at the age of five. He experienced the significant clinical improvement without any complications[7]. Because mild infection occurs occasionally during the neonatal period, the authors did not treat the patient with IVIG. Fortunately, her serum immunoglobulin and protein C level can be elevated spontaneously to subnormal level with time.

Variable expression of 11-q syndrome depends on deletion spanning within the JS region and genotype-phenotype correlation was described in previous studies[2,8-16]. The authors, however, could not identify the breakpoint in this case due to limitation of technology.

Conclusion

Jacobsen syndrome is a rare disease. Complete evaluation should be performed and multidisciplinary management will be required after the diagnosis. Evaluation of the immune system should be undertaken in patients with multiple abnormalities and recurrent infections for allowing better patient care and family counseling. IVIG may be needed in JS with recurrent severe infection.

Consent

Written informed consent was obtained from the patient's mother for publication of this case report and accompanying images.

Authors' contributions

SS made substantial contributions to data acquisition and interpretation, performed the ocular examination, composed the photos for publication, design the study, and drafted the manuscript. AK treated the patient with cranioplasty and composed the photos for publication. NY performed the clinical evaluation and treatment. PY and YY helped to draft the manuscript. SS critically revised the manuscript. All authors read and approved the final manuscript.

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Potential conflicts of interests

None.

References

1. 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: 568-85.
2. Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet J Rare Dis 2009; 4: 9.
3. Azimi C, Kennedy SJ, Chitayat D, Chakraborty P, Clarke JT, Forrest C, et al. Clinical and genetic aspects of trigonocephaly: a study of 25 cases. Am J Med Genet A 2003; 117A: 127-35.
4. Sirvent N, Monpoux F, Pedeutour F, Fraye M, Philip P, Ticchioni M, et al. Jacobsen's syndrome, thrombopenia and humoral immunodeficiency. Arch Pediatr 1998; 5: 1338-40.
5. Ming JE, Stiehm ER, Graham JM Jr. Syndromic immunodeficiencies: genetic syndromes associated with immune abnormalities. Crit Rev Clin Lab Sci 2003; 40: 587-642.
6. von Bubnoff D, Kreiss-Nachtsheim M, Novak N, Engels E, Engels H, Behrend C, et al. Primary immunodeficiency in combination with transverse upper limb defect and anal atresia in a 34-year-old patient with Jacobsen syndrome. Am J Med Genet A 2004; 126A: 293-8.
7. Fernandez-San Jose C, Martin-Nalda A, Vendrell Bayona T, Soler-Palacin P. Hypogammaglobulinemia in a 12-year-old patient with

Jacobsen syndrome. J Paediatr Child Health 2011; 47: 485-6.
8. Evers C, Janssen JW, Jauch A, Bonin M, Moog U. A small terminal deletion 11q in a boy without Jacobsen syndrome: narrowing the critical region for the 11q Jacobsen syndrome phenotype. Am J Med Genet A 2012; 158A: 680-4.
9. Krgovic D, Marcun VN, Zagorac A, Kokalj-Vokac N. Submicroscopic interstitial deletion of chromosome 11q22.3 in a girl with mild mental retardation and facial dysmorphism: Case report. Mol Cytogenet 2011; 4: 17.
10. 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: 486-9.
11. Sachdeva R, Sears JE, Rychwalski PJ. A novel case of bilateral high myopia, cataract, and total retinal detachment associated with interstitial 11q deletion. Ophthalmic Genet 2010; 31: 84-8.
12. Fujita H, Yanagi T, Kosaki R, Torii C, Bamba M, Takahashi T, et al. Transverse limb defect in a patient with Jacobsen syndrome: concurrence of malformation and disruption. Am J Med Genet A 2010; 152A: 1033-5.
13. Manolakos E, Orru S, Neroutsou R, Kefalas K, Louizou E, Papoulidis I, et al. Detailed molecular and clinical investigation of a child with a partial deletion of chromosome 11 (Jacobsen syndrome). Mol Cytogenet 2009; 2: 26.
14. Ye M, Coldren C, Liang X, Mattina T, Goldmuntz E, Benson DW, et al. Deletion of ETS-1, a gene in the Jacobsen syndrome critical region, causes ventricular septal defects and abnormal ventricular morphology in mice. Hum Mol Genet 2010; 19: 648-56.
15. Ye M, Hamzeh R, Geddis A, Varki N, Perryman MB, Grossfeld P. Deletion of JAM-C, a candidate gene for heart defects in Jacobsen syndrome, results in a normal cardiac phenotype in mice. Am J Med Genet A 2009; 149A: 1438-43.
16. Coldren CD, Lai Z, Shragg P, Rossi E, Glidewell SC, Zuffardi O, et al. Chromosomal microarray mapping suggests a role for BSX and Neurogranin in neurocognitive and behavioral defects in the 11q terminal deletion disorder (Jacobsen syndrome). Neurogenetics 2009; 10: 89-95.

รายงานผู้ป่วยเด็กหญิง Jacobsen syndrome ที่พบระดับภูมิคุ้มกันในเลือดต่ำและภาวะพร่อง protein C

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Jacobsen syndrome เป็นกลุ่มอาการที่พบได้น้อย เกิดจากการขาดหายไปบางส่วนของขายาวของโครโมโซมคู่ที่ 11 อาการแสดง ได้แก่ การเจริญเติบโตช้า ระดับสติปัญญาต่ำกว่าปกติ ใบหน้าผิดรูปโรคหัวใจแต่กำเนิด ภาวะเกล็ดเลือดต่ำหรือเม็ดเลือดต่ำทั้งหมด

เด็กหญิงไทย-ออสเตรเลียเกิดมาพร้อมความผิดปกติของร่างกายหลายอย่าง อาการแสดงและผลการตรวจโครโมโซมทำให้ได้รับการวินิจฉัย Jacobsen syndrome ผู้ป่วยมีอาการแสดงที่พบได้ไม่บ่อยนักหลายอย่าง ได้แก่ ภาวะหางตาชี้ขึ้น หลอดเลือดจอตาคดงอและระดับภูมิคุ้มกันในเลือดต่ำ นอกจากนี้ยังพบว่ามีภาวะพร่อง protein C ด้วย ซึ่งภาวะดังกล่าวไม่เคยมีการรายงานในผู้ป่วย Jacobsen syndrome มาก่อน ผู้ป่วยได้รับการรักษาโดยการฉายแสง ให้ยาปฏิชีวนะทางหลอดเลือดและให้เกล็ดเลือดในวัยทารก การผ่าตัดตกแต่งกะโหลกศีรษะเพื่อป้องกันภาวะความดันในสมองสูงทำเมื่อผู้ป่วยมีอายุ 3 เดือน สำหรับการผ่าตัดแก้ไขภาวะตาเขนั้นอยู่ในแผนการรักษาต่อไป