Ultrasonographic findings and prenatal diagnosis of Jacobsen syndrome

A case report and review of the literature

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Abstract
Rationale: Jacobsen syndrome (JBS) is a rare chromosomal disorder with variable phenotypic expressivity, which is usually diagnosed in infancy and childhood based on clinical examination and hematological and cytogenetic findings. Prenatal diagnosis and fetal ultrasonographic findings of JBS are rare.

Patient concerns: A 38-year-old, gravida 3, para 1, pregnant woman underwent clinical ultrasound examination at 22 weeks of gestation.

Diagnoses: Ultrasonographic findings indicated an interventricular septal defect, the presence of septal blood flow, dilation of the left renal pelvis, and a single umbilical artery. Amniocentesis was performed to evaluate possible genetic causes of this diagnosis by cytogenetic and single nucleotide polymorphism (SNP) array analysis.

Interventions: After genetic counseling and informed consent, the couple elected to terminate the pregnancy.

Outcomes: Karyotype analysis showed that the fetal karyotype was 46,XX,del(11)(q23). The SNP array revealed a 6.118 Mb duplication of 11q23.2q23.3 and a 15.03 Mb deletion of 11q23.3q25.

Lessons: Ultrasonographic findings of fetal JBS, including an interventricular septal defect, dilation of the left renal pelvis, and a single umbilical artery, may be associated with a 15.03 Mb deletion of 11q23.3q25. Further cases correlating phenotype and genotype are required to predict the postnatal phenotype.

Abbreviations: DNA = deoxyribonucleic acid, EST-1 = V-ETS avian erythroblastosis virus E26 oncogene homolog 1, JBS = Jacobsen syndrome, OMIM = Online Mendelian Inheritance in Man, SNP = single nucleotide polymorphism.

Keywords: fetus, Jacobsen syndrome, prenatal diagnosis, ultrasonographic findings

1. Introduction

Jacobsen syndrome (JBS), also known as11q23 deletion syndrome, is a contiguous gene syndrome caused by partial deletion of the long arm of chromosome 11.1 JBS is a rare chromosomal disorder with variable phenotypic expressivity,2 and is usually diagnosed in infancy and childhood based on clinical examination and hematological and cytogenetic findings.


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2. Methods

This study was approved by the Ethics Committee of the First Hospital, Jilin University (No. 2018-383). Patient has provided informed consent for publication of the case.
2.1. Cytogenetic analysis

Fetal cells were obtained through amniocentesis after obtaining written informed consent. Then, amniocytes were collected by centrifugation, inoculated in flasks according to laboratory standards, and cultured in carbon dioxide incubators for 10 days. Chromosome analysis using G-band staining was performed as in our previous study.[13] The karyotype was described according to the International System for Human Cytogenetic Nomenclature (ISCN 2013).[14] Twenty metaphases were analyzed.

2.2. SNP array analysis

Genomic DNA was extracted from 10 mL of uncultured amniocytes using a QIAamp DNA Mini kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. SNP array analysis was performed using the Human CytoScan 750K BeadChip (Affymetrix, San Diego, CA). Image data were analyzed using Chromosome Analysis Suite v3.3 software. The final results were analyzed using the Database of Chromosomal Imbalance and Phenotype in Humans using Ensembl Resources (DECIPHER), the Database of Genomic Variants (DGV), OMIM, and NCBI.

3. Case presentation

A 38-year-old, gravida 3, para 1, pregnant woman underwent clinical ultrasound examination at 22 weeks of gestation. Ultrasonographic findings indicated abnormalities of the single live fetus, including a single ventricle in the intracalvarium, the skull ring was completed, the width of the right ventricle was 0.89 cm and the width of the left ventricle was 0.82 cm, the biparietal diameter was 5.3 cm, the head circumference was 19.8 cm, the abdominal circumference was 16.6 cm, the femur length was 3.8 cm, and the amniotic fluid index was 13.3 cm. The main abnormal manifestations on the ultrasound images included an interventricular septal defect, the presence of septal blood flow, dilation of the left renal pelvis, and a single umbilical artery (Fig. 1). After genetic counseling, the woman was offered amniocentesis for cytogenetic and single nucleotide polymorphism (SNP) array analysis at 23 weeks of gestation because of advanced age in combination with these abnormal ultrasound indicators.

Figure 1. Prenatal ultrasound at 22 weeks of gestation showing: A: Interventricular septal defect; B: Presence of septal blood flow; C: Left renal pelvis widening; D: Single umbilical artery.
Karyotype analysis showed that the fetal karyotype was 46, XX,del(11)(q23) (Fig. 2). The SNP array revealed a 6.118 Mb duplication of 11q23.2q23.3 and a 15.03 Mb deletion of 11q23.3q25 (11q23.2q23.3 [113790010–119907572] × 3, 11q23.3q25 [119907627–134937416] × 1) (Fig. 3). The couple underwent cytogenetic detection. The results were both normal. Both the parents were nonconsanguineous and healthy, and their first child was healthy. The mother denied any exposure to smoking, alcohol, infectious diseases, irradiation, or teratogenic agents during this pregnancy. The chromosome aberrations of the fetus arose de novo. This case was diagnosed as JBS according to reports in the literature of JBS with del(11)(q23.3q25). After genetic counseling and informed consent, the couple elected to terminate the pregnancy.

4. Discussion

JBS has an estimated occurrence of 1 in 100,000 births, with a female to male ratio of 2:1.[15] Of the cases reported, 85% arose de novo and 15% may have arisen from inheritance of an unbalanced segregation of a familial balanced translocation.[16] The deletion size ranged from approximately 7 to 20 Mb, and deletion of the breakpoint at 11q23.3 was found in the majority of JBS cases.[2,16,17] Previous studies have shown that the fragile...
The present case was a female fetus with a 15.03 Mb deletion of 11q23.3q25. More cases correlating site in 11q23.3 is susceptible to chromosome deletion in vivo. The present case was a female fetus with a 15.03 Mb deletion of 11q23.3q25 and a 6.118 Mb duplication of 11q23.2q23.3.

For child patients who survive the neonatal period, more attention has been paid to the clinical phenotypes and the genes involved in the deleted regions. Patients with JBS show a wide spectrum of clinical phenotypes, and patients with the more obvious clinical features are diagnosed by the age of one. However, the most severe phenotypes of the patients with deletions vary between patients. Hence, the relationship between genotype and phenotype are required to predict the postnatal phenotype.

A limitation of this study is that fetal autopsy was not performed because the couple refused consent, and so we were unable to confirm the ultrasound findings. We present ultrasonographic findings of JBS in a fetus with an interventricular septal defect, dilation of the left renal pelvis, and a single umbilical artery. These abnormalities were associated with a 15.03 Mb deletion of 11q23.3q25. More cases correlating phenotype and genotype are required to predict the postnatal phenotype.

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References

[1] Jurca AD, Kozma K, Ioana M, et al. Morphological and genetic abnormalities in a Jacobsen syndrome. Rom J Morphol Embryol 2017;58:1331–4.
[2] Afifi HH, Zaki MS, El-Gerzawy AM, et al. Distal 11q monosomy syndrome: a report of two Egyptian sibs with normal parental karyotypes confirmed by molecular cytogenetics. Genet Couns 2008;19:47–58.

Table 1

| Karyotype of the fetus | Deletion | Origin | Gestational age | Ultrasonographic findings | Reference |
|-----------------------|----------|--------|----------------|---------------------------|-----------|
| 46,XX,del(11)(q23)    | 14.38 Mb | De novo | 22 wk         | Intrauterine growth restriction, short femurs, DORV, HLHS, SV agenesis, single umbilical artery, and curly fourth toe of the left foot. | Chen et al[15] |
| 46,XX,del(11)(q23)    | 14.5 Mb  | De novo | 20 wk         | Oligophrymdraminos; reduced movements of the fetus; moderate cerebral ventricular dilatation; two weekgrowth retardation | Boehm et al[16] |
| 46,XY, del(11)(q23)   | NA       | De novo | 20 wk         | Nuchal thickening         | McClelland et al[17] |
| 46,XY,del(11)(q23-qter)| NA       | Maternal: t(11;15) | 28 wk         | Bilateral anterosuperior renal pelvis diameters of 0.5 cm; Left renal pelvis diameters of 0.7cm;Trigonocephaly; Micrognathia and prominent anteverted nares; short femur, polyhydramnios. | Foley et al[18] |
| 46,XY,del(11)(q23-q25) | NA       | Paternal: t(5;11) | 20 wk         | Light increased amount of amniotic fluid; prominent forehead with tight of the metopic suture, open fronto-nasal angle and parieto-frontal overlapping Interventricular septal defect, presence of septal blood flow, dilation of left renal pelvis, single umbilical artery | Valduga et al[19] |
| 46,XY,del(11)(q23)    | 15.03 Mb | De novo | 22 wk         | This study               |           |

NA = not applicable.
Valduga M, Cannard VL, Philippe C, et al. Prenatal diagnosis of mosaicism for 11q terminal deletion. Eur J Med Genet 2007;50:475–81.

Ichimiya Y, Wada Y, Kunishima S, et al. 11q23 deletion syndrome (Jacobsen syndrome) with severe bleeding: a case report. J Med Case Rep 2018;12:3.

Favier R, Akshoomoff N, Mattson S, et al. Jacobsen syndrome: advances in our knowledge of phenotype and genotype. Am J Med Genet C Semin Med Genet 2015;169:239–50.

Ji T, Wu Y, Wang H, et al. Diagnosis and fine mapping of a deletion in distal 11q in two Chinese patients with developmental delay. J Hum Genet 2010;55:486–9.

Younza A, Shaheen K, Aughton DJ, et al. Velopharyngeal insufficiency, submucous cleft palate and a phonological disorder as the associated clinical features which led to the diagnosis of Jacobsen syndrome. Case report and review of the literature. Int J Pediatr Otorhinolaryngol 2013;77:1601–5.

Nalbantoglu B, Donna MM, Nişli K, et al. Jacobsen syndrome without thrombocytopenia: a case report and review of the literature. Turk J Pediatr 2013;55:203–6.

Grossfeld P. Brain hemorrhages in Jacobsen syndrome: a retrospective review of six cases and clinical recommendations. Am J Med Genet A 2017;173:667–70.

Chen CP, Lin SP, Hsu CH, et al. Molecular cytogenetic characterization of Jacobsen syndrome (11q23.3-q25 deletion) in a fetus associated with double outlet right ventricle, hypoplastic left heart syndrome and ductus venosus agenesis on prenatal ultrasound. Taiwan J Obstet Gynecol 2017;56:102–5.

Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet J Rare Dis 2009;4:9.

Penny LA, Dell’Aquila M, Jones MC, et al. Clinical and molecular characterization of patients with distal 11q deletions. Am J Hum Genet 1995;56:676–83.

Jones C, Müllenhbach R, Grossfeld P, et al. Co-localisation of CCG repeats and chromosome deletion breakpoints in Jacobsen syndrome: evidence for a common mechanism of chromosome breakage. Hum Mol Genet 2000;9:1201–8.

Akshoomoff N, Mattson SN, Grossfeld PD. Evidence for autism spectrum disorder in Jacobsen syndrome: identification of a candidate gene in distal 11q. Genet Med 2015;17:143–8.

Grossfeld PD, Mattina T, Lai Z, et al. The 11q terminal deletion disorder: a de novo unbalanced reciprocal translocation. Genet Couns 2012;23:223–9.

Seppänen M, Koihinen H, Mustjoki S, et al. Terminal deletion of 11q with significant late-onset combined immune deficiency. J Clin Immunol 2014;34:114–8.

Seppänen M, Koihinen H, Mustjoki S, et al. Terminal deletion of 11q with significant late-onset combined immune deficiency. J Clin Immunol 2014;34:114–8.

Blažina Š, Ibar A, Lovrečič L, et al. 11q terminal deletion and combined immunodeficiency (Jacobsen syndrome): case report and literature review on immunodeficiency in Jacobsen syndrome. Am J Med Genet A 2016;170:3237–40.

Zhang H, Wang R, Li L, et al. Clinical feature of infertile men carrying balanced translocations involving chromosome 10: case series and a review of the literature. Medicine (Baltimore) 2018;97:e0452.

Shaffer LG, McGowan-Jordan J, Schmid M. ISCN (2013): An International System for Human Cytogenetic Nomenclature. Basel, Switzerland: Karger; 2013.

Chen CP, Wang LK, Wu PC, et al. Molecular cytogenetic characterization of Jacobsen syndrome (11q23.3-q25 deletion) in a fetus associated with double outlet right ventricle, hypoplastic left heart syndrome and ductus venosus agenesis on prenatal ultrasound. Taiwan J Obstet Gynecol 2017;56:102–5.

Mattina T, Perrotta CS, Grossfeld P. Jacobsen syndrome. Orphanet J Rare Dis 2009;4:9.

Penny LA, Dell’Aquila M, Jones MC, et al. Clinical and molecular characterization of patients with distal 11q deletions. Am J Hum Genet 1995;56:676–83.

Jones C, Müllenhbach R, Grossfeld P, et al. Co-localisation of CCG repeats and chromosome deletion breakpoints in Jacobsen syndrome: evidence for a common mechanism of chromosome breakage. Hum Mol Genet 2000;9:1201–8.

Akshoomoff N, Mattson SN, Grossfeld PD. Evidence for autism spectrum disorder in Jacobsen syndrome: identification of a candidate gene in distal 11q. Genet Med 2015;17:143–8.

Grossfeld PD, Mattina T, Lai Z, et al. The 11q terminal deletion disorder: a prospective study of 110 cases. Am J Med Genet A 2004;129A:51–61.

Foley P, McAuliffe F, Mullarkey M, et al. Antenatal diagnosis of deletion chromosome 11(q23-qter) (Jacobsen syndrome). Clin Dysmorphol 2007;16:177–9.

Ye M, Coldren C, Liang X, 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.

Afshar M, Smith AP, Smith NC, et al. Nuchal thickening in Jacobsen syndrome. Ultrasound Obstet Gynecol 1998;12:280–2.