Prenatal Identification and Confirmation of Jacobsen Syndrome: A Series of Four Cases

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ABSTRACT

Jacobsen syndrome (JBS) is a rare contiguous gene disorder caused by partial deletion of the distal part of the long arm of chromosome 11. Only a few prenatal cases of JBS have been reported, and data on prenatal ultrasonographic findings are relatively scarce. We analysed four cases of JBS diagnosed prenatally in our centre. All four cases received ultrasound examination in the second trimester. Cardiac defects and intrauterine growth retardation (IUGR) were present in three cases. Ventriculomegaly, shortened femur length and pyelectasis were found in two cases. According to the literature, IUGR, pyelectasis and ventriculomegaly are common prenatal phenotypes of JBS. In addition, cardiac defects, trigonocephaly and shortened femur are also found. Our presentation of these cases provides more ultrasonic information for the prenatal diagnosis of this rare disease.

Key Words: *Ultrasound, Prenatal diagnosis, Jacobsen syndrome, Chromosomal abnormalities, Fetal malformation.*

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INTRODUCTION

Jacobsen syndrome (JBS, MIM #147791) is a rare chromosomal disorder caused by deletion of 11q23. The occurrence of JBS is about 1 per 100,000 births and over 200 cases have been reported in the literature.[1] There is a large spectrum of clinical phenotypes related to this syndrome, including physical growth retardation, cardiac defects, mental retardation, intellectual disability,[2] behavioural problems,[3] dilation of the renal pelvis,[4] immunodeficiency.[5] All above clinical phenotypes vary from patient to patient.

Most of these patients are only diagnosed in the postnatal stage according to clinical phenotypes and cytogenetics, which is the study of structure, function, and inheritance of chromosomes. The indications of prenatal chromosome examination include multiple abnormalities on fetal ultrasound and unexplained intrauterine growth retardation (IUGR). In the prenatal stage, some cases of JBS have occasionally been detected by ultrasound and follow-up chromosomal studies. But these cases are few, and data of prenatal phenotypes is insufficient. It is not clear whether there are specific ultrasonographic findings of characteristics indicating this rare disease.

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In this report, four cases of JBS diagnosed prenatally in our centre are reviewed retrospectively. The prenatal ultrasound characteristics are identified, and the combination of these characteristics on an ultrasound scan led us to suspect the diagnosis of JBS which was confirmed cytogenetically.

CASES REPORT

Case 1: A 26-year, gravida 1, para 0, pregnant woman was referred to our centre for fetal malformation at 24 weeks of gestation. A structural ultrasound examination showed multiple abnormalities including IUGR (head circumference (HC) =mean-3.4 standard deviation (SD), abdominal circumference (AC) =mean-2.3 SD, femur length (FL) =mean-4.0 SD), increased cardiothoracic ratio, enlarged right cardiac cavity, tricuspid regurgitation, ventricular septal defect (Figure 1A), coarctation of the aorta, and single umbilical artery. Cordocentesis was performed and cord blood cells' karyotype was analysed for the fetus. A karyotype of 46, XN, del (11)(q23) was demonstrated (Figure 2A). Parental karyotyping showed normal results. Chromosome microarray analysis (CMA) was not available at that time. After genetic counselling and informed consent, the pregnancy was terminated. During the next pregnancy, the structural ultrasound examination in the second trimester showed normal results and the couple did not opt for a prenatal diagnosis. Follow-up of the child at age 3 years was normal.

Case 2: A 27-year, gravida 1, para 0, pregnant woman without regular prenatal care was referred to our centre for suspected fetal malformation at 26 weeks of gestation. Multiple fetal abnormalities including IUGR (HC=mean-1.9 SD, AC=mean-3.2 SD,

FL=mean-4.4 SD), pyelectasis (Figure 1B), ventricular septal defect (Figure 1C), dilation of the septum pellucidum cavity, mild ventriculomegaly, trigonocephaly ('lemon-shaped' skull) (Figure 1D), and overlapping fingers were revealed by structural ultrasound examination. Cordocentesis was performed and the karyotyping of cord blood cells showed a deletion of 11q23 (Figure 2B). CMA was not available at that time. Parental karyotyping showed normal results. Considering the poor results of the fetus, the couple decided to terminate the pregnancy. During the next pregnancy, the couple opted for prenatal diagnosis by means of amniocentesis, and karyotyping of fetal cells showed normal results. Follow-up of the child at age 3 years was normal.

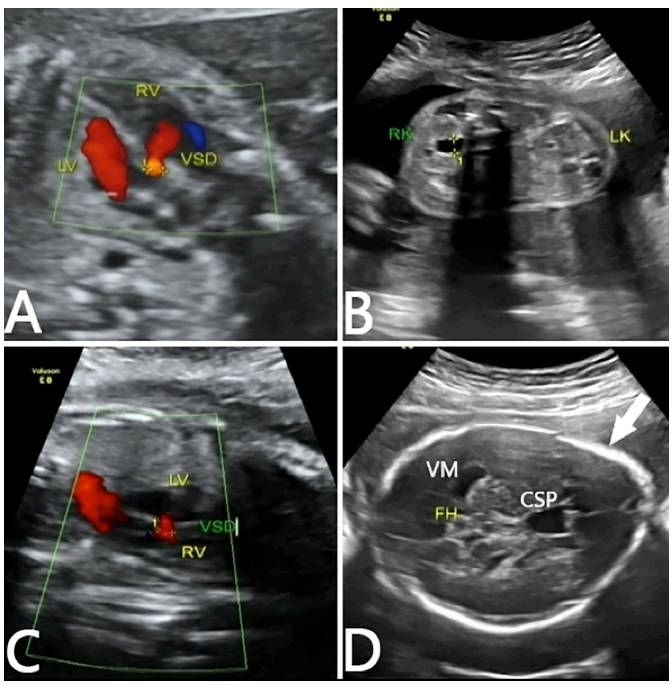

Figure 1: Prenatal ultrasound findings in the study. (A) Ventricular septal defect in case 1; (B) Pyelectasis in case 2; (C) Ventricular septal defect in case 2; (D) Trigonocephaly or 'lemon-shaped' skull (solid white arrow), dilation of the septum pellucidum cavity (CSP) and ventriculomegaly (VM) in case 2.

Case 3: A 22-year, gravida 1, para 0, pregnant woman underwent non-invasive prenatal testing (NIPT) of fetal free-DNA at 20 weeks of gestation. The result of NIPT showed a 13.4 Mb deletion of 11q23.3-25. Ultrasound examination showed IUGR (HC=mean–2.2 SD, AC=mean–2.0 SD, FL=mean–5.5 SD) without structural abnormalities at 23 weeks of gestation. Amniocentesis was performed for fetal karyotype analysis. Cytogenetic studies showed an 11q terminal deletion extending from the 11q23 sub-band to the telomere (46, XN, del(11)(q23.3)) (Figure 2C). CMA was not available at that time. Parental karyotypes were unknown. After genetic counselling, the pregnancy was terminated for the fetal abnormal chromosome.

Case 4: A 28-year, gravida 2, para 0, pregnant woman with normal results of NIPT and nuchal translucency (NT) screening underwent a structural ultrasound examination at 24 weeks of gestation. The ultrasound showed an enlarged right cardiac cavity, tricuspid regurgitation, persistent left superior vena cava, ventricular septal defect of the heart, mild bilateral ventriculomegaly of the brain, and pyelectasis. After genetic counselling, she was suggested to receive amniocentesis. The karyotype and CMA were both analyzed for this fetus. CMA was performed using the Affymetrix CytoScan 750 k platform (Affymetrix, Santa Clara, CA, USA). The arrays were processed according to the manufacturer's protocols and their data were analysed with the CHAS 2.0 software. Marked with more than 50 probes, chromosomal DNA affected at >100 kb length was considered a copy numbers variant (CNV). CNVs were classified as benign, variants of unknown significance (VOUS), or pathogenic according to American College of Medical Genetics (AGMG) guidelines.[6] Fetal karyotype showed an 11q terminal deletion (46, XN, del (11) (q23.3))(Figure 2D) and CMA also showed a deletion of 14.9Mb in 11q23.3-q25 (Figure 3). 19 genes of OMIM are included in this region (SC5D, CLMP, SCN3B, SIAE, ROB03, ROB04, HEPACAM, STT3A, HYLS1, PUS3, CDON, FOXRED1, TIRAP, DCPS, FLI1, KCNJ1, KCNJ5, ST14, OPCML, JAM3, NCAPD3, ACAD8) (Figure 3). Parental karyotyping and CMA showed normal results. After genetic counselling, the pregnancy was terminated.

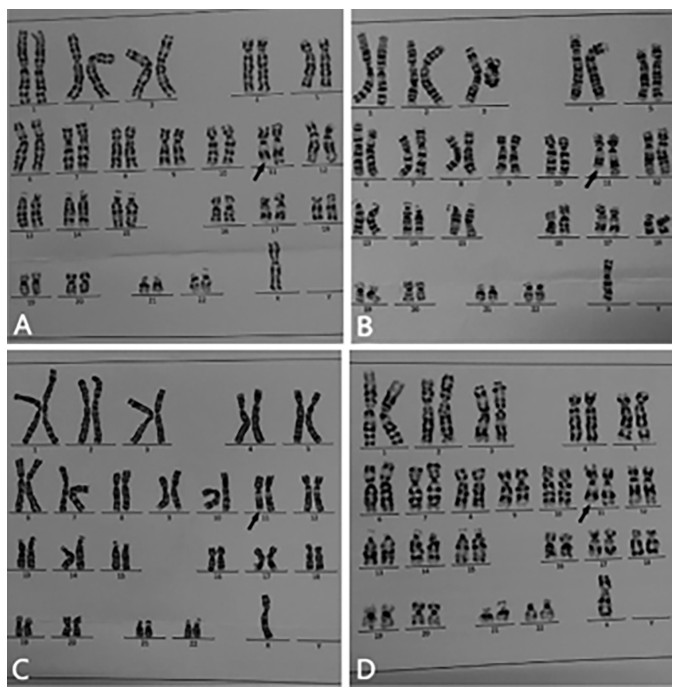

Figure 2: Karyotype findings in the study. Deletion of 11q23 shown in case 1 (A), case 2 (B), case 3 (C), and case 4 (D). The arrows show the breakpoint of 11q23.

DISCUSSION

The deletion of 11q23 is known to be the genetic cause of JBS. Clinical variability and severity depend on the size and the location of the deleted region. It is difficult to discern definite relationships between these regions and phenotypes. Not all JBS cases diagnosed prenatally show structural malformations on ultrasound or soft markers. Case 4 of this study was complicated with IUGR and was diagnosed by NIPT via free fetal cells DNA and subsequent amniotic cell karyotyping. Sheth *et*

al.[7] and Ichimiya *et al*.[8] also reported a case of JBS complicated only with IUGR, respectively. In case 2 of Chen *et al*.,[9] prenatal ultrasound was normal. The IUGR may be the only manifestation among the ultrasonographic findings.

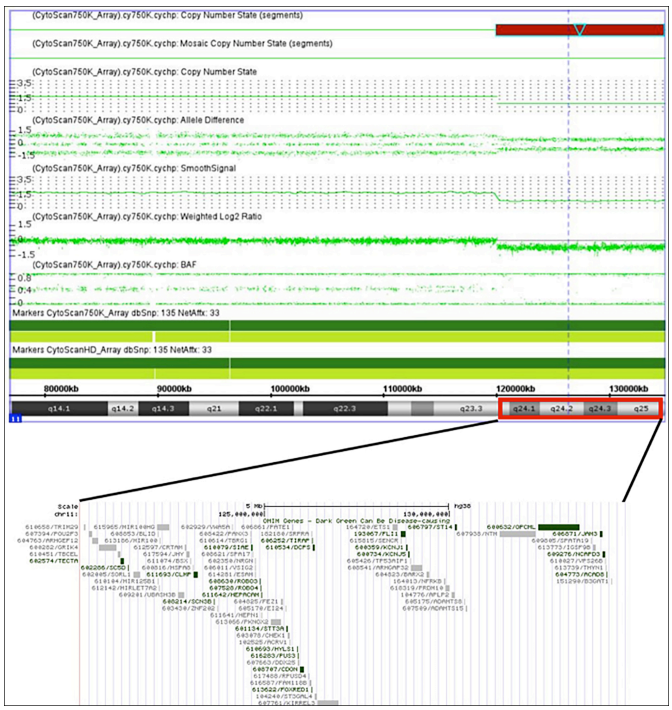

Figure 3: CMA profile of chromosome 11q showing the deleted region and the corresponding genes of OMIM diseases. CMA performed on amniotic cells of case 4 showed an approximately 14.9 Mb deletion at 11q23.3-11q25 (120034951-134937416) in which 19 genes of OMIM diseases were included in this region (SC5D, CLMP, SCN3B, SIAE, ROB03, ROB04, HEPACAM, STT3A, HYLS1, PUS3, CDON, FOXRED1, TIRAP, DCPS, FLI1, KCNJ1, KCNJ5, ST14, OPCML, JAM3, NCAPD3, ACAD8) according to UCSC genome browser (http://genome.ucsc.edu/index.html?org=Human).

Remarkably, the cardiac defects, including the tricuspid regurgitation, enlarged right cardiac cavity, ventricular septal defect, and coarctation of the aorta, emerged as the main ultrasonographic finding in case 1 of this study. Among the four cases in this study, three (75%) were complicated with ventricular septal defects, which supported the notion that cardiovascular malformations are common in this disease. In this study, case 1 and case 4, both had an enlarged right cardiac cavity which may be related to high pressure of left cardia, a sign of hypoplastic left heart syndrome (HLHS). A study by Grossfeld *et al*. showed the prevalence of HLHS in JBS is about 5 -10%. Compared to prenatal cases, postnatal cases often show more congenital heart defects (CHDs).[10,11]

Of the 4 cases in our study, 3 cases manifested as IUGR, which is consistent with other reports.[12,13] Growth delay may be a common sign for JBS. This phenotype can even manifest in the second trimester, which raises the alarm to look for chromosome abnormalities in such cases. In the study by Grossfeld *et al*. developmental delays occurred in 85% of patients, and 25 of 37 (68%) patients had short stature.,[10]

There are three types of ultrasonographic findings, including short femur, pyelectasis, and ventriculomegaly, present in 50% of these four cases. These ultrasonographic findings are also common in other prenatal cases. The pyelectasis can be unilateral or bilateral, and mild pyelectasis (diameter less than 10 mm) or severe (hydronephrosis). Mild pyelectasis is more common than hydronephrosis. In the report of Grossfeld *et al*., also reported a patient complicated with ventriculomegaly with thinning of the corpus callosum.[10] there were 4 cases of hydronephrosis, 5 cases of duplicated ureter, one case of single kidney, and one case of severe dysplastic kidney that required surgical removal, among the 90 cases surveyed. In our case 2, the moderate ventriculomegaly was complicated with dilation of septum pellucidum. Chen *et al*.[14]

In case 2, a characteristic 'lemon-shaped' skull (trigonocephaly) was demonstrated. The trigonocephaly, manifested as a triangular shape of the skull in the top view is caused by premature fusion of the metopic suture. In postnatal cases, the prevalence of trigonocephaly is about 29%.[10] Trigonocephaly is not common in fetuses and should warrant a careful assessment of fetal anatomy and prompt cytogenetic analysis looking for chromosomal aberrations.,[15]

To this day, only about 200 cases of JBS have been reported. The majority of these cases are reported in infancy and childhood based on clinical examination and haematological and cytogenetic findings. The prenatal diagnosis of this disease is rare and difficult. Ultrasound examination is important for the diagnosis. According to the study by Chen *et* al., nearly 71.4% (10/14) of the prenatal JBS cases showed ultrasound findings. Based on our four cases and other prenatal reports, the common ultrasonographic findings of this rare disease include IUGR, pyelectasis, ventriculomegaly, and trigonocephaly. Although nearly all prenatal cases in the literature have ultrasound findings, the deterministic diagnosis depends on cytogenetic examination.[9]

There are some limitations to our study. Firstly, three of four cases were diagnosed only by ultrasound and karyotyping because CMA was not available in the early period. For these three cases, the details of breakpoint and size of deletion are unknown. But the deletion of the 11q terminal obvious in karyotype and the ultrasonographic findings supported this diagnosis. Secondly, all four cases were prenatally diagnosed and ended with termination of pregnancy without an autopsy. The phenotypes of mental development and haematology should be supplemented in future research.

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ETHICAL APPROVAL:
The study was conducted after obtaining approval from the institutional review board of the authors' institute.

PATIENTS' CONSENT:
Informed consents were obtained from all individual participants included in the study.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:

SZ: Study conception, manuscript organization, and data handling.
YD: Manuscript preparation, revision, and supervision.
LX: Cases clinical information collection.
RL: Chromosome microarray examination.
All the authors have approved the final version of the manuscript to be published.

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