**C A S E  R E P O R T**

**Prenatal diagnosis of Pfeiffer syndrome type 2 with increased nuchal translucency**

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**Abstract**

Pfeiffer syndrome (PS) is a rare autosomal dominant genetic disorder characterized by craniosynostosis, broad thumbs/toes. Here, we report a case of PS type 2 with increased nuchal translucency in early trimester.

**KEYWORDS**

increased nuchal translucency, Pfeiffer syndrome, prenatal diagnosis

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**1 INTRODUCTION**

Pfeiffer syndrome (PS, OMIM #101600) is a rare autosomal dominant genetic disorder characterized by craniosynostosis, broad thumbs/toes with an incidence of 1/100,000 live birth. There are three clinical subtypes. Type 1 is associated with midface hypoplasia, broad thumbs, great toes, and is compatible with life, with normal intelligence. Type 2 is characterized by cloverleaf skull, severe ocular proptosis, elbow ankyloses, and large hallucs and thumbs. Type 3 is similar to type 2 except for cloverleaf skull, but with visceral malformation. Fetuses with type 2 or type 3 usually die in utero or in early infancy. With development of ultrasound technology and application of 3-D ultrasound examination, prenatal diagnosis of Pfeiffer syndrome has been reported since 1996. However, craniosynostosis, limb, and visceral malformation are mostly be detected in the second or third trimester. Little is known about the ultrasound manifestation of Pfeiffer syndrome in early pregnancy. Although increased NT has been observed as indirect fetal signs of syndromic or non-syndromic craniosynostosis at first-trimester.
ultrasound examination, Pfeiffer syndrome with increased NT has not been reported so far. Here, we report a case of Pfeiffer syndrome type 2 with increased nuchal translucency in first trimester.

2 | CASE REPORT

A healthy 30-year-old nulliparous woman underwent first-trimester fetal ultrasound scan at 12+1 weeks’ gestation, which showed a single fetus with an increased nuchal translucency (NT) of 3.1 mm (> 99th centile) and a crown-rump-length of 51 mm (Figure 1A). Her husband was 41 years old and healthy. The couple was non-consanguineous. There was no family history of congenital anomalies. Non-invasive prenatal test (NIPT) at 16 weeks’ gestation showed low-risk for fetal Down syndrome.

Morphologic scan at 22 weeks showed acrocephaly, temporal indentation, prominent lateral ventricle with anteroposterior diameter of the posterior horn measuring 10mm, lordosis of the thoracic spine, and broad thumbs and great toes (Figures 1B,C and 2). The fetal sagittal suture was narrow. Its coronal and lambdoid sutures were nearly closed whereas the metopic suture was wide. Pfeiffer syndrome type 2 was suspected based on the typical ultrasound findings. Cordocentesis was performed for molecular diagnosis followed by parents decided to terminate the pregnancy. A 420 g female abortus was delivered. Examination revealed cloverleaf head, proptosis, hypertelorism, low-set ears, flat nasal bridge, abducted broad

FIGURE 1  (A) Increased nuchal translucency of the fetus at 12+1 weeks of gestation. (B) Acrocephaly, protruding forehead, bilateral temporal indentation of the skull and mild ventriculomegaly. (C) Broad thumbs and great toes found by prenatal ultrasound
thumbs, and abducted broad toes along with overriding toes bilaterally (Figure 3). Sacrococcygeal eversion was noted by 3D computed tomography (CT) scan, which was consistent with prenatal ultrasound pictures in retrospect (Figure 2). Whole-exome sequencing showed a heterozygous pathogenic variants on FGFR2 gene [c.870G>T] (located at exon 7), predicted to encode a Trp290Cys substitution. Parental FGFR2 sequencing showed normal findings; therefore, the fetal mutation was de novo.

3 DISCUSSION

There are a number of genetic syndromes with craniosynostosis, such as Apert syndrome, PS, Crouzon’s disease, and Saethre-Chotzen syndrome. With the low incidence and the wide variability of morphological findings, prenatal diagnosis of Pfeiffer syndrome might be challenging. To our knowledge, more than 30 prenatally diagnosed PS have been reported, all were diagnosed at or beyond 20 weeks of gestation. Although cloverleaf skull was one of the most common characteristic noted
in fetal period,7 the typical cloverleaf skull might unlikely be detectable prior to 20 weeks.7,9,10 Gomez-Gomez revealed strawberry-shaped cranium, hypertelorism, a supernumerary bone at frontal level, small thorax, kyphosis and dorsal level scoliosis, and suspicious bladder extrophy at 20 weeks of gestation as clues for the diagnosis.9 Nazzaro detected bilateral temporal indentation and lung system,15 limb,16 cranial sutures,17 and tecting craniosynostosis when fetal skull deformation is minimal,7 which presented in our case. Presence of a saccral appendage and vertebral fusion is also suggestive of PS,12 which also detected in this case.

The ultrasound presentation of PS type 2 in the first trimester has not been described before. In our case, the first abnormal ultrasound appearance was increased nuchal translucency, which might be the first detectable sign in severe craniosynostosis. In fact, increased nuchal translucency has been reported in a case with Apert syndrome, which is also a craniosynostosis syndrome with FGFR2 mutation.13 Thickened nuchal fold (NF) and cystic hygroma with PS were reported presented at 20 weeks and 16 weeks, respectively.7,11 Thickened NF or increased NT is a result of abnormal accumulation of lymph fluid, which might be due to abnormality of blood and lymphatic vessels. In syndromic craniosynostosis, the skull base is smaller and the stenotic jugular foramen causes the crowding of the posterior fossa. Consequently, venous pressure rises and higher cerebrospinal fluid pressure is required to maintain balance, which might explain the severe cases who developed increased NT and ventriculomegaly.14

Another possible association involves molecular mechanisms; fibroblast growth factors (FGFs) are consisted of a family of nine heparin-binding polypeptides which enroll cell proliferation, differentiation, and migration. Any alteration of FGFR can have influence on cellular response to FGFs. FGFR/FGFR genes play a key role in complex branched structures development, such as tracheal bifurcation and lung system,15 limb,16 cranial sutures,17 and angiogenesis.18,19 Mutation in FGFR2 can cause abnormal angiogenesis of fetus, which might also explain the increased NT in this case and David’s case.13

PS mutations have been reported in the ligand-binding region of both FGFR1 and FGFR2. However, mutations affecting the FGFR2 have been reported not only in PS cases but also in other syndrome with craniosynostosis including Crouzon, Apert, and Jackson-Weiss syndromes.20 Combined with our case, 16 of 19 prenatal diagnosed cases of PS with genetic test were found to have mutations in FGFR2 (78.5%), and seven of them were Try290Cys substitution (43.8%).6,8,10,12,21

The correlation between Trp290Cys substitution in FGFR2 and PS has been reported since 1997.10,21-24 The codon 290 exon 7 of FGFR2 is characterized by immunoglobulin-like hoops formed by cys crosslinking, whereas an additional cys at the site caused by a Trp290Cys substitution as our case forms abnormal crosslinking, and changes 3D structure of FGFR2.20 Although cases with such mutations can have variable phenotypes presenting as PS type 2 or type 3,10,21,22,25 their clinical manifestations are always severe as syndromic craniosynostosis.

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CONFLICTS OF INTEREST
There is no any conflict of interest in relation to the work.

AUTHOR CONTRIBUTIONS
Zhi-yang Hu and Sheng Mou Lin involved in conceptualization, methodology, drafting, and writing manuscript. Meng-jie Zhu involved in conceptualization, reviewing, and editing. Cindy Ka-Yee CHEUNG, Tao Liu, and Hong-tao Jin involved in data collection and curation.

CONSENT
Appropriate consent has been obtained from patient, prior to submission, in regards of the publication of images and data.

DATA AVAILABILITY STATEMENT
All data presented and analyzed in this report are included in the published article.

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