Prenatal diagnosis of Pfeiffer syndrome type 2 with increased nuchal translucency

Zhi-yang Hu[1], Sheng Mou Lin[2], Meng-jie Zhu[2], Cindy Ka-Yee CHEUNG[3], Tao Liu[1], and Jin Zhu[1]

[1]Shenzhen People's Hospital
[2]The University of Hong Kong-Shenzhen Hospital
[3]University of Hong Kong-Shenzhen Hospital

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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 at early trimester.

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Zhi-yang Hu[1], Sheng-mou Lin[2,3], Meng-jie Zhu[2], Cindy Ka-Yee CHEUNG[2], Tao Liu[4], Jin Zhu[5]

1Department of Obstetrics, Shenzhen People's Hospital, Shenzhen, China

2Department of Obstetrics and Gynecology, The University of Hong Kong - Shenzhen Hospital, Shenzhen, China

3The First School of Clinical Medicine, Southern Medical University, Guangzhou, China

4Department of Ultrasound, Shenzhen People's Hospital, Shenzhen, China

5Department of Radiology, Shenzhen People's Hospital, Shenzhen, China

Correspondence author: Sheng-mou Lin

Department of Obstetrics and Gynecology, The University of Hong Kong - Shenzhen Hospital, Haiyuan 1st road, Futian District, Shenzhen, China

Telephone number: +86 13500056765

E-mail: linsm@hku-szh.org

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Key Clinical Message

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 at early trimester.

Keywords:Pfeiffer syndrome; increased nuchal translucency; prenatal diagnosis

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 [1]. There are three clinical subtypes [2]. 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 halluces 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 [3]. 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[4,5]. Here we report a case of Pfeiffer syndrome type 2 with increased nuchal translucency at early trimester.

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 3.1mm and a crown-rump-length of 51 mm (Figure 1 A). 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 (Figure 1 B C; Figure2). 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 termination of pregnancy. A 420g female abortus was delivered. Examination revealed cloverleaf head, proptosis, hypertelorism, low-set ears, flat nasal bridge, abducted broad thumbs and toes, and overriding fingers (Figure 3). Sacrococcygeal eversion was noted by 3D computed tomography (CT) scan which was consistent with prenatal ultrasound pictures in retrospect (Figure 2). Whole genome exon 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.

DISCUSSION

There are a number of genetic syndromes with craniosynostosis, such as Apert syndrome, PS, Crouzon's disease, and Saethre-Chotzen syndrome. To our knowledge, 18 prenatally diagnosed PS have been reported [6]. All were diagnosed at or beyond 20 weeks of gestation, and 5 cases were diagnosed before 24 weeks of gestation. The typical cloverleaf skull might not be detectable prior to 20 weeks. Only two prenatal cases mentioned an abnormal skull shape related to Pfeiffer syndrome prior to 21 weeks of gestation [7,8]. Gomez-Gomez revealed strawberry-shaped cranium, hypertolerism, a supernumerary bone at frontal level, small thorax, kyphosis and dorsal level scoliosis, and suspicious bladder exstrophy at 20 weeks of gestation as clues for the diagnosis [7]. Nazzaro detected bilateral temporal indentation and hypertelorism at 20 weeks [8]. Gorincour has reported fetus with PS presenting with a thickened nuchal fold and choroid plexus cysts at 20 weeks' gestation, frontal bossing and temporal indentation at 23 weeks' gestation, and typical cloverleaf skull, broad thumbs and slight hypertelorism at 24.5 weeks' gestation [9]. The relatively late presentation of cloverleaf head might be a result of rapid growth of the brain in the late half pregnancy and craniosynostosis. Among all the prenatal ultrasound features, abnormal fetal skull shape (72.2%) was most frequently reported, while proptosis and hypertelorism were noted in 44.4% cases, whereas malformation of

thumbs and toes were found prenatally in 33.3% and 38.9% [6].

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 [10]. Gorincour's case of PS type 2 was found to have thick nuchal fold (NF) at 20 weeks. Thicken NF or increased NT is a result of abnormal accumulation of lymph fluid which might be due to malformation of blood and lymphatic vessels.

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*. *FGF/FGFR* genes play a key role in complex branched structures development, such as tracheal bifurcation and lung system[11], limb[12], cranial sutures[13], and angiogenesis[14,15]. Clinical researchers have paid great attention to the role of *FGFR* in tumor genesis and targeted it for cancer therapy [16-18]. Mutation in *FGFR2* can cause abnormal angiogenesis of fetus which might explain the increased NT in this case and David's case [10].

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[19]. Combined with our case, 11 of 14 prenatal diagnosed cases of PS with genetic test were found to have mutations in *FGFR2* (78.5%)[6], and five of them were*Try290Cys* substitution (45.5%)[6-8,20].

The correlation between *Trp290Cys* substitution in *FGFR2*and PS has been reported since 1997 [8, 20-23]. 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* [19]. Although cases with such mutations can have variable phenotypes presenting as PS type 2 [8, 20, 21] or type 3 [8,24], their clinical manifestations are always sever. However, a try to *arg* or*gly* mutation at the site seems to have much milder manifestation as previously reported [25,26].

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Conflict of Interest

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

Informed consent

Written informed consent was obtained from the patient.

Authorship List

Zhi-yang Hu: Conceptualization, Methodology, drafting and Writing manuscript.

Sheng Mou Lin: Conceptualization, Methodology, drafting and Writing manuscript.

Meng-jie Zhu: Conceptualization, reviewing and editing.

Cindy Ka-Yee CHEUNG: Data collection and curation.

Tao Liu: Data collection and curation.

Hong-tao Jin: Data collection and curation.

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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.

FIGURE 2. Thoracic spine lordosis and narrow, sacrococcygeal eversion found by prenatal ultrasound (A) and postnatal 3D CT (B).

FIGURE 3. Postmortem examination. (A) Frontal view, showing the typical cloverleaf head, hyertelorism, and contractures of multiple joints. (B) Lateral view, showing the low-set posteriorly rotated ear, mid-face hypoplasia, proptosis. (C-D) Abducted broad thumb. (E) Broad great toes of feet and overriding toes of the left foot.

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