Overlapping Holoprosencephaly-polydactyl syndrome and Asphyxiating thoracic dystrophy, an incidental finding in prenatal ultrasound screening: A rare case report

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Abstract

An obstetric ultrasound of a multi-gravid mother at 37-week of gestation showed a female fetus with alobar holoprosencephaly, polydactyly, short ribs, narrow chest and short upper and lower extremity bones, consistent with Holoprosencephaly-polydactyly syndrome and Asphyxiating thoracic dystrophy overlap. Apgar score was 0 in the first and fifth minutes.

Keywords: alobar holoprosencephaly, polydactyl, short ribs, Jeune syndrome

Key clinical messages: Holoprosencephaly-polydactyly syndrome and asphyxiating thoracic dystrophy rarely overlap but if they do, they have poorer prognosis. Early prenatal detection of multiple congenital anomalies plays a crucial role in the management of pregnancy.

Introduction

Holoprosencephaly is a disorder resulting from failure of septation, cleavage, or differentiation of the midline forebrain structures at various levels or to various degrees. Defects in development of the midfacial region frequently coexist (1). To date, there are four variants of holoprosencephaly according to the degrees of failed differentiation: lobar, semilobar, alobar, and middle interhemispheric variant (syntelencephaly) (2). The various holoprosencephalic abnormalities of the face include cyclopia (single eye or partially divided eye), proboscis (elongated nose), ethmocephalus (narrow-set eyes with an absent nose and abnormal smallness of one or both eyes), cebocephaly (two separate eyes set close together, and a small, flat nose with a single nostril), premaxilla agenesis (least severe form of cebocephaly in the spectrum of facial anomalies is the median cleft lip), median cleft palate/lip, and other less-severe facial dysmorphism (1-3).

Holoprosencephaly–polydactyly syndrome (HPS), also known as pseudotrisomy 13, is one of the less understood congenital syndromes, and the criteria of diagnosis remains controversial. There is some significant overlap of HPS with other disorders such as hydrolethalus syndrome (exclusively from Finland), trisomy 13, which may lead to difficulties in establishing a diagnosis (4, 5).

Asphyxiating thoracic dystrophy (ATD), also known as Jeune syndrome, was first described in 1955 and is a rare autosomal recessive skeletal dysplasia with multi-organ involvement. It characterized by a small, narrow chest and variable limb shortness with a considerable neonatal

mortality as a result of respiratory distress. Other complication of the kidney, liver, pancreas and the eye may occur later in life, if the fetus grows to term (6).

Prenatal ultrasound is an important component of the antenatal care (ANC) package, which can be performed throughout gestational age to check the wellbeing as well as early screening for fetal anomalies (7). Herein, we describe some incidental findings of a rare co-occurrence of HPS and Jeune syndrome diagnosed prenatally through routine obstetric ultrasonography.

Case presentation

In mid 2019, we received a 31-year-old Gravida 3, Para 1+1 (abortion) mother who came for a third trimester routine ANC follow-up in Kawempe National Referral Hospital (KNRH), Kampala, Uganda. She was at her 37weeks by last menstrual period. She received all routine ANC medications, including folic acid, ferrous sulphate, anti-malarial prophylaxis and deworming tablets as per the Ugandan national guidelines. The pregnancy was uneventful. She already had a normal male child who was 3 years old. There was a first trimester abortion (at two months) before this current pregnancy. In her current pregnancy she came once at 24 weeks for her booking ANC and missed her obstetric ultrasound scan. Except for the morning sickness of first trimester, the mother did not have any other complaint throughout her pregnancy. Her blood pressure was consistently in the range of 95/70-110/75mmHg. She added 11kg of weight during the pregnancy (from the 3rd month of the pregnancy to the time of presentation). Both parents were of Ugandan decent and in a non-consanguineous marriage.

On ultrasound examination the fetus was in longitudinal lie and breech presentation. A two-dimensional (2D) ultrasound scan was done on the fetus. The biparietal diameter (BPD) was 119mm (which was above 95th percentile for gestational age). There was absence of brain midline structures with fused thalami. The nasal bone was absent. The neck was short. The ribs were short with narrow chest and four-chambered heart with both right and left ventricular outlets demonstrated (Figure 1 A-F). The diaphragm was present. Double bubble sign, demonstrating a dilated stomach and duodenum was demonstrated in the abdomen. Both kidneys and urinary bladder were seen and normal. The femur, tibia, fibula, humerus, radius and ulna were short (below 5th percentile for gestational age). There was three-vessel umbilical cord. The amniotic fluid index (AFI) was 29cm. The placenta was single lobed and was implanted anteriorly.

A sonographic impression of alobar holoprosencephaly, micromelia, duodenal atresia and short ribs and narrow chest in breech presentation was made. The parents were informed about the abnormalities and the prognosis. They denied the occurrence of similar condition and other abnormalities from both paternal and maternal relations. An elective cesarean section was recommended due to abnormally increased head circumference (as described above) and breech presentation.

A 3.5 kg, phenotypically female baby with Apgar score of zero in the first and fifth minute was delivered through an elective caesarean section. The neonate had six digits and seven digits on the left and right hands respectively. The right and the left feet had five and four abnormally big toes respectively. The head circumference was 45cm and the sutures were widened. The nasal bridge was flat, low set ears, but no cleft lip. The chest circumference was 23cm (less than the 5th percentile). Both upper and lower extremities were abnormally short (Figure 2, A-C). Informed consent was taken from parents for radiological postmortem evaluation.

The postnatal radiography study demonstrated short ribs, short long bones and double bubble sign in the abdomen (Figure 3, A and B).

The whole-body CT scan demonstrated widely open cranial sutures, absent midline structures, postaxial polydactyly of the hands and feet, short and horizontal oriented ribs and narrow chest; and variably short long bones. The phenotypically big toes (5 in the right and 4 in the left feet) showed overlapping phalanges (Figure 3, C-H).

Discussion

Holoprosencephaly is the most common congenital malformation of the forebrain, occurring 1 in 20,000 live births (8). As observed in the present case, the intrauterine fetal death is common among infants with HPS (4). Although the present was phenotypically female , literature suggests that HPS predominantly affect the male sex (4). Despite the fact that, cardiac and genitourinary abnormalities often accompany HPS in a majority of cases (4), this was not observed in the present report. To the best of the authors' knowledge, this is the first case of HPS to be published in Uganda and the first case of HPS-ATD overlap to be reported in the literature.

HPS are heterogeneous group of congenital malformations whose phenotype is consistent with that of trisomy 13 in the context of a normal karyotype- hence often referred to as pseudotrisomy 13 (9). The following diagnostic criteria have been proposed: **a)** a combination of

holoprosencephaly and postaxial polydactyly with or without other characteristics; or **b)** a combination of holoprosencephaly with other characteristics but without polydactyly; or **c)** a combination of postaxial polydactyly, brain defects (microcephaly, hydrocephaly, agenesis of corpus callosum) and other characteristics(10).

In the present case, the diagnosis was made on the basis of phenotypic features and prenatal ultrasound findings. This case is sporadic since there was no similar condition on other sibling. A combination of alobar holoprosencephaly, postaxial polydactyly, absent nasal bone or flat nasal bridge and low set ears was highly suggestive of pseudotrisomy 13. As much as genome wide microdeletion or duplication analysis is ideal for the detection of aneuploidy, it was not done for it was not available in our setting and was not affordable to the parents to do it somewhere else.

Trisomy 13 shows a significant difference from HSP when a detailed phenotypic analysis is performed. In trisomy 13, cystic dysplasia or embryonal lobulation of the kidneys and hydronephrosis occur in 80% cases(10, 11). Grote syndrome has unique combination of holoprosencephaly, tetramelic octodactyly, heart defect, bilateral tibial agenesis, and multivisceral malformations(12). The baby had no cystic dysplasia and neither did it have hydronephrosis nor tetramelic octodactyly.

The definitive diagnosis of HPS remains a challenge. Initially, polydactyly, and normal chromosomal analysis served as the diagnostic criteria of HPS. However, some studies showed that not all cases of HPS have normal chromosomes. This indicated that even in the presence or absence of normal chromosome the diagnosis of HPS is clinical (4).

ATD is a rare autosomal recessive skeletal dysplasia of unknown etiology with multi-organ involvement. Diagnosis is solely based on clinical and radiographic findings. It is clinically characterized by a small, narrow chest and variable limb shortness. Postaxial polydactyly of both hands and/or feet is described as associated congenital abnormalities in 20% case (13). Radiographically it is typical characterized by a narrow, bell-shaped thorax with short, horizontally oriented ribs and irregular costochondral junctions, elevated clavicles, short iliac bones with a typical trident appearance of the acetabula, relatively short and wide long bones of the extremities, and hypoplastic phalanges of both hands and feet with cone shaped epiphyses. In isolated syndromes, the small and narrow thorax often is associated with respiratory distress and recurrent respiratory infections in the postnatal and infancy period respectively (14-16). The present case had small, narrow chest, variable limb shortness and postaxial polydactyly of both

hands on clinical examination. Radiological findings were short, irregular and horizontal oriented ribs, narrow and bell-shaped thorax and short iliac bones. The clinical and radiographic features suggested the presence of an overlapping syndrome other than an isolated HPS in the neonate.

Polymorphisms in several genes including IFT80, DYNC2H1, WDR19, IFT140 and TTC21B have been identified in some families with ATD (6). We were unable to perform molecular genetic testing due to lack of access and affordability of such advanced molecular assays in our setting. ATD and Ellis–van Creveld syndrome are clinically and radiographically similar disorders characterized by skeletal dysplasia. The most important distinguishing feature is, thoracic involvement is less pronounced in Ellis–van Creveld syndrome. Hence it has better prognosis than ATD (17-19). In the present case the chest was profoundly affected.

Visualization of a fluid-filled double bubble on prenatal ultrasound scan is associated with duodenal obstruction secondary to intrinsic or extrinsic cause. It can be associated with VACTERL (vertebral, anorectal, tracheoesophageal, renal, limb), chromosomal anomalies like trisomy 21 or it can be an isolated entity (20, 21). The presence of duodenal atresia was diagnosed on the prenatal late ultrasound and was confirmed by postmortem baby-gram and was found in association with HPS and Jeune syndrome. It hasn't been described in connection with either of these syndromes in the literature.

Conclusion

HPS and asphyxiating thoracic dystrophy rarely overlap but if they do, they have poorer prognosis. Early prenatal detection of multiple congenital anomalies plays a big role in the management of pregnancy, delivery and postnatal complication to the fetus and the mother.

Declaration:

Ethics approval and consent to participate

The neonate's parent provided an informed written consent to participate in the study.

Consent for publication

The neonate's parent provided an informed written consent for this case to be published in a peer-reviewed journal.

Availability of data and materials

The information used and/or analyzed during this case report is available from the corresponding author on reasonable request.

Competing interests

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References

1. DeMyer W, Zeman W, Palmer C. The face predicts the brain: diagnostic significance of median facial anomalies for holoprosencephaly (arhinencephaly). Pediatrics. 1963;34:256-63.
2. Cedrik T-N, Maximilian M, Paul K. Holoprosencephaly Overview. GeneReviews® . 2000.
3. Li-Hsiung C. Alobar Holoprosencephaly: Report of Two Cases with Unusual Findings. Chang Gung Med J. 2003;26 (9).
4. Bous SM, Solomon BD, Graul-Neumann L, Neitzel H, Hardisty EE, Muenke M. Holoprosencephaly-polydactyly/pseudotrisomy 13: a presentation of two new cases and a review of the literature. Clinical dysmorphology. 2012;21(4):183-90.
5. Salonen R, Herva R. Hydrolethalus syndrome. Journal of medical genetics. 1990;27(12):756-9.
6. Jeune M, Béraud C, R. C. Dystrophie thoracique asphyxiante de caractère familial. Arch Fr Pediatr. 1955;12:886–91.
7. Bouman K, Bakker MK, Birnie E, ter Beek L, Bilardo CM, van Langen IM, et al. The impact of national prenatal screening on the time of diagnosis and outcome of pregnancies affected with common trisomies, a cohort study in the Northern Netherlands. BMC Pregnancy and Childbirth. 2017;17(1):4.

8. Chaudhari HD, Thakkar G, Darji P, Khokhani P. Prenatal ultrasound diagnosis of holoprosencephaly and associated anomalies. BMJ Case Rep. 2012;2012:bcr0320126129.
9. Dwight R C, Claude B, Alan L S, Bassem RH. Holoprosencephaly-polydactyly syndrome: in search of an etiology. Eur J Med Genet. 2008;51(2):106–12.
10. Iosif W. L, Eric A. W. Holoprosencephaly-Polydactyly (Pseudotrisomy 13) Syndrome: Expansion of the Phenotypic Spectrum. American Journal of Medical Genetics. 1993;47:405-9.
11. Hodes M, Cole J, Palmer C, Reed T. Clinical experience with trisomies 18 and 13. J Med Genet. 1978;15:48-60.
12. Grote W, Rehder H, Weisner D, Wiedemann H. Prenatal diagnosis of a probable hereditary syndrome with holoprosencephaly, hydrocephaly, octodactyly and cardiac malformations. Eur J Pediatr. 1984;143:155-7.
13. Hennekam R, Beemer F, Gerards L, Cats B. Thoracic pelvic phalangeal dystrophy (Jeune syndroom). Tijdschr Kindergeneeskd. 1983;51:95–100.
14. Cortina H, Beltran J, Olague R, Ceres L, Alonso A, Lanuza A. The wide spectrum of the asphyxiating thoracic dysplasia. Pediatric Radiology. 1979;8(2):93-9.
15. Kajantie E, Andersson S, Kaitila I. Familial asphyxiating thoracic dysplasia: clinical variability and impact of improved neonatal intensive care. J Pediatr. 2001;139:130–3.
16. de Vries J, Yntema JL, van Die CE, Crama N, Cornelissen EAM, Hamel BCJ. Jeune syndrome: description of 13 cases and a proposal for follow-up protocol. European journal of pediatrics. 2010;169(1):77-88.
17. Geneviève B, Martine Le M. Ellis-Van Creveld syndrome. Orphanet Journal of Rare Diseases. 2007;2(27).
18. Kusick V M. Ellis-van Crefeld syndrome and the Amish. Nature Genet. 2000;24:203-4.
19. Takamine Y, Krejci P, Wilcox W. Mutations in the EVC1 gene are not a common finding in the Ellis-van Creveld and Short-Rib-polydactyly type III syndromes. Am J Med Genet. 2004;130A:96-7.
20. Choudhry MS, Rahman N, Boyd P, Lakhoo K. Duodenal atresia: associated anomalies, prenatal diagnosis and outcome. Pediatric Surgery International. 2009;25(8):727-30.
21. Hemming V, Rankin J. Small intestinal atresia in a defined population: occurrence, prenatal diagnosis and survival. Prenat Diagn. 2007;27:1205–11.

Figure Legends

Figure 1. A, B, C, D, E and F – prenatal ultrasound. A) Demonstrates absence of midline structures. B) Demonstrates double bubble sign, narrow chest, short and horizontal ribs. C) Color Doppler demonstrates no flow in the remained brain parenchyma and three vessel cord of umbilicus. D) Demonstrates absence of nasal bone. E) Demonstrates short radius and ulna. F) Demonstrates very short femur, tibia and fibulae.

Figure 2. A, B and C – post-delivery images of the neonate. A phenotypically female neonate with big head, flat nose, low set ears, small chest, invariably short limbs, polydactyly of four limbs

Figure 3. A and B – postnatal radiography study. C, D, and E – CT scan with brain window. F and G - 3D CT bone reformat. H – CT scan in bone window. A and B) demonstrate short and horizontal oriented ribs, bilateral short humerus and femur. C, D and E) demonstrate absent midline structures with frontal lobes and occipital lobe in place. F) Demonstrates widely open cranial sutures. G) Demonstrates short and horizontally oriented ribs. H) demonstrates postaxial polydactyly of the Right hand (RH), Left hand (LH), Right foot (RF) and Left foot (LF).