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CASE REPORT

Fronto-nasal dysplasia and atrio-ventricular canal in a fetus with trisomy 18 identified by absent nasal bones during first trimester screening scan

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ABSTRACT **Failed ultrasonographic visualization of nasal bones is associated with an increased risk of fetal malformations. Maternal ethnicity and chromosomal abnormalities influence the incidence and visualization rate of nasal bones. A case of absent nasal bones with fronto-nasal dysplasia and septated cystic hygroma identified at 13^{+5} weeks' gestation in a trisomy 18 fetus is reported. The crown–rump length was 82 mm and the absent nasal bones were associated with micrognathia and a flattened face. The risks for trisomy 21 and 18 were subsequently calculated. The couple refused chorionic villus sampling. At 19 weeks' gestation a follow-up scan revealed, apart from the resolution of septated cystic hygroma, hypertelorism, a large interventricular septum defect with an atrioventricular canal and an abnormal A wave Doppler pulsation at the level of the ductus venosus. Bilateral choroid plexus cysts were additional ultrasound findings. At that time, an uneventful cordocentesis was performed showing a 47,XY(+18) karyotype. Termination of pregnancy was achieved and pathologic examination confirmed the ultrasonographically detected fetal malformations. When screening the fetal face for the presence or absence of nasal bones during the first trimester pregnancy scan the following points must be taken into consideration: (i) the ethnicity of the mother; (ii) if the nasal bones are absent, measurement of nuchal translucency and risk calculations for trisomy 21 and trisomy 18 should be performed; (iii) if the calculated risks are high, karyotyping should be recommended; and (iv) determine whether the absent nasal bones are an isolated or an associated finding and, in the latter case, discriminate between minor or major fetal malformations.**

Key Words: abnormal karyotype, absent nasal bone, fetal malformation, prenatal diagnosis, ultrasound

INTRODUCTION

Since the work of Cicero *et al*. (Cicero *et al.* 2001) regarding the association between absent nasal bones (NB) and Down syndrome have appeared, many studies in the literature have reported findings of an increased risk of fetal aneuploidies associated with failed ultrasonographic visualization of nasal bones. Today there is a growing body of evidence that introducing the visualization of the nasal bones in the first trimester screening for Down syndrome, as suggested by the Fetal Medicine Foundation 11–14 week scan project, will result in an increased detection rate for Down syndrome from 72% to 75% with nuchal translucency (NT) measurement alone to 83% to 85% with associated NT + NB (Cicero *et al.* 2001).

Taken as an independent ultrasound marker for fetal anomalies, absent nasal bones will result in a 65% sensitivity with a likelihood ratio of 146 (95% CI, 50–434). Out of 3829 fetuses undergoing fetal karyotyping during the first trimester, the fetal profile was examined successfully in 98.9% of cases and was absent in 67% of fetuses with trisomy 21, in 57% of fetuses with trisomy 18, in 32% of fetuses with trisomy 13 and in 8.9% of fetuses with Turner syndrome (Cicero *et al.* 2003). Chromosomal abnormalities as well as maternal ethnicity may influence the visualization rate and the incidence of absent nasal bones. For chromosomally normal fetuses, absent nasal bones have an incidence of 2.8% in Caucasian, 6.8% in Asian and 10.4% in Afro-Caribbean fetuses (Cicero *et al.* 2003).

In a study by Zoppi *et al*. (Zoppi *et al.* 2003) of 5532 fetuses, the visualization of the fetal profile was obtained in 99.8% of fetuses during the first trimester ultrasound NT + NB screening test, with the fetal karyotype available in 3503 pregnancies. There were 40 chromosomal abnormalities diagnosed and the nasal bones were absent in 70% of trisomy 21 cases, 80% of trisomy 18 cases, 66% of those fetuses with Turner syndrome and in only 0.2% of fetuses with a normal karyotype. Odibo *et al*. (Odibo *et al.* 2004) evaluated the fetal nasal bones on 632 fetuses undergoing prenatal diagnosis and found the association between failed nasal bone visualization and aneuploidy to be 41% for total aneuploidy and 44% for trisomy 21. The total number of aneuploid cases were 29 (4.6%) and trisomy 18 accounted for five of these cases (17%).

The authors documented that when using a receiver operating curve (ROC) with a biparietal diameter/nasal bone ratio of 11 or greater, fetal aneuploidy could be identified with a sensitivity of 50%, a specificity of 93%, a positive predictive value of 24% and a negative predictive value of 98%, and concluded that absent or hypoplastic nasal bones are a marker of fetal aneuploidy in a high-risk population.

The case of absent nasal bones with fronto-nasal dysplasia associated with cystic hygroma at 13^{+5} weeks' gestation and an atrioventricular canal in a trisomy 18 fetus is reported here.

CASE REPORT

A 23-year-old Asian gravida 1, para 0 woman, attended first trimester pregnancy scan at 13^{5} week's gestation. She had no relevant past medical, obstetric or family history of note.

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The scan was conducted using a multifrequency 3.5–7.5 MHz transabdominal probe (ATL 3500, Philips, the Netherlands) with a decibel range of 35–60 dB, Thermal Index = 0.1 and Mechanical Index = 0.4. The crown-rump length was 82 mm and the absence of the nasal bones associated with micrognathia and a flattened face was noted (Fig. 1). Additionally, a septated cystic hygroma was seen (Fig. 2). Due to the presence of ultrasonographic markers suspicious of fetal pathology, prenatal counseling was conducted and fetal karyotyping was advised. The couple refused to undergo chorionic villus sampling (CVS) and a serial, follow-up scan was chosen as an alternative management strategy. The patient underwent a thorough scan at 19 week's gestation according to the SIEOG guidelines (SIEOG = Italian Society of Ultrasound in Obstetrics and Gynecology) which revealed the following findings: resolution of the septated cystic hygroma, hypertelorism, micrognathia, clenched hand (Fig. 3) and an atrio-ventricular canal with abnormal Doppler waveform analysis at the level of the ductus venosus (Fig. 4A–C). Bilateral choroid plexus cysts measuring 7.3 mm × 6.6 mm and 5.9 mm × 4.7 mm, respectively, were associated findings (Fig. 5). The couple was again counseled about the fact that a chromosomal abnormality could not be excluded and after informed consent, obtained with the aid of an official translator, an uneventful cordocentesis was performed transabdominally. The result was 47,XY (+18). Due to the presence of both ultrasonographically detected fetal malformations and an abnormal karyotype, the couple chose to undergo a termination of pregnancy (TOP) after giving signed informed consent. The TOP was achieved by vaginal administration of PGE1 (Cervidil©) and the pathologic examination was then performed.

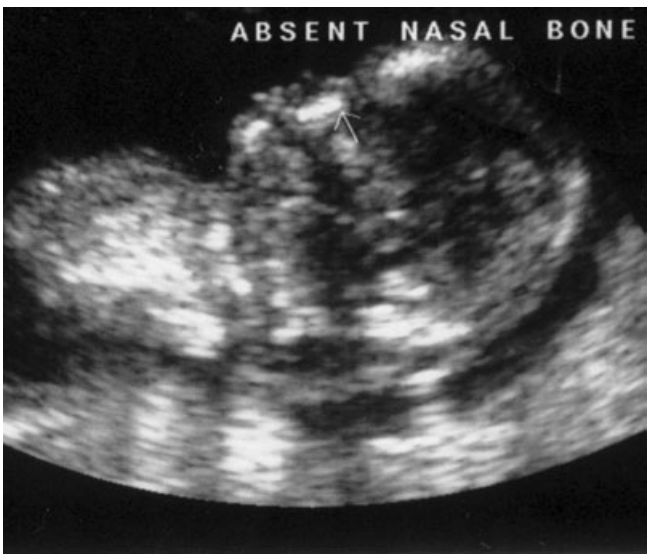

Fig. 1 Sagittal section of the fetal face at 13^{+5} weeks' gestation demonstrating an abnormal profile with a flattened nose, abnormally positioned maxilla and associated micrognathia.

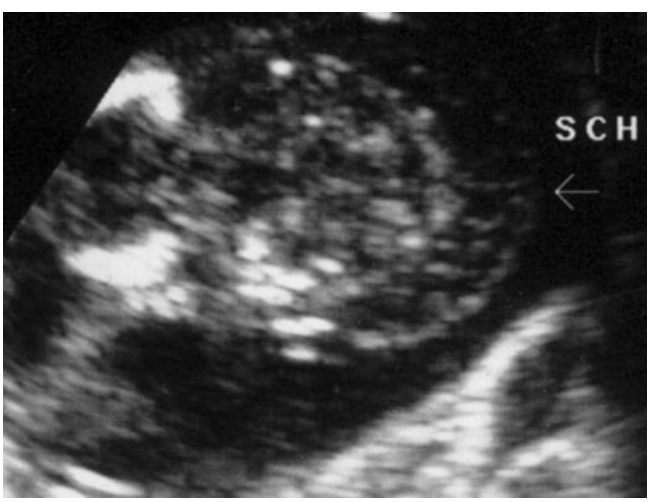

Fig. 2 Transverse section at the level of the cephalic pole revealing the presence of septated cystic hygroma (SCH) at 13^{5} weeks's gestation.

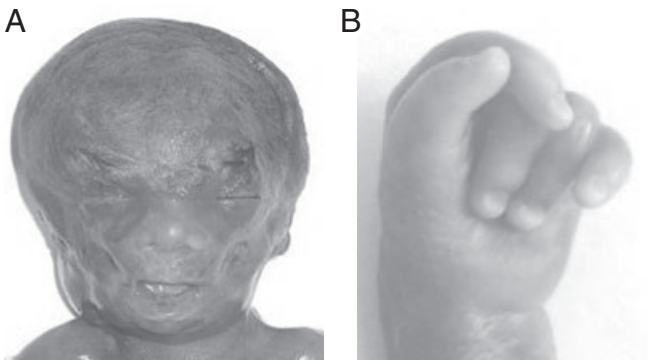

Fig. 3 (A) Post-mortem examination of the fetal face demonstrating the fronto-nasal dysplasia characterized by a flattened nose, hypertelorism and micrognathia. (B) Clenched hand.

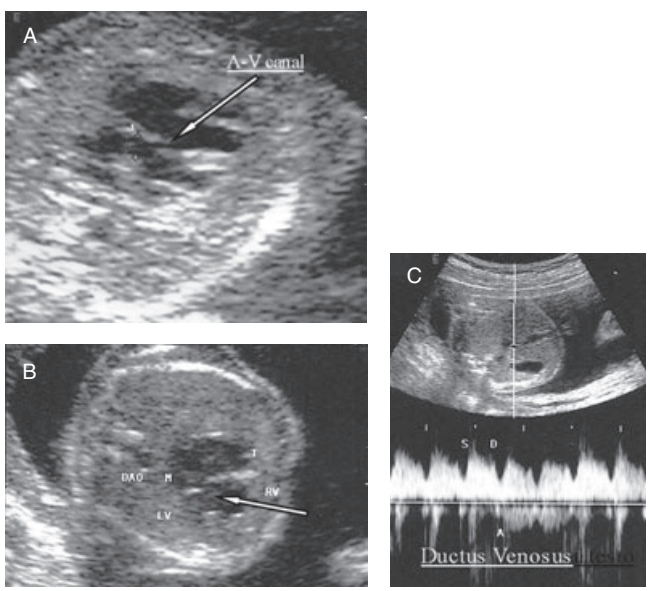

Fig. 4 (A) Prenatal ultrasonographic findings at 19 week's gestation of the fetal heart showing a large interventricular septum defect. LV, left ventricle; RV, right ventricle; DAO, descending aorta. (B) Atrio-ventricular canal. (C) Abnormal ductus venosus Doppler waveform (negative A wave).

DISCUSSION

The nasal bones develop from paired independent ossification centers located in a membrane that covers the cartilaginous nasal capsule (Sandkcioglu 1994). According to Bronshtein (Bronshtein *et al.* 1998) the overall incidence of fetal nasal malformations is reported as 1/1600 and the incidence of trisomy 18 as 1/1500. This incidence is related either to isolated or associated fetal malformations. He reported 15 cases; one diagnosed at 15 week's gestation had associated increased nuchal edema and resulted in trisomy 21, and in another case a tetrasomy 12p was present. Maternal ethnicity is another important variable and it must be taken into consideration that in chromosomally normal fetuses, Asian people are the second most common ethnic group in which absent nasal bones can be identified (occurring in 6.8% of cases) compared to 10.4% for Afro-Caribbean and 2.8% for Caucasian people (Cicero *et al.* 2003). It is also important to note that when screening for the fetal profile at 11–14 weeks gestation there is a variable rate of failed visualization that can be related to: unsatisfactory fetal position (persistent occipito-anterior position); time-to-scan; experience of the sonographer; and the use of the transvaginal approach in the case of a failed transabdominal visualization. In the work of Prefumo *et al.* (2004) on 4492 fetuses undergoing ultrasound assessment of fetal nasal bones at 11–14 week's gestation, the nasal bones could not be examined in 10.3% of cases (460 fetuses). What is essential is to differentiate between a technically unsatisfactory examination of the fetal profile and the failure to visualize the nasal bones because of aplasia, hypoplasia or delayed ossification of the nasal bones themselves.

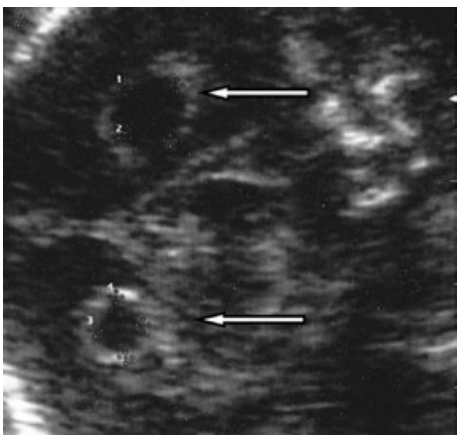

Fig. 5 Transabdominal scan at 19 weeks showing bilateral choroid plexus cysts.

As reported in the work of Cicero *et al*. (2001) on 3829 fetuses undergoing the 11–14 week scan, trisomy 18 is the second most frequently found chromosomal abnormality (57%) associated with absent nasal bones, with a higher incidence observed only for trisomy 21 (67%). The authors concluded that at the 11–14 week scan, the incidence of absent nasal bones is related to the presence or absence of chromosomal defects, crown–rump length, NT thickness and ethnic origin.

Different conclusions have been reached by the FASTER Research Consortium (Malone *et al.* 2004) where 6324 patients underwent nasal bone sonography. There were 11 cases of trisomy 21, and in nine of these (82%) the nasal bones were described as in this report. The only other aneuploidies were two cases of

Table 1 Classification of fronto-nasal dysplasia syndromes

Syndromes and OMIM classification	Inheritance	Associated US anomalies	Fetal karyotype and gene mapping
Robinow syndrome (180700)	Autosomal dominant	Flat face, hypertelorism, short forearms, clinodactyly, macrocephaly	Normal, ROR2 gene
Apert syndrome (#101200)	Autosomal dominant	Flat nose, maxillary hypoplasia, hypertelorism, craniosynostosis, syndactyly	Normal, 10q26 FGFR2
Crouzon syndrome (#123500)	Autosomal dominant	Craniosynostosis, maxillary hypoplasia, hypertelorism	Normal, 10q26l
Aarskog syndrome (100050)	X-linked recessive	Flat nose, hypertelorism	Normal
Rudiger syndrome (268650)	Autosomal recessive	Flat nasal bridge, short	Normal
Stickler syndrome (#108300)	Autosomal dominant	Facial cleft, micrognathia, flat face, osteo-chondrodysplasia, talipes	Normal Type I 12q13.11-q13.2 Type II 1p21 Type III 6p21.3 Gene COL2A1 Gene COL11A1 Gene COL11A2
Achondroplasia	Autosomal dominant	Mid-face hypoplasia, low nasal bridge, rizomelic micromelia	Normal, 4p16.3 FGFR3
Chondrodysplasia puntata (302950)	X-linked dominant	Nasal hypoplasia, scoliosis, asymmetrical shortening of the limbs	Delection/translocation Xp22.3
Binder syndrome (%155050)	Autosomal dominant Autosomal recessive	Flat mid-face, nasal hypoplasia, hypertelorism	Normal, 4p16.3 FGFR3

trisomy 18, and in one of these the nasal bones were described as being absent.

The FASTER study concluded that the absence of nasal bones had a sensitivity for aneuploidy of 7.7%, false positive rate of 0.3% and positive predictive value of 4.5% (Malone *et al.* 2004). Kjaer evaluating the abnormalities of the axial skeleton in 10 human trisomy 18 fetuses showed how the nasal bones were abnormal, either absent or hypoplastic, in eight cases (Kjaer & Keeling 1996). Cusick *et al.* (2004) reported data on 12 aneuploid fetuses with available nasal bone measurements and found that the nasal bones were absent in three fetuses: one case each of trisomy 21, 18 and 13. Viora *et al*. (2003) reported data regarding 1906 consecutive fetuses undergoing the nuchal translucency scan at 11–14 weeks' gestation and showed how the fetal profile visualization was possible in 92% of cases. The nasal bones in this series were hypoplastic/absent in 12 of 19 fetuses with chromosomal abnormalities, of whom 10 cases were trisomy 21. The authors confirm their findings that delayed nasal bone ossification, either in terms of hypoplasia or absence, is a rare feature in chromosomally normal fetuses (1.4%).

Today, there is increasing evidence that absent nasal bones are a marker of fetal pathology. Its first application (Cicero *et al.* 2001) has been utilized in the first trimester screening for Down syndrome, where the inclusion of absent nasal bones in a screening program based on maternal age plus the fetal NT measurement could increase the sensitivity from 72% to 75% of NT alone for a false positive rate (FPR) of 5% to a detection rate of 83% to 85% with a FPR of 1%.

It should be underline that nasal hypoplasia can be encountered in different syndromes, such as chondrodysplasia punctata, which is due to a deletion/translocation of chromosome Xp22.3 X-linked disorders, and Robinow syndrome, which is an autosomal dominant condition characterized by a flat nose, ocular hypertelorism, short forearms, clinodactyly and macrocephaly and others (Table 1).

In summary, when screening for fetal face morphology and the presence or absence of nasal bones during the first trimester pregnancy scan, the following considerations must be born in mind:

(i) the ethnic group of the mother;

(ii) if absent nasal bones are detected, measurement of nuchal translucency and the risk calculation for both trisomy 21 and trisomy 18 should be done whenever possible (both risks are automatically calculated by the Fetal Medicine Foundation 11–14 weeks' scan software);

(iii) if the calculated risk is high (>1:300) fetal karyotyping must be recommended; and

(iv) if the occurrence of absent nasal bones is an isolated or an associated finding and, if so, a distinction between minor and major fetal malformations must be made.

Finally, a thorough search for fetal anomalies should be carried out by an expert, second level sonographer when absent nasal bones have been diagnosed. The detailed description of fetal anatomy would serve as the basis (together with fetal karyotype when obtained) of the parents' counseling and of their decision making process. In cases where a termination of pregnancy is the choice, a complete autopsy examination should be an integral part of the prenatal diagnosis *armamentarium*.

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