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Prenatal Features of Noonan Syndrome

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We report six cases of Noonan syndrome which presented prenatally with sonographic abnormalities. These included increased nuchal fluid, short femora, pleural effusions, hydrops, cardiac and renal abnormalities. A review of all cases of Noonan syndrome seen at two regional genetics centres confirms the association with these sonographic abnormalities. These cases demonstrate the diversity of prenatal presentation of Noonan syndrome and highlight the need to consider this diagnosis, particularly when faced with a fetus with a normal karyotype and varying degrees of oedema or hydrops, with a short femur length. Copyright © 1999 John Wiley & Sons, Ltd.

KEY WORDS: prenatal diagnosis; Noonan syndrome; nuchal oedema; pleural effusion

INTRODUCTION

Noonan syndrome was first described by Noonan and Ehmke (1963). Features include short stature, a typical facial appearance, a broad or webbed neck, and cardiac anomalies (mainly pulmonary stenosis and hypertrophic cardiomyopathy). The incidence of this disorder is between 1 in 1000 and 1 in 2000 of the population (Mendez and Opitz, 1985; Allanson, 1987). Noonan syndrome is inherited in an autosomal dominant manner, although some cases arise *de novo*. The gene has recently been mapped to the long arm of chromosome 12 (Jamieson *et al.*, 1994; Brady *et al.*, 1997).

We report six cases of Noonan syndrome, all of which presented antenatally with increased nuchal fluid and/or pleural effusions, relatively short femora in three cases as well as renal and cardiac anomalies in some cases (Table 1). These cases demonstrate the diversity of prenatal presentation of Noonan syndrome and highlight the need to consider this diagnosis, particularly when faced with a fetus with a normal karyotype and varying degrees of oedema or hydrops, with a short femur length.

CASE REPORTS

Case 1

A 23-year-old primigravida underwent ultrasound examination of 13 weeks' gestation. This demonstrated significantly increased nuchal fluid (Fig. 1). The femur length was just below the 5th centile whilst the head circumference (HC) was on the 25th centile. Chorionic villus sampling was performed. This demonstrated a normal karyotype. Maternal viral studies were negative. Ultrasound examination at 17 weeks' gestation demonstrated complete resolution of the lesion. There were no other obvious anomalies. At 27 weeks' gestation an acute onset of polyhydramnios occurred. Within 24 hours the mother went into premature labour, and a female infant weighting 1380 g was delivered. The infant was oedematous, with low-set ears and widely spaced nipples. There was a patent ductus arteriosus and hypertrophic cardiomyopathy. Despite these complications, the infant survived. Histology of the placenta demonstrated a chorioangioma. A diagnosis of Noonan syndrome, based on the clinical features, was made by the local geneticist.

Case 2

A 27-year-old primigravida was referred at 14 weeks' gestation because of increased nuchal fluid. On assessment at the tertiary unit, the findings were confirmed and femoral length noted to lie on the 5th centile. The karyotype was normal. At 18 weeks' gestation the nuchal fluid had resolved. However, the femoral length remained on the 5th centile whilst other measurements were on or above the 50th centile. Findings were similar for two further scans. On the second of the scans, mild pyelectasis was noted. In view of these findings the parents elected to terminate the pregnancy. At post-mortem examination, a low posterior hairline and low-set ears were noted, in addition to the mild pyelectasis.

The following year, a second child was born after an unremarkable pregnancy. He was well at birth, but at six weeks of age he was noted to have a heart murmur. Echocardiography demonstrated pulmonary stenosis, which was treated by pulmonary valvotomy. He was also noted to have a unilateral undescended testis; a diagnosis of Noonan syndrome was made following a genetics consultation. The mother has facial features consistent with Noonan syndrome, in addition to short stature and some learning difficulties.

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Table 1—Prenatal features of Noonan syndrome

	Nuchal oedema in first trimester	Nuchal oedema in second trimester	Polyhydramnios	Hydrops	Pleural effusions	Cardiac anomaly	Short femur	Other prenatal features	Other postnatal features
Case 1	Yes	No	Yes	No	No	No	Yes		Placental chorioangioma
Case 2[a]	Yes	No	No	No	No	No	Yes	Mild RPD	HOCM
Case 3	?	Yes	Yes	No	No	No	Yes	Single umbilical artery	HOCM
Case 4	No	No	Yes	Yes	Yes	Yes	(No)		Duplex kidney Coarctation of the aorta
Case 5	?	?	Yes	Yes	Yes	No	No	RPD (21 mm)	HOCM
Case 6	?	?	No	No	Yes	No	No		
Genetic centres (n=43)	4		8	3	3	2	?	None recorded	Variable

[a]Termination of pregnancy.
HOCM—hypertrophic cardiomyopathy; RPD—renal pelvic dilatation.

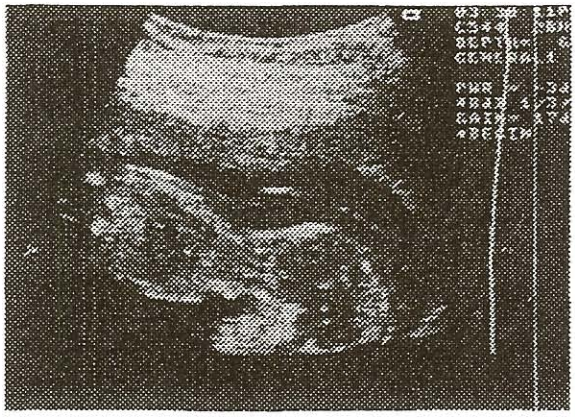

Fig. 1 – Case 1. Longitudinal scan demonstrating increased nuchal translucency at 13 weeks

Case 3

A 38-year-old was referred for anomaly scanning at 20 weeks' gestation. The fetus was noted to have short femora, lying just below the 5th centile. Other measurements were on or above the 25th centile. There were no other obvious fetal anomalies noted at this stage. A scan was arranged for 25 weeks' gestation in view of the short femora. At the 25-week scan, both upper and lower limb measurements were noted to lie around or below the 5th centile whilst other measurements were on or above the 50th centile. In addition nuchal thickening (Fig. 2), polyhydramnios, and a single umbilical artery were noted. The heart and other organs appeared normal. An underlying skeletal dysplasia was felt to be unlikely in view of the normal bone morphology. Chorionic villus sampling was carried out to determine the karyotype of the fetus, which was normal. Ultrasound examination was repeated at 30 and 35 weeks' gestation. The findings were similar at each scan. The limbs remained short but with normal growth velocity. The nuchal oedema and increased liquor volume persisted. In addition, some thickening of the skin over the chest wall was noted. A female baby weighing 2850 g was subsequently delivered at 38 weeks' gestation. At about six weeks of age she developed hypertrophic cardiomyopathy, and died at five months. A diagnosis of Noonan syndrome was made, based on the clinical findings, prior to her death.

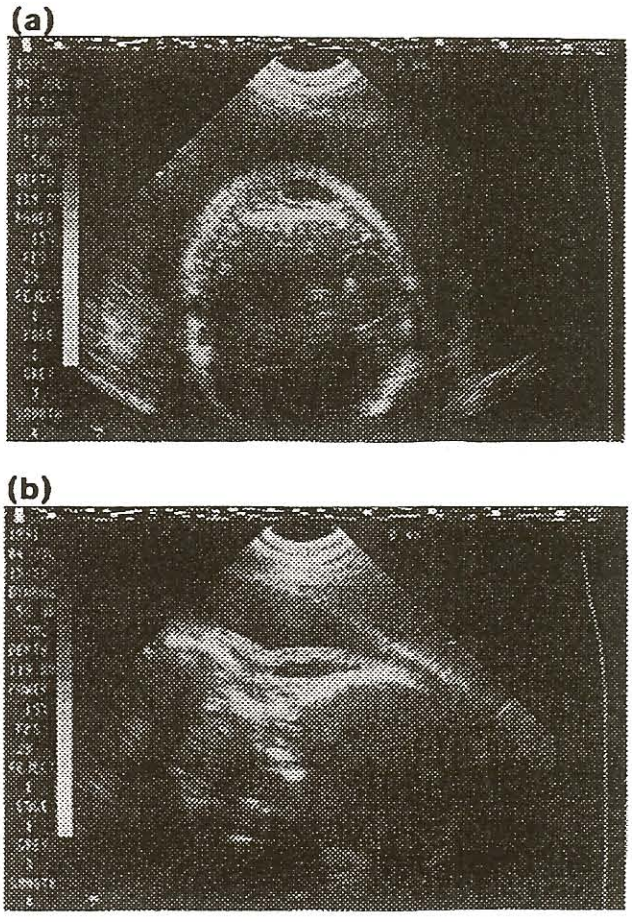

Fig. 2 – Case 3. Views through fetal neck demonstrating increased nuchal fold at 25 weeks: (a) transverse and (b) longitudinal

Case 4

A 23-year-old primigravida with no significant past medical history had two unremarkable routine ultrasound scans at 10 and 20 weeks' gestation. At 29 weeks' gestation a clinical diagnosis of polyhydramnios was made. Ultrasound examination demonstrated hydrops fetalis with polyhydramnios. There was gross skin oedema (Fig. 3(a)), large bilateral pleural effusions (Fig. 3(b)), and thickened ventricular walls of the heart. A fetal blood sampling was performed. The karyotype was normal, and there was no evidence of a viral infection or fetal anaemia. Specialist fetal echocardiography demonstrated a mildly dysplastic pulmonary valve, a subaortic ventricular septal defect and biventricular hypertrophy. At 31 weeks' gestation, ultrasound assessment showed an increase in the pleural effusions. A chest drain was inserted into the left pleural cavity, and a shunt was left *in situ* between the pleural cavity and the amniotic cavity. In addition an amnioreduction was performed. An ultrasound examination later that week demonstrated an improvement in the size of the effusions, although the lungs were not completely re-expanded. Umbilical artery doppler studies demonstrated absent end diastolic flow and serial cardiotocography (CTG) was commenced. Over the next few days, there was deterioration in the CTG and an emergency Caesarean was performed at 32 weeks' gestation. Despite active resuscitation, the insertion of further chest drains, and ventilation, the 2 kg female infant died within 12 hours. Post-mortem examination demonstrated a narrow nose, and webbing of the neck. The pleural effusions and cardiac anomalies diagnosed prenatally were confirmed. In addition there was a right-sided duplex kidney. The mother was of short stature and was noted to have facial features suggestive of Noonan syndrome, a diagnosis which was subsequently confirmed.

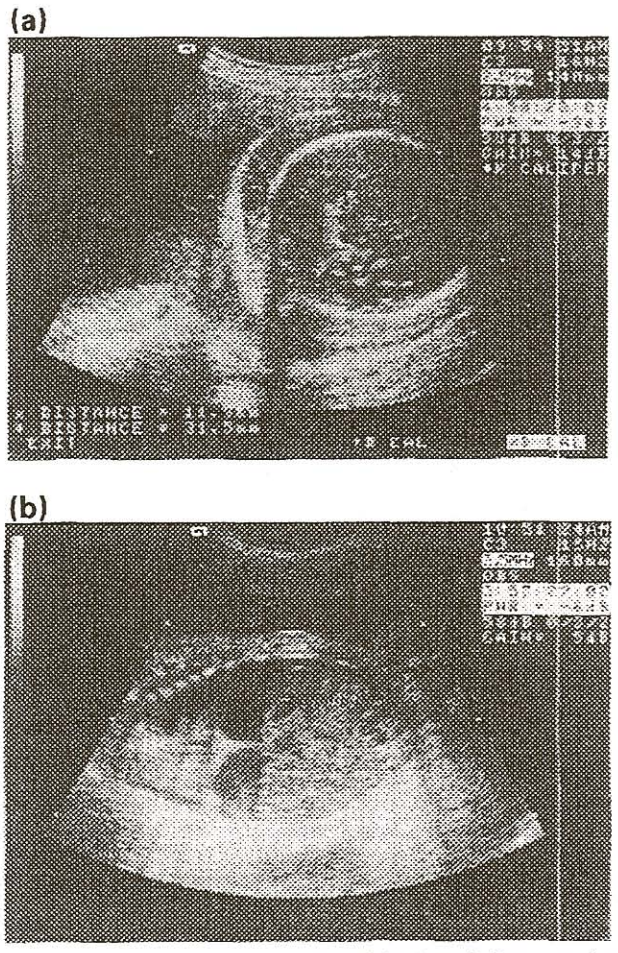

Fig. 3—Case 4. (a) Transverse view of fetal head demonstrating extensive scalp oedema. (b) Longitudinal view through fetal chest demonstrating pleural effusions

Case 5

A 34-year-old para 2 was referred at 31 weeks' gestation because of pleural effusions. Ultrasound assessment demonstrated large bilateral pleural effusions, some skin oedema and polyhydramnios with an amniotic fluid index of 35 cm. In addition there was right renal pelvic dilatation, with the antero-posterior diameter of the renal pelvis measuring 21 mm. A left pleuro-amniotic shunt was inserted and an amniotic fluid sample was sent for cytogenetics. The karyotype was normal. At 32 weeks' gestation the left lung had re-expanded, and a right-sided shunt was inserted. Further ultrasound assessment was carried out at 33 weeks' gestation. There was a moderate effusion on the right, with resolution of the effusion on the left. The liquor volume remained increased. At 34 weeks' gestation the findings were similar. The right renal pelvic dilatation was again noted. Spontaneous labour ensued later that day and a female infant weighting 2977 g was delivered. She had coarctation of the aorta and right ureteric stenosis resulting in right hydronephrosis. She was noted to have some dysmorphic features including hypertelorism, posteriorly rotated low-set ears, a broad neck and skin folds around her wrists and ankles. She developed hypertrophic cardiomyopathy in the neonatal period. The diagnosis of Noonan syndrome was made clinically. The parents were not felt to have any features of the condition, making this likely to be a new mutation.

Case 6

A 24-year-old was referred at 32 weeks' gestation because of bilateral pleural effusions. Ultrasound examination confirmed the presence of isolated moderate bilateral pleural effusions. The liquor volume was normal, and there were no obvious fetal anomalies. Specialist fetal echocardiography was normal. A fetal blood sampling was performed. This demonstrated a normal fetal karyotype, and no evidence of fetal anaemia or parvovirus infection. The mother was of short stature with multiple lentigines and bilateral ptosis. On questioning she said that she had a minor heart abnormality and a diagnosis of Leopard syndrome (the association of multiple lentigines with pulmonary stenosis and deafness, thought by some (Mendez and Opitz, 1985; Sharland *et al.*, 1992), but not all, to be part of the Noonan syndrome spectrum), had been made many years ago. The effusions were noted to increase in size and at 38 weeks *in utero* aspiration was performed under ultrasound guidance. Labour was induced immediately thereafter and a live male infant delivered vaginally. The neonate had features consistent with a diagnosis of Noonan syndrome and did well after further drainage of the effusions on the neonatal unit and a period of ventilation.

DISCUSSION

Noonan syndrome is an important differential diagnosis in any pregnancy complicated by polyhydramnios (cases 1 and 3), increased nuchal fluid (cases 1, 2 and 3), pleural effusions (cases 5 and 6), or hydrops fetalis (cases 4 and 5), particularly when the femora are relatively short. This is particularly so when the fetus is found to have a heart defect characteristic of this condition (such as our case 4).

A variety of prenatal presentations of Noonan syndrome have been reported (Benacerraf *et al.*, 1989; Langer *et al.*, 1990; Izquierdo *et al.*, 1990; Donnenfeld *et al.*, 1991; Johnson *et al.*, 1993; Schulman *et al.*, 1994; Trauffer *et al.*, 1994; Brady *et al.*, 1998). A history of polyhydramnios may be obtained in 33 per cent of mothers of a child with Noonan syndrome (Sharland *et al.*, 1992). The diagnosis of Noonan syndrome in the child is usually made postnatally, unless a parent has an obvious Noonan syndrome phenotype. Noonan syndrome can also present neonatally with serious medical complications, such as hypertrophic cardiomyopathy and chylothorax (Moerman *et al.*, 1993; Baltaxe *et al.*, 1975).

Although fluid accumulation in Noonan syndrome can occur postnatally, it appears to occur most frequently prenatally, often resolving well before the

pregnancy reaches term. The major source of this fluid accumulation is thought to be lymphoedema, resulting from lymphatic vessel dysplasia, the site of which determines the type of fluid accumulation seen postnatally (Witt *et al.*, 1987). However, web neck anomaly, which may occur in Noonan syndrome as a result of a prenatal cystic hygroma or collection of nuchal fluid (Witt *et al.*, 1987), has been noted to affect more infants with both flow and non-flow related heart defects (Berdahl *et al.*, 1995). It has been suggested that the cardiac abnormalities seen in Noonan syndrome may result from lymphatic obstruction and compression of developing structures by dilated lymphatic ducts (Witt *et al.*, 1987). Pulmonary stenosis may be caused by compression of the pulmonary artery and/or right atrium, resulting in reduced right-sided cardiac blood flow (Clark, 1986). It is therefore difficult to know whether the congenital heart disease which affects 66–88 per cent of persons with Noonan syndrome (Allanson, 1987; Sharland *et al.*, 1992) has a causal role in prenatal oedema, or whether it occurs as a result of prenatal oedema.

Noonan syndrome is inherited as an autosomal dominant condition, although many cases are sporadic. Counselling parents about recurrence risks can be made difficult by the more subtle phenotype in adults (Allanson *et al.*, 1985). Sharland *et al.* (1993) studied 117 families of children with Noonan syndrome. One of the parents had typical Noonan syndrome in 14 per cent of families. Overall, 44 per cent of families had one parent either definitely or possibly affected, leaving over half of cases as possible new mutations. They went on to follow these families and calculate the risk of having another child with Noonan syndrome. The recurrence risk was 5 per cent for the 86 per cent of families where the parents had only possible or no signs of Noonan syndrome. All family studies have demonstrated maternal transmission of Noonan syndrome more often than paternal transmission, possibly because of infertility related to cryptorchidism in affected males (Sharland *et al.*, 1993).

As Noonan syndrome is inherited in an autosomal dominant manner (Sharland *et al.*, 1993), it is important to look for features of Noonan syndrome in the parents in cases presenting with prenatal features suggestive of this syndrome. The diagnosis of Noonan syndrome in a parent would help make the diagnosis in the fetus and thus aid prenatal counselling. We reviewed the cases of Noonan syndrome seen at two regional genetic units. There were 43 cases where the prenatal history had been adequately documented. Of these, 18 had a prenatal history comprising one or more of the features described here (Table 1). Whilst these are retrospective data they suggest that Noonan syndrome should be considered in any fetus which has the prenatal findings we have described.

Where a parent has Noonan syndrome, or the couple have had a child with Noonan syndrome before, it would be appropriate to refer them for obstetric ultrasound at 12–14 and 20 weeks' gestation and again in the third trimester. This would not only help to make a prenatal diagnosis of a likely recurrence but it would also assist in the detection of complications so that potentially life-saving treatment can be given. It can also enable parents to prepare themselves if the fetus appears to be severely affected. In view of the frequency of congenital heart disease in Noonan syndrome, fetal echocardiography is also indicated.

In conclusion, Noonan syndrome should be considered in all fetuses with pleural effusions, short femora and increased nuchal fluid with a normal karyotype. It would be interesting to carry out a prospective study of families with Noonan syndrome to help document the number of individuals affected with Noonan syndrome who have an abnormality detected prenatally. If, as suggested by Witt *et al.* (1987), the facial features of Noonan syndrome are largely a result of fetal oedema, one would expect to see oedema at some stage of pregnancy in a substantial number of pregnancies where the fetus has Noonan syndrome.

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