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Poor prenatal detection rate of cardiac anomalies in Noonan syndrome

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ABSTRACT

Background *The wide variation and nonspecific nature of many of the associated ultrasonographic findings complicate prenatal diagnosis of Noonan syndrome. The aim of the present study was to define the rate of prenatal diagnosis of heart malformations in cases diagnosed postnatally with Noonan syndrome.*

Methods *English-language literature review of 29 cases of Noonan syndrome examined prenatally with confirmed postnatal diagnosis and four case reports from our center.*

Results *Cases were evaluated for cervical spine pathologies, cardiac anomalies and other pathological findings, including hydrops fetalis and polyhydramnios. Cardiac anomalies were suspected in only nine of 33 cases; three of these were associated with cystic hygroma. Cardiac anomalies were eventually diagnosed in 31/33 cases postnatally. Polyhydramnios was diagnosed in 19/33 cases in the third trimester, and hydrops fetalis was detected in eight of 33. Cystic hygroma was present in a total of nine cases at mid-trimester.*

Conclusions *Noonan syndrome is characterized by late-onset and progressive pathologies, particularly the associated cardiac anomalies, which develop through the course of gestation and postnatal life. This complicates or precludes prenatal diagnosis at mid-trimester or at any time in the prenatal period, and partly explains the low rate of detection of fetal cardiac lesions in this syndrome.*

INTRODUCTION

Noonan syndrome is an autosomal dominant congenital abnormality having an incidence of between 1 : 1000 and 1 : 2000 in the general population[1,2]. The gene responsible for the defect has recently been located to the short arm of chromosome 12[3–5]. It is characterized by dysmorphic facies, webbed neck, short stature, cardiac anomalies and varying degrees of mental retardation, as well as abnormalities of the lymphatic system. Diagnosis of Noonan syndrome is often only confirmed clinically during the late childhood years; prenatal diagnosis of the syndrome is complicated by the nature of its associated anomalies[6,7].

While the association between Noonan syndrome and lymph system abnormalities is well-established[8–14], during prenatal life, the condition may manifest in many forms, ranging from increased localized cervical spine findings, such as cystic hygroma, to generalized lymph edema as seen in nonimmune hydrops fetalis[9,10,15–19]. The severity of these conditions varies widely among patients and has been found to progress in some cases with gestation and the neonatal period and beyond[1,6,7,11,12]. The webbed neck often observed in Noonan patients probably represents resolving cervical cystic hygroma.

The hydrops fetalis described in Noonan syndrome probably represents the severe end of the spectrum of lymph pathology, but may also result from a cardiac dysfunction sequence[15].

Congenital heart disease may appear in up to 60% of Noonan syndrome patients[6,7,11,20–24]. In fact, cardiac abnormality associated with cervical lymphatic abnormalities may provide the only clues to a diagnosis of Noonan syndrome. Numerous and varied cardiac abnormalities have been described in Noonan syndrome; some are more specific to the syndrome, while others are less so.

As the prenatal diagnosis of congenital heart defects is crucial for the diagnosis of Noonan syndrome *in utero*, we set out to review the current literature on prenatal detection of cardiac anomalies in cases diagnosed with Noonan syndrome.

METHODS

We conducted an English-language literature search in the 'Medline' listing, and reviewed those cases of postnatally

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confirmed Noonan syndrome that were examined by prenatal ultrasound. In addition, we included four cases of the syndrome diagnosed at our center.

RESULTS

Case reports

Case 1

A 31-year-old, gravida 2, para 1, was referred for a mid-trimester scan at 20 weeks of gestation, which was normal. Follow-up at 28 and 34 weeks for suspected intrauterine growth restriction showed no visible abnormality and a normal amniotic fluid volume. The woman delivered at term a male newborn with features of Noonan syndrome and hypertrophic cardiomyopathy.

Case 2

A 22-year-old gravida 1, para 0, who had a normal scan at 20 weeks of gestation, presented for a routine fetal growth assessment at 34 weeks. Mild pulmonary stenosis was identified. The patient delivered a term female; at the age of 5 years, mild pulmonary stenosis and classic features of Noonan syndrome were evident.

Case 3

A 41-year-old gravida 4, para 3, had normal 16-week and 21-week targeted organ scans, and a 34-week fetal growth assessment scan. She delivered a male newborn at term; at the age of 5 years, echocardiography was performed as part of an investigation of short stature and mild mental retardation. Echocardiography revealed mild to moderate pulmonary stenosis and a diagnosis of Noonan syndrome was made.

Case 4

A 23-year-old gravida 2, para 1, who had a normal targeted organ scan at 22 weeks of gestation, was referred for suspected macrosomia at 35 weeks for a fetal growth assessment scan. Pulmonary and aortic stenosis and ventricular hypertrophy were identified. The patient delivered a male at term. Prenatal ultrasound findings were confirmed postnatally by echocardiography.

Table 1 summarizes the current published cases of Noonan syndrome in which prenatal ultrasound examination was performed. The cases are presented in chronological order according to their description in the English-language literature. The last four cases included are those diagnosed in our center. The following criteria were analyzed: (i) cervical spine pathologies; (ii) cardiac anomalies; and (iii) other pathological findings, including hydrops fetalis and polyhydramnios.

Of the 33 cases described here, 19 had polyhydramnios and eight developed hydrops fetalis. Manifestation of cervical pathology was evident in only 14 cases, of which three were diagnosed in the first trimester (including one isolated with increased nuchal translucency). Nine cases of cystic hygroma were diagnosed at midtrimester. Cardiac anomalies were suspected in only nine cases, three of which were reported to be associated with cystic hygroma. All of these cardiac anomalies were confirmed (at least in part) postnatally by echocardiography or by post mortem.

Postnatally, the following cardiac anomalies were diagnosed: ventricular hypertrophy or other cardiomyopathy (n = 13); pulmonary stenosis or dysplasia (n = 13); aortic stenosis (n = 3); ventricular septal defect (n = 5); atrial septal defect (n = 3); atrioventricular valve anomalies (n = 3); coarctation of the aorta (n = 1); atrioventricular canal (n = 1); and tetralogy of Fallot (n = 1). In seven cases, more than one cardiac anomaly was diagnosed.

DISCUSSION

In this review, we have summarized cases diagnosed with Noonan syndrome in which prenatal ultrasound examination was performed. The most common prenatal features of Noonan syndrome are polyhydramnios (19/33), cervical pathologies (cystic hygroma, skin edema or nuchal translucency, 14/33), pleural effusion and hydrops fetalis (11/33). Heart malformations were evident prenatally only in nine cases (27%) of this group. The various cardiac anomalies described here concur with the large series described by Burch *et al.*[20]. Pulmonary valve anomalies (dysplastic or stenotic) and hypertrophic cardiomyopathy are the most common cardiac malformations, with an incidence ranging from 37.5% to 39% in both groups. However, unlike the Burch series, approximately 94% (31/33) of cases discussed here were diagnosed postnatally with cardiac anomalies compared to only 60% of their series. This discrepancy may be explained by the early postnatal follow-up of the cases described in this review. Subtle Noonan cases without cardiac malformation are probably diagnosed later in childhood; cases with cardiac malformation are more readily subjected to thorough diagnostic examination, leading to the diagnosis of Noonan syndrome at an earlier stage in neonatal life.

Analysis of the heart malformations associated with Noonan syndrome may explain the inability to diagnose them more effectively at the prenatal stage. Pulmonary stenosis and hypertrophic cardiomyopathies are typical examples of later onset cardiac malformations, which may appear during the third trimester of pregnancy or even after birth. Moreover, these anomalies may evolve or progress during pregnancy or early childhood from a mild to a severe phenotype of the disease, making diagnosis *in utero* impossible[25–28].

Although 'lymphatic system' abnormalities (e.g. cystic hygroma, skin edema, pleural effusion and hydrops fetalis) are typical features of Noonan syndrome, they are of variable degrees of severity, nonspecific[9,10,15–18] and manifest at varying stages of pregnancy. Thus, the identification of lymphatic system anomalies calls for thorough targeted organ screening, including fetal echocardiography and karyotyping, but these are far from being diagnostic of Noonan syndrome.

Table 1 Summary of prenatal and postnatal findings in Noonan syndrome

Reference	Gestational age at ultrasound diagnosis (weeks)	Prenatal sonographic findings			Postnatal findings	
		Nuchal	Cardiac	Others	Cardiac	Others
Newman *et al.* (1984)[8]	26	CH	—	Hydrops fetalis, IUFD	Coarctation of aorta, VSD (by PM)	Turner phenotype, CH, low-set ears, 46XY; diagnosis of NS
Rahmani *et al.* (1986)[10]	26, 29	CH	—	26 weeks: polyhydramnios, short femur, bilateral club feet	Cardiomegaly	CH, nuchal folds, bilateral club feet, cryptorchidism, forward displaced ears
Brown (1986)[16]	—	—	Structural cardiac anomaly not defined	Non-immune hydrops fetalis	Confirmed	Diagnosis of NS
Bawle *et al.* (1986)[15]						
Case 1	28, 32	—	—	28 weeks: polyhydramnios 32 weeks: hydrops fetalis	PS, aortic stenosis, LVH (by PM)	Generalized edema, bilateral pleural effusion, hypertelorism, depressed nasal bridge, webbed neck, low-set ears, mild retrognathia, undescended testis
Case 2	32	—	—	Polyhydramnios	Small VSD	Generalized edema, posterior set ears, flattened nasal bridge, undescended testis; PM denied
Witt *et al.* (1987)[12]						
Case 1	30, 33	—	—	30 weeks: polyhydramnios 33 weeks: scalp edema	Dysplastic mitral and tricuspid valves, hypertrophic cardiomyopathy, VSD (by PM)	Generalized edema, 'coarse face', low-set ears, webbed neck, 46XX
Case 2	14, 17	13 weeks: CH	—	—	Mild pulmonary valve dysplasia	Redundant skin, SUA, 46XY
Case 3	36	—	—	Polyhydramnios, hydrops fetalis	Undefined cardiomyopathy	At age 3 years: short stature, webbed neck, epicanthal folds, 46XX
Case 4	30, 34	—	—	30 weeks: polyhydramnios 34 weeks: scalp edema	ASD	Diffuse skin edema, 46XY
Case 5	33	—	—	Polyhydramnios	Congestive heart failure, PS	46XY
Case 6	30	—	—	Polyhydramnios, hydrops fetalis	Hypoplasia of all four valves, asymmetrical LVH, ASD	Diffuse skin edema, posterior set ears, nuchal redundant skin, 46XY
Case 7	38	—	—	Polyhydramnios, hydrops fetalis	VSD	46XX
Benacerraf *et al.* (1989)[13]						
Case 1	13, 29, 33	13 weeks: CH	29 weeks: VSD	33 weeks: oligohydramnios	Tetralogy of Fallot	Webbed neck, widely spaced nipples, high arched palate, coloboma of right eye, 46XY
Case 2	20, 24	20 weeks: CH	—	24 weeks: polyhydramnios, scalp edema, mild ascites	Aortic stenosis	Webbed neck, widely spaced nipples, cryptorchidism cleft palate, 46XY
Case 3	20, 27	20 weeks: CH 26 weeks: resolved	Asymmetric ventricular enlargement	27 weeks: polyhydramnios, severe hydrops fetalis	Not described	Severe hydrops fetalis (by PM)
Case 4	29	CH		Hydrops fetalis	PS	—

Continued overleaf.

Table 1 *continued*

Reference	*Gestational age at ultrasound diagnosis (weeks)*	*Prenatal sonographic findings*			*Postnatal findings*	
		Nuchal	*Cardiac*	*Others*	*Cardiac*	*Others*
Sonneson *et al.* (1992)[11]	23, 35	CH	Small primum ASD, echogenicity of mitral valve, abnormal flow over AV valve, modest biventricular hypertrophy; 35 weeks: marked hypertrophy of both ventricles and septum	—	Small primum ASD, mild enlargement of RV, dysplastic pulmonary valve, concentric hypertrophy of LV, no outflow obstruction, thickened mitral valve, abnormal flow over AV valves	—
Silverman *et al.* (1993)[24]	3rd trimester	—	Thickened ventricular wall and septum	Polyhydramnios	Biventricular hypertrophy	At delivery: diagnosis of NS
Hyett *et al.* (1997)[14]	13, 2nd trimester	Increased nuchal translucency	—	—	Mild PS	At delivery: diagnosis of NS
Nisbet *et al.* (1999)[21]						
Case 1	13, 27	CH	—	27 weeks: polyhydramnios, short femur	PDA and hypertrophic cardiomyopathy	Clinical diagnosis of NS, low-set ears, widely spaced nipples, edematous
Case 2	14+	CH			PS	TOP
Case 3	20, 25, 30, 35	Nuchal edema	—	Polyhydramnios, short femur, SUA	Hypertrophic cardiomyopathy	Diagnosis of NS, subsequent demise at 5 months
Case 4	10, 20, 29	—	29 weeks: mildly dysplastic PV, subAO VSD, biventricular hypertrophy	Pleural effusions, polyhydramnios, hydrops fetalis	Prenatally diagnosed cardiac anomalies confirmed by PM	Right-side duplex kidney, webbed neck, pleural effusion; ND
Case 5	31	—	—	Pleural effusion, skin edema, polyhydramnios, right renal pelvic dilatation	Coarctation of AO, hypertrophic cardiomyopathy	Right ureteric stenosis, right hydronephrosis, hypertelorism, low-set ears, clinical diagnosis of NS
Case 6	32	—	—	Bilateral pleural effusion	Normal	Features consistent with NS, drainage of pleural effusion
Achiron *et al.* (2000)[29]						
Case 1	31	—	AV canal	Pyelectasis, skin edema	AV canal	Distinctive facies, effusions
Case 2	13, 18, 20, 28, 32	NT and cysts, resolved	—	Polyhydramnios, skin edema, pleural effusion	PS	Distinctive features, at 2 years: developmental delay and hypotonia
Case 3	12, 24, 28, 32	—	Thickened PV	32 weeks: hydrothorax, polyhydramnios, skin edema	Thickened PV	ND: Distinctive features, respiratory failure, hydrothorax, at PM
Case 4	14, 20, 35	—	—	Polyhydramnios, skin edema	Hypertrophic cardiomyopathy	Distinctive features, cryptorchidism, progressive cardiomyopathy, hepatomegaly, developmental delay
Current study (2000)						
Case 1	20, 28, 34	—	—	—	Hypertrophic cardiomyopathy	Stigmata of NS
Case 2	20, 34	—	Mild PS	—	Age 5 years: mild PS	Age 5 years: stigmata of NS
Case 3	16, 21, 34	—	—	—	Age 5 years: mild PS	Age 5 years: short stature, mild mental retardation, diagnosis of NS
Case 4	22, 33	—	At 33 weeks: PS, AS and ventricular hypertrophy		Findings confirmed by echocardiography	Diagnosis of NS

AO, aorta; AS, aortic stenosis; ASD, atrial septal defect; AV, atrioventricular; CH, cystic hygroma; LV, left ventricle; LVH, left ventricular hypertrophy; ND, neonatal death; NS, Noonan syndrome; NT, nuchal translucency; PDA, patent ductus arteriosus; PM, post mortem; PS, pulmonary stenosis; PV, pulmonary valve; SUA, single umbilical artery; TOP, termination of pregnancy; VSD, ventricular septal defect.

In conclusion, the poor detection rate of Noonan syndrome *in utero* and, specifically, the dismal diagnostic ability of its associated cardiac anomalies is explained by the nonspecific, variable, late onset and progressive nature of the disease, which is only fully manifest after birth.

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