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Abstract

Noonan syndrome is a common genetic disorder characterized by facial anomalies, congenital heart defect, short stature, webbed neck, chest deformities and undescended testes. The phenotypic expression of Noonan syndrome is extremely variable, with some affected subjects showing only minor features of the syndrome. Cardiac malformations are also heterogeneous. Pulmonary stenosis, with or without dysplastic pulmonary valve and hypertrophic cardiomyopathy, are the "classic" cardiac defects reported in Noonan syndrome. However, atrial septal defect, atrioventricular septal defect, left-sided obstructive lesions, tetralogy of Fallot and patent ductus arteriosus have also been described. Autosomal dominant inheritance has been documented in some families, although many cases appear to be sporadic. The diagnosis of Noonan syndrome is at present purely clinical, because a "diagnostic" test is not available. Indeed, although a gene for Noonan syndrome has been recently mapped by linkage analysis to chromosome 12q, the gene or genes of the syndrome have not been yet cloned.

Article

Introduction

Noonan syndrome is one of the most common genetic diseases associated with congenital heart defect, being second for frequency only to Down syndrome. The overall incidence of Noonan syndrome is believed to be between 1/1000 and 1/2000 livebirths.¹ The syndrome was first recognized as a clinical entity in the sixties by Noonan and Ehmke, when they described several patients with pulmonary stenosis associated with characteristic facial anomalies, short stature, webbed neck, chest deformity and undescended testes.^{2,3} Pulmonary stenosis with or without dysplastic pulmonary valve and hypertrophic cardiomyopathy are the "classic" cardiac defects reported in Noonan syndrome, but atrial septal defect, atrioventricular septal defect, left-sided obstructive lesions, tetralogy of Fallot and patent ductus arteriosus have also been described.⁴⁻¹⁷

There is a wide range of variability in the phenotypical expression of Noonan syndrome, with some affected subjects having minimal features.^{18,19} Noonan syndrome affects both males and females, and the karyotype is normal. Autosomal dominant inheritance with variable expressivity has been documented in many families.¹⁹⁻²¹ A gene for Noonan syndrome has been mapped by linkage analysis in several families to the long arm of chromosome 12.²² Nevertheless, the gene has not yet been cloned therefore the diagnosis of Noonan syndrome is purely clinical with no "diagnostic" test available.

Clinical features

The main phenotypical features of Noonan syndrome and their occurrence in our series of 190 children are listed in Table 1.

Table 1: Phenotypical features in 190 patients with Noonan syndrome

Clinical finding	Affected individuals	%
Short stature	62/190	32.6%
Macrocephaly	101/190	53.1%
Facial anomalies	190/190	100%
Hypertelorism	123/190	64.7%
Downslanted palpebral fissures	182/190	95.7%
Ptosis	170/190	89.4%
Epicanthal folds	85/190	44.7%
Low-set ears	176/190	92.6%
Dysmorphic ears	167/190	87.8%
Short neck / Webbed neck	56/190	29.4%
Cardiac defect	160/190	84.2%
Sternal anomalies	102/190	53.6%
Wide-set nipples	81/190	42.6%
Elbow anomalies	51/190	26.8%
Cryptorchidism	71/108	65.7%
Developmental delay	24/190	12.6%

Facial anomalies

Facial features characteristic of Noonan syndrome are hypertelorism, epicanthic folds, antimongoloid slant of the palpebral fissures, ptosis, flat nasal bridge, micrognathia and low-set rotated ears with a thick helix (fig. 1a,b).

Figure 1: Frontal (a) and lateral (b) appearance of a patient with Noonan syndrome, showing hypertelorism, flat nasal bridge, palpebral ptosis, thick lips, and low-set rotated ears with thick helix



Nevertheless, the phenotypical expression is highly variable and may change with age (fig. 2a,b,c).^{18,19, 21,23}

Figure 2a: At 4 months



Figure 2a-c: Facial appearance of a male patient with Noonan syndrome at different ages

Figure 2b: At 3 years



Figure 2c: At 9 years



Facial anomalies can often be difficult to recognise in the newborn (fig. 3). In fact, the mean age at diagnosis from the literature is nine years, and the delay in recognising the distinctive characteristics probably reflects the evolving phenotype.^{1,23} In particular, ocular and nasal bridge anomalies become less evident with increasing age.

Figure 3: Facial appearance of a newborn with Noonan syndrome



It should also be noted that minor facial changes of Noonan syndrome are often found in one of the parents of affected children.^{18,21} In genetic counseling of families with a child with Noonan syndrome, in which one of the parents has mild features of the syndrome, a review of childhood photographs of the mother or the father may be a useful aid, particularly if resemblance to the affected offspring is shown.

Congenital heart defect

The prevalence of congenital heart defect in Noonan syndrome varies from 50 to 80% in the reported series from the literature.⁴⁻⁹ The percentage of occurrence of the different types of cardiac defect in our experience is shown in Table 2. Pulmonary stenosis and hypertrophic cardiomyopathy are generally the most common congenital heart defects found in Noonan syndrome.

Table 2: Cardiac defects found in 160 individuals with Noonan syndrome

Cardiac defect	Affected individuals	%
Pulmonary valve stenosis	64/160	40%
Atrioventricular septal defect	22/160	13.8%
Coarctation of the aorta	20/160	12.5%
Hypertrophic cardiomyopathy	14/160	8.8%
Atrial septal defect (ostium secundum type)	13/160	8.1%
Left atrioventricular valve anomalies	7/160	4.4%
Ventricular septal defect	7/160	4.4%
Tetralogy of Fallot	6/160	3.8%
Patent ductus arteriosus	2/160	1.3%
Pulmonary atresia/intact ventricular septum	2/160	1.3%
Partial anomalous pulmonary venous return	2/160	1.3%
Dilated ascending aorta	1/160	0.6%

Pulmonary stenosis is often associated with a thickened and dysplastic valve. It is usually difficult to obtain a satisfactory result using the transcatheter balloon dilatation of such dysplastic valves, so surgical intervention is more likely to be needed.

Hypertrophic cardiomyopathy involves predominantly the ventricular septum as asymmetric septal hypertrophy, but may also affect the ventricular free walls. Left ventricular outflow tract obstruction may occasionally be produced.

Atrial septal defect, patent ductus arteriosus and tetralogy of Fallot are also found in Noonan syndrome. In our experience, left-sided obstructive lesions and atrioventricular septal defect are also frequently diagnosed. Left-sided anatomic obstruction can occur at the valvular or supra-valvular level,⁹ in the subaortic position

as a result of left atrioventricular valve abnormalities,¹¹⁻¹² or as coarctation of the aortic.¹³⁻¹⁵ Interestingly, the subgroup of patients with Noonan syndrome and aortic coarctation demonstrates male preponderance, and physical manifestations overlapping with those of Turner syndrome, so that the involvement of putative lymphogenic genes located on sex chromosomes has been suggested in these patients.²⁴ The atrioventricular septal defect of subjects with Noonan syndrome is generally "partial" and frequently associated (25% of the cases in our series) with subaortic stenosis.¹⁶ The structural abnormalities causing subaortic stenosis include accessory fibrous tissue and/or anomalous insertion of the left atrioventricular valve and anomalous papillary muscle of the left ventricle. Interestingly, the anomalies of the left atrioventricular valve leaflets and of the subvalvular apparatus in patients with atrioventricular septal defect are similar to those reported in patients with hypertrophic cardiomyopathy.^{25,26}

The pathogenesis of cardiac defects in Noonan syndrome has been attributed to a defect of cardiac jelly and extracellular matrix, in some cases,²⁷ and the same mechanism is probably involved in the pathogenesis of the atrioventricular septal defect.²⁸ Additionally, the development of leaflets and papillary muscles of the left atrioventricular valve is related to the morphogenesis of the left ventricular outflow tract and the atrioventricular and interventricular septations.²⁹⁻³² Thereafter, in some patients with Noonan syndrome, the developmental mechanism of the left ventricular myocardium and the left atrioventricular valve may be altered.

Rare cardiac defects occurring in Noonan syndrome are pulmonary atresia with intact ventricular septum, which should be considered in the spectrum of pulmonary valve stenosis with dysplasia of the leaflets,^{33,34} and dilated ascending aorta.³⁵

Neck anomalies

An obvious and evident webbing of the neck (fig. 4a,b) is generally present in only one fourth of the cases, while an apparent neck shortening with redundant skin on the neck and low posterior hairline are more commonly noted.

Figure 4. Webbed neck (a) and low posterior hairline (b) in a child with Noonan syndrome
Figure 4a: Webbed neck



Figure 4b: Low posterior hairline



Figure 5: Characteristic thoracic and sternal deformities of Noonan syndrome



Skeletal anomalies

Thoracic deformities include the classic sternal changes of Noonan syndrome, often associated with shield chest (Figure 5). Kyphosis and thoracic scoliosis are frequently found, although medical or surgical treatment are rarely required. Bilateral elbow deformity is a frequent upper limb abnormality.

Genital anomalies

Up to three quarters of boys with Noonan syndrome may have undescended testes.²³ Cryptorchidism adversely affects male fertility. Azoospermia or oligozoospermia may occasionally be found following orchidopexy for bilateral undescended testes.³⁶ It remains to be seen whether earlier surgery would improve the outcome. In the presence of normally descended testes, men with Noonan syndrome are likely to be fertile. Pubertal development is delayed in both sexes, and fertility does not appear to be affected in females.

Developmental anomalies

The majority of children with Noonan syndrome (65% to 85% according to different series) have normal mental capacities and attend regular schools.^{1,21,23,37} Early delay in motor milestones could probably be explained by the presence of hypotonia and hyperextensibility in the younger child.

A recent study, investigating patterns of cognitive functioning in school-aged children, showed that Noonan syndrome is not associated with substantial deficits at the level of intellectual functioning.³⁷ However, the correlation between phenotypic and cognitive expression revealed that a severe Noonan syndrome phenotype, i.e. more severe cardiac defect, more evident facial and skeletal anomalies, was associated with a specific pattern of deficits and capacities in cognitive functioning.³⁷ Generally, patients with Noonan syndrome are at risk for speech delay,^{38,39} which could be related to hearing loss or recurrent otitis media that frequently occurs in this syndrome. Tests for hearing are recommended in children with Noonan syndrome, as are tests for vision, because of the association of strabismus and refractive errors in this syndrome.²³

Growth

Growth retardation is an important feature of Noonan syndrome, and short stature is found in 50-70% of cases in previously reported series.^{21,23,40} In our experience (Table 1), the percentage of subjects with height below the 3rd percentile is lower. We believe that in older series, patients with a more complete expression of the syndrome may have been enrolled, while the more recent reports include also patients with milder phenotype Noonan syndrome such that the impact of growth abnormalities may be less evident.

The pattern of growth is similar in males and females, and weight-height ratio is normal. A delayed pubertal growth spurt has been documented in both sexes. Bone age is also usually delayed. The mean adult height reaches, in general, the lowest level of the normal percentiles.

Non-cyanotic heart defects are not found to have any major impact on overall growth patterns.

Coagulation factor deficiencies

Easy bruising after minor trauma and abnormal bleeding are frequently reported in patients with Noonan syndrome, and a variety of coagulation factor deficiencies have been detected.⁴¹ The most common abnormality is a partial factor XI deficiency, but VIII and XII factor anomalies have also been described. Combined coagulation factor

deficiencies may also occur. The involvement of several factors, and the possible presence of combined abnormalities implies that anomalies in regulatory factors of the coagulation system, which is under chromosome genetic control may be the cause.

Familial transmission

Approximately half of the patients are sporadic cases in the families and may represent new mutations. In the remaining 50% of cases, Noonan syndrome is familial, with most of the pedigrees being consistent with autosomal dominant inheritance.^{2,3,15,19,22,42} A mild or subtle phenotype must be searched for in parents of affected children.

A predominance of maternal transmission is noted in familial cases. This has been thought to be due to infertility in affected males, which may be related to cryptorchidism.³⁶

Molecular studies

The result of a linkage analysis of a three-generation family with eight affected individuals and 20 two-generation families performed by Jamieson et al.²² localised a gene for Noonan syndrome to chromosomal region 12q22qter. Nevertheless, the gene is at present not cloned, so that a laboratory test to confirm a clinical diagnosis of Noonan syndrome is not yet available. In searching the gene for Noonan syndrome, it would be interesting to look at candidate genes that might explain cardiac defects, particularly valvular abnormalities and cardiac hypertrophy.

Prenatal diagnosis

Prenatal diagnosis by molecular testing is not possible. Nevertheless ultrasonographic findings can suggest the diagnosis in utero. Reported sonographic signs include cystic hygroma, hydrothorax, polyhydramnios, and congenital heart defect.⁴³ However, Noonan syndrome has an evolving phenotype, since early nuchal region findings can regress in later pregnancy and detectability of characteristic cardiac defects of Noonan syndrome can be low, since pulmonary stenosis can be difficult to diagnose in utero and asymmetric septal hypertrophy is a progressive anomaly that becomes more evident postnatally. The variability of the phenotype must also be taken in consideration, since patients with mild phenotypic expression have only subtle sonographic manifestations, which can be overlooked. Conversely, it has been noted that second-trimester manifestations may predict a severe postnatal course.

Conclusions

Noonan syndrome is a genetic condition with characteristic phenotypic anomalies, but a wide range of clinical expression. Cardiac malformations are also heterogeneous. At present, it is not known whether clinical variability reflects variable expression of the same genetic defect or, on the contrary, genetic heterogeneity may be involved by causing similar phenotypes due to different genetic entities.

It is important to point out that clinical aspects and associated malformations of Noonan syndrome can be early identified and favourably treated. Patients with Noonan syndrome can have good physical health and a normal grade of intelligence, with a positive integration in social life.

Although a gene for Noonan syndrome has been mapped by linkage analysis to chromosome 12q, the gene or genes of the syndrome have not been yet identified. The association of Noonan syndrome with peculiar types of cardiac defects could be used to address the search for the gene of Noonan syndrome to specific cardiac candidate genes. It is hopeful that the rapidly evolving progresses in genetic mapping and identification could lead also to the understanding of the pathogenetic mechanism of this peculiar and fascinating syndrome.

References

1. Allanson JE. Noonan syndrome. *J Med Genet* 1987;24:9-13
2. Noonan JA, Ehmke DA. Associated non cardiac malformations in children with congenital heart disease. *J Pediatr* 1963;63:468-470
3. Noonan JA. Hypertelorism with Turner phenotype. A new syndrome with associated congenital heart disease. *Am J Dis Child* 1968;116:373-380
4. Nora JJ, Torres FG, Sinha AK, McNamara DG. Characteristic cardiovascular anomalies of XO Turner syndrome, XX and XY phenotype, and XO/XX Turner mosaic. *Am J Cardiol* 1970;25:639-641
5. Nora JJ, Lortscher RH, Spangler RD. Echocardiographic studies of left ventricular disease in Ullrich-Noonan syndrome. *Am J Dis Child* 1975;129:1417-1420
6. Siggers DC, Polani PE. Congenital heart disease in male and female subjects with somatic features of Turner's syndrome and normal sex chromosomes (Ullrich's and related syndromes). *Br Heart J* 1972;34:41-46
7. Phornphutkul C, Rosenthal A, Nadas AS. Cardiomyopathy in Noonan syndrome. *Br Heart J* 1973;35:99-102
8. Van der Hauwaert LG, Fryns JP, Dumoulin M, Logghe N. Cardiovascular malformations in Turner's and Noonan's syndrome. *Br Heart J* 1978;40:500-509
9. Burch M, Sharland M, Shinebourne E, Smith G, Patton M, McKenna W. Cardiologic abnormalities in Noonan syndrome: phenotypic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment in 119 patients. *J Am Coll Cardiol* 1993;22:1189-1192
10. Digilio MC, Marino B, Giannotti A, Dallapiccola B. Exclusion of 22q11 deletion in Noonan syndrome with tetralogy of Fallot. *Am J Med Genet* 1996;62:413-414
11. Hirsch HD, Gelband H, Garcia O, Gottlieb S, Tamer DM. Rapidly progressive obstructive cardiomyopathy in infants with Noonan's syndrome. *Circulation* 1975;52:1161-1165
12. Marino B, Gagliardi MG, Digilio MC, Polletta B, Grazioli S, Agostino D, Giannotti A, Dallapiccola B. Noonan syndrome: structural abnormalities of the mitral valve causing subaortic obstruction. *Eur J Pediatr* 1995;154:949-952
13. Marino B, Digilio MC, Giannotti A, Dallapiccola B. Noonan syndrome with left-sided cardiac obstructions. *Am J Hum Genet* 1996;59(suppl):A98
14. Digilio MC, Marino B, Giannotti A, Dallapiccola B. Noonan syndrome with cardiac left-sided obstructive lesions. *Hum Genet* 1997;99:289
15. Digilio MC, Marino B, Picchio F, Prandstraller D, Toscano A, Giannotti A, Dallapiccola B. Noonan syndrome and aortic coarctation. *Am J Med Genet* 1998;80:160-162
16. Marino B, Digilio MC, Toscano A, Giannotti A, Dallapiccola B. Congenital heart diseases in children with Noonan syndrome: An expanded cardiac spectrum with high prevalence of atrioventricular canal. *J Pediatr* 1999;135:703-706

17. Danetz JS, Donofrio MT, Embrey RP. Multiple left-sided cardiac lesions in one of Noonan's original patients. *Cardiol Young* 1999;9:610-612
18. Allanson JE, Hall JG, Hughes HE, Preus M, Witt RD. Noonan syndrome: The changing phenotype. *Am J Med Genet* 1985;21:507-514
19. Sharland M, Morgan M, Smith G, Burch M, Patton MA. Genetic counselling in Noonan syndrome. *Am J Med Genet* 1993;45:437-440
20. Nora JJ, Nora AH, Sinha AK, Spangler RD, Lubs HA. The Ullrich Noonan syndrome (Turner phenotype). *Am J Dis Child* 1974;127:48-55
21. Mendez HMM, Opitz JM. Noonan syndrome: A review. *Am J Med Genet* 1985;21:493-506
22. Jamieson CR, van der Burgt I, Brady AF, van Reen M, Elsayi MM, Hol F, Jeffery S, Patton MA, Mariman E. Mapping a gene for Noonan syndrome to the long arm of chromosome 12. *Nat Genet* 1994;8:357-360
23. Sharland M, Burch M, McKenna WM, Patton MA. A clinical study of Noonan syndrome. *Arch Dis Child* 1992;67:178-183
24. Hasegawa T, Ogata T, Hasegawa Y, Honda M, Nagai T, Fukushima Y, Nakahori Y, Matsuo N. Coarctation of the aorta and renal hypoplasia in a boy with Turner/Noonan surface anomalies and a 46,XY karyotype: A clinical model for the possible impairment of a putative lymphogenic gene(s) for Turner somatic stigmata. *Hum Genet* 1996;97:564-567
25. Klues HG, Roberts WC, Maron BJ. Anomalous insertion of papillary muscle directly into anterior mitral leaflet in hypertrophic cardiomyopathy. Significance in producing left ventricular outflow obstruction. *Circulation* 1991;84:1188-1197
26. Klues HG, Maron BJ, Dollar AL, Roberts WC. Diversity of structural mitral valve alterations in hypertrophic cardiomyopathy. *Circulation* 1992;85:1651-1660
27. Amman G, Sherman FS. Myocardial dysgenesis with persistent sinusoids in a neonate with Noonan's phenotype. *Pediatr Pathol* 1992;12:83-92
28. Clark EB. Mechanisms in the pathogenesis of congenital heart defects. In: Pierpont ME, Moller JM, ed. *The genetics of cardiovascular disease*. Boston: Martinus-Nijhoff, 1986;3-11
29. De La Cruz MV, Giménez-Ribotta M, Saravalli O, Cayré R. The contribution of the inferior endocardial cushion of the atrioventricular canal to cardiac septation and to the development of the atrioventricular valves: study in the chick embryo. *Am J Anat* 1983;166:63-72
30. Garcia Pelàez I, Díaz Gòngora G, Artega Martínez M. Contribution of the superior atrioventricular cushion to the left ventricular infundibulum. Experimental study on the chick embryo. *Acta Anat* 1984;118:224-230
31. Oosthoek PW, Wenink ACG, Wisse LJ, Gittenberger-de Groot AC. Development of the papillary muscles of the mitral valve: morphogenetic background of parachute-like asymmetric mitral valves and other mitral valve anomalies. *J Thorac Cardiovasc Surg* 1998;116:36-46
32. Webb S, Brown NA, Anderson RH. Formations of the atrioventricular septal structures in the normal mouse. *Circ Res* 1998;82:645-656
33. Klinge T, Laursen HB. Familial pulmonary stenosis with underdeveloped or normal right ventricle. *Br Heart J* 1975;37:60-64
34. Dennis NR, Warren J. Risks to offspring of patients with some common congenital heart defects. *J Med Genet* 1981;18:8-16
35. Lin AE, Garver KL, Allanson J. Aortic-root dilatation in Noonan's syndrome. *New Engl J Med* 1987;317:1668-1669

36. Elswawi MM, Pryor JP, Klufio G, Barnes C, Patton MA. Genital tract function in men with Noonan syndrome. *J Med Genet* 1994;31:468-470
37. Van der Burgt I, Thoonen G, Roosenboom N, Assman-Hulsmans C, Gabreels F, Otten B, Brunner HG. Patterns of cognitive functioning in school-aged children with Noonan syndrome associated with variability in phenotypic expression. *J Pediatr* 1999;135:707-713
38. Wilson M, Dyson A. Noonan syndrome: Speech and language characteristics. *J Comm Disorders* 1982;15:347-352
39. Cornish KM. Verbal-performance discrepancies in a family with Noonan syndrome. *Am J Med Genet* 1996;66:235-236
40. Ranke MB, Heidemann P, Knupfer C, Enders H, Schmalz AA, Bierich JR. Noonan syndrome: growth and clinical manifestations in 144 cases. *Eur J Pediatr* 1988;148:220-227
41. Sharland M, Patton MA, Talbot S, Chitolie A, Bevan DH. Coagulation-factor deficiencies and abnormal bleeding in Noonan's syndrome. *Lancet* 1992;339:19-21
42. Collins E, Turner G. The Noonan syndrome - a review of the clinical and genetic features of 27 cases. *J Pediatr* 1973;83:941-950
43. Achiron R, Heggesh J, Grisaru D, Goldman B, Lipitz S, Yagel S, Frydman M. Noonan syndrome: a cryptic condition in early gestation. *Am J Med Genet* 2000;92:159-165

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