ORIGINAL ARTICLE

The natural history of Noonan syndrome: a long-term follow-up study

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Objective: To define better the adult phenotype and natural history of Noonan syndrome.
Design: A prospective observational study of a large cohort.
Results: Data are presented for 112 individuals with Noonan syndrome (mean age 25.3 (range 12–71) years), who were followed up for a mean of 12.02 years. Mutations in *PTPN11* were identified in 35% of probands. Ten subjects died during the study interval; three of these deaths were secondary to heart failure associated with hypertrophic cardiomyopathy. Pulmonary stenosis affected 73 (65%) subjects; 42 (58%) required no intervention, nine underwent balloon pulmonary valvuloplasty (three requiring further intervention) and 22 surgical valvuloplasty (three requiring further intervention). Hypertrophic cardiomyopathy affected 21 (19%) patients, which had remitted in two cases, but one subject required cardiac transplant. No subjects died suddenly or had symptoms suggestive of arrhythmia. The mean final adult height was 167.4 cm in males and 152.7 cm in females. Feeding problems in infancy were identified as a predictor of future outcome. The mean age of speaking in two-word phrases was 26 months for those with no feeding difficulties, compared with 39 months for those with severe problems requiring nasogastric feeding. Attendance at a school for children with special needs for the same groups was 12.5% and 58%, respectively. A statement of special educational need had been issued in 44% overall; however, academic achievement was broadly similar to that of the general population.
Implications: Although the morbidity for some patients with Noonan syndrome is low, early predictors of poorer outcome have been identified, which will help ascertain those most in need of intervention.

Noonan syndrome (MIM 163950) is a relatively common multiple congenital abnormality syndrome characterised by a typical facial appearance, short stature (50–60%) and heart defects, most commonly pulmonary stenosis (50–62%) and hypertrophic cardiomyopathy (HCM, 10–20%). Expression is variable and other recognised aspects of the phenotype include cryptorchidism in males (60–77%), pectus deformities (70–95%) and bleeding diatheses (20%).[1][2] Incidence is estimated to be between 1 in 1000 and 1 in 4000, and Noonan syndrome may be inherited in an autosomal dominant manner, although 60% of cases are sporadic. Linkage was established to a 5-cM region on 12q24 in 1994 and heterogeneity was shown, as not all the families studied linked to this locus.[3] In 2001, mutations were found in *PTPN11* in 6 of the 12 patients studied.[4] This gene encodes the intracellular messenger SHP-2, which is a ubiquitously expressed protein tyrosine phosphatase that is implicated in many developmental pathways.[5] Studies of larger cohorts have found a mutation prevalence of 29–60% and have disclosed a genotype–phenotype correlation, with those carrying mutations in *PTPN11* exhibiting a higher incidence of pulmonary stenosis and a lower incidence of HCM than patients with Noonan syndrome but no mutation.[6–9]

Although the clinical spectrum seen in children with the condition is well recognised,[1][2][10] studies of the adult phenotype have been limited to specific aspects of the condition such as facial features[11] or final height,[12] and have been mostly cross-sectional in nature. There have been no studies to date looking prospectively at long-term outcome in Noonan syndrome to establish the natural history of the overall phenotype.

METHODS

This study was part of an ongoing natural history study conducted by the Noonan Syndrome Research Group at St George's, University of London, London, UK. Between 1989 and 1991, 151 subjects from 123 families were recruited to the study and details of the cohort were published in the *Archives of Disease in Childhood*.[1] Between 2001 and 2003, all families were invited for the follow-up assessment, and travelling expenses were offered to reduce bias. Assessment was done with a structured history questionnaire, clinical examination (by ACS), two-dimensional echocardiography, three-dimensional digital facial photography and analysis of the *PTPN11* gene. Individuals who were unable to travel underwent a partial assessment by postal questionnaire. Diagnosis of Noonan syndrome was reconsidered according to the diagnostic criteria proposed by van der Burgt *et al*.[13] Statistical calculations were performed using SPSS V.12, with significance assumed at 5%. The study was approved by the ethics committee.

RESULTS

Of the 151 patients in the original cohort, 34 (22.5%) dropped out of the study and 10 (6.6%) had died. On assessment of the remaining 107 individuals, three were found to have developed multiple lentigines and were given an alternative diagnosis of LEOPARD syndrome. The phenotype of a further two cases was felt to be inconsistent with Noonan syndrome, and so all five of these individuals were excluded from the analysis. The study cohort therefore comprised 112 individuals (57 males, 55 females) from 92 families, of whom 70 were fully assessed, 32 partially assessed and 10 deceased (for whom hospital records were obtained). The mean (median) age at assessment was 25.3 (22) years (range 12–71 years), and the mean follow-up interval was 12.02 (range 10.7–13.6) years. *PTPN11* analysis was performed in 79 probands and mutations were identified in

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Abbreviations: HCM, hypertrophic cardiomyopathy; SDS, standard deviation score

Table 1 Mutations in *PTPN11* identified in the study cohort

Exon	Nucleotide substitution	Amino acid substitution	Number of probands
2	124A→G	Thr42Ala	2
3	181A→G	Asp61Asn	1
3	182A→G	Asp61Gly	1
3	184T→G	Tyr62Asp	2
3	188A→G	Tyr63Cys	3
3	218C→T	Thr73Ile	2
3	236A→G	Gln79Arg	2
3	317A→C	Asp106Ala	1
7	844A→G	Ile282Val	1
8	854T→C	Phe285Ser	1
8	922A→G	Asn308Asp	10
13	1510A→G	Met504Val	2

28 (35%) patients. Mutations were more common in familial cases and were found in 6 of 12 (50%) probands from affected families (50%) compared with 22 of 67 (33%) sporadic cases (33%). Table 1 gives a list of all identified mutations.

Analysis of the facial features captured by 3D imaging are published elsewhere.[14] Table 2 shows the cause and age of death for the 10 patients who were deceased.

Growth

Height standard deviation score (SDS) was calculated for all individuals with available growth data from ascertainment and follow-up using UK standard data. The mean SDS of 92 subjects at ascertainment was –2.184 (range –6.968 to +0.940), and the mean of 64 subjects at follow-up was –1.755 (range –6.209 to +1.395). Growth data were available from both ascertainment and follow-up on the same individual in 56 cases. Table 3 shows the mean height SDS in these subjects, the data being grouped by growth hormone treatment and genotype. No statistically significant differences were detectable between the two groups. Although the group with *PTPN11* mutations had a similar mean height SDS, the distribution was much narrower, with all cases between –4 and 0 SDS compared with a range of –7 to +1 for the no mutation group.

There were 53 subjects who had reached their final adult height at follow-up. The mean final height of the 25 males and 28 females was 167.4 and 152.7 cm, respectively. Growth hormone treatment had been given to seven men and three women, and once these individuals were excluded, mean final heights were 169.8 cm (male n = 18) and 153.3 cm (female n = 25). The seven men and three women who had been treated with growth hormone in childhood were shorter than the untreated group both before and after treatment, but represent an insufficient sample to perform meaningful analysis. When grouped by genotype, the final height in those with a *PTPN11* mutation was approximately 4 cm less than those without a

Table 2 Mortality in the study cohort

Cause of death	Age (years)
Secondary to severe HCM	0.1
Secondary to severe HCM	5
Halothane-induced hepatitis	5
Road traffic accident	8
Complications after spinal surgery	17
Cerebral haemorrhage	20
Secondary to severe HCM	24
Breast cancer	45
Road traffic accident	45
Ischaemic heart disease	61

HCM, hypertrophic cardiomyopathy.

mutation in both sexes, but the difference was not statistically significant.

The mean adult occipitofrontal circumference was 56.4 cm in males (range 50–64 cm) and 54.9 cm in females (range 52–59 cm).

Cardiovascular

Pulmonary stenosis was present in 73 (65%) individuals overall, and was more prevalent in those with *PTPN11* mutations (table 4). No intervention had been required to relieve the stenosis in 42 (58%) subjects. Percutaneous balloon valvuloplasty had been performed as a primary procedure in nine individuals; three of these went on to have an open valvuloplasty at a later date. Open surgical valvuloplasty was performed as a primary procedure in 22 cases, and three of these individuals required a repeat procedure.

HCM was present in 21 (19%) patients; nine also had pulmonary stenosis, one had an atrial septal defect and one had a ventricular septal defect. Mortality was high in this group, with five subjects dying during the follow-up interval, three from complications relating to their cardiac condition. All the cardiac-related deaths were secondary to progressive heart failure. No subject had a sudden unexpected cardiac arrest or symptoms suggestive of an arrhythmia. Given the mean follow-up interval of 12.02 years, the annual cardiac-specific mortality in the HCM group was 1.2%. β-Blocker therapy had been prescribed in 9 (43%) subjects. Amiodarone had been given to one individual who later had a heart transplant. Two patients had a remission of their HCM, to the point at which β-blocker therapy was withdrawn. Surgical myectomy as a treatment for HCM had been performed in one case at ascertainment and in one further case at follow-up. Heart transplantation had been performed in two subjects at ascertainment and in one further patient at follow-up. Table 4 gives the genotype–cardiac phenotype data.

Feeding difficulties

At ascertainment, infant feeding histories were obtained and a feeding difficulty score derived, based on the level of problems experienced in the first months of life (0 = no problems; 1 = weak suck, each feed takes >1 h; 2 = weak suck and vomiting after 50% of feeds or more; 3 = nasogastric tube feeding for >2 weeks in a term infant). A feeding score obtained from the original study data was available for 104 of the follow-up group. The null hypothesis that feeding score had no long-term association was tested for each outcome measure using the Mann–Whitney U test (ranked feeding score v categorical variable) or Kruskal–Wallis test (ranked feeding score v continuous variable). Table 5 summarises these results.

Education and employment

On enquiry about education, 78 of 107 (73%) individuals reported having attended mainstream school, with 23 of them requiring extra help or tuition, and 29 (27%) reported having attended a school for children with learning difficulties. A statement of special educational need had been issued to 44%. Prevalence of *PTPN11* mutations was similar in each group.

Of the 80 individuals who had completed their education, 13 (16%) had no qualifications, 5 (6%) had completed a life-skills course, 9 (11%) had vocational qualifications, 34 (43%) reached GCSE (UK examination sat at age 16 years) grade C or higher in at least one subject, six (8%) achieved A-level qualifications (UK examination sat at age 18 years) and 13 (16%) had a higher educational qualification. Data from the Office for National Statistics (Newport, UK) for a comparable year (2002) show that 15% of the UK working age population had no qualifications, 14% had vocational or other qualifications, 22%

Table 3 Height standard deviation scores for the 56 subjects with accurate data at both ascertainment and follow-up

		Mean (SD) height	
	n	SDS at ascertainment	SDS at follow-up
All cases	56	−2.07 (1.66)	−1.88 (1.58)
No GH	43	−1.75 (1.47)	−1.67 (1.50)
PTPN11 +	14	−1.99 (1.08)	−1.65 (1.10)
PTPN11 −	27	−1.69 (1.67)	−1.73 (1.72)
GH treatment	12	−3.41 (1.63)	−2.70 (1.74)
PTPN11 +	3	−3.33 (0.60)	−2.27 (0.67)
PTPN11 −	7	−3.40 (2.15)	−2.99 (2.25)

GH, growth hormone; SDS, standard deviation score.

had attained GCSE grades A–C, 24% had A levels and 25% had a higher educational qualification.

Of those with Noonan syndrome who were no longer in full-time education, 32 (60%) were in full-time employment, 7 (13%) in part-time employment, 4 (8%) in sheltered employment, 2 (4%) unemployed and 8 (15%) unable to work due to disability. Of the overall cohort, 26% were registered disabled and 36% received some form of disability benefit.

Quality of life is a subjective variable and is difficult to measure, but most patients felt their quality of life was satisfactory or good, with only 15% reporting it was poor. A lack of social life, or an inability to fit in, was cited as the main problem. Further psychological studies on young adults with Noonan syndrome are ongoing.

Maxillofacial abnormalities

Orthodontic work had been performed in 37 of 72 (51%) patients to correct dental overcrowding, compared with 14% in the general UK population (Office of National Statistics). Dental caries was a common cause of dental morbidity, with 11 of 72 (15%) patients requiring extractions due to caries.

One patient had a mandibular tumour that was surgically resected and histologically confirmed to be a giant-cell tumour. This patient harboured a mutation in exon 3 of *PTPN11* (317A→C), as did two other members of his family who did not have giant-cell lesions. The patient's phenotype was otherwise typical of Noonan syndrome and he did not exhibit any of the unusual features said to be characteristic of Noonan-like/multiple giant-cell lesion syndrome.[15]

Table 4 Prevalence of cardiac abnormalities by *PTPN11* mutation status

	PTPN11 +ve	PTPN11 −ve	Pearson χ^2 p value
PS	27/35 (77%)	35/63 (56%)	0.034
HCM	4/35 (11%)	16/63 (25%)	0.10
Mutations	181G→A		
	218C→T		
	922A→G		
	1510A→G		
ASD	7/35 (20%)	8/63 (13%)	0.336
Mutations (number of cases)	124A→G (2)		
	182A→G (1)		
	922A→G (3)		
	1510A→G (1)		

ASD, atrial septal defect; HCM, hypertrophic cardiomyopathy; PS, pulmonary stenosis.

Infertility/genital abnormalities

Hormone injections had been given to 6 of 97 (6%) individuals to induce pubertal development. In those not receiving exogenous sex hormones, puberty commenced at a mean age of 14.5 years in males and 14 years in females with a range of 10–18 years in both sexes.

Of the 18 individuals who had had or were trying to have children, 12 (67%) had experienced no problems, 2 (11%) had one miscarriage, one had a history of recurrent miscarriages, one pregnancy ended in stillbirth and one woman had difficulty conceiving. One male had a low sperm count. Too few of the subjects had considered starting a family for the effect of cryptorchidism on fertility to be assessed.

Coagulation abnormalities

A history of easy bruising or bleeding tendency was noted at both assessments. Most subjects (n = 70, 79%) gave the same history of bleeding at follow-up. The prevalence of *PTPN11* mutations in those without a history of easy bruising was 19% compared with 47% of those with a history of easy bruising or abnormal bleeding (Mann–Whitney p = 0.015). A subcohort of 72 individuals from the original study had undergone a limited coagulation factor analysis (activated partial thromboplastin time, factors VIII, XI and XII), and these data were compared with genotype data acquired at follow-up. A range of both isolated and combined partial factor deficiencies were identified, but no correlation with genotype was noted.

Ocular abnormalities

Refractive errors affected 71% (39 of 69) patients, of whom 53% had myopia, 14% hypermetropia and 13% astigmatism. There was no relationship between eye abnormality and genotype.

Lymphatic abnormalities

Lymphoedema affected the lower limbs of two patients. One had onset of symptoms in late childhood and had distressing lymph leakage from several sites on the skin; this man had a *PTPN11* (182A→G) mutation. The other individual had severe lower limb lymphoedema from early childhood that affected his mobility, and responded poorly to treatment such as manual lymphatic drainage and bandaging. No mutation was identified in this boy.

One further patient with a 124A→G mutation in *PTPN11* had recurrent problems with lymph leakage from a skin fistula in the inguinal region. He had abnormal lymphatic architecture on lymphoscintogram, but no lymphoedema.

Skeletal abnormalities

Scoliosis was reported in 20 (13%) of the original cohort. Surgical intervention had since been performed in one subject, but the scoliosis remained mild and non-progressive in the

Table 5 Outcome measures compared with infant feeding difficulties score (0–3)

	0	1	2	3	Statistical method	p Value
PTPN11 mutation	11/32	3/12	10/26	8/21	$z=0.416$*	0.677
Underwent speech therapy	8/30	4/14	13/31	15/24	$z=2.718$*	0.007
Statement of special educational need	6/23	3/11	11/25	17/24	$z=3.215$*	0.001
Attended special needs school	4/32	1/14	10/29	14/24	$z=3.923$*	0.000
Mean age of speaking in two-word phrases (months)	26.7 (23.1 to 30.3)	23.9 (20.0 to 27.8)	32.8 (28.3 to 37.4)	39.5 (32.8 to 46.2)	$\chi^2=18.092$†, df=3	0.000
Mean age of walking (months)	18.0 (14.3 to 21.7)	19.8 (13.4 to 26.7)	22.6 (18.4 to 26.8)	26.2 (20.2 to 32.2)	$\chi^2=6.979$†, df=3	0.073

Values in parentheses are 95% CI for the mean.
*Mann–Whitney U test. †Kruskal–Wallis test.

others. Two patients were affected with rheumatoid arthritis, and three patients described a generalised polyarthropathy with onset in their fourth decade.

Neurological abnormalities

Recurrent convulsions were reported in 20 (13%) of the original cohort. Some of these individuals dropped out of the study, and two subjects developed seizures in the follow-up interval, giving a prevalence of 11/112 (10%) in the follow-up sample. Several seizure types were reported and the mean age of onset was 11 (range 3–19) years. PTPN11 mutations were identified in two subjects with seizures.

Hearing impairment

All except four patients, who had hearing loss due to serous otitis media, reported normal hearing at follow-up. These four individuals had unilateral or asymmetric bilateral conductive deafness. Sensorineural deafness affected three patients, and mixed conductive/sensorineural hearing loss was present in two. The symptoms in these five cases had been non-progressive since the initial assessment. One patient with profound sensorineural deafness had a PTPN11 mutation (124A→G). No patient had undergone cranial imaging to investigate the underlying pathology.

DISCUSSION

The adult phenotype of genetic syndromes is inadequately described and follow-up studies are rare. This study has collected longitudinal data on a large and well-characterised cohort of individuals with Noonan syndrome. Of the original 151 patients in the study group, follow-up data are available for 116 (77%). This clearly leaves potential for bias as those who dropped out may comprise a distinct subgroup with different morbidity. However, no differences in phenotype between those who dropped out of the study and those who did not were detectable when comparing data collected at ascertainment.

The prevalence of PTPN11 mutations in the cohort was 35%. Musante et al found mutations in 29% of probands,[8] Sarkozy et al in 32%,[9] Tartaglia et al in 45%[6] and Zenker et al in 60%.[7] The differences between cohorts may be due to ascertainment bias, because of the different diagnostic criteria used and the proportion of cases with pulmonary stenosis (giving a higher mutation prevalence) and HCM (lower prevalence) in each cohort.

The mean final height in this study is greater than reported previously, 169.8/153.3 cm (male/female) compared with 161.0/150.5 cm[16] and 162.5/152.7 cm.[17] This could be due to several factors such as an increase in the background population height over time, ascertainment bias of more severely affected adults in previous studies, or population cohort differences. The correlation between PTPN11 mutations and short stature reported by others[7 18 19] could not be confirmed; rather the non-mutation group had a broader spread of height SDS, perhaps suggesting that they represent a heterogeneous group, compared with the narrow distribution seen in the PTPN11 group.

Although most of those with pulmonary stenosis have required no intervention to relieve the stenosis, about a third have undergone open surgery or repeat procedures. This is comparable to other smaller series of patients with Noonan syndrome, and Noonan syndrome is recognised as a risk factor for progressive pulmonary stenosis because of the high prevalence of valve dysplasia.[20 21] The natural history of the HCM in Noonan syndrome seems to be different from non-syndromic HCM, with a similar annual mortality but with a notable absence of sudden death or rhythm disturbances. This is perhaps surprising given that the histological appearance of myocardial disarray is not distinguishable.[22]

A genotype–phenotype correlation with regard to pulmonary stenosis and HCM in Noonan syndrome is well established[6 8]; however, this and other studies[7 9] have noted HCM in about 10% of subjects with mutations, which is higher than expected. Certain specific mutations that cause LEOPARD syndrome are associated with an even higher prevalence of HCM, but the underlying mechanism for this remains unknown.

Feeding problems in infancy appear to correlate with a delay in developmental milestones and special educational need, and as such may be a neonatal marker of poorer long-term outcome. This has parallels with cerebral palsy, where a history of feeding problems often pre-dates the diagnosis.[23] In Noonan syndrome, it is not clear whether this is due to the effect of suboptimal nutrition on the developing brain, or that feeding problems are simply early markers of a more severe neurodevelopmental phenotype. In children with cerebral palsy, poor nutritional intake may contribute to reduced linear growth,[24] but in the present cohort, no association between feeding score and stature was demonstrable (data not shown). Feeding difficulties in Noonan syndrome are probably an additional feature of developmental delay, a hypothesis supported by an electrogastrographic study of 16 patients with Noonan syndrome and severe feeding difficulties, which showed patterns of foregut dysmotility similar to that seen in premature infants.[25]

Educational achievement was variable, with most individuals attaining GCSE or equivalent qualifications, but a significant number with more marked difficulties attaining no qualifications. Almost half of the individuals had a statement of special educational need, and a quarter attended a school for children with learning difficulties. This proportion is higher than reported at ascertainment, suggesting that educational difficulties are often not recognised in younger children.

This study confirms the association between *PTPN11* mutations and a history of abnormal bruising or bleeding,[7] but finds no correlation with coagulation factor abnormalities. Such abnormalities are recognised to correlate poorly with a history of bleeding,[26] and so it is likely that perturbations of SHP-2 function are influencing coagulation through an as yet unidentified mechanism.

One subject had breast cancer in her 40s, but there were no other cases of malignancy, although many in the cohort remain young. Given the recent studies identifying somatic mutations in *PTPN11* in myeloid malignancies,[27] further follow-up to investigate whether Noonan syndrome conveys a marked long-term cancer susceptibility is important.

Long-term follow-up studies are rare, and this work has added to the knowledge and understanding of Noonan syndrome and shows the importance of delineating the natural history of genetic syndromes.

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What is already known on this topic

- Noonan syndrome is a relatively common multiple congenital abnormality syndrome which is well characterised in children.
- Congenital heart disease, short stature and feeding difficulties are common features, which may have long-term sequelae.

What this study adds

- The natural history of the congenital heart defects in people with Noonan syndrome is different from that of people without the syndrome.
- Feeding problems in infancy are an early marker of delayed language development and long-term educational achievement.