

Noonan Syndrome—Clinical Perspectives and Growth Issues

a report by

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Noonan syndrome is a clinically heterogeneous condition characterized by Jacqueline Noonan et al. in 1963. It comprises a series of features that commonly include a characteristic facial appearance, congenital heart disease, and short stature. Recent genetic investigations have identified mutations in several genes, all involved in the Ras/MAPK (mitogen-activated protein kinase) signal transduction pathway, in patients with the Noonan syndrome phenotype. It is estimated that these mutations can explain approximately 60% of patients with Noonan syndrome. Continued studies are needed to identify the remaining genotypes and to characterize the genotype–phenotype relationships. The aim of this article is to describe the clinical features of this condition, with a particular emphasis on growth.

Clinical Features

Noonan syndrome has an estimated incidence of between 1:1,000 and 1:2,500 live births.¹ Because of the phenotypic variability and the changing phenotype with age,² individuals may be diagnosed at any age. Babies may present with significant peripheral edema and neck webbing with or without congenital heart disease, while other individuals may present in adulthood only after their child is diagnosed with Noonan syndrome. Understandably, it is often difficult to recognize this disorder and establish a diagnosis because of the variability in associated comorbidities and the wide spectrum of phenotypic expression that occurs with age. Thus, it is important for the clinician to understand the spectrum of clinical features and potential comorbidities, not only for the purpose of identifying the condition, but also for managing the array of accompanying clinical issues.

The characteristic facial features include hypertelorism, epicanthal folds, down-slanting palpebral fissures, expressive triangular-shaped eyebrows, and ptosis. Other ocular features may be strabismus, refractive errors, amblyopia, nystagmus, and cataracts, as well as less common findings of optic disc hypoplasia, coloboma, and keratoconus.^{3,4} The most consistent finding in the appearance of the ears is their low-set position. However, they may also be posteriorly rotated, have a thickened helix, be oval-shaped, or have an overfolded and square appearance. The palate may be high arched and dental issues may include overcrowding and malocclusion.^{5,6} The posterior hairline may be low and the neck webbed and/or short.

The skeletal features may include thorax abnormalities of pectus excavatum and/or carinatum, and flat, shield, or funnel chest. Cubitus valgus, kyphosis, scoliosis, vertebral anomalies, genua valgum, pes planus, and syndactyly may also be present.⁷

Cardiovascular abnormalities occur in 50–90% of individuals with Noonan syndrome.^{8–10} The most frequent cardiac lesions are pulmonic stenosis (27–65%),^{5,11} hypertrophic cardiomyopathy (9–25%),^{10,11} and atrial septal defect. Other cardiovascular abnormalities described in Noonan syndrome include ventricular septal defect, patent ductus arteriosus, coarctation of the aorta, mitral valve abnormalities, partial atrio-ventricular canal, dilated ascending aorta, and severe aortic valve stenosis. Additionally, an unusual electrocardiogram (EKG) pattern has been described in Noonan syndrome regardless of the presence or absence of an anatomical cardiac defect, characterized by left axis deviation, an abnormal dominant S wave over the left precordium, and an abnormal Q wave.¹²

Coagulopathies have been described in approximately one-third of patients with Noonan syndrome,¹³ though two-thirds of patients will describe abnormal bleeding and/or increased bruising.¹⁴ Coagulopathies are secondary to a variety of etiologies that include coagulation factor deficiencies (FVIII, FXI, FXII [no bleeding risk]), platelet dysfunction, and/or thrombocytopenia. Other hematological issues may include hepatosplenomegaly, splenomegaly, and juvenile myelomonocytic leukemia (JMML), all of which usually have a transient and favorable outcome.^{10,15,16}

Feeding difficulties in infancy and early childhood occur in most individuals with Noonan syndrome and can be quite problematic for families. Sharland reported results of feeding histories in 144 individuals with Noonan syndrome: 24% had no difficulties, 15% had mild difficulties (defined as the infant having poor suck, with each feed requiring over one hour to complete), 38% had moderate difficulties (defined as a very poor suck, with slow feeding and vomiting with most feeds), and 24% had severe difficulties (defined as a full-term infant



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Table 1: Genes and Loci Associated with Syndromes Involving Mutations in the Ras/MAPK Signal Transduction Pathway

Gene	Name	Locus
<i>PTPN11</i>	Protein-tyrosine phosphatase, non-receptor-type 11	12q24.1
<i>SOS1</i>	Son of sevenless, drosophila, homolog 1	2p22-p21
<i>RAF1</i>	V-raf-1 murine leukemia viral oncogene homolog 1	3p25
<i>KRAS</i>	Kirsten rat sarcoma viral oncogene homolog	12p12.1
<i>HRAS</i>	Harvey rat sarcoma viral oncogene homolog	11p15.5
<i>BRAF</i>	V-raf murine sarcoma viral oncogene homolog B1	7q34
<i>MEK1</i>	Mitogen-activated protein kinase 1	15q21
<i>MEK 2</i>	Mitogen-activated protein kinase 2	7q32

requiring a feeding tube for more than two weeks).¹⁷ Gastrointestinal investigations in 25 children with Noonan syndrome revealed that some of the feeding problems may be attributable to delayed gastrointestinal motor development, and that the feeding difficulties resolve as gut motility matures.¹⁸ Although feeding issues do seem to improve with age, many children continue to be very selective in their food choices, as reported by parents and by Wood et al. in 1995.¹⁹ A recent review by Shaw correlated feeding issues in infancy with delayed developmental milestones and special educational needs, suggesting that feeding issues may be an early marker of poorer long-term outcome.⁵

Lymphatic abnormalities occur in approximately 20% of individuals with Noonan syndrome and can be quite variable.⁷ Dorsal limb lymphedema that disappears in childhood is one of the most common lymphatic dysplasias. However, other significant manifestations of lymphatic abnormalities may include malabsorption secondary to intestinal lymphangiectasia, lymphangiectasia of the lungs, lymphedema of the scrotum or vulva, lymph leakage from skin fistulas, and chylothorax.⁵ Lymphedema may develop in adolescence and adulthood.²⁰

Renal anomalies in Noonan syndrome seem to be less common (10–11%) than other comorbidities and are usually of little significance.^{17,21,22} Solitary kidney, renal pelvis dilation, and duplicated collecting system are some of the findings. Cryptorchidism commonly occurs (up to 80%) in boys and may require surgical attention.¹⁷

Other clinical co-morbidities may include Arnold Chiari malformation, seizures (13%),¹⁷ hearing difficulties, and developmental delays.

Genetics

The inheritance of Noonan syndrome is autosomal dominant, although 60% of cases are sporadic. In 1994, linkage analysis in a large Dutch kindred revealed linkage to chromosome 12q24, and heterogeneity was established as there was absence of linkage in some families.^{23,24} In 2001, mutations in the *PTPN11* gene were found in 50% of those individuals with Noonan syndrome tested.²⁵ This gene encodes the intracellular messenger SHP-2, a ubiquitously expressed protein tyrosine phosphatase and a key component of several transduction pathways that control developmental processes including semilunar valvulogenesis, mesodermal patterning, and hematopoietic cell differentiation. Additional investigations have revealed that *PTPN11* mutations have been detected in 30–60% of individuals with Noonan syndrome, with a significantly higher occurrence of mutations in familial cases.^{26–30} All mutations reported thus far are of the missense exonic variation, with 90% clustering in exons 3, 8, and 12.³¹ In 2006, mutations

in the *KRAS* gene, an effector of activated receptor complexes downstream of SHP-2, were found in a small number (1%) of individuals with Noonan syndrome.^{32,33} It should be noted that some of the individuals with *KRAS* mutations may have a more severe phenotype with features more characteristic of Costello and cardio-facio-cutaneous (CFC) syndromes.³⁴ More recently, mutations in the *SOS1*,^{35,36} *RAF1*,^{37,38} and *BRAF*³⁹ genes were found in individuals with Noonan syndrome. The relative frequencies of these mutations in Noonan syndrome have been observed as follows: *SOS1* 10%, *RAF1* 3–17%, and *KRAS* 1%; the detection rate for *BRAF* in Noonan syndrome is unknown.³⁹ Thus far, mutations in the aforementioned genes explain about 60% of clinical cases of Noonan syndrome.

Despite the recent advances in the molecular genetics of Noonan syndrome, many complexities remain. There are several other genetic syndromes with clinical and genetic overlap with Noonan syndrome. These conditions include CFC, Costello, and LEOPARD syndromes. Common features of these disorders include cardiac defects, facial and skeletal anomalies, growth retardation, and developmental delays. All of these syndromes are caused by gene mutations that affect the Ras/MAPK signal transduction pathway. The genes affected by these disorders include *PTPN11*, *SOS1*, *RAF1*, *KRAS*, *BRAF*, *MEK1*, *MEK2*, and *HRAS* (see Table 1). At present, some of these genes are associated with more than one syndrome (*PTPN11*, *RAF1*, and *KRAS*).⁴⁰ Some patients may have a genotype that is not consistent with their clinical diagnosis. For example, an *SOS1* mutation has been reported in an individual with CFC syndrome, and *BRAF* mutations have been described in individuals with a clinical diagnosis of Noonan syndrome.³⁹

Studies of genotype–phenotype relationships have demonstrated some associations. Individuals with Noonan-syndrome-associated cardiomyopathy have a lower incidence of mutations in *PTPN11*, whereas pulmonic stenosis is significantly associated with individuals with *PTPN11* and *SOS1* mutations.^{27,25} Individuals with mutations in the CR2 domain in exon 7 of *RAF1* have a high incidence of hypertrophic cardiomyopathy (80–95%).^{37,38} The mutation in *PTPN11* of 218C→T (Thr73Ile) is correlated with a high risk of JMML.^{41–43} The 922A→G (Asn308Asp) mutation in exon 8 of *PTPN11* appears to be associated with normal intelligence.^{10,27}

Growth

Approximately 50–70% of individuals with Noonan syndrome are thought to have short stature.^{1,7,17} Although short stature is one of the main characteristics of this condition, some individuals with Noonan syndrome will have completely normal growth and stature. Birth weight and length are typically normal, but there is subsequent retardation of height, weight, and bone development such that heights and weights are below the third centile. The mean delay of bone age behind chronological age is about two years.^{17,44} Puberty is frequently delayed in both sexes, with a decreased pubertal growth spurt.⁴⁴ Noonan-specific growth charts have been published.^{44,45}

Mean adult heights for females have been reported as 152.7cm⁴⁴ and 153.3cm⁵ and for males as 162.5cm⁴⁴ and 169.8cm.⁵ It is important to recognize that these adult height data are in predominantly European populations when using them for individuals with Noonan syndrome from other populations, whose mean population height may differ. In a review of heights in 73 adults in North America with Noonan syndrome,

Table 2: Baseline and Treatment Growth Data from Studies Reporting Adult Height Outcomes in Individuals with Noonan Syndrome Treated with Growth Hormone

Reference	Patients, n (sex)	Baseline Age (years)	Baseline SDS*	Growth Hormone Dose	Therapy Duration (years)	D Height SDS	Height Gain
Municchi, 1995 ⁶³	4 (4 F)	13.5	(-0.6)	0.19mg/kg/week x 1 year, then 0.31mg/kg/week	3.5	(0.48)	NA
Kirk, 2001 ⁶⁶	10 (4 F)	12	-3.1 (-0.7)	0.30mg/kg/week	5.3		3.1cm
Osio, 2005 ⁶²	18 (11 F)	8.6 (M) 7.7 (F)	-2.9 (-0.3)	0.23mg/kg/week (n=10), 0.46mg/kg/week (n=15) x 2 years then dose titration Estimated mean 0.35mg/kg/week	7.5	1.7	13cm (M) 9.8cm (F)
Raaijmakers, 2008 ¹²	24 (NA)	10.2 (median)	-3.24 (median)	0.24mg/kg/week (median) Range: 0.17–0.77mg/kg/week	7.59 (median)	0.61 (0.97)	NA
Noordam, 2008 ⁶⁵	29 (8 F)	11	-2.8 (0.0)	0.35mg/kg/week	6.4 (median)	1.3 (1.3)	9.5cm (M) 9.0cm (F)

Results are mean values unless specified otherwise. *Height standard deviation score (SDS) reported according to population standards and/or (Noonan syndrome standards).

Noonan et al. reported adult heights below the third centile in 54.5% of females (Centers for Disease Control and Prevention [CDC] standards <151cm) and 38% of males (CDC standards <163.2cm).^{46,47}

Reports of growth hormone (GH) secretory dynamics have been inconsistent, and this inconsistency more than likely reflects the heterogeneity of the condition and hence that seen in the study groups. In a large study of 150 individuals with Noonan syndrome in the National Cooperative Growth Hormone Study (NCGS), 45% of individuals had peak GH responses to provocation with <10 μ g/l.⁴⁸ Similarly, Cottrell reported 10 of 27 children (37%) with Noonan syndrome having peak GH levels of <12.5 μ g/l.⁴⁹ Although some studies report abnormal spontaneous GH secretion with high trough levels, suggestive of neurosecretory dysfunction,^{50–52} other studies have reported completely normal GH secretion.^{53,54} Several investigators have reported low levels of insulin-like growth factor 1 (IGF-1) despite normal levels of insulin-like growth factor binding protein 3 (IGFBP-3).^{49,53–55} Mutations in *PTPN11* have been proposed to affect the function of the GH–IGF-1 axis, leading to a deficiency in IGF-1. Of interest is the study of 29 patients with Noonan syndrome by Binder et al., where GH secretion (both spontaneous and stimulated) was significantly higher and IGF-1 levels were significantly lower in *PTPN11*-positive patients (n=16) compared with *PTPN11*-negative patients (n=13), suggestive of mild GH resistance in mutation-positive patients.⁵⁵

Growth Hormone Therapy

Few treatment options are available to improve the physical development of patients with Noonan syndrome. No single treatment exists for the disease as a whole; rather, treatment focuses on individual symptoms. Short stature in children with Noonan syndrome can be treated successfully with GH therapy. The majority of studies with GH therapy in Noonan syndrome have been observational, lacking randomization or control groups, and involving small patient populations with varied enrollment ages, treatment durations, recombinant human GH (rhGH) doses, and responses. A number of studies have reported improved growth velocity in response to GH therapy, with no significant adverse effects.^{48–50,56–58} Most studies have excluded patients with hypertrophic cardiomyopathy. However, many patients have undergone serial echocardiograms, and there have been no reports of abnormal myocardial thickening or development of features of hypertrophic

cardiomyopathy when prospectively measured in patients with Noonan syndrome receiving GH therapy.^{49,59}

Studies with GH therapy in Noonan syndrome have shown that short-term growth acceleration has been comparable to that seen in Turner syndrome.^{48,60} The NCGS enrolled 150 pre-pubertal and pubertal children (53 girls) with Noonan syndrome for GH therapy for a mean of three years, and found significantly greater growth rates from baseline ($p \leq 0.003$) for years one through four of therapy, with annual growth rates in Noonan syndrome children exceeding those in children with Turner syndrome.⁴⁸ A smaller study following the use of rhGH therapy (0.05mg/kg/day) in 23 pre-pubertal Noonan syndrome patients (five girls) 5.4–14.3 years of age over the course of one year showed that the resulting growth response and skeletal maturation was comparable to that seen in a group of 17 similarly treated girls with Turner syndrome (growth rate increase of 4.0 ± 1.6 cm/year from baseline versus 3.6 ± 1.3 cm/year from baseline, respectively).⁶⁰ Recent near adult height data from the NCGS demonstrate comparable growth outcomes to GH therapy in patients with Noonan syndrome and Turner syndrome.⁶¹

Initial concerns about bone age acceleration with GH use in Noonan syndrome have not been substantiated. This apparent acceleration may have been related to the appearance of advancing bone age in children with Noonan syndrome with a very delayed bone age (less than -3SD) at the start of treatment. This change in bone age relative to the degree of bone age delay was reported in 1996, when the ratio of the change in bone age relative to the change in height age for children with Noonan syndrome was compared with the change seen in those with Turner syndrome and idiopathic GH deficiency (IGHD).⁴⁸ It was demonstrated that bone age does not disproportionately advance in Noonan syndrome compared with the bone age delays seen in the other two groups. Because patients with Noonan syndrome have a more delayed bone age, bone age appears to advance at an accelerated rate only due to normalization of bone age under GH therapy. Significant improvements in adult height with GH use in individuals with Noonan syndrome are further evidence that bone age does not advance inordinately.^{56,61–65}

Data on the final or near-final height of patients must be assessed in order to consider the efficacy of GH in Noonan syndrome. Recently, there has been an increasing amount of data concerning adult height in patients with Noonan syndrome treated with GH; these data are summarized in Table 2. Although

these studies report different parameters (i.e. median versus mean values, height SDS based on population standards versus the Noonan-specific standards, varied dosage regimens, etc.), it is still helpful to compare their characteristics relative to the outcomes. Not only were the studies by Municchi and Kirk smaller, but also the patients reaching final or near-final height were older, with mean ages of 13.5 and 12 years, respectively, at the time of initiating GH treatment.^{56,63} The mean duration of therapy was also short (3.5 and 5.3 years, respectively), and poorer outcomes were achieved (Δ height SDS 0.48 and mean height gain 3.1cm, respectively). The 18 patients (11 girls) who reached final height in the study by Osio et al. achieved improved

0.77mg/kg/week, with a median dose of 0.24mg/kg/week. The results from these studies show a wide range of growth in response to GH, and the predictors of good response to GH therapy have yet to be fully established. Both Osio et al. and Noordam et al. show that the number of pre-pubertal years spent on GH treatment is very important.^{62,65} Near adult height data from patients with Noonan syndrome in the NCGS (n=65) revealed comparable height gains to the Osio and Noordam studies, as well as the importance of pre-pubertal GH therapy duration.⁶¹ The findings of improved outcomes with earlier initiation and longer duration of GH therapy have been demonstrated in other conditions as well, including Turner syndrome.^{66,67}

Results of long-term studies of growth hormone (GH) use in patients with Noonan syndrome with short stature demonstrate a significant improvement in adult height. Duration of GH treatment and GH dosage may be important contributors to height optimization.

Considering the involvement of the gene mutations in Noonan syndrome in the Ras/MAPK signal transduction pathway, several studies have looked at GH responsiveness relative to the presence or absence of a mutation in the *PTPN11* gene. Initial short-term data suggested that mutation-positive patients responded 'less efficiently' to GH than mutation-negative patients.⁵⁴ However, longer-term data comparing adult heights between mutation-positive and mutation-negative patients who have been treated with GH demonstrate that there is no difference in outcome.⁶⁵ This difference in GH response between children with and without mutations in *PTPN11* may therefore be significant only in the short-term, and may diminish over long-term GH therapy.

outcomes (Δ height SDS 1.7, mean height gain 13cm for boys and 9.8cm for girls); these patients were comparatively younger at the start of GH treatment and therefore had a much longer treatment duration.⁶² Although this study reported no significant difference between the higher dose of 0.46mg/kg/week over the lower dose of 0.23mg/kg/week, the size of the treatment groups may not have been large enough for dosage comparisons. While the age at GH initiation in the Raaijmakers and Noordam studies were similar (10.2 versus 11 years, respectively), the outcomes were improved in the Noordam study (Δ height SDS 1.7) compared with the Raaijmakers study (Δ height SDS 0.61).^{63,64} This difference in outcome, in spite of a shorter treatment duration, may be related to the higher GH dose of 0.35mg/kg/week used in the Noordam study, whereas the patients in the study by Raaijmakers et al. received dosages ranging between 0.17 and

Conclusions

Noonan syndrome is a clinically and genetically heterogeneous condition characterized by short stature, congenital heart disease, distinct facial features, and many other comorbidities. Mutations in the genes identified in Noonan syndrome are involved in the Ras/MAPK signal transduction pathway, and currently explain about 60% of those with Noonan syndrome. Hence, Noonan syndrome remains a clinical diagnosis. Patients with Noonan syndrome require multidisciplinary evaluations and regular follow-up care for their identified comorbidities. It is still not known how *PTPN11* mutations affect SHP-2, but the apparent result is a disruption of in the GH axis and, ultimately, growth failure. Results of long-term studies of GH use in patients with Noonan syndrome with short stature demonstrate a significant improvement in adult height. Duration of GH treatment and GH dosage may be important contributors to height optimization. ■

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