

Noonan syndrome and related disorders: Alterations in growth and puberty

Jacqueline A. Noonan

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Abstract Noonan syndrome is a relatively common multiple malformation syndrome with characteristic facies, short stature and congenital heart disease, most commonly pulmonary stenosis (Noonan, *Clin Pediatr*, 33:548–555, 1994). Recently, a mutation in the *PTPN11* gene (Tartaglia, Mehler, Goldberg, Zampino, Brunner, Kremer et al., *Nat Genet*, 29:465–468, 2001) was found to be present in about 50% of individuals with Noonan syndrome. The phenotype noted in Noonan syndrome is also found in a number of other syndromes which include LEOPARD (Gorlin, Anderson, Blaw, *Am J Dis Child*, 17:652–662, 1969), Cardio-facio-cutaneous syndrome (Reynolds, Neri, Hermann, Blumberg, Coldwell, Miles et al., *Am J Med Genet*, 28:413–427, 1986) and Costello syndrome (Hennekam, *Am J Med Genet*, 117C(1):42–48, 2003). All three of these syndromes share similar cardiac defects and all have postnatal short stature. Very recently, HRAS mutations (Aoki, Niihori, Kawame, Kurosawa, Ohashi, Tanaka et al., *Nat Genet*, 37:1038–1040, 2005) have been found in the Costello syndrome and germline mutations in *KRAS* and *BRAF* genes (Rodriguez-Viciana, Tetsu, Tidyman, Estep, Conger, Santa Cruz et al., *Nat Genet*, 2006; Niihori, Aoki, Narumi, Neri, Cave, Verloes et al., *Nat Genet*, 38:294–296, 2006) in the Cardio-facio-cutaneous syndrome. Phenotypic overlap between these genetic disorders can now be explained since each is caused by germline mutations that are major components of the RAS-MAPK pathway. This pathway plays an important role in growth factor and cytokine signaling as well as cancer pathogenesis.

Keywords Noonan syndrome · LEOPARD syndrome · Cardio-facio-cutaneous syndrome · Costello syndrome · Short stature · Growth hormone

1 Introduction

Noonan Syndrome (NS) has been recognized for about 40 years [1] but the genetic cause was not found until 2003 when mutations in the *PTPN11* gene were reported [2]. Shortly afterwards LEOPARD syndrome (LS), a rare allelic variant of NS was found to have specific mutations in the *PTPN11* gene [25]. Cardio-facio-cutaneous (CFC) syndrome and Costello syndrome (CS), both rare syndromes, share significant phenotypic overlap with NS especially in infancy. The common features of facial dysmorphism, short stature and similar cardiac findings in all four conditions suggest a similar underlying pathogenesis. In 2005 [6], mutations in the HRAS oncogene were found to be the cause of CS and in 2006 mutations in *KRAS*, *BRAF*, *MEK1* and *MEK2* genes [7, 8] were identified in CFC. All of these germline mutations are components of the RAS-MAPK pathway which plays an important role in growth factors and cytokine signaling. In this review, the clinical findings of the four syndromes will be reviewed. NS will be discussed in more detail since it is common and more clinical studies are available.

1.1 Noonan syndrome

NS is one of the more common non-chromosomal syndromes seen in children with congenital heart disease with an estimated incidence of 1 in 1,500 [1]. Although there is wide phenotypic variation in NS, distinctive facial features include hypertelorism, down-slanting palpebral

J. A. Noonan (✉)
Department of Pediatrics, University of Kentucky
College of Medicine, Lexington, USA
e-mail: jnoonan@uky.edu

fissures, a high arched palate, low set posteriorly rotated ears, malar hypoplasia, ptosis and often a short neck. The phenotype changes significantly with time. In the newborn, there is excessive nuchal skin which is the result of prenatal cystic hygroma. During infancy, the head is relatively large, the eyes are often prominent and round, there is a high nasal bridge which may be flat, and the neck appears short. At 3 to 4 years of age, the body becomes more stocky and the chest more prominent. The chest deformities often become significant. In later childhood, the facial appearance begins to show coarse features and becomes more triangular as the chin lengthens. The eyes become less prominent and the ptosis may be more apparent. In the teenager and young adult, as the neck lengthens webbing may become more apparent, the facial features are more triangular and become sharper, the nose has a pinched root and a thin high bridge. An older adult has prominent nasal labial folds, a high anterior hairline and the skin often appears rather transparent and wrinkled.

In most, the prenatal history is unremarkable but polyhydramnios is frequent. Height and weight are within normal limits at birth but height begins to drop off within a few months and over 70% of patients with NS have significantly short stature. Some patients with NS have significant feeding difficulties with resulting failure-to-thrive and require tube feedings. Although this may contribute to the poor gain in weight, short stature occurs equally in children who have no feeding problems in infancy. Other important findings include a chest deformity which may be in the form of a pectus carinatum or pectus excavatum, apparent widely spaced nipples and a relatively broad chest. Scoliosis and kyphosis occur in about 15% of patients. Muscle hypotonia is frequent and may account for some of the motor delay. Significant mental retardation is uncommon but some degree of learning disability is frequent and may require special help in school. Eye findings, especially strabismus and refractive errors are common and an occasional patient will have a coloboma. All children with NS should have a complete eye examination. Since conductive hearing loss is rather frequent, children should have a hearing evaluation. Over half of the males with NS have either one or both testes undescended and delay in puberty is common for both males and females.

Easy bruising is common in NS and a variety of bleeding problems have been reported [9]. These include deficiency of Factor XI, Von Willebrand's disease, thrombocytopenia and platelet function defects. In addition, low levels of Factor VIII and XII have also been noted. Hepatosplenomegaly, usually unexplained, is present in about 25% of patients particularly in infancy. Lymphatic abnormalities occur in less than 20% of patients but may present serious problems. Over 80% of patients with NS have a cardiac

finding. Pulmonary stenosis is, by far, the most common but nearly every cardiac lesion has been reported. In addition, hypertrophic cardiomyopathy may occur.

It was recognized early on that NS could be transmitted in an autosomal dominant manner. In 1994, Jamieson et al [10] was able to map the gene for NS to the distal part of chromosome 12q. Not all families with NS studied showed this linkage suggesting that more than one gene was likely to be involved in the etiology. In 2002, Tartaglia [2] found a mutation in the *PTPN11* gene to be present in about 50% of patients with NS. This gene regulates the production of a protein called SHP-2 which is essential in several intracellular signal transduction pathways and controls a number of developmental processes including cardiac semilunar valvulogenesis. The protein is expressed throughout the body and it is an important player in cellular response to growth factors, hormones, cytokines and cell adhesion molecules. The *PTPN11* mutations in NS are clustered in interacting portions of the N-SH2 in PTP domains. This mutation results in a gain of function for SHP-2.

Children with NS often present to the endocrinologists because of the short stature, delayed puberty or undescended testes in males. Although height and weight are usually in the normal range at birth, height drops off within the first few months. In general, there is at least a 2-year delay between bone age and chronological age. Continued growth may occur until the early 20s. In both males and females, there is a delay in puberty. Females seem to possess normal fertility. Males, as expected due to undescended testes, appear to have decreased fertility but male transmission is well described and not uncommon.

The cause of short stature in NS is really not clear. After pharmacological stimuli, growth hormone secretion was usually normal in patients studied but a small number showed a subnormal response. Others have shown a neurosecretory growth hormone dysfunction to be present in some patients but this did not appear to have any effect on the response to growth hormone [11]. There have been previous studies looking at the IgF-1 levels which have been below normal for the majority reported. A considerable number of children have undergone treatment with human biosynthetic growth hormone. The majority of studies have shown similar results. There is a significant increase in growth velocity in the first and second year of growth hormone treatment [12–16]. The velocity in growth tends to diminish in succeeding years. Several authors claim that the predicted adult height has been increased in patients treated with growth hormone but there have been no real controlled studies to document the long-term effect of growth hormone on adult height. In those studies where bone age as well as actual height were measured, the increase in bone age was equal or slightly greater than the overall increase in height. If the bone age acceleration

exceeds the acceleration in height, it is even possible that growth hormone therapy could actually decrease the adult height. Since there was little data available regarding adult height in NS, we recently [17] published a study of 73 adults who were all over 21 years of age at the time of their last measurement. Thirty-one percent of males and 32% of females achieved an adult height that was at the tenth percentile or greater which would be considered within a normal range. The remainder all fell below the tenth percentile but importantly 38% of males and 54.5% of females had an adult height below the third percentile. Adult height was unrelated to the presence or severity of cardiac disease and none of the adults achieving a normal height had been treated with growth hormone. Dr. Municchi et al [16] suggests that long-term serial height measurement over years comparing treated and untreated patients is needed to clearly show the benefit of growth hormone therapy on final adult height. There is no question that adult height can be achieved at an earlier age with the use of growth hormone.

With the discovery of the *PTPN11* mutation, it is now possible to study patients with NS positive for a mutation and compare them with NS patients who do not carry a mutation of the *PTPN11* gene. The large cohort reported by Ranke [18] suggested that weight and length were normal in 119 newborns with NS. With the availability of genetic testing, several recent studies have shown that mean birth length for NS patients with a mutation is slightly below normal and is less than that of the non-mutated NS newborns [19, 20]. In a study by Zenker [20], 88% of *PTPN11* positive mutated children older than 3 years of age had a height less than two standard deviations and were significantly shorter than non-mutated children. All recent studies [21] suggest that there is a more severe mechanism acting on growth retardation in NS patients carrying a *PTPN11* mutation. A recent study from France [19] evaluated 35 patients with NS, 20 of whom had a *PTPN11* mutation. There was a trend to a shorter birth length in mutated versus non-mutated newborns and small for gestational age tended to be more frequent in mutated versus non-mutated patients. By 6 years of age, patients with mutations were significantly shorter than patients without mutations. The results of hormonal studies showed a normal growth hormone secretion after pharmacological stimuli and a low serum IgF-1 and ALS concentrations which is in contrast with a normal IgFBP-3 level. Since the *PTPN11* gene has a negative effect on intracellular signaling downstream from several growth factor receptors, a growth hormone post receptor signaling resistance could represent the mechanism of stunted growth in NS. They felt that the lower growth response to growth hormone treatment observed in mutated versus non-mutated patients suggests some degree of resistance to growth hormone.

Another recent study by Binder et al [22] showed a similar pattern. Data from these two studies would be in favor of growth hormone resistance by a late post receptor signaling defect specific for IgF-1 and ALS that does not effect IgFBP-3 stimulation. Changes in height during the first 2 years of growth hormone therapy in the pre-pubertal group show catch-up growth was less pronounced in patients with a mutation compared to those without a mutation. Fortunately, in all the studies using growth hormone, no adverse results have been observed. Many patients have undergone serial echocardiograms and none have shown an increase in their left ventricular mass index during growth hormone treatment [23]. These recent studies suggesting that there may be a primary IgF-1 deficiency in NS has stimulated and been incorporated into a phase II clinical study which will investigate the use of IPLEXtm (mecasermin rinfabate) (rDNA origin) which will be given by injection to treat growth failure due to insulin-like growth factor IgF-1 deficiency. Although we still do not understand how the mutation in the *PTPN11* gene affects SHP-2, the result apparently is a disruption in the growth hormone IgF-1 axis and IgF-1 deficiency which could be the cause of growth failure.

1.2 LEOPARD syndrome (LS)

Gorlin [3], in 1969, introduced the acronym LEOPARD (LS) to describe a rare syndrome that shares many features similar to NS. These include autosomal dominant inheritance, similar facial dysmorphism and similar cardiac defects with an overabundance of hypertrophic cardiomyopathy compared to pulmonary stenosis. The characteristic cutaneous finding of lentigines is the main distinguishing characteristic. In addition, unilateral or bilateral hearing loss is frequent.

Sarkozy et al [24, 25] recently reported clinical and molecular studies in a consecutive study of 30 patients with LS and found mutations in the *PTPN11* gene in 27 of the 30 patients studied. Mutations in LS have all occurred in exons 7, 12 and 13 while the more typical NS have the great majority of mutations occur in exons 3, 8 and 13. It is of interest that the mutations in patients with LS show a loss of function rather than gain a function as is found in the more typical NS patients.

Zenker [20] noted a specific mutation T468M in exon 12 which was also reported by Sarkozy in seven of their patients with LS to have less adverse effects on body growth. Only two of the ten patients with the T468M mutation have short stature.

A cardiac abnormality was present in 71% of the patients with LS, with 80% of those showing hypertrophic cardiomyopathy. Pulmonary stenosis was present in two patients and a partial AV canal in another.

1.3 Cardio-facio-cutaneous syndrome (CFC)

It is often difficult to distinguish an infant with CFC from NS although, with time, the phenotype becomes more distinctive. Patients with CFC [4] have a high forehead, a relatively large head and bitemporal constriction. Like NS, they have a downward slant of the palpebral fissures, posteriorly rotated ears and a flat nasal bridge. The hair is usually sparse, curly and friable and absent eyebrows are frequent. The skin changes are variable but include keratosis pilaris with patchy hyperkeratosis [26]. In time, the phenotype for CFC becomes more distinctive and less Noonan-like. These patients are significantly delayed in both motor and mental skills and, like NS, they are hypotonic, often have failure-to-thrive with frequent gastrointestinal complaints and often require tube feedings. Cardiovascular abnormalities are similar to NS although hypertrophic cardiomyopathy is more common than in the typical NS patient. Although these children appear to be of normal height and weight at birth, they soon fail-to-thrive and short stature is found in 78% [27]. Bone age is significantly delayed and osteopenia is occasionally observed.

Very recently, mutations in four separate genes have been found to be associated with CFC [3, 4]. These four genes include *BRAF*, *KRAS*, *MEK1* and *MEK2*. All of these genes belong to the same RAS-ERK pathway that regulates cell differentiation, proliferation and apoptosis. It is likely that the mechanism causing short stature in NS may be similar to that causing short stature in CFC. This is a very rare disease and there is little information regarding endocrine studies in patients with CFC.

1.4 Costello syndrome

Costello Syndrome (CS) [28] is a rare condition with a distinctive facial appearance which may be difficult to distinguish from NS and CFC in infancy. Although height and weight are normal or above normal at birth, severe growth retardation is the rule postnatally. Like NS, they have a large head, short wide nose and short neck. Unlike NS or CFC, these patients usually have thick and relatively prominent lips and tongue. They also have loose skin on the hands and feet and deep palmar and plantar creases. There is significant mental and motor delay. Cardiovascular abnormalities are found in about 60% and they are remarkably similar to that found in NS and CFC. Pulmonary stenosis, atrial septal defect and hypertrophic cardiomyopathy are the most common lesions [29]. Of particular interest is the high incidence of cardiac arrhythmias noted particularly in infancy [30] that is not characteristic of either CFC or NS.

Recently Aoki et al [4] reported mutations in *HRAS* a proto-oncogene to cause CS. Gripp et al [31] confirmed this finding and reported 33 of 40 patients with a clinical

diagnosis of CS to have a *HRAS* mutation. All the mutations were de novo. Patients with CS are at a significantly increased risk for the development of malignancy, particularly rhabdomyosarcoma, neuroblastoma, ganglioneuroblastoma, and transitional cell carcinoma of the bladder. Although few studies of growth hormone have been carried out in Costello patients, the findings are very similar to that of NS. Response to growth hormone treatment has been variable. Kerr et al [32] have suggested that in CS, hormone treatment may be harmful because of the propensity to tumor formation and the presence of hypertrophic cardiomyopathy. He described two patients, one who had mild left ventricular hypertrophy with normal function before growth hormone was started. After 3 months of treatment, the cardiomyopathy progressed with significant left ventricular outflow tract obstruction with a gradient of 60 mmHg. He was treated with Propranolol. There was no further progression of the cardiomyopathy in spite of continuation of growth hormone. In the second case, growth hormone was started at 12 months and continued until age 26 months when a large pelvic mass was discovered which was proven to be an embryonal rhabdomyosarcoma. Growth hormone was stopped after the tumor was recognized. In spite of extensive chemotherapy, the patient died. Since CS is associated with both subaortic hypertrophic cardiomyopathy and tumors, the role of growth hormone in these two patients is unknown. At the present time, it is unclear whether growth hormone is beneficial or harmful in CS.

2 Conclusion

NS, LS, CFC and CS all have significant phenotypic overlap. Although they may be difficult to distinguish early on in life, in time they can usually be distinguished clinically. Recent studies show that each of these syndromes is caused by a germline mutation in a key component of the highly conserved RAS, RAF-ERK-MAP kinase cascade which is better known for its roles in growth factor and cytokines signaling in cancer pathogenesis. We still do not understand how these specific mutations cause the disease and why there are such distinct phenotypic differences in mutations within the same signaling pathway. Tartaglia et al [33] recently provided evidence that specificity in amino acid substitution is relevant to the functional deregulation of SHP-2 and disease pathogenesis. They showed NS mutations have less potency for promoting SHP-2 gain of function than do leukemia-associated mutations and that Y279C and T468M amino acid substitutions noted in LS engender a loss of SHP-2 catalytic activity. It is not surprising that a mutation in the *HRAS* gene associated with CS has an increased incidence of tumors since these mutations are identical to

the human tumor associated mutations. So far, CFC syndrome has not been associated with malignancy but the number of reported cases is still quite small with long-term follow-up limited. For the endocrinologist, it is interesting that all of the syndromes have a high incidence of short stature. LS, on the other hand, with loss of function appears to have a lower incidence of short stature but the higher incidence of hypertrophic cardiomyopathy. It will be of interest to see how effective IPLEXtm will be in treating the growth failure in NS and perhaps these related syndromes as well. Since the growth failure starts very soon after birth and may indeed start before birth, it is certainly possible that treatment may be necessary very early in life to achieve anywhere near a normal growth stature.

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