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EDITORIALS

Noonan syndrome revisited

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It has been over 30 years since Noonan syndrome was first reported as a multiple malformation syndrome.[1] Affected individuals have characteristic facies, are usually short in stature, and frequently have a chest deformity; congenital heart disease, most often pulmonary stenosis, is frequent. It affects both males and females. The karyotype is normal. Autosomal dominant inheritance with variable expression has been well documented, but many cases appear to be sporadic. Developmental delay is frequent, and mild mental retardation, although relatively common, is not constant. An incidence of 1:1000 to 1:1250 live births is suspected. It has been reported worldwide. In 1985 Allanson [2] reported that the phenotype in Noonan syndrome changes significantly between infancy and adulthood. A parent with mild features of the syndrome may not be recognized as transmitting Noonan syndrome to an affected offspring. However, review of a childhood photograph may show a resemblance to the affected offspring that will prove useful in genetic counseling. Noonan syndrome is often difficult to recognize in the newborn,[3] and so far, accurate prenatal diagnosis is not available. Pulmonary stenosis with or without a dysplastic pulmonary valve is the most frequent cardiac defect noted, but virtually every form of congenital heart disease has been reported.[4] Once cardiac sonography became available, it became apparent that hypertrophic cardiomyopathy [5] was a relatively common finding. The microscopic findings in Noonan syndrome with hypertrophic cardiomyopathy are similar to those in familial, non-syndromic hypertrophic cardiomyopathy. Among infants with symptomatic, severe hypertrophic cardiomyopathy, Noonan syndrome is now recognized as one of the most frequent causes of this serious but uncommon condition.[6]

Two articles on Noonan syndrome appearing in this issue of The Journal demonstrate the worldwide occurrence of this relatively common multiple malformation syndrome. Marino et al[7] found 136 of 157 (86.6%) consecutive subjects with Noonan syndrome to have a cardiovascular abnormality. Although older studies suggested cardiovascular disease to be present in about 50% of patients with Noonan syndrome, a recent study by Sharland et al,[8] in which cardiac sonography was used, also showed over 80% to have a cardiovascular abnormality. Of

particular interest in the report by Marino et al[7] is the high prevalence of partial atrioventricular canal (15%). Such lesions have been previously reported, but with a low prevalence. The prevalence (8.8%) of coarctation of the aorta is also considerably greater than previously reported. On the other hand, the 9.5% prevalence of hypertrophic cardiomyopathy is lower than the 20% reported by Sharland et al[8] and the 33% reported by Ishizawa et al.[9] At present, it is unclear whether these differences in prevalence can be attributed to geographic factors. Clearly, a wide variety of cardiac defects can be found in this syndrome, making it essential that any child with suspected Noonan syndrome undergo a complete cardiovascular evaluation.

The article by van der Burgt et al,[10] which addresses the cognitive functioning of school-aged children with Noonan syndrome, is important because there have been relatively few detailed studies in this area. The reported IQ ranged from 53 to 127 with a mean of 86.14. This is similar to that noted in a smaller study by Money and Kalus.[11] When a verbal-performance discrepancy was observed, no consistent pattern was apparent, but children with moderate Noonan syndrome were more likely to show verbal IQ to exceed performance IQ. The authors identified children with Noonan syndrome to have strengths in non-verbal reasoning, verbal comprehension, social judgment, and visual motor abilities. On the other hand, specific weaknesses were found in spatial knowledge and planning abilities. Frequently, there were problems with organization, memorization, and the ability to pay attention. The study showed a wide range of IQ and a variable pattern of verbal-performance discrepancy, suggesting that each child with Noonan syndrome should have a complete evaluation. There should be emphasis on vision and hearing, as well as a full assessment of intellectual functioning by appropriate testing, which would identify the relative strengths and weaknesses of a particular child. This assessment should be done in the early school years so that needed special attention can be given.

Unfortunately, neither of these articles help to define the mechanism of Noonan syndrome. As in many dominant disorders, there is marked phenotypic variability. The diagnosis is purely clinical at present with no "diagnostic" test available. It is often difficult to recognize in the neonate, and the changing phenotype with time often makes mild Noonan syndrome difficult to recognize in adults. Since Noonan syndrome was described, at least 4 other syndromes that have similar facies and similar cardiac defects have been described. Each has an additional distinctive feature that is considered by many to represent a distinct separate syndrome. These include cardio-facial-cutaneous syndrome,[12] LEOPARD syndrome,[13] neurofibromatosis-Noonan syndrome,[14] and Costello syndrome [15] ; none have a diagnostic test available. In 1994 Jamieson et al[16] mapped a gene for Noonan syndrome to the long arm of chromosome 12. This brought hope that a specific gene would be identified. So far, the gene has remained elusive. Because of the similarities, rather than differences, between Noonan syndrome and the other syndromes mentioned, I have tended to "lump" them together rather than "split" them. That decision is based on recognition that the 22 q 11.2 syndrome now encompasses DiGeorge syndrome, Shprintzen's syndrome, or velocardiofacial and cono-truncal anomaly face syndrome; all are now considered part of the same syndrome,[17] rather than separate entities as previously thought. Indeed, it is now clear that the 22 q 11.2 deletion has a very wide phenotype, ranging from the frequently lethal DiGeorge syndrome to the mild form with subtle facial abnormalities and developmental delay. My own experience includes an infant with severe phenotypic expression and severe congenital heart disease who was born to a mother with mild mental retardation and subtle facial features in whom an isolated right aortic arch was identified by cardiac sonography. Both mother and baby showed deletion of chromosome 22. Recently, Legius et al[18] mapped a large family with the diagnosis of cardio-facial-cutaneous syndrome in several members, whereas others had a phenotype more consistent with Noonan syndrome. All individuals were diagnosed as having Noonan syndrome or cardio-facial-cutaneous syndrome mapped by linkage analysis to chromosome 12 q 24 similar to the family with Noonan syndrome reported earlier by Jamieson et al.[16] Thus there is at least some evidence that Noonan

syndrome and cardio-facial-cutaneous syndrome may share a similar genetic abnormality. With rapidly evolving progress in genetic mapping, it should not be long before we have a better understanding of this syndrome. Once a diagnostic test is available, we will not only be able to identify Noonan syndrome, but hopefully we will understand just what Noonan syndrome is. When this happens, we can replace the eponym *Noonan syndrome* with the identified genetic cause.

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