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Editorial Comment

Noonan syndrome – then and now

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THE REPORT BY DANETZ, DONOFRIO AND Embrey[1] provides an interesting long term follow-up on the first patient diagnosed by me with what is now known as Noonan syndrome. In 1960, when this patient was seen, cardiac ultrasound was unavailable and left-sided cardiac catheterization uncommon. He had severe pulmonary stenosis, and did well following surgery. Unfortunately, his follow-up was not adequate and left-sided obstruction was not recognized until he became symptomatic some thirty years later. Early reports stressed the dysplastic pulmonary valve, with pulmonary stenosis as a common finding.[2] By 1972, the report of Ehlers et al.[3] brought attention to the left-sided involvement in the Turner phenotype. By the late 1970's the eponym, Noonan syndrome, which included many of the patients with the Turner phenotype, became the accepted term for this condition. It is now considered one of the most common non-chromosomal syndromes associated with congenital heart disease. Unfortunately, the diagnosis of Noonan syndrome remains a clinical one, with no diagnostic test yet available.

Left-sided obstructive lesions are well described, including aortic valvar stenosis, subaortic stenosis, coarctation of the aorta, and both obstructive and non-obstructive hypertrophic cardiomyopathy. The hypertrophy may be asymmetric, concentric, or apical, and can range from mild to severe. The hypertrophy regresses in some, progresses in others, and remains stable in most for many years.[4] There is no question that hypertrophic cardiomyopathy is a relatively common finding in Noonan syndrome. Muscular disarray is found similarly to that seen in the non-syndromic form. The course and prognosis is variable and poorly understood.

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Early reports included few symptomatic newborns with Noonan syndrome. This condition may be difficult to diagnosis in early infancy. We now know that hypertrophic cardiomyopathy presenting in infancy is of particular interest because of its serious prognosis. Transient septal hypertrophy presenting in the newborn has been well documented in infants born to diabetic mothers. Metabolic diseases, such as Pompe's disease and a number of mitochondrial disease, may also present with muscular hypertrophy in infancy. Non-syndromic hypertrophic cardiomyopathy must also be considered. In my experience, among patients with hypertrophic cardiomyopathy presenting in infancy, Noonan syndrome is relatively common. Unlike the other forms, patients with Noonan syndrome frequently have right-sided obstruction as well as a dysplastic pulmonary valve, or indeed polyvalvar dysplasia.[5] The phenotypic features of Noonan syndrome are not always recognizable in the newborn, but any infant with hypertrophic cardiomyopathy and valvar dysplasia should be considered suspect.

The present case report emphasizes the variable course of Noonan syndrome. It is my opinion that hypertrophy may develop at any time from prenatal life to early adulthood. I recently saw a patient with Noonan syndrome who, as judged by serial cardiac ultrasound, has had mild pulmonary stenosis and mitral valvar prolapse. Now, at age 30, for the first time, an ultrasound shows mild asymmetric septal hypertrophy. The patient reported here emphasizes the need for long term follow-up in these patients.

Although the gene for familial Noonan syndrome has been linked to the long arm of chromosome 12,[6] the gene or genes for the overall syndrome have not yet been identified. The identification of the abnormality of the elastin gene in Williams syndrome helped to explain the vascular abnormalities, but sheds little light on the phenotypic findings. The

DiGeorge syndrome, "conotruncal anomaly", and velocardiofacial syndrome, all considered separate syndromes, are now known to share a deletion of chromosome 22. In searching for the gene for Noonan syndrome, it would be of interest to look at candidate genes that might explain the valvar abnormalities and the cardiac hypertrophy. On the other hand, it is possible a small chromosomal deletion might be identified. This could demonstrate that a number of syndromes, such as LEOPARD syndrome, Watson syndrome, and other cardio-facio-cutaneous syndromes now considered separate entities, all sharing the many common features, including pulmonary stenosis and ventricular hypertrophy, share a deletion similar to what has been noted in the syndromes related to deletion of chromosome 22. The diagnosis of Noonan syndrome in 1960 was based on clinical findings. Hopefully by the year 2000, we will have a genetic marker, not only to identify, but help us to understand this fascinating condition.

References

1. Danetz JS, Donofrio MT, Embrey RP. Multiple left sided cardiac lesion in one of Noonan's original patient. Cardiology in the Young 1999; 6: 610–612.
2. Noonan JA. Hypertelorism with Turner phenotype. Am J Dis of Child 1968; 16:373–380.
3. Ehlers KH Engle MA, Levin, AR, Delly, WJ. Eccentric ventricular hypertrophy in familial and sporadic instances of 46XX, XY Turner phenotype. Circulation 1972; 45:639–652.
4. Noonan JA, O'Connor W. Noonan syndrome, a clinical description emphasizing the cardiac findings. Acta Paed Jap 1996; 38:76–83.
5. Sreeram, N, Kitchiner, D, Smith, A. Spectrum of valvar abnormalities in Noonan's syndrome: A pathologic study. Cardiol Young 1994;4:62–66.
6. Jamieson, CR, van der Bugt, I, Brady AF. Mapping a gene for Noonan syndrome to the long arm of chromosome 12. Nature Genetics 1994;8:357–360.