Noonan Syndrome or New Autosomal Dominant Condition With Coarctation of the Aorta, Hypertrophic Cardiomyopathy, and Minor Anomalies

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This is a report on a father and his two children with an apparent autosomal dominant condition characterized by craniofacial anomalies, coarctation of the aorta, hypertrophic cardiomyopathy, and other structural heart abnormalities with normal psychomotor development. Some clinical features are reminiscent of Noonan syndrome. Alternatively, this family may have a previously undescribed genetic condition. The family history is suggestive of a new autosomal dominant mutation in the father.

INTRODUCTION

Isolated coarctation of the aorta (CoA) has been ascribed in most cases to multifactorial causes. Occasional reports of familial CoA suggest that autosomal dominant inheritance may be involved in a small number of cases [Vaksmann et al., 1986; Stoll et al., 1999]. CoA is also seen in association with other congenital anomalies as part of a genetic syndrome, for example, Ullrich-Turner syndrome.

The genetic basis of nonsyndromic familial hypertrophic cardiomyopathy (HC) has been elucidated in several cases [Burch and Blair, 1999]. Autosomal dominant mutations in genes coding for sarcomeric proteins are responsible for some forms of familial HC. It is uncommon to see both HC and CoA in the same individual.

In this report, I describe a potentially unique condition in a man and his two children; all three had HC and CoA. Other structural cardiac anomalies were also present. The father and daughter have an unusual appearance with features reminiscent of Noonan syndrome. In this family, there appears to be segregation of an autosomal dominant trait associated with HC, CoA, and minor anomalies. This condition may be distinct from Noonan syndrome.

CLINICAL REPORT

Patient 1

This man (Fig. 1) first came to medical attention at age 13 when it was discovered on a routine physical examination that he had a postductal CoA. He had been completely asymptomatic until then. An ECG showed left ventricular hypertrophy and right bundle branch block. Preoperative cardiac catherization detected a hypertrophied interventricular septum with pulmonic stenosis and bicuspid aortic valve in addition to the aortic coarctation. The conclusion was that the patient had a congenital abnormality of the ventricular myocardium. He was also found to have micrognathia and webbing of the neck. Three different clinical geneticists assessed him over the years. Noonan syndrome was considered in the differential diagnosis, but subsequently rejected because coarctation of the aorta is not commonly associated with this condition.

When next seen at age 22 years, the echocardiogram showed marked systolic thickening of the interventricular septum and the posterior wall of the left ventricle and concentric left ventricular hypertrophy. A small
right ventricular cavity was noted and right ventricular hypertrophy was suspected. He was lost to follow-up until the birth of his son (patient 2) in 1988.

The patient was completely asymptomatic until January 1998, when he experienced a syncopal episode during exercise. He was found to have atrial flutter refractory to oral medication. He underwent successful cardioversion, but required a temporary pacemaker because of asystole. In December 1998, cardioversion was again required because of atrial flutter. In April 1999, he was treated for congestive heart failure. A recent echocardiogram showed cardiomegaly with left-sided predominance, persistent pulmonary venous hypertension, and bicuspid aortic valve. When last seen in August 1999, he was complaining of dyspnea and paroxysmal nocturnal dyspnea. A brief clinical examination at that time confirmed the presence of apparently low-set ears, low posterior hairline, high V-shaped palate with a very small uvula, micrognathia, a short, broad neck, and wide-spaced nipples (Fig. 1). An eye examination detected an early axial posterior subcapsular cataract. He is of normal stature and intelligence. He works as a financial planner. The patient was the youngest of four children born to nonconsanguineous parents of Ukrainian and English descent. There was no history of any congenital heart disease. The paternal age at the time of this patient’s birth was age 50 years.

**Patient 2**

This boy, son of patient 1 (Fig. 2), was born at 40 weeks of gestation by caesarian section because of failure to progress and fetal bradycardia. Birth parameters were normal. An inguinal hernia and a heart murmur were noted on the discharge examination at 3 days of age. He was assessed by pediatric cardiology at age 5 days and found to have two small ventricular septal defects (VSD). He was started on a diuretic for tachypnea. Later, while in hospital for repair of an incarcerated right inguinal hernia, his condition deteriorated and a repeat echocardiogram noted a mildly hypoplastic aortic arch and CoA in addition to the VSDs. Surgical repair of the CoA occurred on day 14 without any complications. Definitive repair for bilateral inguinal hernias and right hydrocele was undertaken at age 5 weeks. At age 9 months, he became increasingly tachypneic and wheezy. Hepatomegaly was noted on examination. Cardiomegaly, a secundum atrial septal defect (ASD), mild mitral valve regurgitation, and slight enlargement of the left atrium was detected on echocardiography. He was found to be in congestive heart failure due to a restrictive cardiomyopathy. At age 10 months, he underwent catheterization; cineangiogram confirmed spongy myocardium with very impaired diastolic function. He was considered and accepted for heart transplantation. He died of early acute graft failure at age 14 months. Autopsy findings showed a restrictive cardiomyopathy with generalized myocardial hypertrophy. All the information on this patient was obtained from the hospital records and the patient was never seen or examined by the author.

**Patient 3**

This girl is the daughter of patient 1 and the sister of patient 2 (Fig. 3). She was born by vacuum-assisted vaginal delivery at 41 weeks of gestational age after an uneventful pregnancy. The Apgar scores were 8 and 9 at 1 and 5 min, respectively. Birth parameters were normal. Given the history of congenital heart defect in her brother and father, an echocardiogram was performed. A small VSD, small patent ductus arteriosus
(PDA), an aneurysm of the atrial septum, and CoA were detected. Cardiomyopathy was suspected on the basis of excessive thickening of the lower two-thirds of the interventricular septum and of the free wall of the right ventricle. At age 19 days, she underwent surgical repair for the CoA. Postoperative complications included a chylothorax and pericardial effusion. At age 7 weeks, the patient had a repeat echocardiogram because of mild cardiac failure. It confirmed the diagnosis of HC and she was started on furosemide. At 2.5 months of age, the patient was found to have a left torticollis that subsequently improved with physiotherapy. Cervical radiographs showed spina bifida occulta at C6 and C7. At age 10.5 months, the patient was noted to have plagiocephaly, a short and webbed neck, and wide-spaced nipples. Plagiocephaly, spina bifida occulta, and facial asymmetry were only present in the daughter.

DISCUSSION

Three individuals in this family have HC and CoA, apparently segregating as an autosomal dominant trait. The full spectrum of congenital heart defects includes bicuspid aortic valve, pulmonic stenosis, septal defects, patent ductus arteriosus, and aneurysm of the atrial septum. Two of the three family members have some features reminiscent of Noonan syndrome, including low-set ears, short broad neck, and wide-spaced nipples. Plagiocephaly, spina bifida occulta, and facial asymmetry were only present in the daughter.

Noonan syndrome is an autosomal dominant condition with similar clinical findings to our cases, including broad neck, wide-spaced nipples, and HC [Allanson, 1987; Sharland et al., 1992]. The clinical features in Noonan syndrome are, however, quite variable even within families and change with age [Allanson et al., 1985]. Pulmonary stenosis is the single most common structural heart defect seen in Noonan syndrome [Allanson, 1987; Sharland et al., 1992]. HC is relatively common and is seen in up to 20% of individuals with Noonan syndrome [Sharland et al., 1992]. The frequency of CoA was <10% in a study of individuals with Noonan syndrome and congenital heart defect [Diglio et al., 1998]. This suggests that CoA, like HC, is a feature of Noonan syndrome. However, it is a relatively uncommon cardiac finding, which might explain the absence of any reports in the literature of familial Noonan syndrome with CoA or Noonan syndrome with CoA and HC.

The father’s appearance is very reminiscent of Noonan syndrome. The daughter has a less obvious Noonan syndrome appearance, but does have a short, webbed neck, and low-set ears (Dr. Judith Allanson, personal communication). Abnormalities of the lymphatic system have been previously described in Noonan syndrome [Mendez and Opitz, 1985; Allanson, 1987; Witt et al., 1987; Sharland et al., 1992; Hasegawa et al., 1996]. The peripheral lymphedema at birth, the pterygium colli, and the postoperative chylothorax in the daughter are consistent with such an abnormality. It has been again noted to have an unusual appearance (Fig. 3). She had an unusual skull shape with prominence of the right parietal region. There was obvious facial asymmetry (left side being smaller than the right), micrognathia, a short and webbed neck, low-set ears, mild thoracic kyphosis, and bilateral pes planus. Her growth parameters were age-appropriate. The echocardiogram showed presence of a bicuspid aortic valve with mild aortic and mitral valve regurgitation. The left ventricle was thickened and diastolic filling of both ventricles was impaired. The atria were dilated. There was a patent foramen ovale with a left-to-right shunt. Her ECG had a pseudoinfarct pattern with nonspecific changes in the ST-T segment in the left chest leads. She had normal eye findings. Chromosomes were normal (46,XX). FISH analysis did not detect evidence of a deletion on the long arm of chromosome 22. The patient was functioning as an average to above average student in a regular school program.

**DISCUSSION**

Three individuals in this family have HC and CoA, apparently segregating as an autosomal dominant trait. The full spectrum of congenital heart defects includes bicuspid aortic valve, pulmonic stenosis, septal defects, patent ductus arteriosus, and aneurysm of the atrial septum. Two of the three family members have some features reminiscent of Noonan syndrome, including low-set ears, short broad neck, and wide-spaced nipples. Plagiocephaly, spina bifida occulta, and facial asymmetry were only present in the daughter. Noonan syndrome is an autosomal dominant condition with similar clinical findings to our cases, including broad neck, wide-spaced nipples, and HC [Allanson, 1987; Sharland et al., 1992]. The clinical features in Noonan syndrome are, however, quite variable even within families and change with age [Allanson et al., 1985]. Pulmonary stenosis is the single most common structural heart defect seen in Noonan syndrome [Allanson, 1987; Sharland et al., 1992]. HC is relatively common and is seen in up to 20% of individuals with Noonan syndrome [Sharland et al., 1992]. The frequency of CoA was <10% in a study of individuals with Noonan syndrome and congenital heart defect [Diglio et al., 1998]. This suggests that CoA, like HC, is a feature of Noonan syndrome. However, it is a relatively uncommon cardiac finding, which might explain the absence of any reports in the literature of familial Noonan syndrome with CoA or Noonan syndrome with CoA and HC.

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suggested that the phenotypic variability in Noonan syndrome may be a reflection of the evolution of the edema and lymphatic involvement [Allanson et al., 1985; Witt et al., 1987].

An alternative hypothesis is that this family does not have Noonan syndrome, but rather some other genetic condition characterized by HC, CoA, and minor anomalies. In support of this hypothesis is the obvious lack of any apparent instances of familial occurrence of Noonan syndrome with CoA in the literature. Thus far, all reported cases of Noonan syndrome with CoA have been isolated [Diglio et al., 1998]. It would appear to be very unusual, though not impossible, to see three Noonan syndrome patients, all from the same family, with both HC and CoA. Two other reported cardiac findings (bicuspid aortic valve and aneurysm of the atrial septum) in this family are not commonly associated with Noonan syndrome [allanson, 1987; Sharland et al., 1992]. Common clinical findings in Noonan syndrome such as cryptorchidism, bleeding diathesis, blue-green irides, and the classic sternal changes were also absent in this family [Allanson, 1987; Sharland et al., 1992].

The family history is suggestive of an autosomal dominant condition with a father and two offspring similarly affected. Given the advanced paternal age (age 50 years) at the time of birth of the father (patient 1) and the absence of other similarly affected individuals in the family, it is likely that a new mutation arose spontaneously in patient 1. This does not in any way help us to resolve the specific diagnosis in our family, as many cases of Noonan syndrome are sporadic and thought to arise from new autosomal dominant mutations [Patton, 1994]. However, this does provide an explanation as to the possible origin if this were a previously unreported genetic condition.

The phenotypic similarities to Noonan syndrome may simply be a reflection of a common pathogenetic mechanism, namely, an abnormality of the lymphatic system. This has been raised as a possible explanation for the clinical similarities between Noonan and Ulrich-Turner syndromes [Clark, 1984; Mendez and Opitz, 1985; Sharland et al., 1992; Hasegawa et al., 1996]. Features described in patient 3 support some involvement of the lymphatic system in this condition.

In summary, a family with HC, CoA, and clinical features reminiscent of Noonan syndrome is described. This family may represent a rare presentation of Noonan syndrome or a previously undescribed condition presenting with similar clinical features because of an abnormality of the lymphatic system. The picture may become clearer when the daughter reproduces and/or the gene(s) for Noonan syndrome are identified.

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