CASE REPORT

Rapidly Progressive Obstructive Cardiomyopathy in Infants with Noonan’s Syndrome

Report of Two Cases

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SUMMARY
Two patients with hypertrophic obstructive cardiomyopathy and Noonan’s syndrome are presented. Both patients were found at postmortem examination to have gross malformation of the mitral valve and obliteration of the left ventricle due to muscle hypertrophy. Each case demonstrated similar clinical, echocardiographic, and angiographic findings. The poor response to medical and surgical therapy are noted.

OBSTRUCTIVE CARDIOMYOPATHY is rare in children. Its association with Noonan’s syndrome has been described in sporadic and familial cases. We have recently seen two infants with Noonan’s syndrome and hypertrophic cardiomyopathy who rapidly developed progressive left ventricular outflow tract obstruction over the first year of life. Postmortem examinations also revealed abnormality of the anterior papillary muscle and mitral valve not previously reported in association with Noonan’s syndrome. These patients had similar electrocardiographic, echocardiographic, and angiographic findings.

Case Reports

Patient 1
This 23-month-old white boy was first admitted to Jackson Memorial Hospital, Miami, Florida, at one day of age. He had been the product of a normal pregnancy and delivery, and weighed 3.97 kg at birth. At another hospital he was noted to be cyanotic and heart murmur was heard. A sibling had died of heart failure at two weeks of age. On admission the patient was noted to be cyanotic only when crying. The blood pressure was palpated at 80 mm Hg in the upper and lower extremities. Ptosis of the left eyelid, low-set ears, and webbed neck were noted. The shoulders were narrow, the nipples appeared widely-spaced, and there was the "shield-like" configuration of the anterior chest. A grade 3/6 long systolic ejection murmur was heard at the upper and mid-left sternal border. The pulses were strong throughout, and the liver was palpated 2 cm below the right costal margin.

The electrocardiogram revealed left axis deviation, left atrial and left ventricular hypertrophy; the chest X-ray revealed cardiomegaly and normal pulmonary vascularity. Lymphocyte karyotype revealed the normal male pattern. Cardiac catheterization was done at four days of age (table 1). Cineangiograms suggested moderate infundibular pulmonic stenosis and there was increased left ventricular free wall thickness. There was no systolic pressure gradient between the left ventricle and the systemic arterial pressure. The patient’s condition stabilized over the next several days and his cyanosis resolved.

At six months of age the infant began having intermittent episodes of limpsness associated with crying, and tachypnea when he attempted to crawl. Physical examination at this time revealed a greatly accentuated first heart sound, an atrial gallop, a grade 3/6 systolic ejection murmur along the left sternal border, and a grade 2/6 mid-diastolic rumble at the apex. The electrocardiogram and chest X-ray were unchanged. Repeat cardiac catheterization at 15 months of age demonstrated a 46 mm Hg gradient across the right ventricular outflow area and 90 mm Hg gradient on the left (table 1). Angiography revealed septal encroachment into the right and left ventricular outflow areas. Because of the diagnosis of obstructive cardiomyopathy the patient was given propranolol at 1 mg/kg/day. He improved symptomatically. Echocardiograms done at ages 14 and 22 months showed increased mobility of the septum and left ventricular hypertrophy with outflow tract obstruction (fig.
Table 1

Hemodynamic Data

<table>
<thead>
<tr>
<th>Catheter position</th>
<th>Patient 1</th>
<th>Age 4 days</th>
<th>Pressure (mm Hg)</th>
<th>Age 13 months</th>
<th>Pressure (mm Hg)</th>
<th>Patient 2</th>
<th>Age 5 months</th>
<th>Pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC</td>
<td>m = 6</td>
<td>a = 6, m = 6</td>
<td>m = 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RA</td>
<td>a = 12, m = 6</td>
<td>m = 4.5</td>
<td>m = 5, a = 7</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RV in</td>
<td>42/8</td>
<td>74/10</td>
<td>110/7</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>RV out</td>
<td>28/10</td>
<td>60/5</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>MPA</td>
<td>28/10</td>
<td>20/12</td>
<td>16</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RPC</td>
<td>m = 12</td>
<td>V = 22</td>
<td>m = 14</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>LA</td>
<td>m = 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>LV in</td>
<td>100/12</td>
<td>180/20</td>
<td>160/10</td>
<td></td>
<td></td>
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<tr>
<td>LV out</td>
<td>90/10</td>
<td>75/12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aorta</td>
<td>80/40, m = 64</td>
<td>75/50, m = 60</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>RFA</td>
<td>95/62, m = 80</td>
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</tbody>
</table>

Abbreviations: SVC = superior vena cava; LV in = left ventricle inflow; RV in = right ventricle inflow; LV out = left ventricle outflow; RV out = right ventricle outflow; RFA = right femoral artery; RA = right atrium; RPC = right pulmonary artery; LA = left atrium; MPA = main pulmonary artery; m = mean pressure.

1), although asymmetric septal hypertrophy was not evident. Serum propranolol levels were 100 and 75 ng/ml at two and four hours respectively after an oral dose and the heart rate ranged between 80 and 100 beats per minute.

At 22 months of age the infant was readmitted due to recurrence of his syncopal episodes and sinus bradycardia which persisted after discontinuance of propranolol. Left ventricular septal myomectomy was performed using cardiopulmonary bypass and coronary perfusion. However, low cardiac output occurred after the procedure and the patient expired at surgery.

Postmortem examination revealed the left ventricle to be concentrically hypertrophied with an extremely small cavity. The thickened anterior mitral leaflet inserted directly into a flattened, markedly fibrotic papillary muscle and extended into the left ventricular outflow tract. Several short chordae connected the posterior mitral leaflet to a flattened fibrotic posterior papillary muscle. Viewed from above, the mitral valve ballooned into the left atrium. Microscopic examination defined left atrial and left ventricular subendocardial hemorrhage, focal necrosis, and endocardial fibrosis. Severe myocardial hypertrophy involved the septum and left ventricle. The mitral and tricuspid valves were thickened by a loose myxomatous stroma.

Patient 2

A nine-month-old boy was admitted because of cough, tachypnea, and fever. He had been born six weeks prematurely and weighed 2.73 kg at birth. At twenty-four hours of age he was noted to have an ejection murmur at the mid left sternal border. At two months of age he had developed tachypnea and poor feeding and was digitalized at another institution. Chromosome study then was unremarkable. Cardiac catheterization at five months of age revealed a gradient of 90 mm Hg across the right ventricular outflow tract and 85 mm Hg across the left ventricular outflow tract (table 1). The left ventricular angiogram and echocardiogram were identical to those of patient 1.

Figure 1

Echocardiogram obtained by sweeping the sound beam along the long axis of left ventricle demonstrates the aorta (Ao) and narrowing of the distal left ventricular outflow tract (LVOT) (4 mm). The interventricular septum (IVS) is extremely dynamic and appears to contribute to the narrowing of the left ventricular outflow. There is diastolic apposition of the anterior mitral valve leaflet (AMV) with the interventricular septum. The lower one-third of the IVS and posterior LV wall are not shown in this illustration. LA = left atrium; RV = right ventricle.
Tachypnea recurred at eight months and improved on a regimen of diuretics and propranolol.

Physical examination revealed an acyanotic tachypneic infant with ptosis of the right eyelid, narrow shoulders, and a webbed neck. Dullness to percussion and rales were noted over the left chest. The point of maximal cardiac impulse was displaced to the left. The first heart sound was increased, the second exhibited wide splitting. There was a harsh grade 3/6 systolic ejection murmur and a rough mid-diastolic murmur in the second to the fourth left intercostal spaces. The liver was 4 cm below the right costal margin and the spleen was palpable. Pulses were equal in upper and lower extremities and non-pitting edema of the feet was present. There was cryptorchidism on the right. Neurologically the baby had fair head control, sat with support, and had normal reflexes.

The electrocardiogram revealed left axis deviation, right atrial enlargement, and biventricular hypertrophy. Chest X-ray demonstrated cardiomegaly, increased pulmonary venous pattern, and a small left pleural effusion. The infant received antibiotic therapy, oxygen and diuretics. However he deteriorated rapidly and died within 12 hours of admission.

Postmortem examination demonstrated heart failure and hemorrhagic pneumonitis. There was dilatation of right and left atrium, endocardial fibroelastosis of the left atrium and left ventricular hypertrophy which resulted in a very constricted left ventricular chamber. The mitral valve was thickened, prolapsed into the left atrium but did not appear to obstruct the orifice. In addition, abnormal chordae inserted directly into the septum producing obstruction below the aortic valve (fig. 2). An area of infarction was found at the left ventricular apex. Microscopic findings included myocardial hypertrophy, fibrosis, and necrosis. Some muscle bundles were oriented in a convergent pattern. Interruption of the internal elastic lamina of some arteries was associated with a basophilic infiltration of media and intima. The mitral valve was thickened due to deposition of a myxomatous material which proved to be acid mucopolysaccharide.

Discussion

Since the original description by Noonan and Ehmke in 1963, observations have found a wide variety of cardiac lesions in patients who have the physical features of Turner’s syndrome and a normal complement of chromosomes. Hypertrophic cardiomyopathy has been reported and symptoms of left ventricular outflow tract obstruction have usually

Figure 2

Upper panel: The mitral valve as viewed from the left atrium appears thickened and the leaflets appear asymmetrical. There is marked prolapse of the anterior leaflet. In the lower panel, the mitral valve is retracted upward and a probe has been passed into the ascending aorta. The left ventricular outflow area is obstructed by septal thickening and abnormal septal attachments of the mitral valve. At the left ventricular apex, an area of infarction can be identified.
appeared in later childhood or adulthood, although
Ehlers described a fatal case five months of age.3

The two cases presented were similar in somatic
habitus, rapid progression of symptomatology, and
similar findings on clinical examination, catheteriza-
tion, angiography, echocardiography and postmortem
examination. The first patient presented offered
the unique opportunity to observe that nonobstrusive
hypertrophic cardiomyopathy was present at birth
and became obstructive over the first year of life. The
theory of the development of left ventricular outflow
tract obstruction in children with hypertrophic car-
diomyopathy had been offered by Bloomfield and
Liebman,1 and this case appears to support this view.

Both infants presented auscultatory findings com-
patible with mitral stenosis, probably on the basis of
decreased ventricular compliance and similar to find-
ings in adults with left ventricular inflow obstruction4
where these findings are viewed as an ominous sign.

The particular abnormalities of the mitral valve and
the fibrous replacement of the anterior papillary mus-
cle seen in these patients has not been previously
reported to our knowledge in infants with Noonan’s
syndrome, although Roberts6 has described fibrosis of
the anterior papillary muscle in postmortem ex-
aminations of adult cases of obstructive cardiomyopathy.
Cooley and associates10 have also en-
countered fibrosis of the anterior papillary muscle in
patients undergoing mitral valve replacement for
obstructive cardiomyopathy, although the appearance
of the subvalvar apparatus in their example did not
resemble the changes found in our patients. Similar
gross deformity of the mitral valve leaflets was found
in both cases, and the additional subaortic obstruction
due to abnormal chordae tendineae which attached
directly to the septum was found in the second
patient.

This type of abnormality was described by Bjork et
al. in 196111 in adults with subaortic stenosis. How-
ever, they proposed the mitral valve anomaly to
be responsible for the left ventricular hypertrophy
seen in their cases, while we suggest that the mitral
valve anomalies are part of a more generalized dis-
order in these infants. According to Van Mierop12 the
ventricular cavity is formed by progressive centrifugal
diverticulation and trabecular formation in the
developing myocardium. Some of these trabecular
coalesce and form the papillary muscles and other
structures. Similarly, the chordae form by gradual
thinning of the fibrous bands that are continuous with
the valve cusps. The combined abnormalities noted in
our patients: diffuse myocardial hypertrophy, small
ventricular cavity, abnormally inserting mitral valve,
and fibrous replacement of papillary muscles with ab-
normal or fused chordae may be the result of arrested
embryological development of left ventricle. The
rapid progression of symptoms in infants would then
follow in this more severe form of hypertrophic car-
diomyopathy. Any additional obstruction due to an
abnormality of the mitral valve may act to hasten the
unfavorable progress of the disease in infants.

The disappointing results of long-term beta
adrenergic blockade and surgery for the disease in in-
fants may be due to the diffuse underdevelopment of
the left ventricular chamber. Propranolol has proven
useful in adults6,7 and one report of successful use in an
infant was found.14 In our patients there was clinical
improvement with propranolol; however, this proved
to be temporary. Surgery to relieve the left ventricular
obstruction was not successful in our first patient, and
others have reported a poor surgical result in an infant
whose right ventricle was predominantly involved.15

The recognition of hypertrophic cardiomyopathy in
association with Noonan’s syndrome is important
because it may be familial. Screening of other
relatives and genetic counseling should be offered
when the diagnosis is made. Since the clinical and
angiographic features14 have appeared quite similar,
early recognition is feasible. There is some danger of
overlooking the left-sided obstruction at cardiac
catherization, since significant infundibular
pulmonic stenosis may be present, and the left heart
structures and hemodynamics must be specifically
defined.

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