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52. NOONAN SYNDROME: A CLINICAL DESCRIPTION EMPHASIZING CARDIAC FINDINGS 199

5) 38, 76-83

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With best wishes
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Feature Article

Noonan syndrome: A clinical description emphasizing the cardiac findings

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Noonan syndrome (NS) is one of the most common non-chromosomal syndromes seen in children with congenital heart disease.[1] Affected individuals have characteristic facial features, usually short stature, a chest deformity and a cardiac abnormality. Although many cases are sporadic, autosomal dominant inheritance has been documented in a number of families. The diagnosis, at present, rests solely on clinical criteria. As the majority have some form of congenital heart disease, pediatric cardiologists should be aware of the variable clinical picture and the characteristic cardiac findings.

History

The first report of what is now called NS was a 20 year old male reported by Kobylinski[2] in 1883. Ullrich in 1930[3] described a number of patients with a webbed neck and short stature, some of these probably had NS. Turner in 1938[4] noted sexual infantilism in a number of females who also had a webbed neck and short stature. Later the patients described by Turner were recognized to have a sex chromosome abnormality. Flavell in 1943[5] reported a male with a phenotype similar to that reported by Turner and used the term 'male Turner' syndrome (TS). In 1963 JAN reported nine patients, six males and three females with short stature and characteristic facies which included hypertelorism, ptosis and low-set ears. Several males had undescended testes and all had valvular pulmonary stenosis and a normal karyotype. Dr John Opitz suggested the term NS be used to describe such patients. He felt that the observation that the syndrome occurs in both sexes, is associated with normal chromosomes and could be inherited, justified the eponym.[6]

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Received 30 June 1995; revision 1995; accepted 1995.

Genetics

Although there is a superficial resemblance between NS and TS, no abnormality of the chromosome has ever been found in patients with NS. Some patients with neurofibromatosis have been reported to have a Noonan phenotype and valvular pulmonary stenosis (PS) suggesting that NS might be linked to chromosome 17 as is found in neurofibromatosis. Genetic studies, however, have shown no linkage.[7] Recently investigators from London[8] studied a large, three generation family with NS and 20 smaller two generation families and mapped a gene for NS to the distal part of chromosome 12q (12q 22-qter). Future studies will hopefully identify the gene and allow for a more significant diagnosis than is currently available.

Family studies have shown great variability in expression so that mildly affected individuals who carry the gene may be difficult to identify. Allanson has shown that the phenotype in NS changes between birth and adulthood.[9] A parent may not resemble the affected child, but review of past photographs may show a surprising resemblance of the parent to the affected child when compared at a similar age.

Family history should include a careful examination of both parents and siblings as well as review of past family pictures in order to evaluate whether the affected child is sporadic or a familial case with a mildly affected parent. There is a 50% recurrence risk for subsequent offspring if a parent is affected, while in a sporadic case only the offspring of the affected individual are at risk. Prenatal diagnosis of NS is not possible, but there are several reports describing *in utero* fetal edema and cystic hygroma in patients who subsequently could be diagnosed with NS.[10,11]

Epidemiology

The exact incidence of NS is unknown, but a frequency of 1 per 1000 live births is most frequently quoted.[12] There appears to be no racial predilection and cases have been

reported world-wide. There are no significant sex differences. The variability of the clinical picture makes it difficult to distinguish mild cases from a normal variant. Several other syndromes focusing on heart and skin have been called the cardio-facio-cutaneous syndromes[13] and include Watson syndrome[14] and LEOPARD syndrome.[15] Such patients overlap with NS and until a specific diagnostic test is available, we tend to label some of these patients as NS. The NS phenotype is not specific and there is considerable overlap with other conditions including a few chromosomal abnormalities as well as the fetal alcohol syndrome. Over 1% of children[16] with congenital heart disease have NS, making it one of the most common non-chromosomal syndromes associated with congenital heart disease. Over 5% of children requiring treatment for pulmonary stenosis have NS. Among infants with hypertrophic cardiomyopathy (HCM) NS is a common association, but the incidence is not yet determined.

Diagnosis

To diagnose NS a careful history and physical examination is essential.

History

The majority of patients with NS have an unremarkable prenatal history, but about one-third of pregnancies are complicated by polyhydramnios.[17] Fetal ultrasound may reveal cystic hygroma or fetal edema in a few. Birthweight is usually normal, but excessive weight loss shortly after birth suggests some degree of fetal edema may be quite common.

Over half of the children with NS have moderate or severe feeding problems in early infancy. We have seen a number of young infants who have been hospitalized with lethargy, vomiting and poor feeding with suspected, but unconfirmed diagnosis of sepsis. Usually the feeding problems resolve by 4 to 6 months of age, but some children are subjected to many diagnostic procedures for failure to thrive which are usually non-revealing. NS should be suspected in a dysmorphic appearing infant with hypotonia, poor feeding and failure to thrive.

In general, mild motor delay is common. Sharland[17] reported a mean age for sitting at 10 months, walking 21 months and talking 31 months. Often some learning disability will be reported in school age children. Mental retardation, usually mild, is relatively common, but by no means constant. Graduation from college and achievement of a PhD degree are reported. Conduction hearing loss is also frequent.

Short stature is present in over 80% and is often a reason for referral. This growth failure is postnatal in origin because the length at birth is usually normal. In general there is a 2 year delay between bone age and chronological age. As a result, some catch up growth occurs up to the early twenties. The mean height for males is about two standard deviations below average with most males achieving a height of about 5 feet, 5 inches. In general the mean adult height for females is one standard deviation above those with TS and most achieve a height of about 5 feet. Delayed puberty is common, but normal sexual development is usual. Females appear to have normal fertility. Among males with undescended testes, there is often a decrease in fertility.

As mentioned earlier, a careful family history may be very helpful in diagnosis, but sporadic cases are frequent and mildly affected parents may be difficult to recognize.

Physical examination

The characteristic facies of NS change with age. The newborn is difficult to diagnose. The forehead is often sloping and broad and the ears may be thick and rotated posteriorly. Apparent ocular hypertelorism, anti-mongoloid palpebral fissures and a deep philtrum may also be present (Fig. 1). An occasional infant presents with edema and excessive nuchal skin and the female may be confused with TS. Unless the newborn is severely affected, NS is usually not diagnosed at birth.

In infancy through to the age of 2 years, the head often appears relatively large. The malar eminences are flat, the eyes become more prominent and round. The nasal bridge is flat and the neck short (Fig. 2). By 12 to 24 months, the body becomes more stocky and the chest deformity more prominent. In early childhood the facial appearance appears coarser, but the face assumes a more triangular appearance, mainly due to lengthening of the chin. The eyes are less prominent and ptosis more apparent. As the neck becomes longer webbing may become more obvious. In teenage years and young adulthood the facial features are sharper with the nasal bridge thin and high. The older adult has prominent nasolabial folds, high anterior hairline and transparent wrinkled skin (Fig. 3).

In our experience careful attention to the eyes is helpful in diagnosis. In a study by Lee[18] hypertelorism was present in 74%, ptosis in 48%, epicanthal folds in 48% and an anti-mongoloid slant in 38%. In addition strabismus is present in 48%. An occasional patient will have a coloboma. In addition very light blue or green irides are also frequent.

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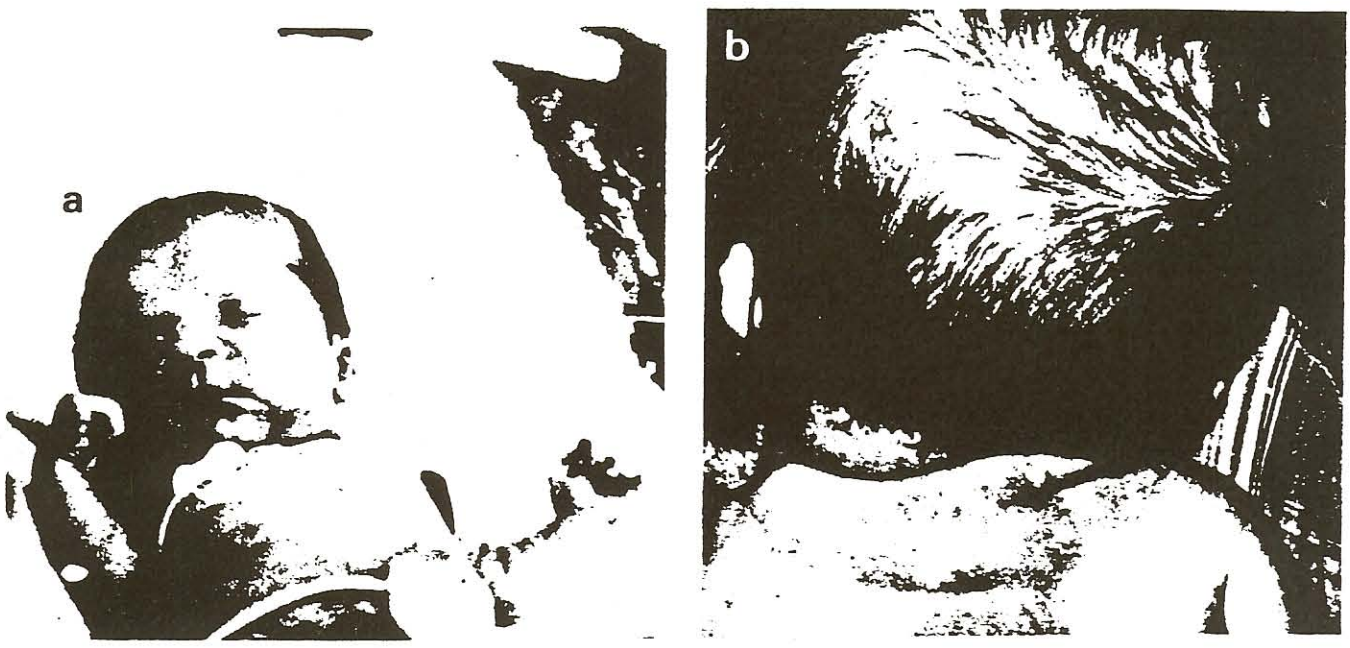

Fig. 1 (A) Newborn with Noonan syndrome. (B) Redundant nuchal skin (Reprinted with permission from *Clinical Pediatrics* 1994; 548–55).

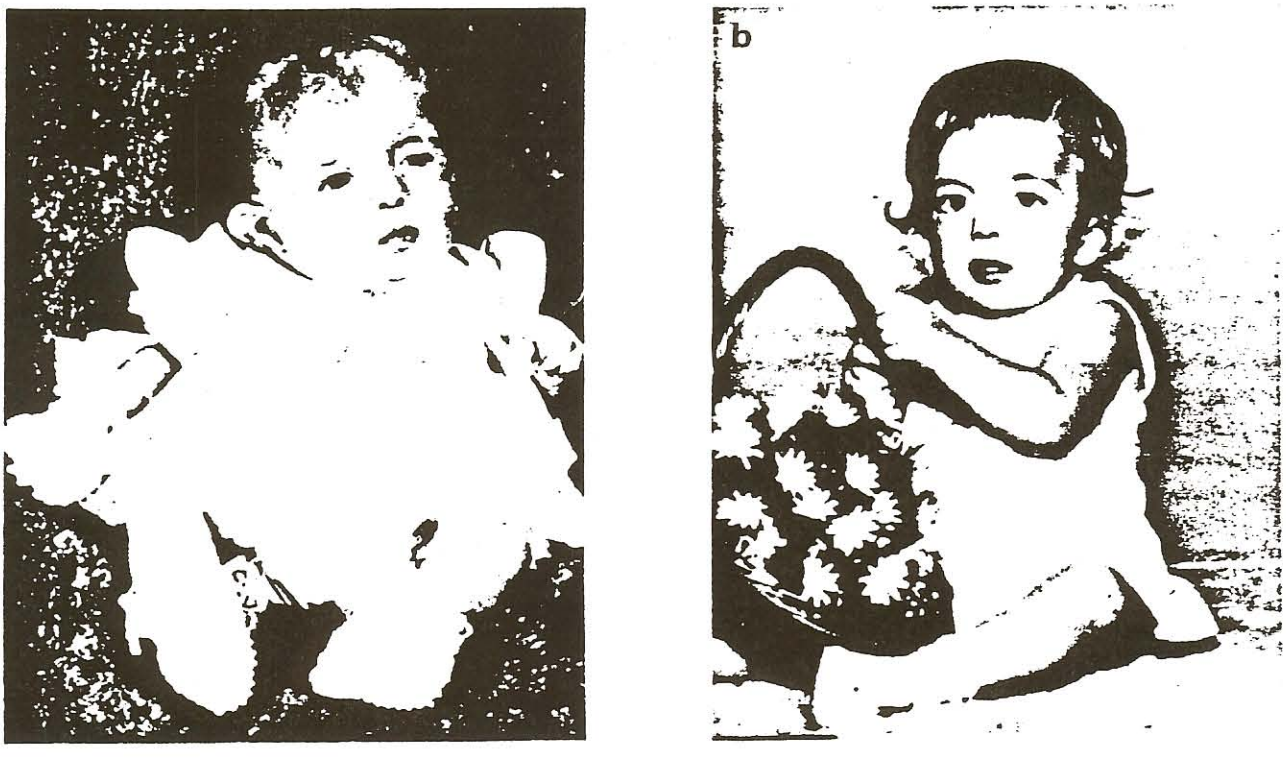

Fig. 2 (A) Patient with Noonan syndrome shown here at 2.5 months. (B) Same patient at 10 months of age (Reprinted with permission from *Clinical Pediatrics* 1994; 548–55).

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Fig. 3 Mother with Noonan syndrome and affected infant (Reprinted with permission from *Clinical Pediatrics* 1994; 548–55).

Over 90% of patients with NS have a chest deformity, the most characteristic being pectus carinatum (Fig. 4). Pectus excavatum is also frequent. The chest is often shield-like with widely spaced nipples. Scoliosis occurs in 10–15% and talipes equino-varus in 10–15%. Hyper-extensible joints and muscle hypotonia is frequent. An increased carrying angle at the elbow and a short, curved fifth finger are also seen.

Careful attention to the skin and hair may also provide clues. Curly hair is frequent, but in some both hair and eyebrows are sparse. Nevi and freckles are common and may be similar to Watson or LEOPARD syndrome. Keratosis pilaris[19] is often noted. Prominent fetal pads on the fingers and toes are seen in some patients. In my experience extensive keloids may occur following a surgical procedure. Puffy hands and feet are relatively frequent in the newborn. In some, lymphedema may develop later in childhood and persist. Lymphangigraphy has demonstrated hypoplasia or absence of superficial

Fig. 4 Young male with Noonan syndrome showing webbed neck, chest deformity and a few nevi.

lymphatic channels.[20] Lymphatic abnormalities occur in less than 20%. Besides extremity edema, both intestinal[21] and pulmonary lymphangiectasia[23] are occasionally seen and may lead to protein-losing enteropathy and/or chylothorax.

Abdominal examination will reveal hepatosplenomegaly in about 25%. Thus far, no explanation for this finding has been identified. Undescended testes, either one or both, is present in about half of affected males.

Cardiac problems

The majority of patients with NS have some cardiac abnormality. A dysplastic, often stenotic pulmonary valve is the most characteristic lesion, but virtually every type of cardiac defect has been described. Of particular interest is the HCM, both obstructive and non-obstructive, which is present in 20–30% of such patients.[23] Patients with NS should have a complete cardiac evaluation including physical examination, electrocardiogram (ECG) and cardiac ultrasound.

The ECG is of particular interest. Left axis deviation and a dominant S wave over the precordial leads is very frequent and may be present in patients with no other evidence of cardiac disease. The cause of this ECG finding is unknown. Although the pulmonary valve in NS is frequently dysplastic there is great variability in the degree of dysplasia and obstruction. In many the valve is only dysplastic and no significant obstruction or regurgitation ever results. Typical non-syndromic PS, if mild or moderate, generally does not progress after the age of 2 years; however, some patients with NS show rapid progression of valvular obstruction. One of our patients had a right ventricular pressure of 65/10 at the age of 2 years which progresed to 160/10 by the age of 6 years. Unfortunately simple valvotomy might not be adequate to relieve the obstruction and often complete excision of the valve, resection of anomalous muscle bundles and sometimes an outflow tract patch will be required. Although balloon valvuloplasty may reduce the gradient, it is seldom successful in abolishing the RV outflow obstruction in a patient with a dysplastic pulmonary valve. The majority of children with NS who have significant PS will require surgical treatment. Associated atrial septal defects and pulmonary artery branch stenoses may coexist with valvar PS.

Atrial septal defect, ventricular septal defect and tetralogy of Fallot are among the more frequent defects reported but valvar aortic stenosis, subaortic stenosis, coarctation of the aorta, patient ductus arteriosus, total anomalous pulmonary venous return, ostium primum and Ebstein's malformation have all been reported. We have seen two patients with a discrete subaortic membrane who, in addition, had a tunnel type subaortic stenosis as well as HCM. Both had relief of obstruction with resection of the membrane and a myectomy. In both patients the subaortic membrane recurred and progressive obstruction developed within 2 years of the surgical procedure. Re-operation has been carried out in one patient and is planned in the other. Echocardiogram has demonstrated mitral valve prolapse, both isolated or in association with additional cardiac lesions, in a significant number of patients. In one such patient there was considerable mitral regurgitation at cardiac catheterization as well as mild, non-obstructive HCM at age 3.5 years. Without any specific therapy, mitral regurgitation had disappeared on a follow-up echocardiogram at age 12 years and only mitral valve prolapse was found.

Some degree of HCM occurs in 20 to 30% of NS patients.[23] The course and prognosis of HCM is variable and not well understood. We are particularly interested in HCM presenting in infancy which we feel may be associated with NS more frequently than is appreciated. Transient HCM has been well documented in some infants born to diabetic mothers and is probably the most commonly diagnosed cause of asymmetric septal hypertrophy in the newborn. This condition is transient and usually resolves without therapy.[24] Metabolic diseases, such as Pompe's disease, are another cause of septal hypertrophy in the young infant. A number of other metabolic and mitochondrial diseases have also been shown to have HCM and must be considered in any infant who presents with HCM. Non-syndromic famial HCM, usually transmitted as an autosomal dominantly inherited disorder, must, of course, also be considered. Maron,[25] in his report of HCM presenting in infancy, noted that right ventricle hypertrophy and often right ventricle outflow obstruction is frequent in this group of patients. Of the 20 patients he reported who presented with signs of HCM in infancy (aged 1 day to 10 months) nine died between 1 and 11 months of age. All had signs of congestive cardiac failure. Two of these died suddenly and unexpectedly while two others died following resection of right ventricle muscle to relieve obstruction. Seven patients had no symptoms related to HCM and remained free of cardiac symptoms. Four were symptomatic in infancy, but two who had congestive cardiac failure improved and were asymptomatic 9 and 11 years later. Two others with a history of syncope underwent successful surgical relief of obstruction at 16 and 21 months and were doing well at the age of 5 and 12 years. It is of interest that only six of these patients had evidence of a familial transmission of HCM. We suspect that some of these infants may have had NS in association with their HCM, but no description of the infants was provided.

HCM presenting in infancy has been reported in relatively few patients diagnosed with a diagnosis of NS. Ehlers[26] reported in 1972 of an infant dying of congestive cardiac failure at the age of 5 months. Hirsch[27] reported in 1975 on two infants who had evidence of severe pulmonary stenosis as well as HCM diagnosed shortly after birth. One infant showed some transient improvement with propranolol, but

because of syncope underwent surgery at 22 months and died during that procedure. The second patient developed congestive cardiac failure at 2 months and was shown to have gradients across both the right and left ventricle outflow tracts. Although there was transient improvement with propranolol, at 9 months he presented with congestive heart failure and died. Both of these patients, had, in addition to bi-ventricular HCM and severe valvular PS, abnormal mitral and tricuspid valves. In 1994 Sreeram[28] reported on four infants presenting in the first year of life. One died at 7 months awaiting surgery for severe PS. Another died at 14 months during a repeat balloon valvuloplasty for a severely dysplastic obstructed pulmonary valve. Two others died during surgery at 14 months and 5.5 years in an attempt to relieve the outflow obstruction. At post mortem examination all four valves were thickened and dysplastic in three patients, while one had a normal aortic valve. Bilateral HCM was present in all four. Our experience is similar to Sreeram. Polyvalvular dysplasia has been frequent in patients studied at post mortem. NS is often difficult to diagnose in the newborn and it may not be considered when HCM is recognized. In infants with HCM the presence of associated right ventricular outflow tract obstruction and a dysplastic pulmonary valve, tricuspid valve and occasionally mitral valve and aortic valve should suggest NS, as these are not expected findings in the other known causes of HCM presenting in infancy.

We have also seen very rapid progression of HCM in patients with NS. One recent patient showed evidence of mild asymmetric septal hypertrophy at 2 days of age. A transient condition was suspected and NS was not considered. At 9 days of age a repeat ECG showed a left ventricular outflow tract gradient of 51 mmHg and a thick pulmonary valve. We saw her first at the age of 6 weeks and diagnosed severe NS. An ECG then showed a left ventricular outflow tract gradient of 78 mmHg and a right ventricular outflow tract gradient of 36 mmHg and the septal thickness had increased from 0.5 to 0.7 cm. By 3.5 months the left ventricular gradient had increased to 100 mmHg, the right ventricle to 105 mmHg and the septum measured 1.0 cm. Treatment with a beta-blocker brought no improvement. She was dyspneic, had spells of apparent pain, was oxygen dependent and required tube feedings. By 5 months the gradient had increased to 162 mmHg across the left ventricular outflow tract and a 117 mmHg across the right ventricle outflow. The septum measured 1.2 cm. A chest X-ray showed gross cardiac enlargement and pulmonary congestion. Surgical relief was attempted. Anomalous right muscle bundles were resected. The pulmonary valve was dysplastic, but not obstructive. A septal myectomy was carried out through the aortic valve. A post-operative ECG revealed the left ventricular outflow gradient reduced to 41 mmHg and the right ventricular outflow tract gradient to 38 mmHg. Unfortunately the infant developed renal failure and died 10 days following surgery. Typical muscle disarray was present in the surgical specimen.[29]

However, most NS patients with both obstructive or non-obstructive HCM remain asymptomatic and stable for many years. One patient followed from infancy was quite stable, but developed increasing symptoms of shortness of breath at 12 years of age. The right ventricular outflow tract gradient increased from 20 mmHg at 7.5 years to 58 mmHg at 12 years of age. The left ventricle outflow tract gradient increased from 50 to 100 mmHg. All valves appeared dysplastic with striking tricuspid valve prolapses on angiography. She underwent surgical treatment which included resection of the anomalous right ventricle muscle bundles and a left ventricular myectomy. A follow-up ECG at the age of 9 years continues to show bi-ventricular hypertrophy with systolic anterior motion of the mitral valve, but no gradient is present across the right ventricular outflow tract and only a 22 mmHg gradient across the left ventricular outflow tract. She has continued on a calcium channel blocker and remains stable. One of our patients undergoing post mortem examination had severe right ventricular hypertension at 12 months with a right ventricular pressure of 142/7 mmHg and a left ventricular pressure of 80/8 mmHg. The left ventricle appeared normal by angiography. At operation the dysplastic pulmonary valve and anomalous muscle bundles were resected and an outflow tract patch was placed. He did well but on follow-up ECG at the age of 7 years mild HCM without a significant gradient was noted. By 9 years he had developed a peak gradient of 30 to 40 mmHg. At the age of 10 he died suddenly on the playground. At post mortem he had an unsuspected skull fracture with a small subdural. Impressive HCM was found (Fig. 5). Similar to non-syndromic HCM the majority of patients show an asymmetric pattern of hypertrophy. One of our patients, however, had marked non-obstructive concentric hypertrophy. Microscopic examination from either surgical specimens or post mortem examination reveal findings very similar to that seen in non-syndromic HCM. There is marked muscle disarray, thick wall intramural coronary arteries, but, unlike the non-syndromic HCM, polyvalvular dysplastic valves are frequently noted (Fig. 6).

The natural history of HCM in NS is not yet well defined. From our experience it is apparent that there is marked variability. The HCM may become symptomatic and rapidly progressive in infancy. It may remain stable for many years and may develop, or at least become recognized, late in childhood. Familial non-syndromic

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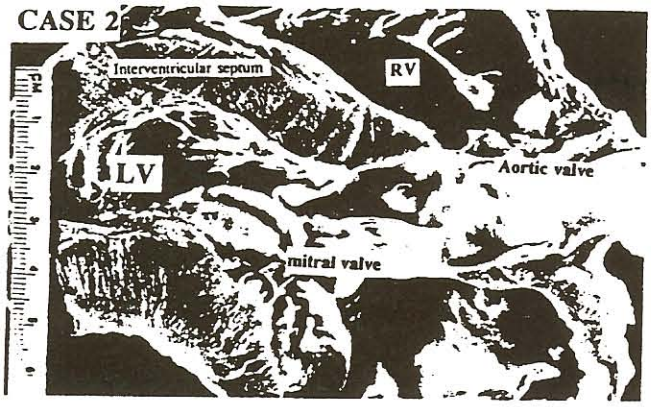
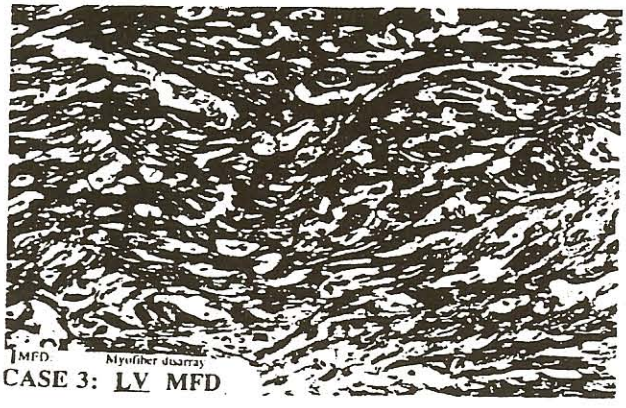


Fig. 5 Marked hypertrophic cardiomyopathy in a boy dying suddenly at age 10 years.



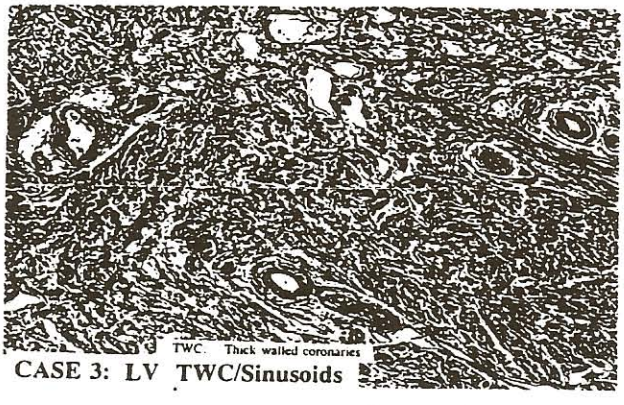


Fig. 6 (A) Pathological specimen showing marked muscle disarray. (B) Same patient showing thick walled intramural coronary arteries. (Reprinted with permission from *Clinical Pediatrics* 1994; 548–55).

HCM is characterized by a significant incidence of sudden death even in childhood.[30] Most deaths have occurred after the age of 8 years. Symptomatic HCM in NS is associated with a significant mortality, even in infancy. The risk of sudden death in NS patients who are asymptomatic is not yet known. We recently, however, saw a 20 month old, asymptomatic child with NS, who by ECG had HCM and a 51 mmHg peak gradient across the left ventricular outflow tract. He died suddenly in his sleep a few months later. Another patient reported to me recently was noted to have a systolic murmur at birth and moderate symmetrical HCM. She was asymptomatic but developed progressively severe PS and at 14 months of age she underwent an operation to correct the right ventricular outflow tract obstruction. A pulmonary valvectomy, right ventricular outflow patch and closure of a small atrial septal defect was carried out with no complications and she did well following surgery. Approximately 1 month after surgery, she became apneic and lost consciousness while being held by her father. She was rushed to the hospital and was unable to be resuscitated. This child, therefore, had sudden death probably related to her underlying asymptomatic HCM. It will be important to follow a large number of children with NS and HCM before the risk of sudden death can be assessed in children with NS. Treatment for HCM in NS is similar to that in non-syndromic HCM. A few children with NS and severe cardiomyopathy have under gone cardiac transplantation. Surgical relief of the symptomatic patient with obstructive cardiomyopathy has been quite successful in the older child, but the risk is very high in infancy. We have had no experience in the use of dual chamber pacing for patients with NS and HCM, but would suspect it would be similar to that seen in the non-syndromic form.

Other findngs

For patients undergoing a surgical procedure, it is important to be aware that bleeding problems may occur in patients with NS. Witt *et al.*[31] reported a variety of bleeding problems including factor 11 deficiency, von Willebrand disease, thrombocytopenia and platelet function defects. Others have found low levels of a wide variety of clotting factors with no specific patterns. In our experience bleeding is not usually a problem in patients undergoing open heart surgery because the frequent use of fresh, frozen plasma probably corrects the deficiencies. However, a recent patient undergoing scoliosis surgery did bleed excessively although routine studies showed only a mild increase in partial thromboplastin levels. If there is any suspicion of a bleeding problem a prothrombin time,

partial thromboplastin bleeding time and platelet count should be obtained. Aspirin and aspirin containing products should be avoided.

An occasional patient with NS will have abnormal pulmonary lymphatics resulting in prolonged pleural effusions post-operatively. Renal abnormalities occur in about 10% of NS patients and are usually of little clinical significance. Renal ultrasound may be helpful in recognizing such anomalies.

Conclusion

Children with NS are special. They usually have a pleasant personality, but may be a little immature because of their small size. The majority grow up to function normally as adults, but there is a 50% chance that their offspring may be affected. We still have a lot to learn about the natural history of NS. When the basic genetic factors are identified it will be possible to have a specific test to diagnose NS with certainty. In the meantime reliance on clinical findings is required.

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