Clinical Characterization of Left Ventricular Noncompaction in Children
A Relatively Common Form of Cardiomyopathy

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Background—Left ventricular noncompaction (LVNC) is a reportedly uncommon genetic disorder of endocardial morphogenesis with a reportedly high mortality rate. The purpose of this study was to identify the clinical characteristics of children with LVNC.

Methods and Results—We retrospectively reviewed 36 children with LVNC evaluated at Texas Children’s Hospital (TCH) from January 1997 to December 2002. Five children had associated cardiac lesions. There were 16 girls and 20 boys. The median age at presentation was 90 days (range, 1 day to 17 years). The median duration of follow-up was 3.2 years (range, 0.5 to 12 years). Twenty-seven patients (75%) had ECG abnormalities, most commonly biventricular hypertrophy (10 patients, 28%). Both ventricles were involved in 8 patients (22%) and only the left ventricle in 28 patients (78%). Left ventricular systolic function was depressed in 30 patients (83%), with a median ejection fraction of 30% (range, 15% to 66%) at diagnosis. Nine patients presenting in the first year of life with depressed left ventricular contractility had a transient recovery of function; however, ejection fraction deteriorated later in life, at a median interval of 6.3 years (range, 3 to 12 years). Two patients had an “undulating” phenotype from dilated to hypertrophic cardiomyopathy. Two patients (6%) were identified with an underlying G4.5 gene mutation. Five patients (14%) died during the study.

Conclusions—LVNC does not have an invariably fatal course when diagnosed in the neonatal period. A significant number of patients have transient recovery of function followed by later deterioration, which may account for many patients presenting as adults, some manifesting an “undulating” phenotype. (Circulation. 2003;108:2672-2678.)

Key Words: ventricles ■ myocardium ■ cardiomyopathy ■ heart failure

Oncompaction of the ventricular myocardium (NCVM), also known as left ventricular noncompaction (LVNC), represents an arrest in the normal process of myocardial compaction, resulting in persistence of multiple prominent ventricular trabeculations and deep intertrabecular recesses.1 The disorder has only recently been recognized as a distinct form of cardiomyopathy. It was previously termed “spongy myocardium,” although this term has been abandoned because it underscores the hypothesis that the basic morphogenetic abnormality may be arrest of normal compaction of the loose interwoven mesh of myocardial fibers in the embryo.2,3 To date, LVNC has been reported in approximately 50 children.4–6 It typically involves the left ventricle, although involvement of the right ventricle has been reported.7 Clinical presentations include depressed systolic and diastolic function, systemic embolism, and the development of ventricular tachyarrhythmias, both in adult and pediatric populations.4–13 This study sought to determine the clinical features, genetic causes, and natural history of children diagnosed with LVNC at a single institution.

Methods

The echocardiogram database of Texas Children’s Hospital (TCH) was searched for all children with the diagnosis of LVNC between January 1997 and December 2002. Medical records were reviewed to document clinical presentations, including symptoms, primary diagnosis, New York Heart Association classification (NYHA), associated dysmorphic features, presence of arrhythmia, and a positive family history. Echocardiograms were analyzed for ejection fraction.
mitral and tricuspid inflow velocities, and ventricular dimensions, as well as features of congenital heart disease. The posterior wall myocardial thickness from parasternal short-axis view was obtained in end-diastole. Myocardial thickness was also determined at the site of the most prominent trabecular meshwork. Holter monitors and 15-lead ECGs were also examined for evidence of arrhythmia. All first-degree relatives of children affected underwent echocardiograms to screen for LVNC. Myocardial and skeletal muscle biopsy reports were examined when available, as were genetic studies.

Diagnostic Criteria
LVNC was diagnosed when 3 criteria were established: (1) the presence of multiple echocardiographic trabeculations, (2) multiple deep intertrabecular recesses communicating with the ventricular cavity, as demonstrated by color Doppler imaging and the recesses demonstrated in the apical or middle portion of the ventricle, and (3) a 2-layered structure of the endocardium with a noncompacted to compacted ratio >1.4.14

Results
Patient Population and Demographics
Thirty-six cases of LVNC were identified from ~50 000 echocardiograms performed during the study period on just over 26 000 patients. Three hundred forty-four cases of cardiomyopathy were diagnosed during this period, with LVNC accounting for 9.5% of cases. Of the 36 patients with LVNC, 16 were girls and 20 were boys. The median age at presentation was 90 days (range, 1 day to 17 years), and the median duration of follow-up was 3.2 years (range, 0.5 to 12 years).

Clinical Presentation
Twenty of the 36 patients (56%) were diagnosed in the first year of life. Dysmorphic features were obvious in 5 of the patients (14%). The underlying reason for initial referral and subsequent diagnosis of LVNC are outlined in Table 1. The most common presenting symptom was tachypnea, secondary to low cardiac output/congestive heart failure (CHF), which was noted in 14 patients (39%). Less common presentations included cyanosis, syncope, dysmorphic features, or failure to thrive. Fifteen patients (42%) were either asymptomatic (4 patients) or referred because of an abnormality on ECG or chest radiography without the presence of other symptoms (11 patients). NYHA classification evaluation demonstrated grade I-II in 22 patients and grade III-IV in 14 patients. One patient presented with sudden cardiac death after echocardiographic diagnosis during the study period. Five patients had associated congenital cardiac anomalies (14%). Three patients had isolated ventricular septal defects, one of which underwent surgical repair. A fourth patient was diagnosed with hypoplastic right ventricle with pulmonary valvar stenosis and underwent placement of a Blalock-Taussig shunt in the first week of life. The fifth patient had hypoplastic left heart syndrome and underwent a Norwood procedure. In all patients who underwent surgical intervention, LVNC was diagnosed by echocardiography after the surgical intervention.

Five patients had evidence of dysmorphic features. One child had DiGeorge syndrome, confirmed by fluorescent in situ hybridization (FISH) analysis demonstrating 22q11 deletion but no underlying congenital heart disease (CHD). One patient had congenital adrenal hyperplasia. In the remaining 3 patients, no genetic syndrome could be determined after chromosomal analysis, FISH for 22q11 deletion, and formal genetic evaluation. In 7 children (19%), there was a first-degree relative with a history of cardiomyopathy. Three of these children were siblings with LVNC whose father had a history of dilated cardiomyopathy. There were 3 other children with a paternal family history of dilated cardiomyopathy and 1 child with a paternal history of hypertrophic cardiomyopathy.

Electrocardiographic Findings
A high prevalence of ECG abnormalities in affected subjects was noted; with 27 patients (75%) manifesting ECG abnormalities. The most prominent feature was marked biventricular hypertrophy in 10 patients (28%), with extreme QRS voltage similar to that seen in Pompe’s disease (Figure 1). Other patterns included isolated or diffuse T-wave inversion in 7 patients (19%), Wolff-Parkinson-White syndrome (WPW) in 6 patients (17%), and premature atrial and ventricular contractions in 2 patients each (11%) (Table 2). Two patients with WPW had documented supraventricular tachycardia (SVT), and 1 child underwent radiofrequency ablation for refractory supraventricular tachycardia. An intracardiac defibrillator was implanted in another child with recurrent ventricular tachycardia.

Two-Dimensional Echocardiography
Characteristic noncompaction morphology was found in both ventricles in 8 patients (22%) and was isolated to the left ventricle in 28 patients (78%) (Table 2). There were no cases of right ventricular noncompaction without involvement of the left ventricle. Use of color Doppler in the parasternal short-axis and apical 4-chamber views improved visualization of the trabeculations within the left ventricular endocardium, which characterize this disorder, and MRI also accurately delineated ventricular morphology (Figures 2 and 3). The median noncompacted-to-compacted left ventricular myocardial ratio was 2.13 (range, 1.4 to 2.44). Left ventricular systolic function was depressed in 30 patients (83%) at diagnosis, with a median ejection fraction of 30% (range, 15% to 66%) (Table 2). Mitral inflow velocities demonstrated a decrease in E/A ratio consistent with restrictive left ventricular physiology in 15 patients (42%). There was only 1 patient with evidence of left ventricular thrombus identified.

TABLE 1. Clinical Presentation in 36 Children With LVNC

<table>
<thead>
<tr>
<th>Reason for Presentation</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low CO/congestive cardiac failure</td>
<td>14</td>
</tr>
<tr>
<td>Syncope</td>
<td>1</td>
</tr>
<tr>
<td>Murmur</td>
<td>2</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>2</td>
</tr>
<tr>
<td>Failure to thrive</td>
<td>1</td>
</tr>
<tr>
<td>Dysmorphic</td>
<td>1</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal ECG</td>
<td>6</td>
</tr>
<tr>
<td>Cardiomegaly on chest radiograph</td>
<td>6</td>
</tr>
</tbody>
</table>

CO indicates cardiac output.
in our study cohort. In 2 patients, the cardiac phenotype changed from dilated to hypertrophic during the study course (Figure 2), demonstrating an “undulating phenotype” (Table 2). Two patients had hypertrophic cardiomyopathy initially with depressed systolic function, which normalized, and 3 patients had hypertrophic cardiomyopathy with increased left ventricular end-diastolic diameter and depressed ventricular function, which later normalized.

Genetics
Two patients (6%) were identified to have previously reported underlying gene mutations (Table 2). Both patients had mutations in the G4.5 gene. Patient 4 was a 1-month-old boy who presented with severe left ventricular dysfunction and left ventricular dilation. Screening also revealed the presence of 3-methylgluconic aciduria and neutropenia consistent with Barth syndrome. Single strand conformational polymorphism (SSCP) analysis, with primers for exon 10 of G4.5 used, identified an abnormal conformer in the proband and mother. DNA sequence analysis identified a T→A substitution at the intron 10 splice donor site (IVS10+2→A). Patient 20 was a 5-month-old infant with a dilated hypertrophic heart with poor systolic function and heart failure; he also had 3-methylgluconic aciduria and neutropenia. SSCP screening of G4.5 with exon 4 primers identified an abnormal conformer in the mother and child. DNA sequence analysis demonstrated a T→C missense substitution at nucleotide 353, resulting in an amino acid change from cysteine to arginine at codon 118 (C118R). None of the patients had mutations in α-dystrobrevin, a gene previously identified in patients with LVNC associated with congenital heart disease.

Skeletal Muscle Analysis
Five patients underwent skeletal muscle biopsy during the study period. In all patients, there was evidence of mitochondrial proliferation and morphological abnormalities, including inclusions with myopathic changes (Figure 4). In one patient there was confirmed partial deficiencies in complexes I-III of the mitochondrial respiratory chain in association with elevated citrate synthase and succinate dehydrogenase.

Medical Therapy
Treatment of CHF consisted of diuretics in 13 patients, cardiac glycosides in 16 patients, and afterload reduction in 18 patients. Thirteen patients suspected of having an underlying mitochondrial myopathy were maintained on a “metabolic cocktail” including coenzyme Q10, thiamine, riboflavin, and carnitine. β-Blockers were used to treat SVT in 5 patients, amiodarone was required in 1 patient with SVT, and sotalol was given in 1 patient with ventricular tachycardia. Twelve patients were treated with β-blockade for CHF symptoms, including metoprolol in 9 patients and carvedilol in 3 patients.

Clinical Course
Nine patients who presented in the first year of life with depressed left ventricular function had a significant improvement in left ventricular ejection fraction with near normalization. Their median ejection fraction at diagnosis was 25% (18% to 32%), which improved to 47% (39% to 59%), with later deterioration to 23% (18% to 29%) at a median age of 6.3 years (range, 3 to 12 years). There were no reported episodes of systemic embolism. Five patients (14%) died during the study period (Figure 5). One patient...
had a history of ventricular tachycardia, and despite being treated with sotalol, died suddenly, presumably secondary to arrhythmia. Four children died of CHF and/or multiorgan failure despite maximal intravenous inotropic support. Necropsy was performed in 3 patients, which confirmed LVNC. Four patients underwent orthotopic heart transplantation (patients 7, 12, 20, and 32; Table 2). Overall survival on follow-up at a mean follow-up duration of 3.2 years was 78%.

Discussion

Over the last decade, LVNC has been recognized as a distinct form of cardiomyopathy with a distinct underlying cause and prognosis.1 LVNC is believed to represent an arrest in endomyocardial morphogenesis, which normally occurs between weeks 5 to 8 of fetal life and is characterized by gradual compaction of the myocardium, transformation of large intertrabecular spaces into capillaries, and evolution of the coronary circulation.6 The process of compaction typi-
cally progresses from epicardium to endocardium and from the base of the heart toward the apex. This study reports the largest series of children with LVNC from a single institution to highlight some discrepancies in the clinical presentation and natural history compared with those previously reported.

Recently, echocardiographic criteria for the diagnosis of LVNC have been proposed. Our patients fulfilled most of these criteria with the exception of the absence of CHD and differences in noncompaction-to-compaction ratio. It is clear that patients with LVNC may also manifest coexistent congenital heart lesions, as was seen among several patients in our study cohort. The presence of CHD does not exclude the diagnosis of LVNC. Although the majority of children with LVNC had a noncompaction-to-compaction ratio >2, there were 3 patients with a ratio between 1.4 to 2.0. Fulfillment of echocardiographic features of LVNC in children may not necessarily require a noncompaction-to-compaction ratio >2, as suggested in the adult literature.

Medical treatment depends on associated comorbidities, including systemic embolism and arrhythmia. All patients should be treated with aspirin therapy; in our study cohort there were no cases of systemic embolism after this strategy. Low-molecular-weight heparin or coumarin therapy should be initiated if systemic embolism is confirmed. Interestingly, there was a significant prevalence of mitochondrial morphological abnormalities and inclusions among patients who underwent skeletal muscle biopsy; this highlights the potential association of LVNC with underlying mitochondrial disorders, which has not previously been described. We recommend patients be treated with a metabolic cocktail including thiamine, coenzyme Q10, riboflavin, and carnitine if there is concern of underlying mitochondrial myopathy; 13 of our patients were treated with such a regimen, and in 3 cases, there was subsequent improvement in systolic ventricular function. Patients with decreased ventricular systolic function should be treated with afterload reduction and/or β-blockers. Patients with a hypertrophic phenotype without depressed ventricular function should be treated with either β-blockade or Ca²⁺ channel blockers. In this study, there was a family history in 19%, which is lower than previously reported by Ichida et al, who found that 44% of Japanese cases had a family history. Likewise, the frequency of dysmorphic children with LVNC (14%) was significantly lower than previous reports of 37% and 66%, respectively.

In certain cases, isolated LVNC is an X-linked disorder with genetic linkage localizing the disorder to the Xq28 region, where other myopathies with cardiac involvement have been localized. In those cases, mutations in the G4.5 gene or tafazzin, the same gene causing Barth syndrome with its associated cardiomyopathy, have been identified. There has been a reported association with Barth syndrome and LVNC and loss of function mutations in the G4.5 gene, such that it was concluded that LVNC is a severe allelic variant of Barth syndrome with a specific effect on the heart. This finding provides further structure-function information about the G4.5 gene product and has implications for idiopathic cases of severe infantile hypertrophic cardiomyopathy in boys. Genetic mutations in α-dystrobrevin responsible for the autosomal dominant form of LVNC associated with congenital heart disease has been described by our own group, but other elusive genes remain to be identified. In this study, one family with autosomal dominant transmission from a father with dilated cardiomyopathy to 3 children is notable, but no mutations in α-dystrobrevin have been identified, suggesting further genetic heterogeneity.

Specific gene mutations may be responsible for patients who have an “undulating phenotype” or who demonstrate
serial alterations in systolic ventricular function. The potential for patients with LVNC to have depressed systolic left ventricular contractility followed by a period of recovery and then further deterioration in systolic left ventricular function appears to be a prominent clinical pattern among the patients in our study and has been previously described. This process also may provide a logical explanation for the late presentation of many adults with LVNC. Such patients may have depressed systolic function early in life, which then resolves until adulthood, when they present with the disease. Recent reports have also highlighted that the lack of awareness of this disease process may also in fact result in numerous patients being misdiagnosed with hypertrophic cardiomyopathy. Although echocardiography is usually dramatic when one is specifically looking for the trabeculation and recess pattern of noncompacted myocardium, occasionally other modalities such as MRI may help to delineate LVNC (Figure 3).

Conclusions
LVNC is not a uniformly fatal disorder when diagnosed in infancy, as previously suggested. Patients may demonstrate an “undulating phenotype” with recovery in systolic ventricular function for a variable period of time before having further deterioration, which may account for many patients presenting as adults. Although ECG abnormalities are prominent, dysmorphic features and systemic embolism are not. LVNC needs to be carefully excluded in cases of severe biventricular hypertrophy, and this disorder is probably significantly underdiagnosed or misdiagnosed as hypertrophic or dilated cardiomyopathy, with LVNC probably being relatively common. In our study, LVNC was responsible for 9.5% of cardiomyopathies over this 5-year period. Skeletal muscle biopsy commonly demonstrates abnormalities, and in most cases should obviate the need for endomyocardial biopsy. Autosomal recessive, X-linked recessive, or autosomal dominant inheritance may underlie this disorder, and many of the underlying gene defects remain to be determined.

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