

Coffin–Lowry Syndrome and Left Ventricular Noncompaction Cardiomyopathy With a Restrictive Pattern

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Coffin–Lowry syndrome (CLS) is an X-linked dominant condition characterized by moderate to severe mental retardation, characteristic facies, and hand and skeletal malformations. The syndrome is due to mutations in the gene that encodes the ribosomal protein S6 kinase-2, a growth factor-regulating protein kinase located on Xp22.2. Cardiac anomalies are known to be associated with CLS. Left ventricular noncompaction (LVNC) is a clinically heterogeneous disorder characterized by left ventricular (LV) myocardial trabeculations and intertrabecular recesses that communicate with the LV cavity. Patients may present with a variety of clinical phenotypes, ranging from a complete absence of symptoms to a rapid, progressive decline in LV systolic and diastolic function, resulting in congestive heart failure, malignant ventricular tachyarrhythmias, and systemic thromboembolic events. Restrictive cardiomyopathy is an uncommon primary cardiomyopathy characterized by biatrial enlargement, normal or decreased biventricular volume, impaired ventricular filling, and normal or near-normal systolic function. We describe a patient with CLS and LVNC with a restrictive pattern, as documented by echocardiography and cardiac catheterization. To our knowledge, there have been no previous reports of concomitant CLS and LVNC. On the basis of our case, we suggest that patients with CLS be screened not only for congenital structural heart defects but also for LVNC cardiomyopathy.

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Key words: Coffin–Lowry syndrome; left ventricular noncompaction; restrictive cardiomyopathy

INTRODUCTION

Coffin–Lowry syndrome (CLS) is a rare, but well-established, X-linked disorder that entails a constellation of clinical findings, including characteristic facial features (prominent forehead; orbital hypertelorism; downslanting palpebral fissures; epicanthal folds; large, prominent ears; thick, everted lips; thick nasal septum) and

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skeletal abnormalities (kyphoscoliosis, pectus carinatum/excavatum, tapered fingers, fleshy hands), as well as short stature and developmental delay [Massin et al., 1999; Coffin, 2003; Facher et al., 2004; Pereira et al., 2010]. The syndrome is caused by heterogeneous mutations in the *RPS6KA3* gene, which encodes the ribosomal protein S6 kinase-2 (RSK2) [Trivier et al., 1996; Hanauer and Young, 2002]. To date, *RPS6KA3* is the only gene associated with CLS; a mutation can be identified in 90–95% of cases [Hunter and Abidi, 2009; Pereira et al., 2010].

Because CLS is an X-linked disorder, its expression differs between the sexes: the syndrome is more severe in males, who share similar characteristic clinical findings; affected females display more phenotypic variability. Cardiac anomalies are known to be associated with CLS and have been reported in approximately 14% of affected males [Hunter, 2002]. Some reports have described cardiac abnormalities, including structural abnormalities of the mitral valve and dilated cardiomyopathy [Massin et al., 1999], as well as heart failure due to restrictive cardiomyopathy [Facher et al., 2004]. Although the number of reported cases of CLS associated

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with cardiomyopathy has increased, this fact is underappreciated by cardiologists and medical geneticists.

Left ventricular noncompaction (LVNC) is a genetically and clinically heterogeneous disorder characterized by prominent left ventricular (LV) myocardial trabeculations and intertrabecular recesses that communicate with the LV cavity [Sasse-Klaassen et al., 2004]. This disorder may be found in isolation or as a feature of several malformation syndromes [Johnson et al., 2006]. It represents a developmental arrest of normal embryologic compaction of the LV myocardium [Richardson et al., 1996]. Since LVNC's initial description in the medical literature in 1984 [Engberding and Bender, 1984], heightened awareness and advances in cardiac imaging (i.e., echocardiography, magnetic resonance imaging, and computed tomography) have led to an increased detection rate [Lipshultz et al., 2003; Nugent et al., 2003]. In one pediatric study of children with primary cardiomyopathy of all types, isolated LVNC was present in 9.2%, making it the third most common type of primary cardiomyopathy, after dilated cardiomyopathy and hypertrophic cardiomyopathy [Andrews et al., 2008].

Patients with LVNC may present with varied phenotypic expression in regard to myocardial involvement, ventricular function, and clinical course. Even within members of the same family who share a common genetic etiology, the phenotype may vary considerably. [Lorsheyd et al., 2006; Andrews et al., 2008]. Its symptomatology spans the entire spectrum of severity, from a complete absence of clinical symptoms to a rapid, progressive decline in LV systolic and diastolic function, resulting in congestive heart failure, malignant ventricular tachyarrhythmias, and systemic thromboembolic events. Improvement in ventricular function and/or symptoms after diagnosis has also been reported [Andrews et al., 2008].

We describe a boy with CLS that was diagnosed clinically and confirmed by *RPS6KA3* gene sequencing. Cardiac findings included LVNC with restrictive physiology. To our knowledge, the literature contains no previous reports regarding the concomitant presence of these two cardiac abnormalities in a single patient.

CLINICAL REPORT

During the boy's first year of life, he was referred to the Department of Human and Molecular Genetics at Baylor College of Medicine because of a developmental delay. At age 3 years, he had a cardiopulmonary arrest while undergoing induction of anesthesia for an elective inguinal hernia repair. He was successfully resuscitated but had neurologic injuries with long-term sequelae, including further severe developmental delay and marked persistent left-sided weakness.

The day after his cardiopulmonary arrest, he was referred to the Section of Pediatric Cardiology at Texas Children's Hospital for cardiac evaluation. His initial echocardiogram showed mild to moderate biventricular dysfunction but also suggested chronically elevated pulmonary artery pressures. In addition, his mitral valve appeared abnormal (irrespective of the ventricular dysfunction): the anterior leaflet was elongated, thickened, and redundant; the mitral valve underwent prolapse, with mild to moderate regurgitation; and the left atrium was mildly dilated.

Hemodynamic data obtained by means of cardiac catheterization (performed 4 days after the cardiopulmonary arrest) confirmed these findings. The right ventricular and pulmonary artery pressures were approximately 75% systemic. Both atria had elevated A waves (right atrium, 20 mmHg; left atrium, 24 mmHg) with corresponding elevated right ventricular and LV end-diastolic pressures (20 and 24 mmHg, respectively). Pulmonary vascular resistance was elevated (approximately 22 Wood units in room air) and only mildly responsive to inhaled pulmonary vasodilators (high-dose nitric oxide and 100% oxygen). In light of these findings, it was concluded that the patient had a restrictive cardiomyopathy, as well as pulmonary hypertension and moderate mitral regurgitation.

Within 1 year after cardiopulmonary arrest, his ventricular function and right ventricular pressure returned to normal, as documented by qualitative and quantitative echocardiographic measurements. The mitral valve remained abnormal, with persistent mild prolapse of the anterior leaflet, limited excursion of the posterior leaflet, and associated regurgitation that was initially mild; the mildly dilated left atrium remained unchanged.

Over the next 4 years, the patient developed a restrictive physiology, with an altered mitral inflow pattern. His left ventricle met the criteria for ventricular noncompaction (Fig. 1). The mitral regurgitation and left atrial dilatation gradually grew more severe. The right ventricle again became hypertensive and hypertrophied, with mildly depressed function. The right ventricle and right atrium also became more dilated.

When the patient was 9 years old, repeat cardiac catheterization confirmed the presence of a restrictive physiology and of pulmonary hypertension: the right ventricle was approximately 66% systemic, pulmonary vascular resistance was elevated (16 Woods units) and nonreactive to inhaled pulmonary vasodilators, and the mean wedge and right atrial pressures were mildly elevated (13 and 10 mmHg, respectively).



FIG. 1. Apical four-chamber echocardiographic view with evidence of trabeculations at the apex of the left ventricle [arrows]. LA, left atrium; RV, right ventricle; LV, left ventricle; LVNC, left ventricular noncompaction.

The patient was referred back to the Department of Human and Molecular Genetics at Baylor College of Medicine. At that time, his physical findings and history were consistent with CLS, and DNA sequencing of the *RPS6KA3* gene revealed an A > G change at nucleotide 1000-2 in intron 12 (c.1000-2A > G), which is predicted to lead to abnormal splicing and to produce a transcript with an 11 base pair deletion. Maternal genetic analysis revealed that this mutation was de novo.

At the patient's last follow-up visit, at age 13 years (Figs. 2 and 3), echocardiography showed persistent suprasystemic pulmonary arterial pressures, severe tricuspid regurgitation (peak velocity, ~5.7 m/sec), mitral valve thickening (mean gradient, 8 mmHg), severe mitral regurgitation, moderate biatrial dilatation, and mild right ventricular hypertrophy and dilatation. His medications included aspirin, an angiotensin-converting enzyme inhibitor (enalapril), metoclopramide, sildenafil, guanfacine, and ambrisentan.

DISCUSSION

We have described a boy with CLS and LVNC with a restrictive pattern. The diagnosis of LVNC was based on echocardiographic findings, with a 2:1 ratio of noncompacted to compacted endocardium. Color Doppler interrogation revealed flow between the LV trabeculations.



FIG. 2. At 13 years of age, the patient displayed the characteristic facial features of CLS, including a large nose; large, low-set, thick ears; a broad forehead; hypertelorism; anteverted nares; and a thick, everted lower lip.



FIG. 3. At 13 years of age, the patient's hands have a puffy appearance, and a broad proximal part of his fingers is tapered distally. Such tapering is usually seen both in males with Coffin-Lowry syndrome and in female heterozygotes.

Noncompaction of the LV myocardium is characterized by a distinctive “spongy” morphologic appearance. The distal or apical portion of the LV chamber develops deep intertrabecular sinusoids that communicate with the ventricular cavity [Pignatelli et al., 2003; Maron et al., 2006]. The mainstay for diagnosing LVNC is anatomic definition of the ventricular myocardium by means of two-dimensional echocardiography [Eidem, 2009]. The natural history of LVNC is largely unresolved but may range from a complete absence of symptoms to LV systolic dysfunction, heart failure, thromboemboli, arrhythmias, and even sudden death [Sasse-Klaassen et al., 2004; Lorscheid et al., 2006; Ichida, 2009]. Its hemodynamic sequelae and associations are also unpredictable, whereas many LVNC patients demonstrate features similar to those of dilated cardiomyopathy with compromised ventricular systolic function and a dilated left ventricle, a small number of patients have shown features of restrictive cardiomyopathy [Sasse-Klaassen et al., 2004; Lorscheid et al., 2006; Ichida, 2009].

Restrictive cardiomyopathy is a rare primary cardiomyopathy that accounts for 2.5–5% of pediatric cardiomyopathies [Denfield and Webber, 2010]. It is characterized by biatrial enlargement, normal or decreased biventricular volume, and impaired ventricular filling, with normal or near-normal systolic function [Maron et al., 2006]. Systemic disorders that have been implicated as common causes of restrictive cardiomyopathy include glycogen storage diseases, mucopolysaccharidoses, sarcoidosis, scleroderma, and hemochromatosis [Rivenes et al., 2000; Nihoyannopoulos and Dawson, 2009]. Previous cases of restrictive cardiomyopathy in CLS patients have been reported [Facher et al., 2004], although LVNC in CLS patients has not been reported.

Our case involves a unique constellation of CLS, LVNC, and restrictive physiology without evidence of any systemic conditions known to cause restrictive cardiomyopathy. In addition, our case corroborates previous evidence that mitral valve malformations can occur in patients with CLS [Massin et al., 1999]. We initially suspected the restrictive pattern when echocardiographic findings

suggested chronic elevation of the pulmonary artery pressure (e.g., dilated main and branch pulmonary arteries, hepatic veins, inferior vena cava, and right atrium). However, the myocardium at that time had not yet become noncompacted. Although the relationship between the RSK2 pathway and LVNC has not been clearly delineated, the ribosomal protein S6 kinase-2 is highly expressed in striated muscle. Whereas RSK2 is most strongly expressed in skeletal muscle [Zeniou et al., 2002], it represents the predominant isoform of *RPS6K* in cardiac myocytes [Wagner, 2004]. Therefore, as a specialized form of skeletal muscle, cardiac muscle differentiation, and development may be directly affected by the RSK2 mutation in CLS.

In addition, contrary to other MAPK pathway factors—such as Raf1, RafB, Mek1, Erk2, and Rsk1—that are significantly down-regulated during embryogenesis, RSK2 levels do not appear to exhibit postnatal changes in protein expression [Kim et al., 1998]. Moreover, during terminal muscle differentiation, insulin-like growth factor 1 (IGF-1)—a strong RSK2 activator—along with insulin can promote complete maturation of the myogenic program and induce myotube hypertrophy, which is mediated by p42/p44 MAPK and p90RSK [Pelosi et al., 2007]. In the heart, IGF-1 exerts a prohypertrophic and antiapoptotic function, and administration of IGF-1 in a delta-sarcoglycan-deficient hamster model of cardiomyopathy preserves ventricular wall thickness and improves cardiac function [Serose et al., 2005]. Therefore, decreased or malfunctioning RSK2 may reduce the beneficial effect of IGF-1 and affect both cardiac embryogenesis and compaction through altered MAPK-mediated signaling pathways for cell proliferation/differentiation and apoptotic activation [Pearson et al., 2001].

An alternative and perhaps more tenable hypothesis is that the genetic backdrop in CLS patients lends itself to varied phenotypic outcomes from gene–gene and/or gene–environment interactions. Exposure to environmental stressors such as proinflammatory markers, ischemia, and hypoxia, in combination with the RSK2 mutation, may impair myocardial morphology and function. The process may ultimately result in a hypertrabeculated phenotype that is identical to LVNC caused by known gene mutations such as those in *TAZ* (*G4.5*) or α -dystrobrevin [Captur and Nihoyannopoulos, 2010].

In our present case, we also observed mitral valve prolapse, with mild to moderate regurgitation, at the patient's initial presentation. Both the mitral valve abnormality and LVNC may be phenotypic expressions of our patient's genetic milieu. Given the known deleterious interaction between mitral valve regurgitation and LV dysfunction, the coincidental presence of these findings provides the substrate for a vicious cycle, whereby one can worsen the other: significant mitral valve insufficiency induces LV dysfunction and congestive cardiomyopathy, which further stretches the mitral valve annulus and exacerbates mitral insufficiency. Therefore, we agree with Massin's conclusion that if primary myocardial disease has a proven association with mitral valve anomalies in CLS, surgery should be considered at an early stage [Massin et al., 1999].

To our knowledge, our case of CLS is the first instance of concomitant LVNC and restrictive cardiomyopathy to be reported in the literature. This case suggests that in addition to undergoing initial echocardiography for the detection of structural abnormali-

ties, patients with CLS should undergo continued monitoring by a pediatric cardiologist for the development of cardiomyopathy.

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