Clinical Report
Cardiomyopathy in Coffin–Lowry Syndrome

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Coffin–Lowry syndrome (CLS) is a rare but well-documented X-linked disorder characterized by small size, developmental delay/mental retardation, and characteristic facial and skeletal findings in affected males. The phenotype in affected females is far more variable and can include developmental differences, obesity, and characteristic facial and skeletal differences. Cardiac anomalies are reported in less than 20% of affected males, with cardiomyopathy being one of the rare but reported complications of this disorder. However, cardiomyopathy is not well characterized in CLS. Here, we report on a 14-year-old boy with physical and developmental findings consistent with CLS who presented with a relatively sudden onset of signs of congestive heart failure due to a restrictive cardiomyopathy; an endomyocardial biopsy demonstrated non-specific hypertrophic myocyte alterations consistent with cardiomyopathy. This is the first description of the histology and electron microscopy of cardiomyopathy in CLS.   © 2004 Wiley-Liss, Inc.

KEY WORDS: Coffin–Lowry syndrome; cardiomyopathy

INTRODUCTION

Coffin–Lowry syndrome (CLS; MIM 303600) is a rare but well characterized X-linked syndrome comprising mental retardation, growth retardation, skeletal and facial anomalies [Delaunoy et al., 2001]. Affected males also manifest hypertelorism and downslanting palpebral fissures, broad nose with thick nasal septum and anteverted nares, large mouth with everted lips, and dental anomalies [Hunter, 2002]. Other common findings are short, fleshy hands with tapering fingers and a hypothenar crease, progressive kyphoscoliosis, pectus carinatum/excavatum, and sensorinural hearing loss [Hunter et al., 1982; Young, 1988]. Mutations in the *RSK2* gene (located at Xp22.2 and encoding a growth-factor-regulated protein kinase) are known to cause CLS. Most mutations cause premature translation termination and likely loss of function of the mutant allele [Delaunoy et al., 2001; Zeniou et al., 2002].

Cardiac anomalies have been described in approximately 14% of males with CLS and include anomalies of the mitral, aortic and tricuspid valves, and pulmonary and aortic root dilatation [Hunter, 2002]. Cardiomyopathy was described in a few cases, but with no consistent sub-type (cases with obstructive, dilated, and with endomyocardial fibroelastosis have all been reported, [Gilgenkrantz et al., 1988; Massin et al., 1999]).

Here we report on a 14-year-old boy with physical and developmental findings suggestive of CLS who presented with congestive heart failure due to restrictive cardiomyopathy. This is the first study of restrictive cardiomyopathy in CLS and it was confirmed by the pathologic findings of an endomyocardial biopsy and electron microscopy.

Fig. 1.   The propositus, at age 14 years.

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CLINICAL REPORT

B.D. was born at term after an uncomplicated pregnancy of 30-year-old non-consanguinous Caucasian parents. At birth he weighed 2.7 kg and, was approximately 48 cm long; the parents remember a normal head circumference. B.D.'s parents became concerned when he was approximately 1-year-old, as he was not yet sitting nor achieving motor development like their older daughters. A developmental evaluation determined significant sensorineural hearing loss (SNHL). He was diagnosed with Williams syndrome (WS) due to his developmental delay and his facial appearance (note: FISH testing for WS was not yet clinically available). Cardiac evaluation demonstrated a murmur that was thought to be benign, and an echocardiogram was reported as normal. B.D.'s development remained considerably delayed; he walked at age 3 years, never developed language and at 14 years cannot read or write and is not toilet trained.

B.D. physically healthy without hospitalizations or cardiac symptoms until age 14 years when he presented with a 1–2 month history of hand, face, and leg edema, decreased urination, non-productive cough without fever, and decreased physical activity. Height and weight were within the 5–10th centile. He had wide-set eyes, a wide, flat nasal bridge with anteverted nares; a wide mouth, a midline groove of the tongue and full lips (Fig. 1). His hands were short with tapered fingers, doughy skin, and bilateral hypothenar creases. A diagnosis of CLS was made. To rule out the diagnosis of WS, FISH analysis was performed for the chromosome 7q11.23 deletion with normal results.

Subsequently, analysis of the *RSK2* gene revealed a three amino acid deletion at position 1428–1430 (thymidine-adenine-thymidine) in exon 16. This alteration, which is predicted to result in the loss of an isoleucine, has not been reported previously. (Note: testing in other family members has been declined to date, so the clinical significance of this alteration is uncertain.)

Cardiac Evaluation

Chest radiograph showed bilateral pleural effusion, and echocardiography demonstrated severe bi-atrial enlargement with normal ventricular size and systolic performance. Chest MRI did not suggest the presence of constrictive pericarditis. Echocardiography demonstrated moderate mitral and tricuspid regurgitation with the Doppler pattern across the mitral valve suggested restrictive physiology. This was confirmed at cardiac catheterization, with findings of elevated right and left ventricular end-diastolic pressures of 22 and 27 mm Hg, respectively, and a severely depressed cardiac index at 1.4 L/min/M2. A characteristic diastolic "square-root sign" was evident in the ventricular pressure tracing. Right ventricular endomyocardial biopsy was performed.

Endomyocardial Pathology

Histologic assessment of the right ventricular endomyocardial fragments showed marked myocyte hypertrophy and mild interstitial fibrosis. Endocardial thrombosis or fibrosis was absent; however, focal endocardial fibrosis was observed (Fig. 2A). Special staining showed no abnormal glycogen or amyloid deposition. Electron microscopy demonstrated enlargement of myofibers related to an increased complement of normal-appearing mitochondria and myofilaments with mild degenerative cellular changes (Fig. 2B). Myofiber disarray, as described in hypertrophic cardiomyopathy, abnormal storage materials or lysosomal alterations, inflammatory lesions and etiologic agents, such as viruses, were absent. While nonspecific, the findings were consistent with cardiomyopathy.
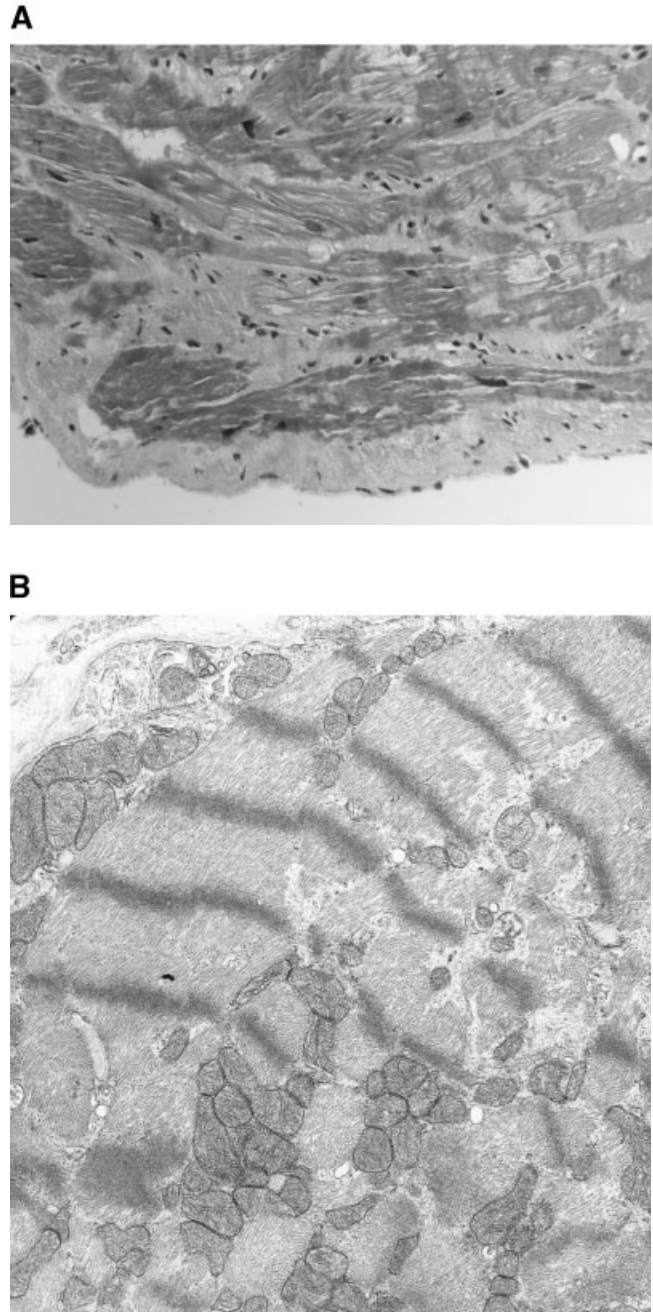
Fig. 2. **A**: Thickened fibrosed endocardium and underlying hypertrophied myocardial fibers (H&E, Original magnification ×400). **B**: Electron microscopy showing myofiber with increased myofilaments and normal-appearing mitochondria. Original magnification ×16,0003.

B.D.'s parents were made aware of the poor prognosis and relatively ineffective treatment. The family declined consideration for cardiac transplantation and B.D. was released on hospice care.

DISCUSSION

Based on our literature review, we think that this is the first documented case of restrictive cardiomyopathy in CLS. There are three major types of cardiomyopathy. Dilated

cardiomyopathy is the most common, and results from damage-induced weakening of the chamber walls and subsequent dilatation of the heart chambers. Hypertrophic cardiomyopathy results from thickening of the chamber walls due to disorganized growth of heart muscle cells within the ventricles. Restrictive cardiomyopathy is characterized by impaired ventricular filling and decreased or normal diastolic ventricular volumes [Richardson et al., 1996]. Restrictive cardiomyopathy is the least common form cardiomyopathy, and is quite rare in children. In most cases, a pathogenesis cannot be identified. Such was the case with our patient, as the histopathologic/EM evaluation demonstrated nonspecific changes consistent with idiopathic, non-infiltrative cardiomyopathy.

We cannot say how long the process had been active in patient. He had had a normal echocardiogram at age ~3 years, and onset of symptoms only 1–2 months prior to presentation at age 14 years. His signs and symptoms were typical of restrictive cardiomyopathy: breathlessness, fatigue, nonproductive cough, and peripheral edema and ascites. Once symptoms develop, there is a substantial risk of progressive pulmonary hypertension, arrhythmias and sudden death, with cardiac transplantation being the only effective therapeutic option [Rivenes et al., 2000; Chen et al., 2001; Weller et al., 2002].

While cardiac anomalies are common in CLS, occurring in approximately 14% of cases [Hunter, 2002], cardiomyopathy is rare, with only a few reported cases [Gilgenkrantz et al., 1988; Massin et al., 1999]. These were uncharacterized, without the advanced studies detailed in this case. However, it may be that cardiomyopathy is more common in CLS than has been previously recognized. Unexplained sudden death has been reported to occur in CLS patients [Hunter, 2002]. As sudden death is a recognized presentation for cardiomyopathy (due to cardiac conduction abnormalities), and since many of these cases may not have had complete post-mortem studies, it may be that that some were due to undiagnosed cardiomyopathies. Furthermore, this may imply an as yet unrecognized role for the *RSK2* gene in cardiac function.

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