Combined obstructive hypertrophic cardiomyopathy and double outlet right ventricle in an infant with Down syndrome

Patient: Male, 2
Final Diagnosis: Obstructive hypertrophic cardiomyopathy
Symptoms: Congestive heart failure
Medication: —
Clinical Procedure: Left ventricular septal myectomy • repair of congenital heart disease
Specialty: Cardiology

Objective: Rare disease
Background: Hypertrophic cardiomyopathy (HCM) is uncommon in Down syndrome (DS). When combined with congenital heart disease (CHD) both morbidity and mortality may be greater compared to CHD alone. Whether HCM in DS patients is related to having trisomy 21 versus a second site mutation is unknown.
Case Report: We report a case of severe HCM in an infant with DS in combination with double outlet right ventricle (DORV) who required surgery for relieving obstruction and congestive heart failure. We predicted that this infant would have a second site mutation involving either a sarcomeric protein or metabolic disorder as a cause for his HCM. Using current genetic and metabolic testing as well as histologic assessment of excised cardiac tissue we sought to further characterize the nature of the HCM. A successful resection of sub-aortic stenosis and DORV repair was performed. Genetic and metabolic testing was negative for gene defects and/or syndromes commonly associated with familial HCM. Excised cardiac tissue from the ventricular septum exhibited myocyte hypertrophy and sub-endocardial fibrosis but no sarcomeric disarray, myocyte fibrosis or glycogen storage. Metabolic testing for common forms of mitochondrial disease was negative. Post-operative echocardiograms show persistent, non-obstructive septal hypertrophy.

Conclusions: Unlike prior reports, this child required a surgical intervention to relieve his sub-aortic obstruction. Thus, HCM in this population can be more serious than previously suspected. Although testing did not reveal the cause of his HCM, we still suggest screening for known causes of HSC until the etiology of the HCM in DS is well understood.

Key words: conal-truncal defect • hypertrophic cardiomyopathy • Down syndrome

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Background

Hypertrophic cardiomyopathy (HCM) is usually an isolated and familial disease [1]. However, there are a growing number of reports describing infants with non-familial, primary HCM in combination with genetic syndromes (polysomy/metalic disease) with or without congenital heart defects (CHD, [2–4]). Among these reports, at least 2 were diagnosed with the combination of Downs, HCM and CHD {atrioventricular canal defect (AVC), Tetralogy of Fallot (TOF) [5,6]}. To date, no unifying hypothesis appears to account for the seemingly diverse pathways affecting these individuals and their heart. Although CHD is common in DS, it is unclear if trisomy 21 is simply coincidental or related to development of HCM. Indeed, primary HCM can coexist in non-DS patients with conal-truncal defects. Interestingly, most of the non-DS infants are male and most exhibit additional developmental and/or physical congenital anomalies [3]. Feltes et al. [7] described one infant with multiple, non-specific minor physical deformities as well supernumerary ring of chromosome 1 origin (significance unclear) as well as global developmental delay. In a second infant, the karyotype was normal and the 22q11 FISH was negative. However, a mitochondrial cytomyopathy was suspected. It is unknown if DS and non-DS patients develop HCM by similar mechanisms. In either case, HCM in combination with CHD is thought to complicate pre- and postoperative outcomes. Specifically, investigators report the development of profound cyanosis (in the setting of TOF), heart failure (when intracardiac shunts are present) or the development of left ventricular outflow gradients following ventricular septal defect (VSD) repair [3]. At least two deaths have been reported [6,7].

We describe an infant with combined DS, HCM, and Double Outlet Right Ventricle (DORV) who developed severe congestive heart failure and severe sub-aortic stenosis that prompted an early surgical intervention. We hypothesized that this child would have a commonly recognized form of HCM such as a sarcomeric gene mutation or metabolic disease. The purpose of this report was to further characterize this incompletely understood HCM using contemporary genetic testing for heritable HCM as well as histologic analysis of excised hypertrophic tissue. If we could identify his type of HCM, we believed we could better manage long-term risks and provide counseling for possible heritable disease to the family.

Case Report

Pediatric Cardiology follows a 2-year-old male with DS born to a 33-year-old female at 38-week gestation with no known prenatal complications or gestational diabetes. The family history was negative for CHD, HCM, sudden death or arrhythmia. On exam he was acyanotic and exhibited typical Down facies and had palmer creases. There was mild respiratory distress. Biventricular precordial activity was moderately increased. Cardiac auscultation revealed a normal S1, a loud P2, an S3 apical gallop, a 2/6 systolic regurgitant murmur (mid-left sternal border), a 3/6 systolic murmur (upper left sternal border) and a mitral flow rumble. The liver edge was 3 cm below the right costal margin. There was no edema and pulses were normal.

An echocardiogram revealed severe asymmetric septal hypertrophy (ASH, 1.4cm, Z-score 9) with borderline left posterior wall hypertrophy (0.5–0.6 cm, Z-score 2–3) and mild right ventricular hypertrophy (Figure 1A, B). Initially there was no subaortic gradient. There was a large inlet ventricular septal defect (VSD, 1.0 cm) with perimembranous extension (Figure 1A, C), a d-malposed and mildly dilated aortic root, mild dynamic right ventricular outflow obstruction (22 mmHg), a moderate secundum atrial septal defect (ASD, 0.6 cm), and a large patent ductus arteriosus. The left ventricular endocardium was mildly echo dense. Ventricular function was hyper-dynamic (shortening fraction 50%). The EKG showed sinus rhythm, right atrial enlargement, and biventricular hypertrophy with a left strain pattern. The QTc was normal and there was no ventricular preexcitation (serial EKG’s during first year of life). The cardiac MRI did not reveal myocardial fibrosis.

Down syndrome was suspected clinically and confirmed by karyotype. Testing for 18 common gene mutations associated with HCM (GeneDX, Gatherburg, MD) was negative. State of Kansas newborn screening for metabolic disease (organic/amino/fatty acid oxidation disorders, and thyroid) was negative. Urine organic acids, urine amino acids, lactate, pyruvate, an acylcarnitine profile, plasma amino acids were all negative. No muscle or skin biopsy was performed. Lactate levels were normal in the peri-operative period as well.

Despite anti-congestive therapy (Lasix, Digoxin, Propranolol) he exhibited refractory congestive heart failure and failure to thrive. At 2 mo age he also developed mild sub-aortic stenosis that rapidly progressed to severe (60–80 mmHg) by 3 mo. A cardiac catheterization confirmed this finding as well as reactive pulmonary hypertension. A surgical intervention was performed consisting of patch closure of the VSD and ASD, ligation of the ductus, and septal myectomy. Intra-operative inspection of the great vessel relationship suggested DORV. The child did well post-operatively and has not re-acquired sub-aortic obstruction. However, moderate residual hypertrophy persists. No family members underwent HCM screening as heritable disease was not suspected.

The microscopic evaluation of excised cardiac tissue revealed several areas with significant subendocardial fibrosis varying between 1 to 2.5 mm in thickness. The underlying myocardial
cells showed occasional hypertrophy. There was no evidence of myocardial fibrosis, acute or chronic inflammatory infiltrate or other pathologic abnormalities. The vascular structures appeared normal. In addition to Hematoxylin and Eosin (H&E) staining (Figure 2A), other special stains including Periodic acid-Schiff stain (PAS) with and without digestion (not shown) and Trichrome (Figure 2B) were applied. The H&E stain was not diagnostic for myocyte/sarcomeric disarray. The PAS stain was negative for glycogen inclusions or other carbohydrates. The Trichrome stain revealed the extensive subendocardial fibrosis but no cellular fibrosis or deposits.

**Discussion**

Down syndrome is the most common human chromosomal aneuploidy (1/700–750 live births [8,9]). The elevated expression of trisomic genes is believed to disrupt the normal paths...
of development of various organ systems [10]. Even though it would seem that a trisomy would result in a consistent phenotype it is more typical to see variable penetrance of the DS associated anomalies. Nearly 310 genes may be present on the extra chromosome. The resulting phenotype is thought to be dependent upon individual gene dosage [10]. The Down syndrome consensus region (DSCR) is an example of a locus of DNA that may be responsible for many of the Down syndrome features including heart defects. The DSCR1 gene was once thought to strongly contribute to the specific features of DS such as the heart (TOF, AVC). Interestingly, restoration of DSCR1 to disomic levels in Ts16 mouse models of trisomy 21 did not rescue animals from the development of CHD [11]. Other studies suggest that DSCR1 is a regulatory protein involved in the calcineurin/NFAT pathway. This protein appears to inhibit calcineurin phosphatase activity and consequently, could block calcineurin dependent cardiac hypertrophic signaling pathways [12]. Furthermore, cardiac hypertrophy does not appear to be an expected phenotypic finding in Ts16 mouse models. Taken together, it was not certain that the DS and HCM were linked. As such, we elected to use a multifaceted approach to screen for known causes of HCM using genetic, metabolic, and histologic analyses.

This report is similar to others describing a primary HCM that is unexpectedly associated with a genetic syndrome and congenital heart disease [4–7]. Likewise, this infant’s condition was adversely affected by HCM. In particular, the rapid onset and degree of pulmonary congestion was likely due to a combination of left to right shunt and to left ventricular diastolic dysfunction. In contrast to other cases, this child developed severe sub-aortic stenosis that required an urgent intervention. Despite a good surgical outcome, his hypertrophy has not regressed and we suspect this child will have ongoing diastolic function and pulmonary venous hypertension. Long-term treatment with Propranolol (and possibly pulmonary vasodilators) may be necessary.

Cardiomyocyte hypertrophy is thought to result from a cellular response to a pathologic molecular or biomechanical stress. Although the acute hypertrophic response is considered adaptive for maintaining cardiac output, chronic hypertrophy is not always beneficial. Over time, chronic hypertrophy can promote ventricular diastolic dysfunction, congestive heart failure and increase risk for arrhythmogenic sudden death [1].

Clearly some infants with congenital heart disease may acquire cardiac hypertrophy due to overload stress. The cellular histology would reveal increased cell size as opposed to abnormal sarcomere development or myocyte inclusions or deposits [1,8]. It is expected that hypertrophy would slowly regress once the stress is removed. While increased cell size is consistent with our findings, there was no early obstruction that would explain severe ASH seen in this infant. Moreover, the child in our case has not shown improvement in ASH during the 1st year following his surgery.

Gene expression in cardiac tissue from right ventricles of infants with conal-truncal defects has been analyzed [13]. In addition to changes in expression of normal developmental genes (WNT and Notch signaling), tissues also expressed higher levels of glucocorticoid responsive natriuretic peptide precursors A and B (NPPA, NPPB) that are thought to promote hypertrophy and cellular proliferation. This infant did have infundibular hypertrophy along with mild right sided outflow obstruction. Thus, right hypertrophy in our patient might be explained by the above signaling pathways. However, left ventricular gene expression was not assessed in the study and it is unknown whether the same mechanism could cause ASH. We did not have enough tissue to perform a microarray analysis on our patient.

There are a number of commercially available gene panels that only require blood or saliva for testing. For those presenting with childhood onset HCM, mutations can be identified in up to 55% of patients [14]. The most common cause of familial HCM is an autosomal dominant mutation in one of the genes encoding sarcomeric proteins. Mutations (sporadic or familial) can involve thick or thin filaments as well as numerous other regulatory sarcomeric proteins. The β-myosin heavy chain (MYH7) is the most common mutation found in familial disease [1,15]. Studies suggest that these types of gene mutations reduce cardiac contractility resulting in the release of growth factors that promote hypertrophy and fibrosis [15]. Although HCM can involve any wall of the heart, 67% of patients with familial HCM show asymmetric hypertrophy, usually affecting the subaortic portion of the interventricular septum. Prior to our ability to perform genetic testing, sarcomeric disease was classically identified by histologic evidence for myocyte and myofibrillar disarray [1,15]. Myocytes, normally arranged in parallel bundles, are found at unusual angles to each other in HCM patients. Areas of fibrosis may also be present [17]. Our echocardiography findings were consistent familial HCM. However, the genetic testing for commonly known mutations was negative. Moreover, the H&E analysis of our patient’s tissue did not show myocyte disarray. Trichrome staining detected only subendocardial fibrosis, however, this may have been a consequence of coronary flow insufficiency as a result of the severe hypertrophy. Myocardial fibrosis could develop later in life.

Although less common, inborn errors of metabolism can be associated with HCM. In such cases, large amounts of metabolic products may accumulate within the cardiomyocytes [1,18,19]. This finding has led many to believe that these products directly cause hypertrophy. For example, cardiac glycogen storage disease may be mediated by AMP-activated protein kinase.
mutations (PRKAG2 gene). This enzyme complex normally plays a role in energy balance within healthy cells. Exactly how mutations within the regulatory subunit promote intracellular glycogen accumulation is unknown. While certain individuals exhibit marked HCM and positive PAS (glycogen) staining of the myocardium, recent findings suggest that hypertrophy can be present without significant glycogen deposition or fibrosis [18]. The PRKAG2 mutations are also of clinical interest due to a possible association with a Wolf-Parkinson-White-like syndrome and supraventricular tachycardia [18]. Using mouse models of PRKAG2 mutations, investigators have demonstrated that the source of pre-excitation was a result of disruption of the valve annular junctions by tracks of glycogen engorged cells rather than having a classic bypass tract [19]. Similar mechanisms for ventricular pre-excitation probably exist for other storage disease such as Danon’s, Pompe’s, and Fabry’s disease [18]. Interestingly, pre-excitation in PRKAG2 mice was uncommon at birth but was found in 88% by 4 weeks of life [20]. For our patient, PRKAG2 genetic testing was negative, all EKG’s were normal (up to 18 months of life), and there was of no evidence for glycogen storage by PAS tissue staining.

With regard to other metabolic diseases that are known to be associated with HCM, the state screening (disorders of fatty acid metabolism), metabolic and genetic screening (Fabry, LAMP2) and histology staining did not suggest an obvious metabolic disorder, storage disease or amyloidosis. Indeed, mitochondrial cytopathies may be more difficult to detect clinically. Although neither skin nor muscle biopsies were performed, a normal lactate (pre and post-operative period) helped exclude some mitochondrial oxidative phosphorylation defects [1]. Genetic testing for certain mitochondrial transfer RNA mutations [21] was also negative. As this child’s development is progressing well, a mitochondrial cytopathy is not so far suspected. Dysregulation of Caveolin 3 (muscular dystrophy), or Noonan syndrome (altered calcineurin signaling) [22] are also associated with HCM. However, neither was evident based upon our evaluation.

Interestingly, WKY/NCrj rat models have been shown to exhibit ASH with or without congenital heart disease (AVC, TOF) [23]. The majority of rat cardiac tissues demonstrate diffuse myocyte fibrosis (70%) while fewer also show sarcomeric fiber disarray. These findings in the rat model are in contrast to our histology findings for this patient. However, it is possible that such changes may be evident later in life. So far, it is not clear whether the combination of HCM and CHD in humans develops along the same path as the rat model. Regardless, the use of this animal model along with fetal echocardiography and molecular analysis may provide insight into the evolution of the disease process.

Conclusions

We report individual with Down syndrome, primary HCM and a conal-truncal defect. To our knowledge this is the first case where genetic, metabolic and histologic analyses are presented together. Results suggest that he likely does not have a common, heritable form of HCM or obvious metabolic disease. The fact that the child required a myectomy suggests that the disease process can be more serious than previously suggested.

Clearly contemporary testing cannot exclude all possible forms of known HCM. It is also possible that a novel molecular signaling process caused his HCM during development. Nevertheless, until the disease process is better understood, we suggest patients undergo testing for various forms of HCM as a positive finding may assist with risk stratification for the patient and family.

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