Noncompaction of the Ventricular Myocardium and Hydrops Fetalis in Cobalamin C Disease

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Abstract Cobalamin C disease (*cbLC*), a form of combined methylmalonic acidemia and hyperhomocysteinemia caused by mutations in the *MMACHC* gene, may be the most common inborn error of intracellular cobalamin metabolism. The clinical manifestations of *cbLC* disease are diverse and range from intrauterine growth retardation to adult onset neurological disease. The occurrence of structural heart defects appears to be increased in *cbLC* patients and may be related to the function of the *MMACHC* enzyme during cardiac embryogenesis, a concept supported by the observation that *Mmachc* is expressed in the bulbus cordis of the developing mouse

heart. Here we report an infant who presented with hydrops fetalis, ventricular dysfunction, and echocardiographic evidence of LVNC, a rare congenital cardiomyopathy. Metabolic evaluations, complementation studies, and mutation analysis confirmed the diagnosis of *cbLC* disease. These findings highlight an intrauterine cardiac phenotype that can be displayed in *cbLC* disease in association with nonimmune hydrops.

Introduction

Cobalamin C disease (*cbLC*), a form of combined methylmalonic acidemia and hyperhomocysteinemia, may be the most common inborn error of intracellular cobalamin metabolism and is caused by mutations in *MMACHC* gene located on chromosome 1p34 (Lerner-Ellis et al. 2006). In the “early onset” form of *cbLC*, infants present with failure to thrive, developmental delay, visual impairment, and hematologic problems (Carrillo-Carrasco et al. 2011; Rosenblatt et al. 1997). Malformations including congenital microcephaly and congenital heart diseases are frequently present (Andersson et al. 1999). While the phenotypic spectrum of *cbLC* disease is broad and age of onset is variable, encompassing prenatal and adult presentations, a prenatal cardiac presentation of right ventricular dilated cardiomyopathy in the third trimester has been documented in one infant with *cbLC* disease (De Bie et al. 2009). Here, we describe a patient with *cbLC* disease who presented with the combination of hydrops fetalis and left ventricular noncompaction (LVNC), review the previous reports of cardiomyopathy in *cbLC* disease, and highlight the need to consider the diagnosis of *cbLC* disease in the setting of nonimmune hydrops fetalis, especially when cardiac disease is present in the fetus.

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Case Report

Clinical investigations were conducted through NIH study 04-HG-0127 “Clinical and Basic Investigations of Methylmalonic Acidemia and Related Disorders” (clinicaltrials.gov identifier: NCT00078078) in compliance with the Helsinki Declaration. The patient was born to a healthy 35-year-old primigravida. A routine prenatal ultrasound at 12 weeks showed an increased nuchal translucency and subsequently chorionic villus sampling demonstrated a normal female karyotype, 46,XX. At 20 weeks, a prenatal ultrasound showed a thickened nuchal fold. Fetal echocardiography suggested possible tricuspid atresia and insufficiency with poor right ventricular function. Repeat evaluation at 24 weeks demonstrated questionable pulmonic stenosis and impaired biventricular function. Significant hydrops fetalis was also noted and the fetus was not expected to survive. At 30 weeks, a fetal echocardiogram revealed poor right ventricular function with preserved left ventricular systolic function. Deep trabeculations of both ventricles with a thickened septum were clearly visualized at the apex (Fig. 1a). Surprisingly, the hydrops nearly resolved by 35 weeks.

This infant was delivered at 38 weeks by scheduled Cesarean section. The birth weight was 2.72 kg (10th percentile), birth length was 49.3 cm (50th percentile), and head circumference was 34 cm (50th percentile). Clinical heart failure manifested shortly after birth and required inotropic support including dopamine, dobutamine, and digoxin. An echocardiogram on the first day of life demonstrated bilateral poor ventricular function, hypertrabeculation of the left ventricle, perfusion of trabecular recesses by Doppler color flow, and > 2:1 ratio of compacted to noncompacted myocardium, consistent with left ventricular noncompaction (LVNC). A screen for metabolic disorders was conducted and revealed methylmalonic aciduria (urine methylmalonic acid (MMA) 330 $\mu\text{mol}/\text{mmol}$ creatinine; normal < 5.1), hyperhomocysteinemia (total homocysteine (tHcy) 180 $\mu\text{mol}/\text{L}$; normal 5–13), and hypomethioninemia (methionine 6 $\mu\text{mol}/\text{L}$; normal 8–51) consistent with a diagnosis of an intracellular vitamin B12 disorder. Hydroxycobalamin, betaine, carnitine, folate, and aspirin were administered and a reduced protein diet was prescribed. After treatment, the levels of urine MMA and plasma tHcy decreased significantly (urine MMA 165 $\mu\text{mol}/\text{mmol}$; creatinine and tHcy 59.2 $\mu\text{mol}/\text{L}$), and plasma methionine increased to the normal range (22 $\mu\text{mol}/\text{L}$). The diagnosis of *cb1C* was established by cellular biochemical studies in the laboratory of Dr. David Rosenblatt (McGill University, Montreal, Canada). Her fibroblasts demonstrated diminished incorporation of propionate and methyl-THF, diminished synthesis of adenosyl- and methylcobalamin, and failed to complement cells of the *cb1C* class.

Fig. 1 Selected echocardiographic images. **(a)** Fetal echocardiography at 30 weeks (parasternal short axis view) showed hypertrabeculation (arrows) of both ventricles. **(b)** Echocardiography at 1 month (parasternal long axis view) revealed a globular apex. **(c)** Echocardiography at 1 month (parasternal short axis view) shows multiple deep trabeculations at the apex of the left ventricle

Sequence analysis of the *MMACHC* gene detected a homozygous mutation, c.271dupA. To rule out the possibility that uniparental disomy (UPD) at the *MMACHC* locus was present in the patient, 21 markers spaced along chromosome 1 that mapped 8.3 Mb telomeric and

1.0 Mb centromeric to the *MMACHC* gene were analyzed. The patient was heterozygous at 19 informative markers indicating there was no evidence of UPD or microdeletion around the *MMACHC* locus (data not presented). Other postnatal genetic investigations included a high-resolution karyotype and subtelomere FISH studies, both of which were normal.

At 1 month of age, an echocardiogram demonstrated poor left ventricular (LV) function, with estimated ejection fraction (LVEF; 43%) and decreased LV fractional shortening (LVFS; 20%). Noncompaction was noted at the apex of the LV (Fig. 1b, c). At 8 months, LV function had improved (70% EF and 40% LVFS), but noncompaction was still evident at the apex of the LV. At 30 months of age, ventricular function had stabilized and the cardiac morphology, except for a mild globular appearance of the left ventricle, appeared normal. Digoxin therapy had been initiated in early life and was continued.

Other clinical findings consistent with *cbIC* deficiency, such as feeding difficulties, macular changes, and developmental delay were present. Both parents had normal echocardiograms.

Discussion

Cardiac manifestations of *cbIC* disease have been described and include several congenital abnormalities (Andersson et al. 1999; Martinelli et al. 2010; Profitlich et al. 2009), cardiomyopathy (Martinelli et al. 2010; Profitlich et al. 2009), and endocardial fibrosis (Baumgartner et al. 1979; Geraghty et al. 1992; McCully 1969). At least 15 patients with *cbIC* have been reported with cardiomyopathy (Table 1; Baumgartner et al. 1979; Brandstetter et al. 1990; Carmel et al. 1980; Chenel et al. 1993; De Bie et al. 2009; Longo et al. 2005; Geraghty et al. 1992; Ogier de Baulny et al. 1998; Profitlich et al. 2009). However, the specifics regarding the type and echocardiographic manifestations of the cardiac lesions have not been fully delineated. Only three out of fifteen previously reported patients were diagnosed with LVNC (Profitlich et al. 2009); one additional patient displayed prominent left ventricular apical trabeculation but did not meet the criteria of noncompaction cardiomyopathy (Profitlich et al. 2009). Although an association with the underlying disorder has been assumed, none of the previously reported patients were evaluated for familial and genetic causes of noncompaction and, except for this report, parental echocardiograms were not performed. Biochemical and molecular genetic data (Table 2) have not uniformly been documented, although in several instances, the patients have had mutations and a clinical course consistent with “early onset” disease (Rosenblatt et al. 1997). Cobalamin C disease has also been documented in a single patient who

presented with dilated cardiomyopathy, diminished systolic function, hypocontractility of the left ventricle, and intra-uterine growth retardation (De Bie et al. 2009). Left ventricular noncompaction (LVNC) was not described in this infant. It therefore remains to be determined whether LVNC is present in all *cbIC* patients, if there is a correlation with *MMACHC* genotype(s), an association with the magnitude of metabolite elevations and/or the age of diagnosis or treatment.

Left ventricular noncompaction is a genetically heterogeneous condition that occurs because of failure of normal myocardial maturation during cardiac embryogenesis (Chin et al. 1990; Ichida 2009) and results in prominent trabeculations, particularly in the left ventricle (Chin et al. 1990; Ichida. 2009). LVNC can occur in patients with malformation syndromes, including velocardiofacial syndrome (Madan et al. 2010), Sotos syndrome (Martinez et al. 2011), as well as states of aneuploidy and mosaicism (Beken et al. 2011; McMahon et al. 2005; Sellars et al. 2011; Wang et al. 2007). Furthermore, LVNC has been reported in association with several distinct inborn errors of metabolism (IEM) including Barth syndrome (Bleyl et al. 1997); Pompe disease (Finsterer et al. 2006); Fabry disease (Stöllberger et al. 2003); cobalamin C disease (Profitlich et al. 2009); numerous mitochondrial disorders including Leber’s hereditary optic neuropathy (LHON) (Finsterer et al. 2002); mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome as well as less well-defined mitochondriopathies (Finsterer et al. 2006; Stöllberger et al. 1999). In at least one case, isolated LVNC has manifested as fetal hydrops (Richards et al. 2009).

There are several genes associated with isolated LVNC including G4.5 (*TAZ*), dystrobrevin (*DTNA*), LIM domain-binding protein 3 (*Cypher/ZASP: LDB3*), Lamin A/C (*LMNA*), *SCN5A*, and sarcomere proteins (β -myosin heavy chain, α -cardiac actin (*ACTC*), cardiac troponin T [*TNNT2*], tropomyosin 1 [*TPM1*]) (Xing et al. 2006; Ichida 2009; Chang et al. 2011). These gene products have functions related to cytoskeletal and/or mitochondrial function (Tang et al. 2010). Another six loci located on chromosomes 1p36 (Thienpont et al. 2007), 1q43 (Kanemoto et al. 2006), 5q35 (Pauli et al. 1999), 8p23 (Blinder et al. 2011), and 11p15 (Sasse-Klaassen et al. 2004) also have been linked to the phenotype of nonsyndromic LVNC. While a number of genes and candidate loci have been reported with LVNC, only a minority of affecteds have been found to harbor causative mutations (Finsterer et al. 2004; Ichida 2009; Tang et al. 2010; Xing et al. 2006). Although we and others have not able to rule out other genetic causes of LVNC in manifesting patients, that fact that other *cbIC* patients have been diagnosed with LVNC (Profitlich et al. 2009) and that the parents were unaffected in the case reported here provides some support for an association between *cbIC* disease and LVNC.

Table 1 Clinical features of congestive heart failure and cardiomyopathy in *cb1C* disease

Reference	Number of patients	Cardiac manifestations	Echocardiography	Pathology
Baumgartner et al. 1979	1	Congestive heart failure	N/A	Endocardial fibrosis, intima, and inner elastic membrane destruction of the coronary arteries
Carmel et al. 1980	1	Congestive heart failure	Cardiomyopathy	N/A
Brandstetter et al. 1990	1	Congestive heart failure	Right ventricular dilated cardiomyopathy	N/A
Geraghty et al. 1992	1	Congestive heart failure	N/A	Patchy endocardial fibrosis, intimal proliferation in the coronary arteries
Chenel et al. 1993	1	Congestive heart failure	Cardiomegaly, hypertrophic ventricular septum	N/A
Ogier de Baulny et al. 1998	3	Cardiomyopathy	N/A	N/A
Longo et al. 2005	2	Cardiomyopathy	N/A	N/A
Profitlich et al. 2009	4	Asymptomatic with low LV shortening fraction	Left ventricular noncompaction ($n = 3$), prominent left ventricular trabeculation ($n = 1$)	N/A
De Bie et al. 2009	1	Symmetrical intrauterine growth retardation	Thickened right ventricle, dilated cardiomyopathy, and small perimembranous ventricular septal defect	N/A
This report	1	Hydrops fetalis	Left ventricular noncompaction	N/A

Table 2 Enzymatic, biochemical, and molecular aspects of *cb1C* patients with congestive heart failure and cardiomyopathy

Reference	Number of patients	Cellular biochemistry/ molecular genetics	Plasma total homocysteine (tHcy)($\mu\text{mol/L}$; normal = 3–9.8)	Homocysteine plasma ($\mu\text{mol/L}$; normal = 0) (P) or urine(U) (mmol/mol Cr; normal = 0)	Plasma methionine ($\mu\text{mol/L}$; normal = 8–51)	Urine MMA (mmol/mol Cr; normal < 10)
Baumgartner et al. 1979	1	–	N/A	P = present U = high	Low	High
Carmel et al. 1980	1	+	N/A	P = present U = 151.7	7	4,751
Brandstetter et al. 1990	1	+	N/A	P = present U = 3.1	3	1,705
Geraghty et al. 1992	1	-	N/A	P = 37 U = N/A	0	1,187
Chenel et al. 1993	1	+	N/A	P=25 U=1,800	8	2,000
Ogier de Baulny et al. 1998	3	–	N/A	P = N/A U = N/A	N/A	N/A
Longo et al. 2005	2	+	71	P = N/A U = N/A	N/A	285
		+	52	P = N/A U = N/A	N/A	170
Profitlich et al. 2009	4	271dupA/271dupA	95	P = N/A U = N/A	N/A	266
		271dupA/271dupA	107	P = N/A U = N/A	N/A	196
		547_8delGT/285dupA	64	P = N/A U = N/A	N/A	31
		608G>A/608G>A	42	P = N/A U = N/A	N/A	20
De Bie et al. 2009	1	271dupA/271dupA	236 or 45	P = 66 U = N/A	5	High
This report	1	271dupA/271dupA	55	P = 2 U = N/A	42	250

The presence of LVNC in utero with cardiac dysfunction in the propositus is consistent with a model in which the MMACHC gene product may play a role in cardiac development. In a recent study, *Mmachc* mRNA was present and highly expressed in the bulbus cordis and endocardial cushion at E11 in mice (Pupavac et al. 2011). The role of MMACHC in development is unknown but given that MMADHC, a related enzyme in the pathway and a MMACHC binding partner (Plesa et al. 2011), was not expressed in the same temporal/spatial pattern may indicate a unique role for MMACHC in cardiac physiology and/or development (Pupavac et al. 2011). Other factors related to the biology of MMACHC may be contributory: MMACHC can localize to mitochondria (Pagliarini et al. 2008) and *cbfC* patients and their fibroblasts have increased markers of oxidative stress suggesting underlying mitochondrial dysfunction (Richard et al. 2009; Mc Guire et al. 2009). In addition, patient-derived cells display global dysregulation of cytoskeletal proteins, such as actin, lamin A/C, and collagen VI (Hannibal et al. 2011). Therefore, it seems reasonable that MMACHC deficiency could result in developmental cardiac defects, possibly by inducing secondary cellular ultrastructural changes and/or mitochondrial dysfunction. This hypothesis is consistent with the observation that genes responsible for LVNC have functions associated with cytoskeletal and/or mitochondrial metabolism, a finding that perhaps could be investigated in experimental animal models of *cbfC* disease.

To our knowledge, this is the first case of LVNC presenting prenatally in a patient with *cbfC* disease. The fact that a number of other *cbfC* patients have also been reported to have cardiomyopathy (Table 1) extends the hypothesis of a disease association between *cbfC* and cardiac pathology (McCully 1969; Profitlich et al. 2009) and highlights the importance of assessing all patients with *cbfC* for cardiac disease. The findings in the patient reported here also emphasize that a metabolic evaluation for *cbfC* should be considered in the setting of nonimmune hydrops fetalis, especially if fetal cardiomyopathy is present.

Synopsis

A case report of prenatal onset left ventricular noncompaction and hydrops in cobalamin C disease.

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