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Cardiomyopathy, an uncommon phenotype of congenital disorders of glycosylation: Recommendations for baseline screening and follow-up evaluation

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Abstract

Conflict of interest statement

The authors report no conflict of interest.

Ethical statement

Patients included in this work were enrolled in the Frontier in CDG Consortium (FCDGC) natural history study after consents were obtained from the legally authorized representatives of the patients (Institutional Review Board 19–005187; https://clinicaltrials.gov/ct2/show/NCT04199000?cond=CDG&draw=2&rank=4). For those patients who were deceased prior to the initiation of this study, legally authorized representatives agreed to the publication of their data.

Introduction: Congenital disorders of glycosylation (CDG) are a continuously expanding group of monogenic disorders that disrupt glycoprotein and glycolipid biosynthesis, leading to multi-systemic manifestations. These disorders are categorized into various groups depending on which part of the glycosylation process is impaired. The cardiac manifestations in CDG can significantly differ, not only across different types but also among individuals with the same genetic cause of CDG. Cardiomyopathy is an important phenotype in CDG. The clinical manifestations and progression of cardiomyopathy in CDG patients have not been well characterized. This study aims to delineate common patterns of cardiomyopathy across a range of genetic causes of CDG and to propose baseline screening and follow-up evaluation for this patient population.

Methods: Patients with molecular confirmation of CDG who were enrolled in the prospective or memorial arms of the Frontiers in Congenital Disorders of Glycosylation Consortium (FCDGC) natural history study were ascertained for the presence of cardiomyopathy based on a retrospective review of their medical records. All patients were evaluated by clinical geneticists who are members of FCDGC at their respective academic centers. Patients were screened for cardiomyopathy, and detailed data were retrospectively collected. We analyzed their clinical and molecular history, imaging characteristics of cardiac involvement, type of cardiomyopathy, age at initial presentation of cardiomyopathy, additional cardiac features, the treatments administered, and their clinical outcomes.

Results: Of the 305 patients with molecularly confirmed CDG participating in the FCDGC natural history study as of June 2023, 17 individuals, nine females and eight males, were identified with concurrent diagnoses of cardiomyopathy. Most of these patients were diagnosed with PMM2-CDG (n=10). However, cardiomyopathy was also observed in other diagnoses, including PGM1-CDG (n=3), ALG3-CDG (n=1), DPM1-CDG (n=1), DPAGT1-CDG (n=1), and SSR4-CDG (n=1). All PMM2-CDG patients were reported to have hypertrophic cardiomyopathy. Dilated cardiomyopathy was observed in three patients, two with PGM1-CDG and one with ALG3-CDG; left ventricular non-compaction cardiomyopathy was diagnosed in two patients, one with PGM1-CDG and one with DPAGT1-CDG; two patients, one with DPM1-CDG and one with SSR4-CDG, were diagnosed with non-ischemic cardiomyopathy. The estimated median age of diagnosis for cardiomyopathy was 5 months (range: prenatal–27 years). Cardiac improvement was observed in three patients with PMM2-CDG. Five patients showed a progressive course of cardiomyopathy, while the condition remained unchanged in eight individuals. Six patients demonstrated pericardial effusion, with three patients exhibiting cardiac tamponade. One patient with SSR4-CDG has been recently diagnosed with cardiomyopathy; thus, the progression of the disease is yet to be determined. One patient with PGM1-CDG underwent cardiac transplantation. Seven patients were deceased, including five with PMM2-CDG, one with DPAGT1-CDG, and one with ALG3-CDG. Two patients died of cardiac tamponade from pericardial effusion; for the remaining patients, cardiomyopathy was not necessarily the primary cause of death.

Conclusions: In this retrospective study, cardiomyopathy was identified in ~6% of patients with CDG. Notably, the majority, including all those with PMM2-CDG, exhibited hypertrophic cardiomyopathy. Some cases did not show progression, yet pericardial effusions were commonly observed, especially in PMM2-CDG patients, occasionally escalating to life-threatening cardiac tamponade. It is recommended that clinicians managing CDG patients, particularly those with PMM2-CDG and PGM1-CDG, be vigilant of the cardiomyopathy risk and risk for potentially life-threatening pericardial effusions. Cardiac surveillance, including an echocardiogram and EKG,

should be conducted at the time of diagnosis, annually throughout the first 5 years, followed by check-ups every 2–3 years if no concerns arise until adulthood. Subsequently, routine cardiac examinations every five years are advisable. Additionally, patients with diagnosed cardiomyopathy should receive ongoing cardiac care to ensure the effective management and monitoring of their condition. A prospective study will be required to determine the true prevalence of cardiomyopathy in CDG.

Keywords

congenital disorders of glycosylation; cardiomyopathy; inborn error of metabolism; N-glycans; phenotyping

Introduction

Glycosylation plays a crucial role in various cellular processes, including cell recognition, adhesion, migration, resistance to proteases, and host defense mechanisms.[1] Congenital Disorders of Glycosylation (CDG) are a genetically and clinically heterogeneous group of rare inherited metabolic disorders, caused by defects in various steps of the complex process of glycosylation occurring in the endoplasmic reticulum, Golgi apparatus, and the cytosol. Glycosylation is the covalent attachment of oligosaccharide residues to proteins or lipids, which is crucial for cellular structure and function.[2,3] The first CDG was reported in 1980,[4] and 200 distinct types of CDG have been identified to date.[5,6] The broadening in their diagnosis has been largely attributed to advancements in glycosylation biochemical assays, including transferrin isoelectric focusing and mass spectrometry, and the advent of genomic testing, including exome sequencing (ES) and genome sequencing (GS). Most of the monogenic disorders are inherited in an autosomal recessive manner, but autosomal dominant and X-linked forms have been reported as well.[2,7–9]

Given the ubiquitous nature of glycosylation in human biology, CDG can lead to a wide range of clinical symptoms, often presenting as multisystemic diseases. The phenotypic spectrum is broad, and the severity of symptoms is diverse, both within and between types. CDG patients often present with developmental delay, intellectual disability, failure to thrive and feeding problems, neurologic abnormalities, hepatopathy, and coagulopathy. Affected individuals may also show signs of ocular and dermatological conditions, distinctive facial features, and cardiac disease.[2,10,11]

Cardiomyopathies, a diverse group of heart muscle disorders, are defined by abnormal myocardial structure or function not due to ischemic conditions or external stress factors, and can be familial (inherited) or non-familial (acquired). With over 100 associated genes identified, estimates suggest that more than 60% of hypertrophic and 30–35% of dilated cardiomyopathies are monogenic in origin.[12–14] The initial link between cardiomyopathy and CDG was established in 1992, and numerous instances of cardiomyopathy in CDG patients have been documented since then, although these have not been thoroughly delineated.[15] In a recent systematic review, the authors offered a comprehensive overview of inherited metabolic disorders linked to carbohydrate metabolism that present with cardiomyopathies, arrhythmogenic disorders, and/or structural cardiac defects.[14] They

identified 29 that clinically present with cardiac manifestations in patients with CDG.[6] Twenty-three of the identified disorders presented with cardiomyopathy, categorized by their genetic defects: N-glycosylation defects include *ALG3, ALG6, ALG9, ALG12, GMPPB, NPL, PGM1*, and *PMM2*; O-glycosylation defects include *B3GALTL, FKRP, FKTN, POMT1,* and *POMT2*; defects in dolichol-phosphate synthesis are found in *DOLK, DPM3, MPDU1*, and *SRD5A3*; GPI anchor synthesis defects are associated with *PIGA, PIGN*, and *PIGT*; COG complex defects with *COG1*; and V-ATPase complex defects with *ATP6V1A* and *ATP6V1E1*. Another systematic review from 2017 reported cardiac involvement in 20% of patients with CDG, including cardiomyopathies, structural defects, and arrhythmogenic disorders.[1] This review cataloged cardiomyopathy cases across various CDG disorders as follows: PMM2-CDG featured 11 patients with hypertrophic cardiomyopathy, alongside reports of cardiomegaly and cardiac dilation. FKRP-CDG was the most prevalent CDG type affected with cardiomyopathy, with 81 patients displaying mostly a dilated phenotype. DOLK-CDG had 22 patients with dilated cardiomyopathy and one with biventricular hypertrophy. PGM1-CDG featured 11 patients with dilated cardiomyopathy. For FKTN-CDG, 6 patients had dilated cardiomyopathy, with additional cases showing cardiomegaly and cardiac dilation variants. Less frequent were ALG12-CDG, ALG9-CDG, POMT1-CDG, POMT2-CDG, SRD5A3-CDG, PIGA-CDG, PIGN-CDG, PIGT-CDG, COGI-CDG, ATP6V1A-CDG, and ATP6V1E1-CDG, each documenting one to two patients with various forms of hypertrophic and dilated cardiomyopathy, or more nonspecific abnormal dilation or hypertrophy of individual cardiac chambers.

Despite the impact of cardiac disease on morbidity and mortality in CDG, there is a lack of detailed descriptions regarding the clinical manifestations and progression of cardiomyopathy in CDG. In this retrospective case series, we aimed to identify the prevalence of cardiomyopathy and the common cardiomyopathy patterns found among a large cohort of patients with a broad spectrum of genetic causes of CDG, and to propose recommendations for clinical surveillance. This work could enhance the early ascertainment and management strategies for cardiomyopathy in CDG patients.

Methods

Subjects

Three hundred and five patients with molecular and clinical confirmation of CDG were enrolled in the prospective and memorial arms of the Frontiers in Congenital Disorders of Glycosylation Consortium (FCDGC) Natural History study as of June 2023. The enrollment process for the natural history study included both retrospective and prospective data collection, and patients were followed up annually by standard of care. As part of the current study, the retrospective clinical data for those molecularly confirmed patients in the registry were reviewed for the presence of cardiomyopathy and collected for the preparation of this manuscript.

Clinical studies

All patients with a confirmed molecular diagnosis of CDG were evaluated by clinical geneticists at their respective academic centers belonging to FCDGC. This comprehensive

evaluation included a full history and physical examination, along with molecular testing and carbohydrate-deficient transferrin analysis. Imaging studies, when clinically indicated, such as X-rays, echocardiography, abdominal ultrasounds, electroencephalograms, and brain MRIs, were also performed.

Cardiomyopathy was ascertained by echocardiogram, and patients were referred to the Cardiology service at the primary institution. The duration of cardiac follow-up ranged from the time of cardiac disease diagnosis to the last known follow-up visit. Details were recorded regarding the type of cardiomyopathy, the patient's age at the initial presentation of cardiomyopathy, additional cardiac features, the treatments administered, and the clinical outcomes. For some patients, echocardiography results were also available and recorded in this study.

The Nijmegen Progression CDG Rating Score (NPCRS) was administered to fourteen patients in the study. Patient #06010, diagnosed with ALG3-CDG, passed away at 7 weeks of age, and due to his early age, the NPCRS could not be administered. NPCRS was not available for two patients (Patient #05007 and Patient #M08006). The NPCRS is a clinical instrument designed to quantify the clinical severity of CDG patients in a holistic manner and has been validated for all age groups.[16,17]

Echocardiographic data

Data for the study were extracted from written echocardiogram reports. Echocardiogram images were largely unavailable for direct review. Measurement of the left ventricular ejection fraction (LVEF) was primarily conducted using Simpson's biplane method, with the bullet method serving as a secondary approach when the former was not applicable.

Statistical analysis

We used descriptive statistics to investigate the characteristics of the entire cohort of patients with CDG and cardiomyopathy.

Results

Subjects

Of the 305 patients with molecularly confirmed CDG participating in the FCDGC natural history study, 17 individuals (5.6%) - nine females and eight males - were identified with concurrent diagnoses of cardiomyopathy. The median age at diagnosis of CDG was 9.5 months (range: 10 days to 4 years), and the median age of clinical assessment at enrollment to FCDGC natural history study was 2.25 years (range: 3 months-27 years). Most of these patients were diagnosed with PMM2-CDG (n=10). However, cardiomyopathy was also observed in other diagnoses, including PGM1-CDG (n=3), ALG3-CDG (n=1), DPM1-CDG (n=1), DPAGT1-CDG (n=1), and SSR4-CDG (n=1). All but one variant were known to be pathogenic or likely pathogenic. One patient had a novel homozygous variant in *ALG3* which was classified as a variant of uncertain significance favoring pathogenicity due to its bioinformatic scores, functional validation using carbohydrate-deficient transferrin analysis, and the patient's clinical phenotype. When tested, all variants were inherited. One

patient had a sibling with DPAGT1-CDG while the others had no family history of CDG. Consanguinity was reported for the parents of a patient with PGM1-CDG but not in other families.

Cardiac findings

Clinical information was available for all patients (Table 1). Ten patients with PMM2-CDG were reported to have hypertrophic cardiomyopathy. Dilated cardiomyopathy was observed in three patients, two with PGM1-CDG (Patient #01081 and Patient #01130) and one with ALG3-CDG (Patient #06010). Left ventricular non-compaction (LVNC) cardiomyopathy was diagnosed in two patients, one with PGM1-CDG (Patient #01265) and one with DPAGT1-CDG (Patient #M03005). Additionally, two patients, one with DPM1-CDG (Patient #05007) and one with SSR4-CDG (Patient #01051), were diagnosed with non-ischemic cardiomyopathy. Further information to allow complete characterization of their non-ischemic cardiomyopathy was not available. (Figure 1) The estimated median age of cardiomyopathy onset was 5 months (range: prenatal–27 years). Additional cardiac findings were observed in fourteen patients, with the most common presentation being pericardial effusion (n=9). The median duration of cardiac follow-up was 20 months (range: 1 month-26.5 year). Cardiac improvement was observed in three patients with PMM2-CDG. Five patients showed a progressive course of cardiomyopathy (two patients with PGM1-CDG, one patient with PMM2-CDG, one with DPM1-CDG, and one patient with ALG3-CDG), while the condition remained unchanged in eight individuals. One patient with SSR4-CDG (Patient #01051) has been recently diagnosed with cardiomyopathy; thus, the progression of the disease is yet to be determined. Nine patients received medical treatment for their cardiac manifestations. Patient #M03002, with PMM2-CDG and hypertrophic cardiomyopathy, underwent pericardiocentesis at 4 months of age due to a large pericardial effusion. Patient #M03005, with DPAGT1-CDG and LVNC cardiomyopathy, received a VVI epicardial pacemaker for bradycardia, and Patient #01265, diagnosed with PGM1-CDG and non-compaction cardiomyopathy, underwent mitral valve surgery, was placed on ECMO, and eventually received a cardiac transplant at the age of one. Seven patients have passed away, five with PMM2-CDG, one with DPAGT1-CDG, and one with ALG3-CDG. The causes of death varied: two patients with PMM2-CDG suffered cardiac tamponade, another with PMM2-CDG experienced culture-negative shock, and a fourth from the same group died of peritonitis. A newborn with ALG3-CDG succumbed to sepsis and subsequent multi-organ failure. The causes of death for two patients, one with DPAGT1-CDG and another with PMM2-CDG, were not recorded.

Echocardiographic data

Echocardiogram reports were accessible for seven patients (Patients: #03002, #03014, #M03001, #M03002, #M03003, #M03004, #M08006) with PMM2-CDG diagnosed with hypertrophic cardiomyopathy (Table 2, Figure 2). The median age at the initial time of the imaging study was 4 months (range: birth – 3 years). The qualitative left ventricle function was normal for all seven patients. The level of hypertrophy was mild for five patients, moderate for Patient #M03003, and progressed from mild to moderate for Patient #M03004. Moderate left ventricular outflow tract obstruction (LVOTO) was noticed in Patient #M08006, with a peak velocity of 3.5m/s and a peak gradient of 31mmHg. Patient

#M03004 exhibited dynamic LVOTO at 10 months of age, with a peak gradient of 50mmHg during agitation and tachycardia, and 35mmHg when calm (Figure 2A–B). Six of the seven patients experienced pericardial effusion, and three of these cases progressed to tamponade, leading to the death of two patients (Figure 2C–E). Patient #M03004 and Patient #M08006 were observed to have moderate mitral regurgitation and systolic anterior motion of the mitral valve leaflet.

Extra-cardiac manifestations

Prenatal history among CDG patients with cardiomyopathy was variably complicated by multiple congenital anomalies, neural tube defects, cleft lip or palate, polyhydramnios, fetal growth restriction, maternal infections, preterm labor, and preterm delivery; however, no consistent pattern of prenatal complications was observed among these patients (Supplemental Table 1).

All patients exhibited dysmorphic features characteristic of CDG, and all except one presented with neurological symptoms, including hypotonia, ataxia, and seizures. Microcephaly was diagnosed in six patients, while developmental delay or intellectual disability, with varying levels of functionality, were identified in fourteen patients. The most frequent ocular abnormalities were strabismus and nystagmus, with two patients showing optic nerve hypoplasia and another two diagnosed with congenital cataracts. Hearing loss at various levels was identified in four patients.

Endocrine abnormalities were present in most patients (n=16), encompassing conditions like hypothyroidism, adrenal insufficiency, hyperinsulinism leading to hypoglycemia, and delayed puberty. Respiratory complications were observed in eight patients. Skeletal abnormalities, including short stature, scoliosis, contractures, hip dislocation, overlapping digits, and foot deformities, were noted in nine patients. Gastrointestinal issues, such as feeding difficulties, failure to thrive, gastroesophageal reflux, enteropathy, constipation, ascites, and peritonitis, were prevalent in all patients, with ten requiring tube feeding or total parenteral nutrition. Hepatopathy was reported in fourteen patients, and genitourinary anomalies were identified in eight. Low cholesterol levels were observed in three individuals. Infections were a common presentation for CDG patients (n=11). Eleven patients had hematologic abnormalities or vascular disorders, with anemia and hypercoagulability with low antithrombin III being the most frequent. Abnormal fat pads were the most common skin manifestation.

Nijmegen Progression CDG Rating Scale (NPCRS)

Fourteen individuals were evaluated using the Nijmegen Progression CDG Rating Scale at their institution at baseline (Supplemental Table 1).[16] The NPCRS scales patients into mild (0–14), moderate (15–25) and severe (>25) categories. Nine patients scored in the severe range, three in the moderate range, and two in the mild range. The total median was 30.5, ranging from 5 to 43.

Biochemical and molecular studies

Carbohydrate-deficient transferrin profiling was performed for all patients. All patients underwent molecular testing with a confirmed diagnosis of CDG. Of these, nine patients underwent proband or trio ES, three were tested with a gene panel specific to CDG, three received Sanger sequencing with deletion and duplication analysis of the *PMM2* gene, one had sequencing of the *PGM1* gene, and another had the *DPM1* gene sequenced. Single-gene testing was conducted due to high clinical suspicion based on typical syndromic presentation. The most common genetic variants found in PMM2-CDG were c.422G>A (p.Arg141His) (8/20), c.357C>A (p.Phe119Leu) (5/20), and c.691G>A (p.Val231Met) (3/20) (Table 1). The most prevalent genotype in our cohort was p.Arg141His | p.Phe119Leu, accounting for four individuals. Three patients with ALG3-CDG, PGM1-CDG, and SSR4-CDG had homozygous variants.

Discussion

Glycomics-based studies focusing on cardiomyocytes indicate that glycosylation plays a crucial role in regulating and modulating the structural development and function of the heart.[18–20] Despite the significant role of cardiac disease in the morbidity and mortality associated with CDG, detailed accounts of the clinical presentation and evolution of cardiomyopathy in these disorders remain scarce. In our research, we sought to uncover the prevalence of cardiomyopathy within a large group of molecularly confirmed CDG patients recruited to the FCDGC Natural History study, the different patterns of cardiomyopathy, the clinical progression of the disease, its prognosis, and to suggest recommendations for clinical monitoring. Our findings have the potential to improve early detection, establish follow-up guidelines, and intervention approaches for managing cardiomyopathy in individuals with CDG.

In this retrospective study, cardiomyopathy was identified in ~6% of patients with CDG enrolled in the FCDGC Natural History study. CDG can be associated with several types of cardiomyopathies, including hypertrophic, dilated, LVNC, and non-ischemic cardiomyopathy. There was no sex preference in the patients who were diagnosed with cardiomyopathy. Additional cardiac findings were observed in fourteen patients, with the most common presentation being pericardial effusion. Cardiac improvement was observed in three patients with PMM2-CDG. Five patients showed a progressive course of cardiomyopathy, while the condition remained unchanged in eight individuals. Nine patients (53%) received medical treatment for their cardiac manifestations, predominantly heart failure medications, including beta-blockers, ACE inhibitors, and diuretics. Three patients underwent surgical interventions, including pericardiocentesis, VVI epicardial pacemaker placement for bradycardia, and cardiac transplantation. Seven patients have passed away, five of whom died in their first year of life. While two patients passed away of cardiac tamponade from pericardial effusions, cardiomyopathy was not the primary cause of death for the remaining patients.

PMM2-CDG is the predominant genetic cause among diagnosed CDG, and as such, accounts for more than half of the cardiomyopathy cases in our cohort. Consistent with previously reported cases,[1,14,21–23] all patients with PMM2-CDG were diagnosed with

hypertrophic cardiomyopathy. This indicates the potential association between certain genetic causes of CDG and a specific pattern of cardiac involvement. Additionally, half of these patients passe d away, most often within their first year of life. However, the cardiac status improved in three of these patients. Dilated cardiomyopathy was observed in three patients, two with PGM1-CDG and one with ALG3-CDG. To date, 30 patients with confirmed PGM1-CDG have been reported with cardiac involvement.[14,24] Cardiac involvement included dilated cardiomyopathy (15 patients), in some cases restrictive cardiomyopathy, cardiomegaly, left ventricular dilation, left ventricular hypertrophy, aortic coarctation, ventricular septal defect, mitral prolapse, arrhythmia, and even cardiac arrest.[14,25,26] Cardiovascular involvement has been reported in 15 patients with ALG3-CDG, including hypertrophic obstructive cardiomyopathy, biventricular hypertrophy, cardiomegaly, right descending aorta, aortic root dilatation, tricuspid valve regurgitation, and other structural defects.[14,27,28] The presented case represents the first instance of a patient with ALG3-CDG accompanied by dilated cardiomyopathy, thereby broadening the known phenotypic spectrum of the disorder. In our study, LVNC was identified in two patients: one with PGM1-CDG and the other with DPAGT1-CDG. While PGM1-CDG was associated with dilated cardiomyopathy, left ventricular dilation, and hypertrophy, the observed occurrence of LVNC cardiomyopathy in our study is regarded as a phenotypic expansion for PGM1-CDG. However, this type of cardiomyopathy has been previously described in association with other CDG, as it was reported in a patient with PIGN-CDG.[1] Additionally, two patients were diagnosed with non-ischemic cardiomyopathy: one with DPM1-CDG and another with SSR4-CDG. Additional information to allow further classification of their cardiomyopathy was not available. There are no reports of non-ischemic cardiomyopathy in patients with CDG. While it is possible that the patients with non-ischemic cardiomyopathy may represent an expansion of the cardiac phenotype observed in patients with CDG, it is not clear from these data whether this diagnosis truly represents a phenotype expansion or whether this finding could be classified into a more specific cardiomyopathy phenotype. In this report, we describe for the first time the occurrence of cardiomyopathy in patients with DPAGT1-CDG, DPM1-CDG, and SSR4-CDG. Consistent with prior reviews, the majority of cardiomyopathy cases in our study manifested within the first year of life and were linked to a high rate of morbidity and mortality.[22,29]

The muscular component of the heart, the myocardium, is composed of highly specialized contractile cells. To fulfill the energy needs of the contractile apparatus within these cells, the biochemistry of the human myocardium has evolved to facilitate continuous energy production from various substrates, predominantly lipids and carbohydrates.[14] Glycoproteins make up approximately 50% of the body’s protein composition, with glycosylation being critical to their functionality. One hypothesis is that hypoglycosylation of glycoproteins may induce alterations of the dystrophin-associated glycoproteins in the sarcolemmal plasma membrane.[22] The significance of glycosylation in controlling and modulating cardiac structure and function has been confirmed through the analysis of glycome profiles in cardiomyocytes.[1] The glycome profile has been observed to change during development between atrial and ventricular cells.[18] In a buffalo heart, hypoglycosylation of galectin-1 (a glycosylated protein found in numerous cardiac

structures and tissues) caused a significant deviation from the regular secondary structure of the protein and impaired its functional integrity.[19] Nagai-Okatani and Minamino demonstrated that the gene and glycoproteome expression in the rodent model of hypertension-induced cardiac hypertrophy exhibited significant changes in glycosylation pattern, specifically upregulation of mucin-type O-glycosylation, and downregulation of core fucosylation on N-glycans.[20] Furthermore, the expression of B-type natriuretic peptide (BNP) and proBNP protein are highly regulated by glycosylation and have been consistently associated with heart failure.[30] ProBNP has been identified to possess seven potential O-glycosylation sites, which regulate the cleavage of this peptide, thereby influencing the production of activated BNP and amino-terminal proBNP.[31] These studies underscore the important role of glycosylation in regulating and controlling cardiac function.[1]

Sporadic reports have identified CDG-associated genes, such as *PGM1* and *B3GAT3*, that impact cardiac function, but their role in disease pathology requires additional exploration. A potential mechanism for cardiac symptoms, particularly dilated cardiomyopathy, in PGM1-CDG patients, was proposed by Arimura et al.: when rat cardiomyocytes were subjected to stress, PGM1 bound directly to an anchoring protein named Z-band alternatively spliced PDS-motif protein (ZASP, homolog of LDB3 in humans), suggesting a potential compensatory cardioprotective mechanism. Therefore, loss of function of PGM1 can result in dilated cardiomyopathy.[32] The *B3GAT3* gene has been expressed in the aortic tissue of mice and the human heart.[33] Its messenger RNA analysis in murine and humans revealed that this protein is highly expressed in the brain, kidney and heart cells.[34,35] In an in vitro model, *B3GALTL* knockdown resulted in decreased secretion of ADAMTSL2 protein, a metalloendopeptidase found to be expressed in human cardiomyocytes.[36] Furthermore, glycoprotein glycans are recognized as primary regulators of ion channels, particularly voltage-gated channels, which are prevalent in cardiac cells and crucial for optimal cardiac function.[1] Therefore, disruptions in glycosylation and sialylation likely impact ion channel function, leading to compromised cardiac performance.[37] Specifically, the deletion of *ST3Gal4*, a gene crucial for sialylation, has been shown to affect sodium channel functionality, thereby contributing to cardiac disease by impacting ventricular myocyte electrical signaling.[38] Moreover, dilated hearts were frequently observed in *Srd5a3* homozygous null mice with impaired dolichol formation.[39] Disruption of the integrity of the cardiac myocyte intercalated disc, which is composed of gap junctions, adhesion junctions, and desmosomes, may lead to cardiomyopathy.[29] LIMP-2 is a component of the cardiac myocyte intercalated disc, and is known to be a glycosylated protein. Schroen et al. demonstrated that a complete loss of LIMP-2 leads to failure to mount a hypertrophic response to hypertension in a LIMP-2 null mouse model, resulting in cardiomyopathy. Therefore, dilated cardiomyopathy may be secondary to the dysglycosylation of glycoproteins involved in the cardiac myocyte intercalated disc structure.[40] Although the molecular mechanisms underlying cardiomyopathy are not fully understood, these observations confirm the significant role of genes and proteins involved in glycosylation in the heart physiology and pathology.

Based on mostly retrospective data from this natural history study, along with previous case reports and systematic reviews, there is notable variability in the incidence and

pattern of cardiac involvement across different types of CDG. Cardiac involvement can vary widely, from subclinical conditions to severe cardiomyopathy. Most patients with CDG are diagnosed with cardiomyopathy in their first months of life, and even upon birth, which might impact the prognosis.[41] As the disease progresses, it is critical to implement appropriate therapeutic measures and ensure diligent follow-up. Management of CDG-associated cardiomyopathy may include medical therapy for heart failure, such as beta-blockers, ACE inhibitors and diuretics, lifestyle modifications, and in some patients, surgical intervention and even cardiac transplantation. Our patient with LVNC cardiomyopathy and PGM1-CDG represents the sixth reported case of successful heart transplantation in individuals with CDG and cardiomyopathy, following four with severe dilated cardiomyopathy due to DOLK-CDG and one with severe dilated cardiomyopathy and PGM1-CDG.[24] Clinicians caring for patients with CDG, particularly for those with PMM2-CDG and PGM1-CDG, should be aware of the risk of cardiomyopathy, and conduct baseline and regular cardiac evaluations, including echocardiogram and EKG, especially upon the emergence of clinical symptoms. Based on previous studies and current cases, we suggest annual cardiac surveillance until the age of 5 years, followed by check-ups every 2–3 years if no concerns arise until adulthood. Afterward, routine cardiac examinations every five years are advisable. Additionally, CDG patients with diagnosed cardiomyopathy should receive ongoing cardiac care to ensure the effective management and monitoring of their condition for other cardiac involvement and complications. In our cohort, pericardial effusions were notably prevalent, mostly for patients with PMM2-CDG. This finding underscores the propensity for pericardial effusions within this population and indicates a need for vigilant screening. Given that pericardial effusions can rapidly evolve into cardiac tamponade, a condition with life-threatening implications, their commonality and importance cannot be overlooked. This alarming potential for acute progression heightens the importance of our discovery and necessitates a proactive approach to monitoring and intervention to preempt severe outcomes. An increasing frequency of clinical evaluation and echocardiographic surveillance, with a lower threshold for interventions such as pericardiocentesis and/or pericardial window creation, may help reduce morbidity and improve outcomes. The recurrent presentation of pericardial effusion as a cardiac manifestation and its cause of death in some CDG patients highlights it as a key finding of our research and a critical area for clinical attention. Therefore, a multidisciplinary team should be involved in the care of these patients and determine the frequency of clinical evaluations and imaging follow-ups. Furthermore, children with cardiomyopathy and evidence of multi-organ involvement should be screened for CDG, especially as implemented treatment becomes more etiology-oriented, and timely diagnosis is crucial. The recommendations provided are based on the integration of both empirical data and expert clinical insights.

Although the data were extracted from the FCDGC natural history study, its limitations should be acknowledged. We encountered incomplete records, such as missing echocardiogram reports or limited phenotypic descriptions. Given that patients are enrolled at various stages of their disease and have been followed by different institutions throughout their lives, there is a potential for recall bias stemming from inaccurate recollections of history or medical documentation. Variations in treatment protocols and follow-up practices

over time and between institutions can lead to inconsistent data. Furthermore, we lack information about patients who have been lost to follow-up and may have subsequently developed cardiomyopathy over the course of their disease. The retrospective clinical nature of this study precludes us from making definitive conclusions about potential mechanisms for cardiomyopathy in patients with CDG. Prospective studies that monitor the progression of cardiomyopathy in CDG patients over time, trials of new therapeutic interventions, and molecular studies aimed at elucidating the precise pathways by which glycosylation defects affect cardiac tissue, are warranted.

In conclusion, in this retrospective study, cardiomyopathy was identified in ~6% of patients enrolled in the FCDGC Natural History study. The majority, including all those with PMM2-CDG, exhibited hypertrophic cardiomyopathy. Some cases did not show progression, yet pericardial effusions were commonly observed, occasionally escalating to life-threatening cardiac tamponade. A significant proportion of patients passed away in their first year of life, although cardiomyopathy was not necessarily the primary cause of death. It is recommended that clinicians managing CDG patients, particularly those with PMM2-CDG and PGM1-CDG, acknowledge the cardiomyopathy risk and conduct cardiac evaluations upon confirmation of CDG diagnosis and perform periodic surveillance cardiac evaluations as mentioned, with increasing frequency upon the emergence of clinical symptoms. Additionally, patients with diagnosed cardiomyopathy should receive ongoing cardiac care to ensure the effective management and monitoring of their condition. A collaborative approach to the care of CDG patients with cardiomyopathy, involving cardiologists, geneticists, and other specialties to ensure comprehensive and effective treatment is justified. Ongoing research is essential to further delineate the mechanisms underlying the association between CDG and cardiomyopathy, and to develop more effective strategies for the management of patients with CDG and cardiomyopathy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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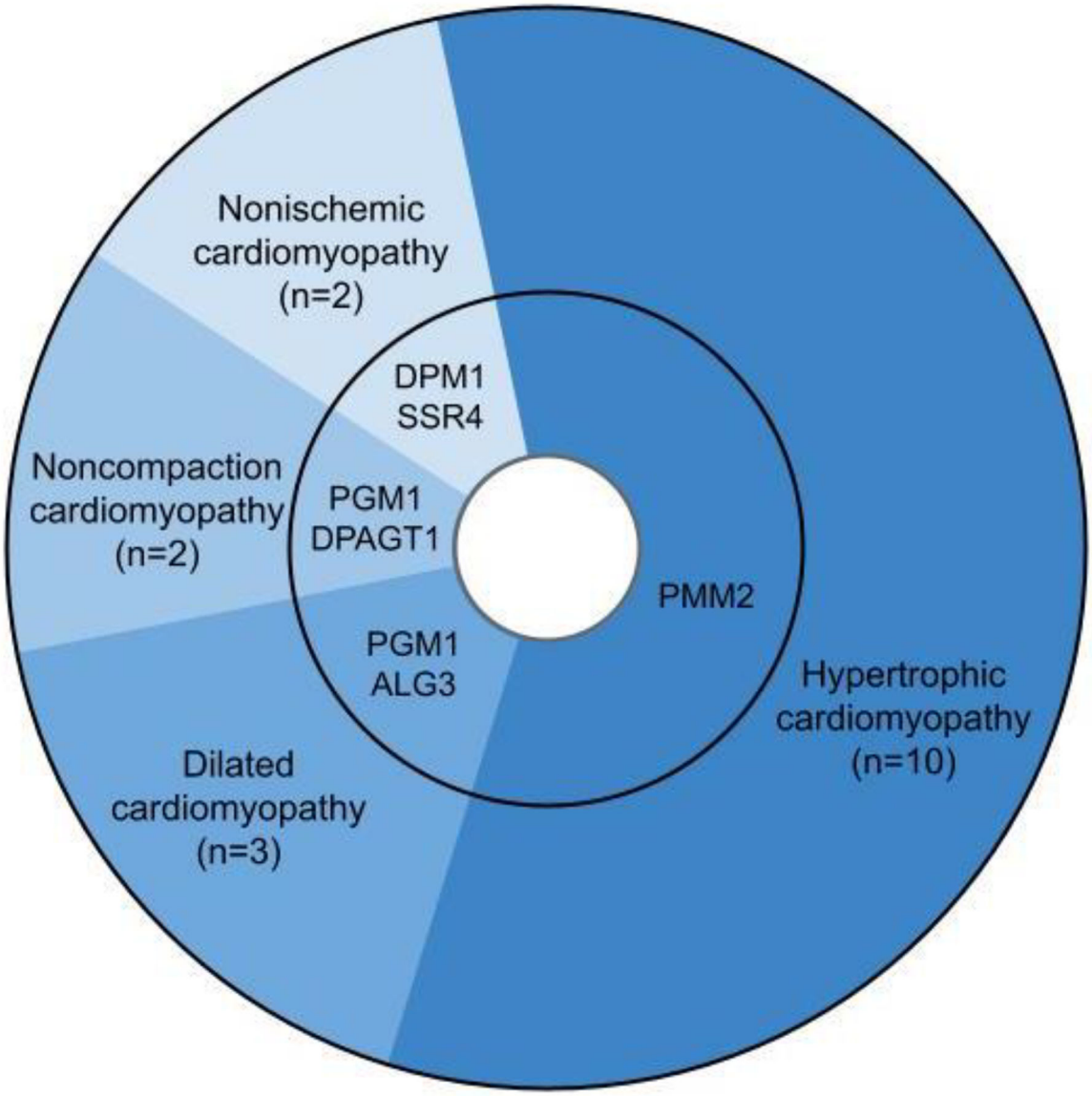

Figure 1: Types of cardiomyopathy and genetic etiology

Cardiomyopathies are rendered by frequency, and the associated CDG genes are included for each type of cardiomyopathy.

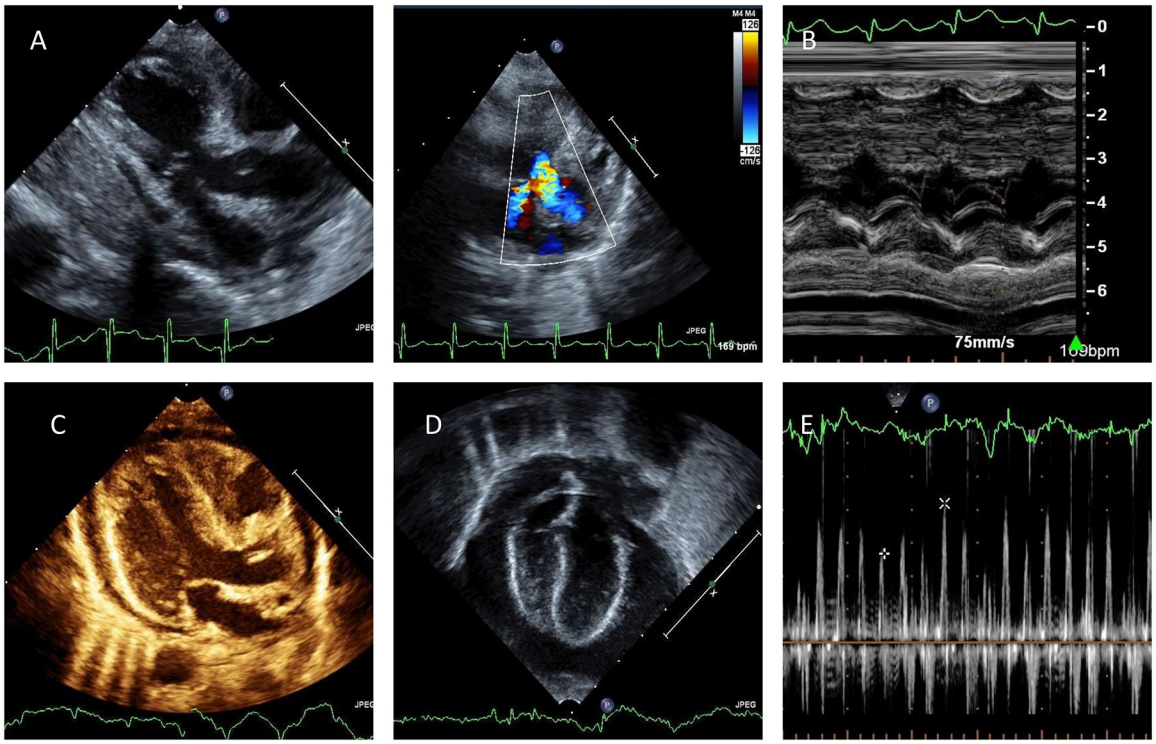

Figure 2.

Echocardiogram images

Representative echocardiograms from Patient #M03004 at 11 months, including A) off-axis parasternal long axis without (left) and with (right) color demonstrating asymmetrical septal hypertrophy with outflow tract obstruction and mild-to-moderate mitral regurgitation. B) M-mode of parasternal short axis demonstrating left ventricular hypertrophy (e.g. diastolic intraventricular septal dimension (IVSd, 7.2mm, z= +3.73). C) long axis image of Patient #M03003 at one month of age demonstrating moderate asymmetric LVH (IVSd 8.1mm, z=+5.5) as well as trace pericardial effusion. D) Apical four-chamber view at two months of age with large, global pericardial effusion measuring 2.2cm maximally, evidence of right atrial collapse, and E) mitral valve inflow pattern with 36% respiratory variation suggestive of tamponade physiology.

Table 1:

ic involvement in CDG patients

nt er	Sex	Diagnosis (CDG type)	Genotype	Protein change	Age at CDG diagnosis	Family history of CDG	Age at diagnosis of cardiac involvement	Cardiomyopathy phenotype	Duration of Cardiac Follow Up	Additional Cardiac Findings	Medications Used	Surgery / Interventions	Status of cardiomyopathy	Outcome
nt 02	F	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	1.5 years	No	2 years	Hypertrophic	9 years	Chronic PCE	None reported	None reported	Static	Alive, age 11 years
nt 14	M	PMM2-CDG	c.385G>A; c.422G>A	p.Val129Met;p.Arg141His	9 months	No	5 months	Hypertrophic	6.5 years	Chronic PCE	None reported	None reported	Static	Alive, age 7 years
nt 001	F	PMM2-CDG	c.160dupG; c.385G>A	p.Glu54fs; p.Val129Met	5 months	No	5 months	Hypertrophic	<1 month	PCE with tamponade	None reported	None reported	Static	Died at age 5 months due to cardiac tamponade
nt 002	F	PMM2-CDG	c.691G>A; c.422G>A	p.Val231Met;p.Arg141His	3 months	No	1 month	Hypertrophic	4 months	PCE with tamponade	None reported	Pericardiocentesis at 4 months for large PCE	Static	Died at age 5 months from culture-negative shock
nt 003	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	1 month	No	15 days	Hypertrophic	1.5 months	PDA; PCE with tamponade	None reported	None reported	Static	Died at age 2 months due to cardiac tamponade
nt 004	F	PMM2-CDG	c.691G>A; c.422G>A	p.Val231Met; p.Arg141His	2.5 months	No	3 months	Hypertrophic	8 months	Chronic PCE; Dynamic LVOTO	None reported	None reported	Progressive	Died at age 11 months due to peritonitis
nt 73	M	PMM2-CDG	c.357C>A; c.639–1479C>T	p.Phe119Leu; cryptic splice site creation and insertion of 123 base pairs of normally intronic sequence between exons 7 and 8 (does not translate into a stable protein)	2 years	No	4 years	Hypertrophic	23 years	Aortic stenosis; Mild AR	Propranolol in childhood	None reported	Improved	Alive, age 27 years
nt 29	M	PMM2-CDG	c.422G>A; c.357C>A	p.Arg141His; p.Phe119Leu	7.5 months	No	5 months	Hypertrophic	1.5 years	PCE	Beta-blocker (not specified)	None reported	Static	Alive, age 2 years. Large PCE

nt er	Sex	Diagnosis (CDG type)	Genotype	Protein change	Age at CDG diagnosis	Family history of CDG	Age at diagnosis of cardiac involvement	Cardiomyopathy phenotype	Duration of Cardiac Follow Up	Additional Cardiac Findings	Medications Used	Surgery / Interventions	Status of cardiomyopathy	Outcome
nt 31	M	PMM2-CDG	c.357C>A; c.422G>A	p.Phe119Leu; p.Arg141His	12 months	N/A	3 months	Hypertrophic	20 months	Pericarditis	None reported	None reported	Improved	Alive, age 23 months. History of pericarditis
nt 006	F	PMM2-CDG	c.422G>A; c.691G>A	p.Arg141His; p.Val231Met	2 years	No	3 years	Hypertrophic	2 years	Dynamic LVOTO; PCE	Enalapril	None reported	Improved	Died at age 5, cause of death not available. History of PCE
nt 31	F	PGM1-CDG	c.1129G>A; c.988G>C	p.Gle377Lys; p.Gly330Arg	2 years	No	4 years	Dilated	23 years	WPW syndrome; History of endocarditis	Aldactone, torsemide, bisoprolol	None reported	Progressive	Alive, age 27 years. Mildly depressed systolic function (EF 45%)
nt 30	F	PGM1-CDG	c.787G>T; c.988G>C	p.Asp263Tyr;p.Gly330Arg	4 years	No	12 months	Dilated	26 years	None reported	Digoxin, enalapril, spironolactone, furosemide, rivaroxaban	None reported	Static	Alive, age 27 years. History of heart failure
nt 65	F	PGM1-CDG	c.1544G>A; c.1544G>A	p.Arg515Gln; p.Arg515Gln	10 months	N/A	At birth	Non-compaction	27 months	Dysplastic pulmonary valve with valvar stenosis	Captopril, diuretics (not specified)	Mitral valve surgery, ECMO, eventual cardiac transplant at 1 year of age	Progressive	Alive, age 27 months
nt 005	M	DPAGT1 CDG	c.324G>C; c.692T>G	p.Met108Ile; p.Phe231Cys	Unknown	Yes	7.5 months	Non-compaction	10 months	PCE; Prolonged QT; Bradycardia; MR; LV dilation	Enalapril, captopril	VVI epicardial pacemaker for bradycardia	Static	Died at age 17 months, cause of death not available
nt 10	M	ALG3-CDG	c.1226T>C; c.1226T>C	p.Leu409Pro; p.Leu409Pro	10 days	No	Prenatal presentation	Dilated	7 weeks	Large PDA (preterm neonate); Severe PHT; Dilated RV with depressed function; LV dysfunction	Epinephrine, milrinone, furosemide and bumetanide	None reported	Progressive	Died at 7 weeks due to multi-organ failure, sepsis

Patient Number	Sex	Diagnosis (CDG type)	Genotype	Protein change	Age at CDG diagnosis	Family history of CDG	Age at diagnosis of cardiac involvement	Cardiomyopathy phenotype	Duration of Cardiac Follow Up	Additional Cardiac Findings	Medications Used	Surgery / Interventions	Status of cardiomyopathy	Outcome
Patient 7	F	DPM1-CDG	c.274C>G; c.173_174del	p.Arg92Gly; p.Tyr58*	12 months	No	23.5 years	Non-ischemic	1.5 years	None reported	Lisinopril	None reported	Progressive	Alive, age 25 years
Patient 51	M	SSR4-CDG	c.302G>A (hemizygous)	p.Trp101*	7 months	No	27 years	Non-ischemic	26.5 years	None reported	None reported	None reported	Recently diagnosed	Alive, age 27 years

ic regurgitation; ECMO: extracorporeal membrane oxygenation; EF: Ejection fraction; LV: left ventricle; LVH: left ventricular hypertrophy; LVOTO: left ventricular outflow tract obstruction; MR: gurgitation; N/A: not available; PCE: pericardial effusion; PDA: patent ductus arteriosus; PHT: pulmonary hypertension; RV: right ventricle; RVH: right ventricular hypertrophy; SAM: systolic motion of mitral valve leaflet; WPW: Wolff-Parkinson-White

Table 2:

Echocardiographic findings (available for P1-P6 and P16 only)

Patient Number	Cardiomyopathy Phenotype	Diagnosis (CDG Type)	Age at Initial Imaging Study	Qualitative LV Function	LV EF (%)	LVOTO	LVEDD (mm)	LVEDD (z-score)	PWD (mm)	PWD (z-score)	IVSD (mm)	IVSD (z-score)	Trend			
													Hypertrophy	LVOTO	PCE	Other
Patient #03002	Hypertrophic cardiomyopathy	PMM2-CDG	14 months	Normal	65%	None. Prominent bulge of muscle present	25.2	−0.54	4.2	−0.84	5.9	−1.14	Stable, did not worsen	None observed	Small PCE at 15 months, persistent over the next 2 years. No tamponade observed	Mild hypokinesis of mid antero-septum noted at 8 years
Patient #03014	Hypertrophic cardiomyopathy	PMM2-CDG	5 months	Normal	68%	None	24.0	0.24	5.0	0.92	4.0	−1.15	Qualitative mild hypertrophy on initial studies. Stable, did not worsen	None observed	Trivial PCE present at diagnosis, increased to small-moderate by 7 months, remained small subsequently. Gone at 5 years. No tamponade observed	N/A
Patient #M03001	Hypertrophic cardiomyopathy	PMM2-CDG	4 months	Normal	N/Q	None	14.0	−3.11	5.0	1.55	7.0	4.18	Qualitative mild RVH and moderate LVH on initial study	None observed	Trivial PCE present at diagnosis, progressed to moderate by 5 months. Died from tamponade	N/A
Patient #M03002	Hypertrophic cardiomyopathy	PMM2-CDG	3 months	Normal	70%	None	20.0	−1.23	5.5	1.93	6.6	3.00	Qualitative mild LVH and asymmetric IVS hypertrophy on initial study	None observed	Trivial PCE present at 3.5 months. Progressed to large PCE with tamponade at 4 months	N/A
Patient #M03003	Hypertrophic cardiomyopathy	PMM2-CDG	Birth	Normal	N/Q	None	20.2	−0.76	4.5	0.42	8.1	5.51	Qualitative moderate RVH & LVH with asymmetric IVS	None observed	Trivial PCE present at 7 days, increased to small by 1 month of	Moderate-sized PDA with left to right shunting on echocardiogram at birth, trivial in

Patient Number	Cardiomyopathy Phenotype	Diagnosis (CDG Type)	Age at Initial Imaging Study	Qualitative LV Function	LV EF (%)	LVOTO	LVEDD (mm)	LVEDD (z-score)	PWD (mm)	PWD (z-score)	IVSD (mm)	IVSD (z-score)	Trend			
													Hypertrophy	LVOTO	PCE	Other
													hypertrophy on initial study		age, moderate by 6 weeks of age, large with tamponade at 7 & 8 weeks of age. Died from tamponade	size at 7 days of life
Patient #M03004	Hypertrophic cardiomyopathy	PMM2-CDG	3 months	Normal	N/Q	None	22.0	0.34	4.3	0.13	3.9	−1.06	Qualitative mild LVH on initial study, IVS demonstrated mild hypertrophy (z score 2.86) by 5 months of age, increasing to moderate (z score 3.71) by 6 months of age	Dynamic LVOTO observed at 10 months of age, peak gradient 50mmHg when agitated & tachycardic, 35mmHg when calm	Trivial PCE present on initial study, increased to small 3 days later. Remained small-trivial over follow up period	SAM observed at 10 months of age with moderate MR
Patient #M08006	Hypertrophic cardiomyopathy	PMM2-CDG	3 years	Normal	N/Q	Mild LVOTO (peak velocity 2.8m/s, peak gradient 31mmHg)	24.6	−2.97	4.5	−0.43	7.5	3.62	Mild concentric LVH, asymmetric hypertrophy of the IVS	Mild initially, not seen on subsequent echocardiograms, moderate dynamic LVOTO (peak velocity 3.5m/s, peak gradient 52mmHg) seen with valsalva	None noted	Mild/moderate MR due to SAM, mild/ moderate TR that persisted over several echocardiograms

IVSD – interventricular septal dimension in diastole; LV - left ventricle; LV EF – left ventricular ejection fraction; LVEDD – left ventricular end-diastolic dimension; LVH – left ventricular hypertrophy; LVOTO – left ventricular outflow tract obstruction; MR - mitral regurgitation; N/Q - not quantified; PCE – pericardial effusion; PWD – left ventricular posterior wall dimension in diastole; RV - right ventricle; RVH - right ventricular hypertrophy; RVOTO - right ventricular outflow tract obstruction; SAM - systolic anterior motion of mitral valve leaflet; TR - tricuspid regurgitation.