Lay Language Summary of the Article "Cardiac complications of congenital disorders of glycosylation (CDG): a systematic review of the literature"

Propose title for the lay summary:

Heart involvement in congenital disorders of glycosylation

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"A sweet heart works better" – Are sugars (glycans) important for cardiac health?

Yes, the process through which sugars (glycans) are attached to proteins and fats is called glycosylation. Indeed, many essential heart proteins have been found to need attached sugars to work properly, having missing sugars been associated with heart failure. Sugars are so important for the accurate function of many heart proteins that they are needed during the embryonic development (early pregnancy stages).

To fully understand the impact and range of heart problems in congenital disorders of glycosylation patients, we reviewed all the information contained in the literature.

Take home messages

- At least 16% of all CDG types present with heart complications;

- Predominant heart disorders are cardiomyopathy (diseases that affect the heart muscle), valvular and septal defects (heart structural anomalies), arrhythmogenic disorders (diseases that cause abnormal heart beating), and pericardial effusion (excess of fluid around the heart). Some types of heart defects are more frequent in some CDG, such as structural (valvular and septal) defects in B3GAT3-CDG, pericardial effusions in ALG9 and PMM2-CDG, dilated cardiomyopathy in DOLK-CDG and PGM1-CDG, and ventricular dysfunction (a type of cardiomyopathy) in FKRP-CDG.

- Healthcare professionals are still widely unaware of CDG and of the underlying heart complications found in these patients;

- Heart function should be assessed and monitored in all CDG patients to better understand the incidence, evolution and importance of heart problems in CDG as well as to improve the diagnosis, management and treatment strategies;

- Heart disease has been effectively controlled with specific regimens of medication, and/or specific exercise programs (controlled aerobic training);

- Heart transplant has been successfully performed in CDG patients, currently being an approved therapy in Europe for DOLK-CDG patients;

- The extent and importance of heart affectation in CDG is very likely underestimated and has been overlooked. This is corroborated by sudden deaths caused by heart disease or late diagnosis of heart problems in CDG patients;

- CDG testing should be done, when a heart disorder is associated with other symptoms, particularly neurological symptoms.

The main findings were:

- Heart diseases are associated with sudden and premature deaths in CDG;
- Some patients can remain asymptomatic for long periods of time, while in other types of CDG it seems that heart problems develop only in late childhood or adolescence;
- 21 CDG types were reported to have heart problems (currently there are 133 CDG recognized, thus around 16% of all CDG have heart involvement);
- Heart problems found in CDG patients could be grouped into 3 main categories: cardiomyopathies, structural defects, and arrhythmogenic disorders;
- CDG types with cardiac involvement were also divided according to the associated type of glycosylation (sugar attachment mechanism): N-glycosylation, O-glycosylation, dolichol synthesis, glycosylphosphatidylinositol (GPI)-anchor biosynthesis, COG complex, V-ATPase complex, and other glycosylation pathways.

Table 1 – Types of heart defect identified per CDG. (X) marks the presence of the heart defect

	Type of heart defects		
CDG with heart affectation	**Cardiomyopathies**	**Structural defects**	**Arrhythmogenic disorders**
N-Glycosylation CDG			
ALG9-CDG		x	x
ALG12-CDG		X	
PMM2-CDG	X	X	X
O-Glycosylation CDG			
B3GALTL-CDG		X	
B3GAT3-CDG		X	
FKRP-CDG	X	X	
FKTN-CDG	X		
POMT1-CDG	X		
POMT2-CDG	X		
XYLT2-CDG		X	
Dolichol synthesis CDG			
DOLK-CDG	X	X	X
SRD5A3-CDG	X	X	
GPI-anchor biosynthesis CDG			
PIGA-CDG	X	X	X
PIGL-CDG		X	
PIGN-CDG		X	
PIGT-CDG	X	X	
COG Complex CDG			
COG1-CDG	X	X	

COG7-CDG		X	
Multiple pathways CDG			
PGM1-CDG	X	X	X
V-ATPase complex CDG			
ATP6V1A-CDG	X	X	
ATP6V1E1-CDG	X	X	

- There are reports of some patients, for whom the diagnosis of cardiomyopathy was only made after the identification of another patient within the family;
- Troponin levels (a marker of cardiac damage), lactate dehydrogenase levels (indicative of heart cell death), the ratio between creatine kinase and creatine kinase-MB (monitors damage to heart cells), aspartate aminotransferase (high levels may indicate damaged heart cells), and myoglobin (protein that binds to oxygen and is release after heart infarction) are important biomarkers (measurable indicators of normal biological processes, disease processes or pharmacological responses) predictive of heart dysfunction in CDG;
- In terms of clinical importance and number of patients, cardiomyopathies predominate among the heart disorders in CDG patients affected by defects in N-glycosylation, O- glycosylation, and dolichol synthesis. Structural defects are common in CDG patients with associated defects in GPI-anchor biosynthesis and COG complex. CDG associated with defects in V-ATPase complex and PGM1-CDG present a mixed spectrum with cardiomyopathies and structural cardiac defects

Taking into account our findings, we recommend that a heart check-up should be performed in all CDG patients with and without known heart problems, so that a greater understanding of the frequency, onset and evolution of heart diseases in CDG patients can be achieved.