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Cardiac Involvement in Children with Glycogen Storage Diseases

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Abstract:

Introduction: The heart is a highly active metabolic organ and can be negatively impacted by inherited metabolic disorders. Glycogen storage diseases (GSDs) encompass a group of genetic conditions resulting from defects in enzymes and transporters responsible for glycogen metabolism. Glycogen primarily accumulates in the liver, muscles, and kidneys.

Aim of the study: To evaluate cardiac involvement in infants and children diagnosed with GSD.

Subjects and Methods: This cross-sectional study was performed at the Children's Hospital of Fayoum University between October 2021 and May 2023. A total of 27 children diagnosed with GSD participated in the study. Each child underwent an ECG, conventional echocardiography, and tissue Doppler imaging.

Results: Among the 27 GSD patients, 11 (33.33%) exhibited a prolonged QT interval. Pulmonary hypertension was observed in Four patients (14.8%), while congenital heart disease was present in three cases (11.1%). Left ventricular hypertrophy (LVH) was detected in 51.8% of the patients, with one case involving HOCM. Impaired left ventricular (LV) diastolic function was found in 15 children (55.5%), whereas all patients (100%) exhibited impaired right ventricular (RV) diastolic function.

Conclusion: Children with GSD are at risk of developing cardiac abnormalities, including prolonged QT intervals, LVH, pulmonary hypertension, and impaired diastolic function of both the left and right ventricles.

Keywords: Glycogen storage disease; Echocardiography; Cardiac.

1. Introduction

GSDs encompass a group of inherited disorders caused by defects in transporters and enzymes responsible for regulating the synthesis and breakdown of glycogen. Storage of Glycogen is primarily in the kidneys, muscles, and liver. However, muscle tissue lacks glucose-6-phosphatase, preventing it from producing glucose for systemic use. Hepatic GSDs (types XI, IX, VI, III, I, and 0) primarily manifest as hypoglycemia, whereas muscle GSDs (Kindes III, II, V, IV, X, and VII) typically present with muscle weakness and/or cramps [1].

GSDs are a significant cause of hypertrophic cardiomyopathy (HCM) in children, identified by glycogen-filled vacuoles in cardiomyocytes. Several GSD types are associated with HCM, with the most notable being Danon disease (GSD type IIb), Pompe disease (GSD type IIa), PRKAG2 syndrome, and Cori–Forbes disease (GSD type III) [2].

Management of cardiac complications in GSD patients is challenging and depends on the specific type and severity of cardiac involvement. Enzyme replacement therapy (ERT) has shown significant benefits in certain forms of GSD, such as Pompe disease, by reducing glycogen accumulation and improving cardiac function. Additionally, supportive treatments, including beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics, may help manage heart failure symptoms and arrhythmias. Lifestyle modifications and regular cardiovascular monitoring are also essential to optimize patient outcomes and prevent disease progression [3, 4].

In patients with late-onset Pompe disease (LOPD), approximately 75% exhibit tall QRS complexes and a short PR interval on ECG. Additionally, echocardiography can detect hypertrophic cardiomyopathy in the early stages of LOPD [3]. Elevated wall thickness and left ventricular (LV) mass are commonly observed in GSD IIIa; however, they are less frequent in GSD IIIb, despite both subtypes maintaining normal ventricular systolic function [4].

Cardiac involvement in GSD IV presents with a broad spectrum of cardiomyopathy, ranging from dilated cardiomyopathy (DCM) to HCM, with

clinical manifestations varying from asymptomatic cases to decompensated heart failure [5]. In contrast, cardiac involvement is uncommon in GSD IX. Reported cases include a small patent foramen oval that did not require medical intervention and incomplete right bundle branch block (RBBB) without significant impact on cardiac function [6].

2. Subjects & Methods

2.1. Subjects

This cross-sectional research was carried out at the Children's Hospital of Fayoum University between October 2021 and May 2023. A total of 27 pediatric participants who suffered from GSD were included. The study got approval from the Research Ethics Committee of the Faculty of Medicine, Fayoum University, Egypt (IRB: M481).

Informed consent was acquired from caregivers, and the study adhered to the ethical principles outlined in the Declaration of Helsinki.

Inclusion criteria

- Both male and female children diagnosed with GSD

Exclusion criteria

- Those with acquired heart disease, patients with electrolyte imbalance were excluded.

2.2. Methods

All patients underwent a comprehensive clinical evaluation, including detailed medical history, thorough physical examination, and laboratory investigations such as alanine aminotransferase (ALT), complete blood count (CBC), serum bilirubin, and aspartate aminotransferase (AST) levels. GSD diagnosis was confirmed via liver biopsy, performed using the percussion-guided or blind method. Typing was conducted for selected cases, with GSD types I, II, III, and IX identified.

Cardiac evaluation included electrocardiography (ECG), conventional echocardiography, and tissue Doppler imaging.

A. ECG: A standard 12-lead ECG was recorded with a speed of 25 mm/s and an amplitude of 1 mV/cm while the patient was in a supine position. The following parameters were analyzed: heart rate, rhythm, QRS and T axes, QRS-T angle, P axis, P-R interval, QRS duration, QT and

QTc intervals (calculated using Bazette's formula), ST segment, and T wave [7].

B. Conventional echocardiography was conducted using a Vivid-5 color Doppler ultrasound system (General Electric) with 3.75 MHz or 5 MHz transducers. A complete echocardiographic evaluation was done to rule out congenital heart disease, with a focus on right ventricular (RV) dimensions, left ventricular (LV) internal dimensions, global function, and LV ejection fraction (EF). Standard transthoracic views were utilized to measure LV end-systolic diameter (LVESD), LV posterior wall thickness (LVPW), EF, and LV end-diastolic diameter (LVEDD).

C. Tissue Doppler echocardiography was conducted using the same ultrasound system. Transmitral early (E) and late (A) wave velocities were averaged to obtain mean values. The myocardial performance index (MPI) was calculated as follows: RV MPI = (IVRT + IVCT) / RVET. LV MPI = (IVRT + IVCT) / LVET
RV and LV functions were assessed using MPI, where an elevated MPI indicated the occurrence of global myocardial dysfunction (8).

2.3. Statistical Methods

The gathered data were systematically analyzed, tabulated, and organized using SPSS version 22 (SPSS Inc., USA). Quantitative data were demonstrated as standard deviation (SD), mean, and range, with independent t-tests used to compare groups. Qualitative data were presented as percentages and frequencies, with chi-square ($\chi 2$) tests employed for significance testing. Pearson correlation analysis evaluated relationships between the Tei index and other study parameters.

3. Results

The study involved 27 patients, 12 of whom were females and 15 males. The mean age at the time of the study was 6.2±2.8SD years with a range of 1-12 years. old). For cardiac examination, 25 patients (92.6%) had normal auscultation, 2 patients (7.4%) had accentuated S1, 3 patients (11.1%) had accentuated S2, and 3 patients (11.1%) had a systolic murmur. The routine laboratory investigations of the studied

group are summarized in **Tables 1** & 2. Notably, anemia was present in 11cases (40.7%) and elevated ALT and AST were present in all our cases.

Table 1: CBC and liver function tests in the studied patients

Variables		**Mean ± SD**	**Range**
CBC	*platelets*	366.78±93.55	205-534
	Hemoglobin	10.75±1.41	7-12.5
	TLC	9.85±3.65	4-15
Variables		Number of cases	%
Anemia		11	40.7
Elevated ALT		27	100.0
Elevated AST		27	100.0
Elevated direct bilirubin		1	3.7

Electrocardiogram findings among our patients mean heart rate was 108.59±23.97 with a range of 110-141beats/ min. the mean QTc was 446.65±40.97 with a range of 400-531 msec. Prolonged QTc interval was found in 11 patients (40.7%) of all our cases.

Data of Echocardiography of the studied patients are demonstrated in **Tables 2**& 3. The mean PAP was 32.48±11.74. The mean FS was 38.41±6.29 in GSD. 11.1% of our GSD patients had CHD in the form of small ASD, small VSD and PDA. We found that 51.8% of our GSD cases had LV hypertrophy, and one of them had LVH with obstruction. pulmonary hypertension was present in 4 cases (14.8 %), one of them had severe pulmonary HTN, about 75mmHg. Impaired systolic function was present in 3 cases (11.1%). Impaired RV diastolic function was found in all our cases. and impaired LV diastolic function was in 15 cases (55.5%). Tissue Doppler findings are summarized in **Table 4**.

Table 2: Conventional Echo measurements of the studied participants

Variables	**Mean ± SD**	**Range**
AO	2.3±0.42	1.3-3.5
LA	2.27±0.41	1.2-3.5
PAP	32.48±11.74	25-87
LVEDD	3.12±0.84	1.9-6.4
LVESD	1.91±0.79	1-5.4
FS	38.41±6.29	15-46
EF	90.3±113.19	65.75-75

Table 3. Conventional Echo findings of the studied participants.

Variables		**Number**	**(%)**
Valvular affection	Absent	25	92
	MR	2	8.0
Congenital Heart Diseases	Absent	24	88.9
	ASD	1	3.7
	PDA	1	3.7
	VSD	1	3.7
Left ventricle	LV dilatation	3	11.1
	LVH without obstruction	13	44.4
	LVH with obstruction	1	3.7
pulmonary HTN	Present	4	14.8
Impaired function	Impaired systolic function	3	11.1
	RV diastolic dysfunction	27	100
	LV diastolic dysfunction	15	55.5

Table 4: Tissue Doppler Echo study of the studied groups.

Variables		**Mean± SD**	**Range**
RV	IVCT	51.59±8.83	40-70
	IVRT	78.41±25.28	50-120
	ET	276.81±45.52	200-390
	Tie index	0.45±0.07	0.38-0.64
LV	IVCT	50.37±4.06	40-60
	IVRT	74.48±25.44	50-140
	ET	275.07±22.56	220-316
	Tie index	0.44±0.06	0.36-0.57
TAPSE		1.69±0.42	1.2-2.9
E/A ratio		1.73±0.25	(0.8-2)
velocity of S PRIMME m/s		0.06 ± 0.01	0.04-0.08
velocity of E PRIME m/s		0.09±0.01	0.07-0.11
velocity of A PRIME m/s		0.05±0.01	0.03-0.07
E\e prime ratio		9.57±1.61	6-12

4. Discussion

Cardiac involvement in children with GSDs is a significant clinical concern due to the metabolic disruptions that affect myocardial function. These inherited disorders, characterized by abnormalities in glycogen synthesis and degradation, lead to excessive glycogen accumulation in various organs, including the heart. The extent of

cardiac involvement varies among different GSD subtypes, with some exhibiting severe HCM and conduction abnormalities, while others display milder cardiac manifestations [9].

The identification of cardiac manifestations is primarily reliant on echocardiographic and ECG assessments. Electrocardiograms are effective in detecting heart rhythm disorders and conduction abnormalities, while echocardiography serves as a widely accessible imaging modality for evaluating structural cardiac defects. Basic imaging methods, such as X-rays, can help identify cardiac enlargement, whereas cardiac magnetic resonance imaging and endomyocardial biopsy are useful for ruling out other underlying conditions [9].

Our study is a cross-sectional descriptive study, which included 27 pediatric cases diagnosed with GSD in the Children's Hospital, Fayoum University. CHD was found in three cases (one PDA, one VSD and one ASD) out of 55 patients with GSD (5.4%) in a study by Seol et al. (2023) [13]. In our study, three cases (11.1%) of GSD patients had CHD in the form of small ASD, small VSD and PDA.

Long QT syndrome (LQTS) is a rare hereditary cardiac electrophysiological condition characterized by dysfunctional ion channels in myocardial cells, leading to prolonged repolarization. This dysfunction can trigger Torsades de Pointes (TdP) and potentially fatal ventricular tachyarrhythmia. On an electrocardiogram (ECG), LQTS typically appears as a prolonged QT interval with T-wave abnormalities. In our study, a prolonged QTc interval was observed in 11 patients (40.7%) (10). Similarly, a study by Ben Chehida et al. (2018) reported a prolonged QTc interval in 65% of GSD cases [11].

The relationship between GSD and pulmonary hypertension (PHTN) remains poorly understood. However, PH has been reported in association with GSD Types I, II, and III. It is suggested that endothelial dysfunction resulting from metabolic disturbances in glucose may contribute to the development of PHTN [12]. According to our study, pulmonary hypertension was present in 4 cases (14.8%), one of them had severe pulmonary HTN. In a study by Seol

et al. (2023), it was found that none of their GSD patients had pulmonary HTN [13]. A case report with GSD was reported to have pulmonary HTN by Torok et al. (2017) [14]. To date, the incidence of PH is unknown in glycogen storage disease [15].

In GSD, an abnormal form of glycogen called dextrin builds up between the myofilament bundles in muscle tissue, leading to hypertrophic cardiomyopathy, which may further develop into asymptomatic left ventricular hypertrophy [16]. We found that 51.8% of our GSD cases had LV hypertrophy, and one of them had LVH with obstruction. In a study by Vertilus et al. (2010), 38.8 %of GSD cases were associated with LVH [17]. Also, in a study by Chong-Nguyen et al. (2018), 43% of their GSD cases had LVH [18].

Metabolic disorders can lead to functional or structural myocardial disease due to metabolic imbalances. Elevated blood glucose levels and the accumulation of triglycerides (TGs) and free fatty acids may act as pro-inflammatory agents, resulting in myocardial toxicity. In our study, impaired systolic function was observed in three GSD patients (11.1%). In a study by Seol et al. (2023), none of the GSD patients had impaired systolic function [13].

Despite advances in the understanding and management of cardiac involvement in GSDs, several challenges remain. Future research should focus on the development of gene therapy approaches aimed at correcting the underlying genetic defects responsible for these disorders. Additionally, new pharmacological agents targeting glycogen metabolism and mitochondrial function may offer promising therapeutic options. Longitudinal studies evaluating long-term cardiac outcomes in treated and untreated GSD patients are necessary to refine treatment strategies and optimize patient care.

5. Conclusion

Patients with GSD usually develop LVH. Pulmonary HTN is infrequent but can be severe in GSD. Valvular affection is not a common echocardiographic finding in our GSD cases. Impaired RV diastolic function was reported in 100% of our GSD patients. Impaired LV may be present in patients with GSD. Patients with GSD may have prolonged QTc. Early recognition and

appropriate management are critical to improving patient outcomes. Advances in ERT, metabolic control, and emerging gene therapies hold promise for better prognosis and quality of life for affected children. Continued research and collaboration among metabolic and cardiovascular specialists are essential to further enhance our understanding and treatment of these complex disorders.

Ethical committee approval: This investigation was carried out with ethical approval from the research ethical committee of the faculty of medicine at Fayoum University. Patient consent was taken after explaining the procedure. Patients had the right to withdraw from the trial at any time.

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Author's contributions: DBA: protocol development, Data collection and management, manuscript writing/editing. MAE: protocol development, Data collection and management, manuscript writing/editing. SIA: protocol development, Data collection and management, manuscript writing/editing.

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