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A case of an 8-year-old girl affected by Glycogen Storage Disease type III: can diet interfere with severe hypertrophic cardiomyopathy's progression?

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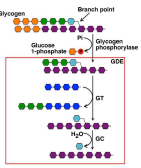
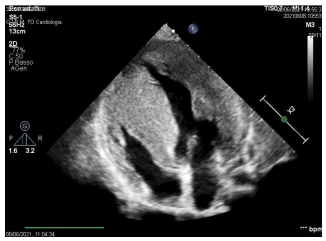
INTRODUCTION

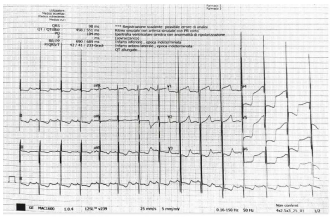
Glycogen Storage Disease type III (GSD III) is a rare autosomal-recessive metabolic disorder characterized by mutations in the AGL gene that encodes the glycogen debranching enzyme and this leads to an accumulation of abnormal glycogen called "limit dextrin" (LD) in affected tissues. Four clinical types of GSD III are described. The most common form is subtype IIIa (85% of cases) that shows hepatic, skeletal muscle and cardiac involvement. Cardiac storage of LD is described in 58% of GSD IIIa affected patients and it can evolve to a severe cardiomyopathy in 15% of cases. Herein we present a challenging case of an 8-year-old girl affected by GSD III.



OUR CASE

At 2 years of age, the girl presented significant hepatomegaly and recurrent hypoglycemia, so she underwent further investigations and received a molecular diagnosis of GSD III (c.3304G>A/C.2681+1G>A mutation).
A six-month multidisciplinary follow-up was started (pediatric, metabolic, gastroenterological, nutritional and cardiological).
At 3 years of age, the echocardiographic examination showed an initial myocardial thickness (IVSd 10 mm, z score +3,47 and LVPWd 12 mm, z score +4,52) with a mild obstruction gradient on left ventricular outflow tract (LVOT). Beta-blocker therapy was postponed not to worse and hide hypoglycemia crisis.
During the years, she continued her multidisciplinary follow-up, showing slow progression of the disease.





June 2021, last hospitalization:

- worsening of **symptoms** in the latest months: lower limb pain, fatigue and poor exercise tolerance;
- normal glycemic levels with a **dietary regimen** based on frequent high-carbohydrate meals associated with cornstarch
- **echocardiography:** worsening of cardiomyopathy
  - marked increase in the thickness of the interventricular septum (IVSd 30 mm, z score +14.94) and the left ventricle posterior wall (LVPWd 20 mm, z score +6.78),
  - mild dynamic gradient (basal: 30 mmHg, during Valsalva maneuver: 40 mmHg) on the LVOT
  - severe diastolic disfunction (TDI lateral E/E': 29);
- **ECG:** marked biventricular hypertrophy with a significant ST-tract depression in all leads, especially from V4 to V6 (max 26 mm) and prolonged QTc (480 ms);
- **Holter-ECG:** negative for arrythmia;
- elevated **cardiac enzymes**: NTpro-BNP value was 5273 ng/L (n.v.<450), troponin I hs was 1086 ng/L (n.v. <16), total CK value was 1861 UI/L (n.v. 25-140) and CK-MB value was 51,6 mcg/L (n.v <3.1).

Due to the worsening of clinical symptoms and the difficulty to discriminate between a cardiac cause from the starting of a concomitant myopathy, neurological investigations were performed, too.

DISCUSSION

The case was discussed for cardiac transplantation but after a careful and thorough review of literature, we decided to attempt a modification of the current dietary regimen in favor of a high-fat, high-protein and low-carbohydrate diet.
In the literature we found six pediatric cases and two adult cases (see Table1) of GSD III and severe myocardiopathy that after a minimum of 12 months of ketogenic diet showed a significant improvement of IVSd and LVPWd thickness, cardiac enzymes and reversal of cardiac symptoms, avoiding cardiac transplantation.

Study	Patient age	Diet	Follow up	Heart function	Heart transplant
Valayannopoulos V., et al. (2011)	2 mo	2:1 KD and 3OHB	24 months	Improved	No
Brambilla A., et al. (2014)	5 y 7 y	High fat (60%), high protein (25%), low CHO (15%)	12 months	Improved	No
Sebene M., et al. (2104)	9 y	MAD	32 months	Improved	No
	11 y		26 months	Improved	No
Dagli A.I., et al. (2009)	16 y	High protein (30%), low CHO	12 months	Improved	No
Francini-Pesenti F., et al. (2019)	32 y	24-h protein enriched nasogastric feeding: protein (37%), CHO (61%), fat (2%)		Improved	No
Sentner C. P., et al. (2011)	34 y	MAD	12 months	Improved	No

TABLE 1. Literature review of outcome data from case reports on KD in GSDIII. KD: Ketogenic Diet; 3OHB: 3 hydroxybutyrate (synthetic ketone bodies); CHO: carbohydrates; MAD: Modified Atkins Diet (10g carbohydrate per day, proteins and fatty acids ad libitum)

CONCLUSION

The girl continues a close follow-up and starts a prophylactic beta-blocker treatment and a strict ketogenic diet, which is described in few case reports to be a beneficial treatment for GSD III-related cardiomyopathy.

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