Clinical Nutrition Experimental 28 (2019) 83–91

Contents lists available at ScienceDirect

Clinical Nutrition Experimental

journal homepage: http://www.clinicalnutritionexperimental.com

Original Article

Ketogenic diet treatment in adults with glycogenosis type IIIa (Morbus Cori)

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ARTICLE INFO

Article history:
Received 29 July 2019
Accepted 28 September 2019
Available online 7 November 2019

Keywords:
Morbus Cori
Glycogenosis type III
Glycogen storage disease
Modified atkins diet
Ketogenic diet
Nutrition therapy

SUMMARY

Background: Glycogen storage disease type IIIa (GSDIIIa) is a defect of the debranching enzyme (amylo-1,6-glucosidase) in glycogenolysis and has an effect on the muscles and the liver. The guidelines for diagnosis and management of GSDIIIa primarily recommend a nutritional therapy to avoid hypoglycaemia. For adolescents and adults, the recommendation is a diet high in protein (25 E%) and moderate or low in carbohydrates (<50 E%) while avoiding simple sugars and fasting. There are some indications that a ketogenic diet, such as the modified Atkins diet (MAD), could present a good approach to nutritional therapy for GSDIIIa.

Methods: This report is a retrospective evaluation of the nutritional and clinical data of two adult patients with GSDIIIa. The effect of a diet according to the guidelines and a ketogenic diet (MAD) were compared in both cases. Patient compliance during the nutrition therapy is also described.

Results: The MAD led to a reduction of CK and a stabilization of blood glucose as well as to an unwanted weight loss. The progression of the disease was decelerated, but existing complaints could not be improved. Compliance to the MAD decreased over time and re-training was necessary.

Conclusions: The MAD presents a good option for nutritional therapy for glycogenosis with muscle involvement like in GSDIIIa.

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https://doi.org/10.1016/j.yclnex.2019.09.004
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The food composition takes the metabolic defect into account and could have a positive effect on progression.

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1. Introduction

In 1952, Illingworth and Cori described enzymatically different types of glycogen storage disease for the first time [1]. At almost the same time, Forbes publicized a case report of a young girl with conspicuously short outer glycogen chains in liver and muscle tissue. Forbes suspected a defect of the debranching enzyme to be the trigger for the observed glycogen modification [2]. A few years later, the enzyme amylo-1,6-glucosidase (debranching enzyme) from glycogenolysis was finally detected as the cause of this glycogen storage disease in cases with abnormally short outer chains of glycogen in heart and skeletal muscle. It was assumed that the absence of enzyme activity could be the reason for the abnormal structure and the accumulation of glycogen in tissues [3]. In accordance with the first description, the glycogen storage disease type III (GSDIII) is the same as Morbus Cori, Forbes disease or amylo-1,6-glycosidase deficiency (OMIM 232400; ICD-10-CM: E74.03) [1–3]. Glycogenosis type III is divided into subgroups. The most common type IIIa affects the liver and muscles, and type IIIb affects the liver only. Additional types like IIIc and IIId were described but occur very rarely [4].

The nutritional therapy in the guidelines for diagnosis and management of glycogen storage disease type III aims at avoiding hypoglycaemia. Complex carbohydrates like corn starch should therefore be preferred. Frequent small feedings, comprising of complex carbohydrates while avoiding simple sugars and protein, are used to stabilize blood sugar especially in children. When hypoglycaemia is present the application of corn starch is possible. In adult patients an intake of high protein (20–30 percent of daily energy [E%]), normal or slightly reduced fat (20–35%), and normal or limited carbohydrates (35–55 E%) with emphasis on complex carbohydrates is recommended. In summary, the dietetic recommendations in the guidelines for adolescents and adults are high protein (25 E%), moderate or low carbohydrates (<50 E%) as well as avoidance of fasting and simple sugars [5]. The macro nutrient intake recommendations are predominantly based on case reports in children as mentioned in the guidelines [5–7]. In an adult patient with GSDIIIa, an improvement of cardiomyopathy and a decrease in creatinine kinase (CK) level effected by a high protein diet (30 E%) and reduction of corn starch was described [8]. Another case sample report with two adults on a high-protein diet (20–25 E%) presented in one patient a pronounced, in the other one a mild improvement of muscle performance [7].

An alternative approach in the nutritional therapy of GSDIII is the ketogenic diet. The main idea is the reduction of carbohydrate intake with a reduction of glycogen storage in the muscle. Muscle cells use up to 90% of the energy requirement under aerobic condition from fatty acid metabolism. The mildest available form is the modified Atkins diet (MAD). The implementation of the MAD affected a decrease of CK, and an improvement of cardiomyopathy in the patients. Except for an initial hypoglycaemia, no further side effects were reported and the diet was well tolerated [9]. The intake of a high-protein and high-fat diet, comparable to MAD, and additional treatment with D-/L-β-hydroxybutyrate (βHB) in an infant led to an improvement of cardiomyopathy and to a normalization of liver size. During the therapy, growth returned to normal and no adverse effects were reported [10].

In this case study, the nutritional treatment with MAD in two adult brothers with GSDIIIa is described. To our knowledge, there are only case reports on children with MAD nutritional therapy available. This is the first report about a switch from guideline recommended diet to MAD in adult GSDIIIa patients.

2. Methods

The report is based on a retrospective analysis of clinical data.

2.1. Patients medical history

The 37 and 40 year old male brothers are the first and third children of healthy Turkish stock parents. Their sister (second child) has no metabolic disorder. First diagnosis of the older brother was glycogenosis type 6b in the early eighties. After the birth of the younger brother with similar symptoms, like jumpiness and tremors in the morning, the diagnosis was controlled and showed a α-1,6-amylo-glucosidase activity in erythrocytes of 0 units. In later years, genetical analyses confirmed the diagnosis caused by a homozygote mutation of AGL (c.753_756delCAGA; p.ASP251Glufs*23). The disease had a higher progression rate in the younger brother. At the age of 4 years, signs of left hypertrophy were already present. At the age of 9 the diagnosis of hypertrophic cardiomyopathy was confirmed. The present pronounced hypertrophic non-obstructive cardiomyopathy (HNOCM) led to diastolic restrictions. The formation of crypts and the resulting thrombi led to two episodes a cerebrovascular stroke without permanent cognitive impairments. The older brother was diagnosed with myopathy and cardiomyopathy at the age of 10. Moderate hypertrophic cardiomyopathy resulted in no functional impairment. Due to progressive myopathy, both brothers have been dependent on a wheelchair for mobility from around the age of 30. There are no cognitive limitations in either of them. In the following text the younger brother is denoted as A and the older brother as B.

2.2. Nutritional therapy

2.2.1. Guideline diet

At first (A ~ 32 years; B ~ 35 years), the diet was based on guidelines for GSD. An important part of the diet was the prevention of hypoglycaemia, especially by use of corn starch. In adulthood, a high-protein diet was used in addition to starch supplementation.

2.2.2. MAD

The start of the diet took place during an in-patient stay at the University Hospital in Münster. The reduction of carbohydrates and increase of fat took place gradually. For the long-term implementation, a carbohydrate intake of 65–70 g (A) and 50–55 g (B) per day was initially determined for the patients. Approximately one year later, carbohydrates were reduced further to a maximum of 40–45 g per day for both patients. No further adjustments or restrictions were made hereafter. A dietary support by the intake of MCT was given during the entire duration of the MAD depending on the individual tolerance.

2.3. Training and training materials

For MAD follow-up trainings, course materials that took the Turkish descent into consideration were prepared. For cooking courses, country-specific recipes were modified into a ketogenic variant and the family was included. All information materials were specifically targeted at the patients. The training sessions were followed by a verbal evaluation and discussion. Additional training took place every 3–6 months after the start of the MAD.

3. Results

3.1. Guideline diet

The diet according to the guidelines was carried out at an average of 15.6 ± 4.9 E% protein, 22.1 ± 11.1 E% fat and 61.8 ± 12.7 E% carbohydrates respectively for patient A. Patient B received a similar nutrient composition (18.3 ± 3.5 E%; 23.7 ± 10.2 E%; 58.1 ± 8.7 E%). Supplementation with corn starch reached a maximum of 345 g/d (B) due to increasing age and weight. A late meal was necessary to ensure the high intake and to avoid hypoglycaemia overnight. The administration of corn starch in milk or curd cheese was a critical factor due to the poor mouth feel and daily quantity.

No stabilization of blood sugar could be achieved in the overall course. (B) also showed an increase in weight up to BMI 29.6. The younger brother (A) showed a stable weight development within the normal BMI range (Fig. 1). During the diet according to the guidelines, an increase in muscle destruction was observed based on the creatine kinase values (CK). (A) reached a maximum CK value of 8470 U/L and (B) of 5850 U/L (details see Fig. 3).

3.2. MAD

The start of the ketogenic diet was controlled by daily urine ketone measurements. After day six both patients reached a value of 50 mg/dL ketone bodies in urine (see Table 1). No adverse effects were detected during the induction of the MAD. The macronutrient composition was between 5 and 20 E% carbohydrates, 70–78 E% fat and 9–23 E% of protein in accordance to the recommended daily energy intake. Proportion of MCT on the total daily fat ingestion was 11–23 E%.

Patient A showed a feeling of weakness, tachycardia, stress dyspnoea, tremor and a vertigo after about 2 weeks. In order to stabilize the patient, the ketogenic diet was readjusted on an inpatient basis over a period of 2 weeks. Daily measurements of βHB in capillary blood were taken during the adjustment period and showed a strong variation throughout the day (Fig. 2). No further side effects occurred after readjustment of the MAD. The target value for ketosis was 1–2 mmol/L D-βHB for the implementation at home. Both patients received a meter for glucose and D-βHB in capillary blood for the control at home.

Immediately after the start of the diet, a considerable decrease in the CK value was observed in both patients. The CK level, previously above 3000 U/L, was reduced to up to <1000 U/L (Fig. 3). An improvement of the existing physical impairments could not be achieved, but the further progression was decelerated.

An unwanted side effect was weight loss in both patients. In the case of A, the diet led to a BMI of approx. 18 kg/m^2 (Fig. 1). By further training, the body weight was stabilized and a further weight reduction avoided.

It is evident that stabilization of the blood sugar in both individuals was achieved only after the introduction of the MAD. During the diet according to the guidelines, there were strong fluctuations in

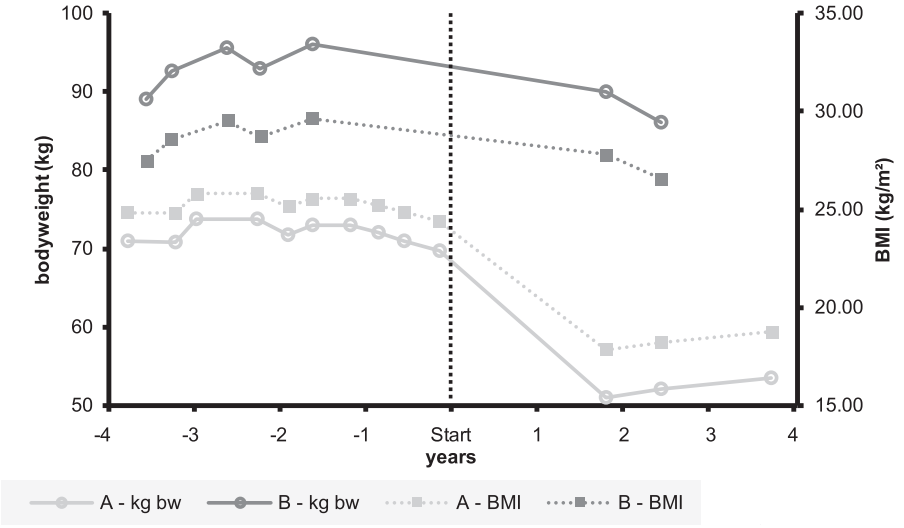

Fig. 1. Weight development of two brothers (A, B) with glycogenosis type IIIa during a diet adapted on guideline and a ketogenic diet (MAD; start marked in diagram…).

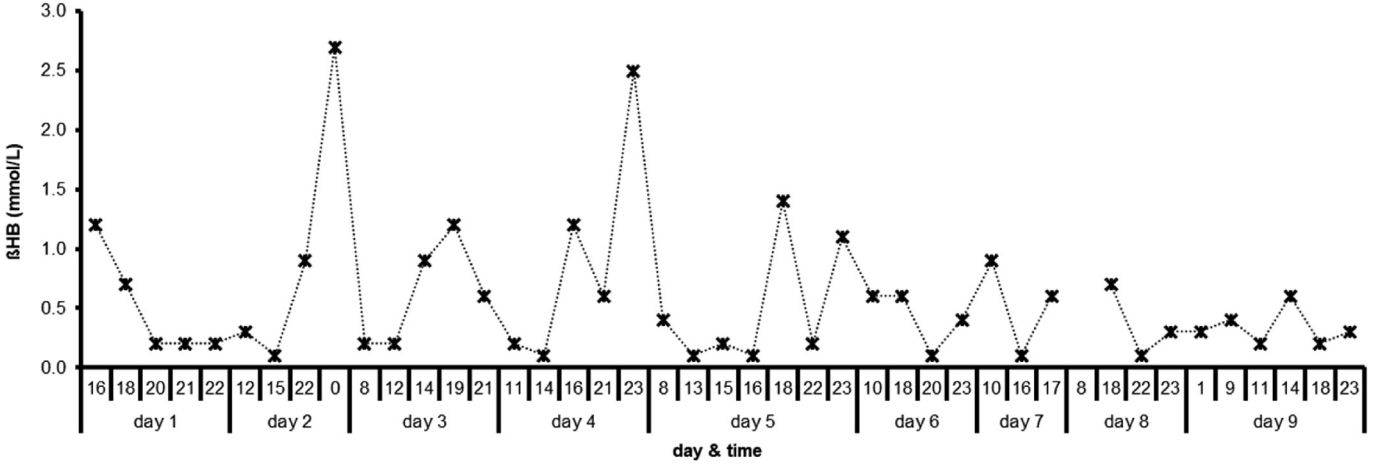

Fig. 2. Detection of D-βHB (mmol/L) in capillary blood during readjustment of a MAD in a patient with glycogenosis type IIIa.

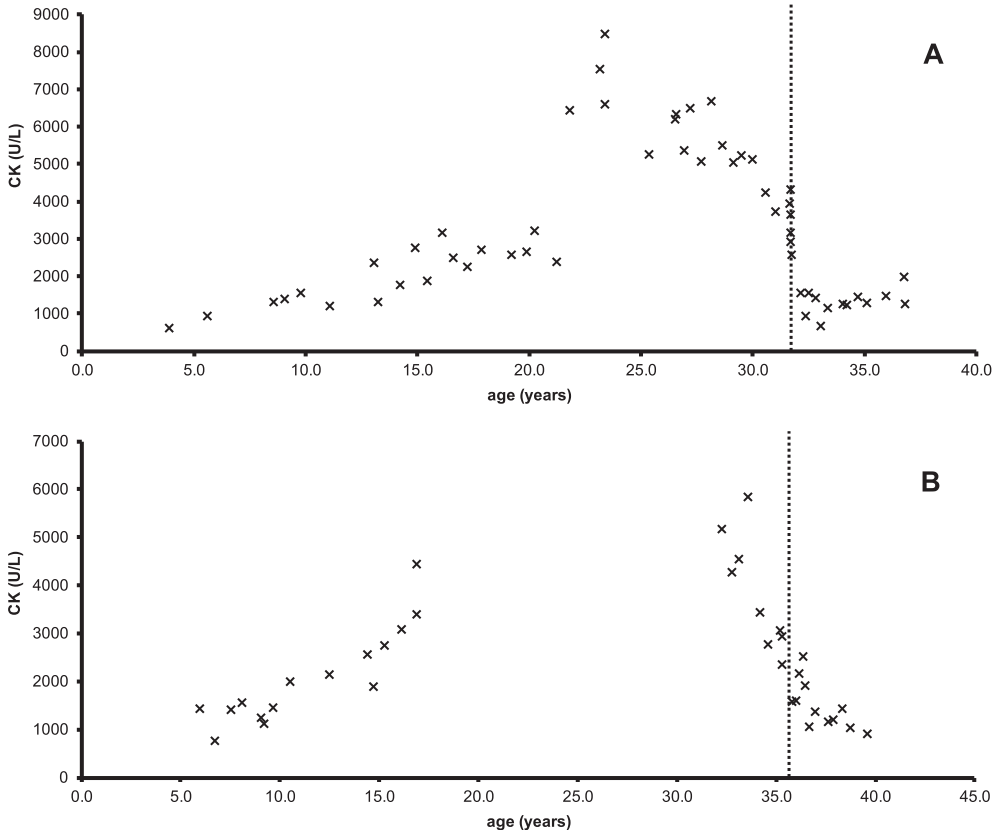

Fig. 3. CK levels (U/L) of two brothers (A, B) with glycogenosis type IIIa during a diet adapted on guideline and a ketogenic diet (MAD; start marked in diagram…).

blood sugar and occasionally a hypoglycaemia. Particularly in A, a clear improvement in stabilization of blood sugar levels was reported (Fig. 4).

3.3. Problem of non-compliance

Compliance decreased steadily with the length of the MAD. In discussions with the nutritionists, it was constantly explained by the patients that a permanent implementation of the diet was impossible

Table 1
Ketone bodies (mg/mL) measured in urine during induction of a ketogenic diet (MAD) in two patients with glycogenosis type IIIa (- = no measurement).

day	A	B
	mg/dL	mg/dL
1	neg	Neg
2	5	5
3	–	5
4	5	15
5	15	15
6	50	50

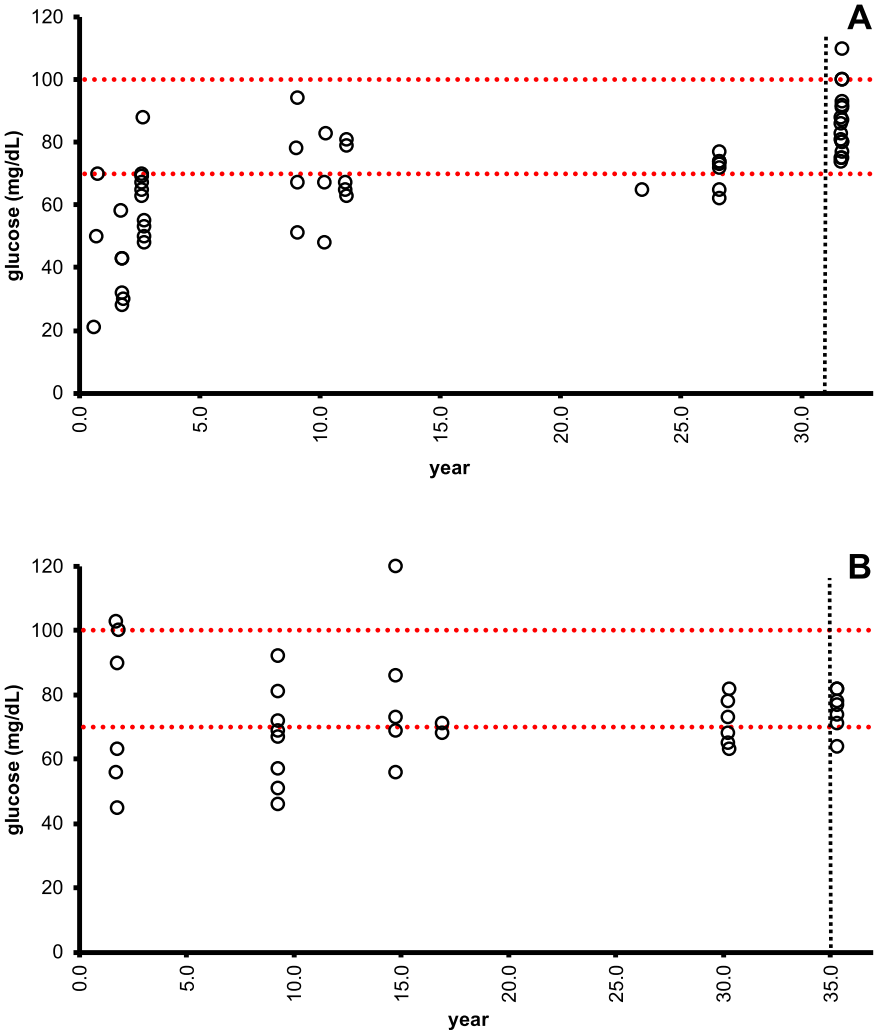

Fig. 4. Blood glucose levels (mg/dL) of two brothers (A, B) with glycogenosis type IIIa during a diet adapted on guideline and a ketogenic diet (start MAD marked…; Normal blood sugar levels [70–100 mg/dL] marked in diagram…).

and that no effect of the diet could be observed. Particularly the older brother, who has fewer health problems, showed insufficient willingness to follow the diet. The trainings that were conducted only led to a short improvement. Approximately every 3–6 months, new training and control dates were necessary.

4. Discussion

The application of the MAD showed a considerable improvement of clinical parameters, such as a decrease in CK in both cases. Other reports already showed positive results in the use of a ketogenic diet in children with GSDIII without adverse effects [9,10]. The ketogenic diet implemented by Valayannopoulos et al. corresponds approximately to a MAD in terms of macronutrient composition. In the case of Mayorandan et al. a typical MAD was performed with a stricter carbohydrate limitation as

described in this report on adult patients. The mild form of MAD was chosen to ensure sufficient diet compliance in both brothers. The carbohydrate intake was clearly above the classical MAD which is used, for example, to reduce seizures in epilepsy [11]. For precision, the implemented nutritional therapy was a diet inspired by the MAD and not a classical MAD. Accordingly, high levels of ketone bodies in the blood are not to be expected in this mild ketogenic diet, as shown in Fig. 2. Patient A showed side effects like muscle weakness after the first adjustment of the diet. These problems could be eliminated in a re-training, and the diet was well tolerated in further course.

There are indications that a high protein diet could be beneficial for patients with GSDIII [6,7]. The MAD has an increased protein content with reduced carbohydrates at the same time. Main energy source in the MAD is fat at approximately 65 E% [11]. A potential positive effect of protein in the nutritional therapy is also guaranteed with a MAD. The additional low intake of carbohydrates could be a meaningful method to avoid an increased storage of glycogen.

In both cases no symptomatic hypoglycaemia occurred during MAD. On the contrary, a stabilization of blood glucose levels during MAD was present. The often described usage of corn starch to maintain a blood sugar above 70 mg/dL was not necessary [5,12]. MAD was a useful alternative to high intakes of starch and/or a high protein diet in adult GSDIII patients.

The unwanted weight loss is a well-known side effect of ketogenic diets. Possible reasons for the weight loss include not eating or food refusal, resulting in a caloric deficit [13,14]. Another cause could be a reduction of appetite through ketogenic diets [15]. The influence of ketogenic diets on appetite is currently under discussion and not completely clarified. Extreme weight loss can be avoided through close monitoring and care of the patients.

A fundamental problem of ketogenic diets is the partially difficult compliance. With increasing stringency the willingness and motivation to carry out the diet usually decreases [16]. Especially adults have greater problems with compliance in ketogenic diets than children [17]. In addition to medical reasons, such as a perceived lack of efficiency, there are also non-medical causes of non-compliance, such as the time investment in food preparation [18]. In the present case, lack of compliance has been a critical part over the years and additional training was necessary. Through cooking events and dietary training, the motivation was renewed. Another aspect was supportive and open discussions with the patients about the experienced problems in implementing the diet.

5. Conclusion

In summary, the MAD is an efficient nutritional therapy in GSDIII. The fact that the protein content in the MAD is usually high, the therapy does not conflict with the dietary recommendations for GSDIII. Through the diet, a stabilization of blood glucose and a reduction of CK levels could be achieved. For good performance of the diet, periodic patient contact and trainings are necessary to maintain compliance.

Consent

Report was performed with the written consent of the patients.

Authors's contributions

TF evaluated the data and wrote the publication, HN supported the data evaluation and the linguistic examination of the manuscript, UO look after the dietary advice, IK created the data set from clinical data, TM is the attending physician and supported the data evaluation including manuscript preparation.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgement

None.

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