Dietary carbohydrate modification in Niemann-Pick Type C

Case series of dietary treatment during miglustat (Zavesca®) therapy

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Abstract

Niemann-Pick Type C is a neurodegenerative disease with a lethal disease course. The only approved treatment is oral administration of miglustat (Zavesca®), a glucose derivative that competitively inhibits the first step of glycolipid biosynthesis. The main side effect that most patients experience is diarrhea, which is attributable to the inhibition of disaccharidases in the gut — sucrase-isomaltase in particular.

In two example cases, this complication was almost completely eliminated through strict reduction of disaccharides and oligosaccharides in the daily diet. In the study, the two patients were given disaccharide-free nutrition containing glucose as the sole source of carbohydrate. For the infant, this was given as bottle feed, and the adolescent female patient received it via tube feeding.

In the long term, the selection of foods the patients eat could be based on a diet that is very low in carbohydrates, such as the modified Atkins diet, or on a diet that specifically avoids large amounts of critical carbohydrates (such as sucrose, maltose, and starch). Essentially, the extent to which disaccharides must be restricted in the diet in order to reduce gastrointestinal side effects must be decided on an individual basis for each patient.

Keywords: Niemann-Pick Type C, miglustat, disaccharides, ketogenic diet, modified Atkins diet, carbohydrate reduction

Introduction

Niemann-Pick Type C

Niemann-Pick Type C disease (Acronym: NPC; ICD10-CM: E75.242; OMIM: 607623) is a neurodegenerative, autosomal recessive, heritable lysosomal storage disease. In 95% of cases, the NPC1 gene is affected, and in only 5% of cases, the NPC2 gene is affected [1]. The incidence of the disease is estimated at 1 in 92,000 for NPC1 and 1 in 2,900,000 for NPC2. Taking into account forms of NPC that manifest later, the combined incidence is 1.12 per 100,000 population [2].

NPC1 is an integral membrane glycoprotein of the late endosomes . The much smaller NPC2 protein can be found within the lysosomes in dissolved form [3]. If there is a fault in either of these two proteins, intracellular transport of lipids out of the lysosomes is disrupted, leading to accumulation [1, 4]. The excessive amounts of mixed lipids (mainly cholesterol and glycosphingolipids) stored in the cells causes an intensive accumulation of lipids in the brain and other organs (lipid storage disease) [3].

The first clinical signs of NPC can occur at various ages. A distinction is made depending on the age at onset: perinatal, in early childhood, in late childhood, in adolescence, or in adulthood. The clinical signs of NPC are very heterogeneous. It is common to find a combination of neurological impairments (including devel-

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[1] Endosome = a vesicle in a cell that is created through endocytosis (incorporation of particles from outside the cell through invagination of the cell membrane). Late endosomes are endosomes that are mature. They are found in the middle of the cell, unlike early endosomes, which are still located near the cell membrane.

[2] Lysosome = an organelle in the cell with an acidic pH value that contains digestive enzymes (proteases, lipases, nucleases) for the breakdown of substances originating from the cell itself or from foreign substances.

opmental delay, cataplexy [short-term muscle weakness], and cerebral seizures), psychiatric impairments (schizophrenia, depression, psychosis), and systemic impairments (including splenomegaly, liver damage, and cholestasis) [1, 4]. Diagnosis involves a complex mix of history-taking, clinical examinations, and in the case of relevant suspicions-targeted laboratory tests [4].

Side effects of treatment with miglustat (Zavesca®)

In 2006, the drug miglustat (Zavesca®) was approved in Europe for the treatment of NPC. It reduces glycosphingolipid biosynthesis in the brain and thus reduces the neurological damage that this process causes. The drug has had marketing approval from the European Commission for the treatment of the rare disease Gaucher type I since November 2002 [5]. Miglustat (N-butyl-deoxynojirimycin) is an iminosugar (♦ Figure 1) that has an inhibiting effect on glycolipid biosynthesis [6].

It remains unclear whether the use of miglustat leads to improvement of cognitive function in NPC. However, a long-term study showed stabilization of other neurological manifestations [7].

Due to its structural similarity to glucose, the active substance has an additional undesirable inhibiting effect on alpha-glucosidases (disaccharidases) in the gut. This undesirable effect causes gastrointestinal symptoms such as diarrhea, flatulence, nausea, and insufficient digestion of disaccharides. The main substances affected by this are sucrose, maltose, and isomaltose as a breakdown product of starch. Disaccharides with beta-glycosidic bonds, such as lactose, only cause malabsorption and the associated symptoms to a small extent, and only at high doses of miglustat [8, 9]. The inhibition mechanism of the disaccharidases is reversible in the presence of mainly competitive and partially non-competitive inhibition [8]. Therefore, it is currently assumed that the indigestion effect is mainly acute in nature and is expected to have only mild lasting effects on carbohydrate digestion [10]. In addition to its influence on the enzymatic cleavage of disaccharides, the molecule is also described as inhibiting glycogen breakdown in the liver [9].

In randomized controlled trials (RCT), gastrointestinal side effects were frequently observed with miglustat in addition to the stabilization or improvement of clinical markers in NPC. In the case of the pediatric patients, in the short-term and long-term study (12 vs. up to 52 months), a total of 67% had diarrhea, 33% flatulence, 42% vomiting, and 25% weight loss [11, 12]. Adults exhibited a greater tendency towards gastrointestinal symptoms than children [11].

In order to avoid the side effects, it is advisable to implement a special diet with reduction of certain disaccharides, which should reduce the development of osmotic diarrhea and altered fermentation products of the gut bacteria [13]. This can improve tolerance of miglustat treatment and help prevent weight loss [14]. What follows is a description of the development and testing of a special diet using two NPC patients as examples. The aim of the adapted diet was to reduce gastrointestinal side effects when taking miglustat. In addition, this article will discuss which types of diet are fundamentally possible for the ongoing treatment of patients with NPC, and will present lists of possible foods that could be used.

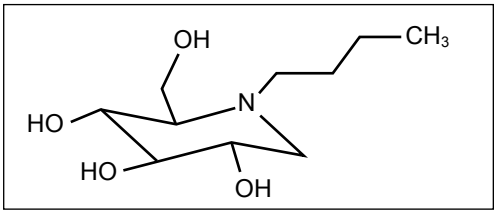

Fig. 1: **Structural formula of miglustat (n-Butyl-deoxynojirimycin; [2R,3R,4R,5S]-1-Butyl-2-[hydroxymethyl]piperidin-3,4,5-triol) [IUPAC]**

Methodology

For two patients (6 months and 19 years) with Niemann-Pick type C disease, a diet based on a carbohydrate-free product with added glucose that met the patients' dietary needs was developed for use during drug therapy with miglustat. The basis for documenting the success of the new diet was the evaluation of the existing patient data prior to the intervention. Of particular interest was the documentation regarding gastrointestinal side effects, history with regard to body weight, and a subjective assessment of well-being prior to the intervention.

The quantities of macronutrients and micronutrients that each child would need based on their nutritional requirements were calculated using the nutritional software Prodi [Version 6.7]. The food was prepared under strict hygienic conditions by the milk kitchen of *Universitätsklinikum Münster* [Münster University Hospital]. In both cases, the food was administered under inpatient conditions the first time.

The approach was determined following a systematic literature search in the online portal PubMed with the terms "Niemann-Pick Type C", "Miglustat", and related keywords in the period from December 2017 to February 2018.

Case study

Case 1

The 19-year-old was a girl; the second child of parents of German origin. She was diagnosed with Niemann-Pick Type C at the age of 10. In the same year, miglustat treatment

Amount	Ingredients	P g	F g	CH g	Energy kcal
	1,200 mL of nutrition				
1,000 g	drinking water	0.0	0.0	0.0	0
150 g	Milupa basic-ch. almost carbohydrate-free	42.4	87.0	0.2	968
150 g	glucose	0.0	0.0	149.7	608
	total (g)	**42.4**	**87.0**	**149.9**	**1,575**
	nutrient ratio in E%	**11.0**	**50.0**	**39.0**	**100.0**
	g/kcal per 100 mL	**3.5**	**7.3**	**12.5**	**130.0**
	g/kcal per kg body weight	**0.9**	**1.9**	**3.2**	**34.0**

Tab. 1: **Overview of nutrient composition (PEG tube) for a female patient (starting from 14 years of age) with Niemann-Pick Type C during treatment with miglustat**
CH = carbohydrate; E% = energy percentage; F = fat; P = protein

Amount	Ingredients	P g	F g	CH g	Energy kcal
	600 mL of nutrition				
540 g	drinking water	0.0	0.0	0.0	0
42 g	Milupa basic-ch. almost carbohydrate-free	11.9	24.4	0.0	271
48 g	glucose	0.0	0.0	47.9	194
	total (g)	**11.9**	**24.4**	**47.9**	**465.0**
	nutrient ratio in E%	**10.0**	**47.0**	**43.0**	**100.0**
	g/kcal per 100 mL	**2.0**	**4.1**	**8.0**	**78.0**
	g/kcal per kg body weight	**2.5**	**5.1**	**10.0**	**97.0**

Tab. 2: **Overview of nutrient composition for an infant (starting from the 4th month of life) with Niemann-Pick Type C before and during treatment with miglustat**
CH = carbohydrate; E% = energy percentage; F = fat; P = protein

was initiated (3 mg/kg body weight [bw] at first, then 5 mg/kg bw) with simultaneous implementation of a low-lactose, low-maltose diet. During this period, gastroenterological problems were reported only occasionally and weight gain was satisfactory.

Due to the progressive neurological problems, the patient's ability to independently consume a diet that met her needs markedly diminished, so at the age of 12.5 years, a percutaneous endoscopic gastrostomy (PEG tube) became necessary. Like most of the usual tube feeding products on the market, the main carbohydrate source in the tube feeding product that was administered was maltose. The tube feeding led to increased diarrhea and to a negative effect on weight gain (growth curve ♦ Figure 2).

In order to avoid a deterioration in the patient's physical condition, at 14 years of age, a low-disaccharide tube feeding diet was established for her. Compared to the German Nutrition Society (DGE) reference values, the glucose-based diet has a sufficient protein content to cover the patient's needs (11 energy percent [E%]), an elevated fat content (50 E%) and a reduced carbohydrate content (39 E%; ♦ Table 1).

The patient was previously receiving 1,200 mL of normal tube feeding nutrition, spread out over 6 intervals throughout the day. When the diet was changed, the original volume was maintained. When performing the calculations for the diet, the manufacturer's dosing recommendations were followed. The amount of glucose to be administered was calculated at 80% of total needs because the patient was still able to consume small amounts of solid food. The food selected was to be as low in disaccharides as possible in order to avoid gastrointestinal side effects. An informational discussion was conducted with the parents to inform them about the disaccharide content of various foodstuffs and a nutritional specialist identified critical ingredients in ready-made foods. When performing calculations for tube feeding nutrition and when manufacturing it, it is important to bear in mind that there is a limit to how high the energy content per 100 mL can be increased because increasing it too much can cause excessive osmotic concentration of the food, leading to osmotic diarrhea. Based on ex-

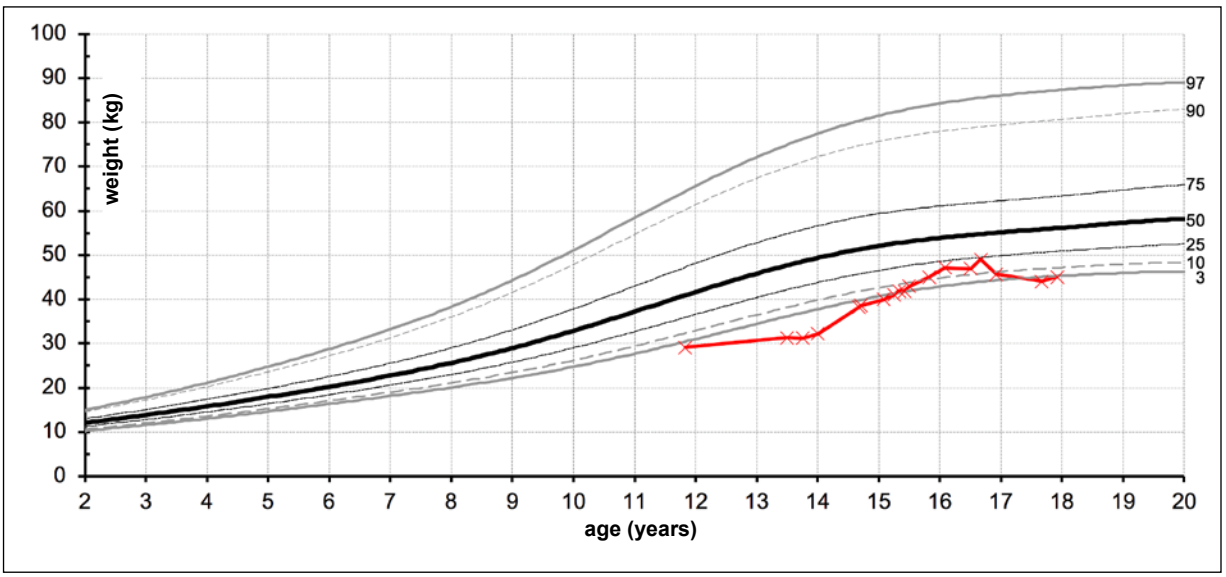

Fig. 2: **Diagram showing the body weight history for a female patient with Niemann-Pick type C**
The red line shows the individual measured values over the entire course of the therapy.
For the diagram the percentile values for girls aged 2 to 20 years (according to: Kromeyer-Hauschild K, Wabitsch M, Kunze D et al. [2001] Monatsschr Kinderheilk 149: 807–818) were used.

perience, 100–150 kcal/100 mL is tolerated well. The tube feeding nutrition used in this case contained 130 kcal/100 mL.

Case 2

The 6-month-old infant was a boy, the first child of parents of German origin. He was diagnosed with Niemann-Pick Type C 3 months after birth. Miglustat treatment was initiated in the fourth month of life. At this point in time, the infant was not able to achieve the required daily liquid food intake and was therefore put on tube feeding via a nasogastric tube to achieve this. When miglustat treatment was initiated, the infant had watery stools even though only a very small dose of the drug was administered (1 mg/kg bw/d) in order to introduce it gradually. This meant that the drug dose could not be increased for the time being.

In order to prepare for another attempt at increasing in the miglustat dose, at the age of 4 months, a special disaccharide-free tube feeding diet that was adapted to the infant's energy needs was initiated (see Case 1 and ♦ Table 2). In this case too, the manufacturer's recommended standard dose for powdered nutrition was used (Milupa basic-ch = fully balanced infant nutrition, almost carbohydrate-free). The required carbohydrate intake was calculated based on the content of breast milk and standardized infant nutrition (7–8 g carbohydrate/100 mL). Glucose was the only source of carbohydrate. The tube feeding was spread out over 6 feeds per day, about every 4 hours, similar to how feeding is spread out through the day for healthy infants. Overall, the diet was tolerated well and it was possible to increase the miglustat dose (10 mg/kg bw) without this causing watery stools. Starting from the middle of the fifth month of life, the infant became able to take the nutrition orally from a bottle, so it was possible to remove the nasogastric tube.

Results

Case 1

A comparison between the micronutrients and macronutrients administered and the D-A-CH reference values (♦ Table 3) shows that the use of the adapted tube feeding diet allowed an adequate supply to be achieved. The total energy supply was deliberately calculated below total energy needs because the patient was able to consume additional small portions of food orally. The increased supply of fats is due to the fact that ready-made food was used and this was the main component of the energy supply.

Before the optimized nutrition was implemented, it was not possible to achieve weight gain, mainly due to the existing gastrointestinal symptoms. Immediately after introduction of the adapted diet (at approximately 14 years of age), the patient's weight increased compared to the baseline weight (♦ Figure 2). After about a year, the patient was above the 3rd percentile and her weight stabilized. In the course of the last 5 years of treatment (ages 13–18), only a slight dip under the 3rd percentile was observed, and this was successfully remedied through adjustment of the daily diet. Just one day after introduction of tube feeding with glucose as the sole sugar source, there was no longer any diarrhea. This improved

Ingredient		Actual	Target	Achieved	Compensation	exceeding/undercutting (%)
Energy	kcal	1,575	2,000	79%	+425	
Protein	g	42	48	88%	+6	
Fat	g	87	65	135%	–22	
Carbohydrates	g	150	285	53%	+135	
Calcium	mg	1,134	1,200	94%	+67	
Iron	mg	11.7	15.0	78.0%	+3.3	
Vitamin B_1	mg	0.9	1.1	81.8%	+0.2	
Vitamin B_2	mg	2.0	1.2	162.5%	–0.8	
Vitamin B_6	mg	1.1	1.2	87.5%	+0.2	
Vitamin C	mg	152	90	168%	–62	
Vitamin E	mg	17.7	12.0	147.5%	–5.7	
Zinc	mg	8.2	7.0	116.6%	–1.2	
Linoleic acid	g	9.0	5.4	167.4%	–3.6	
Linolenic acid	g	1.7	1.1	153.5%	–0.6	
Vitamin B_{12}	µg	3.9	3.0	130.0%	–0.9	

Tab. 3: **Comparison of actual and target intakes of micronutrients and macronutrients in a female patient with Niemann-Pick Type C based on D-A-CH reference values for a girl aged 15 to 19 years**
A PAL of 1.4 was established for the calculation. The share of the reference value reached is shown as a percentage, the compensation required to reach the reference value is shown in the respective unit of measurement, and the extent to which the values exceed or fall short of the reference values is shown as a bar chart.

condition was maintained throughout the entire nutritional therapy intervention. A consultation with the relatives providing care revealed that there was a marked improvement in the patient's well-being. There were no further abnormal gastrointestinal symptoms.

Case 2

A direct comparison between the patient's actual intake of energy, vitamins, and minerals since introduction of the disaccharide-free diet and the target intakes (based on D-A-CH reference values) shows that the supply was fully adequate throughout the treatment (♦ Table 4). Both during and after tube feeding, the calculated recommended liquid food intake for the infant was achieved without any major problems. In this second case, it was possible to maintain a macronutrient ratio that corresponded to the reference values. The main energy source was fat (47 E%). This was followed by glucose (43 E%) and a protein content that covered nutritional requirements (10 E%). The intake of micronutrients exceeded the recommended amounts because a powdered diet that is suitable for several age groups was used.
Thanks to the early diagnosis and the quick implementation of the disaccharide-free diet, weight was kept stable at above the 3rd percentile throughout the entire course of treatment. The critical phase with liquid stools was kept short thanks to the quick nutritional intervention, and as soon as this diet was started, no more diarrhea occurred. In this case, the only reason it was possible to increase the dosage of miglustat was that the diet had been adjusted. If standard feed or breast milk were used, this would not have been possible due to the high amounts of water and electrolytes lost through the severe diarrhea. The stabilization was maintained throughout the rest of the course of treatment, and no further abnormal gastrointestinal symptoms occurred. The infant exhibited a balanced clinical picture overall, especially compared to the period prior to the intervention, during which he had to be ventilated and fed through a tube due to his inadequate nutritional condition.

Discussion

In both cases, it was found that the gastrointestinal symptoms caused by the use of miglustat immediately reduced after introduction of the special disaccharide-free diet. As the treatment went on, it was possible to maintain this condition in a stable manner and increase the patient's well-being. For infants, it is possible to put the same tube feeding nutrition in a bottle and use it for bottle feeding without any problems, and this covers all micronutrient needs. In order to optimize treatment with the drug, the disaccharide-free diet should be implemented as soon as gastrointestinal symptoms start under miglustat treatment so that it is possible to increase the dose up to the desired dose and avoid gastrointestinal problems in the initial period. In the long term, use of this diet can help avoid undesired weight loss. In the cases presented here, increased intake of the monosaccharide

Ingredient		Actual	Target	Achieved	Compensation	exceeding/undercutting (%)
Energy	kcal	465	550	85%	+85	
Protein	g	12	14	85%	+2	
Fat	g	24	28	87%	+4	
Carbohydrates	g	48	55	88%	+7	
Calcium	mg	336	220	153%	–116	
Iron	mg	3.3	0.5	660.0%	–2.8	
Vitamin B_1	mg	0.3	0.2	126.0%	–0.1	
Vitamin B_2	mg	0.6	0.3	182.0%	–0.3	
Vitamin B_6	mg	0.3	0.1	294.0%	–0.2	
Vitamin C	mg	42	20	212%	–22	
Vitamin E	mg	5.0	3.0	165.2%	–2.0	
Zinc	mg	2.3	1.0	229.4%	–1.3	
Linoleic acid	g	2.5	2.4	106.5%	–0.2	
Linolenic acid	g	0.5	0.3	156.1%	–0.2	
Vitamin B_{12}	µg	1.1	0.4	273.0%	–0.7	

Tab. 4: **Comparison of actual and target intakes of micronutrients and macronutrients in a male infant with Niemann-Pick Type C based on D-A-CH reference values for a boy aged 0–4 months**
The share of the reference value reached is shown as a percentage, the compensation required to reach the reference value is shown in the respective unit of measurement, and the extent to which the values exceed or fall short of the reference values is shown as a bar chart.

glucose did not cause any problems such as osmotic diarrhea. However, if any further increase in glucose concentration in the diet is needed, this should be done in a stepwise manner in order to avoid the possible side effects. One practical advantage of the addition of monosaccharides to the almost carbohydrate-free powder diet is its improved solubility when mixed with water.

In a study with 29 patients (21 of whom had NPC), it was also demonstrated that modification of disaccharide intake was associated with a reduction in gastrointestinal side effects. The study participants were divided into three groups (no modification, low-lactose diet, and low disaccharide diet). In this study, the low lactose diet produced a very small improvement compared to standard nutrition. The best results in terms of increase in body weight and reduced gastrointestinal symptoms were found in the group that was on a reduced disaccharide diet. However, there were no significant differences between the groups in terms of change in weight. In 60% of patients, mild flatulence occurred in the initial phase of the treatment despite the low disaccharide diet [14].

Compared to the complete removal of disaccharides from the daily diet as described in the present study, in this case, depending on the patient, even small amounts of disaccharides appeared to cause gastrointestinal symptoms. The poor efficacy of a low lactose diet can be explained by the fact that only alpha-glucosidases are affected by inhibition through miglustat, and not beta-glucosidases. Thus, the drug inhibits sucrase (cleaves sucrose), maltase (cleaves maltose), and isomaltase (involved in breakdown of starch: amylopectin, alpha-D1,6-glycosidic cleavages), but not lactase (cleaves lactose) [8].

Another study in human subjects focused on the use of yeast as a supplement to improve tolerance of miglustat. Overall, there was no evidence of a significant effect in terms of efficacy [15].

The manufacturer of miglustat also recommends adapting the diet by reducing intake of sucrose, lactose, and other carbohydrates if gastrointestinal symptoms (diarrhea) and/or weight loss occur. Furthermore, the manufacturer also mentions the additional use of antidiarrheal drugs such as loperamide [16]. In addition, there is a dietary advice booklet with a food diary and recipe cards available for patients, and this is specifically aimed at reducing disaccharides in the diet [17]. In the recipes and informational brochures, the limitation of disaccharides mainly refers to restriction of lactose, sucrose, and maltose. It is also clearly highlighted that miglustat should not be taken with a meal, but rather always two hours before or after a meal, however this is often difficult to implement in everyday life in practice. In summary, a diet with a low disaccharide and carbohydrate content is recommended [17].

Limitations of the dietary concept

The dietary concept presented here is limited in sense that it can only be used in infants or in phases of tube feeding. The solution

Follow-up diet options

There are various nutritional concepts that could be used for the introduction of complementary food in the first year of life or for increasing orally-ingested food in the case of tube feeding. The disaccharide-free tube/bottle feeding presented here is only suitable for long-term use to a limited extent. In the first instance, an attempt should be made to switch the patient to normal oral food intake as far as possible.

An adapted form of the Modified Atkins Diet (MAD) may serve as a suitable long-term diet. Here, the main source of energy is fat (approximately 65 E%), and the protein content (up to 30 E%) covers nutritional needs. Daily carbohydrate intake is between 10 and 60 g (~ 5–10 E%) and can be adapted to the individual [18, 19]. With sufficient information and training, supplementation of micronutrients is not necessarily required, however it should be considered if needed. The main adaptation that should be made to MAD for the diet required here is the avoidance of foods that contain a large amount of disaccharides. Because this diet already reduces carbohydrate intake, and because foods with a high disaccharide or starch content are additionally eliminated, gastrointestinal side effects can be kept to a minimum. An additional advantage is that the basic training concept for MAD is relatively simple, and it can be easily incorporated into everyday life.

Another option is to recommend that the patient avoid the problematic disaccharides (sucrose and maltose) and starch, without reducing carbohydrate intake as low as in MAD. An important aspect of this kind of dietary treatment is using trial and error to determine the individual's physiological limits with regard to carbohydrate intake. These modifications result in a diet that is rich in protein and fat, but which has a much higher carbohydrate content than an adapted MAD (up to approximately 40 E%). For example, regular household sugar can be replaced with glucose. Overall, products with a high dietary fiber content (such as wholemeal bread instead of white bread) are advantageous. Foods with a high content of critical carbohydrates should be avoided, or permitted only in very small amounts.

Food swap tables could help the patient identify the best possible foods and create a balanced daily menu.

♦ Table 5 shows an overview of recommended products and unsuitable products. Industrially produced ready-made foods (such as ketchup, sauces, and instant products) cannot be integrated into the diet due to the added sugar. In terms of fruit and vegetables, it is particularly important to make the patient/the relatives aware of sensible alternatives to products that contain large amounts of carbohydrates.

♦ Table 6 provides an overview of possible low-carbohydrate plant-based foods. The selection focuses mainly on products that can be used for infant nutrition. In principle, small amounts of potatoes can be consumed (sucrose: 0.3 g/100 g, starch 14.3 g/100 g), and they offer a good alternative to foods such as pasta (sucrose: 0.1 g/100 g, starch: 25.6 g/100 g) or rice (sucrose: 0.0 g/100 g, starch: 27.1 g per 100 g), which all have a much higher starch content.

used here, made up of carbohydrate-free tube feeding/liquid nutrition and added glucose, is not suitable for administration by the oral route only as the sole source of nutrition in the long term. In the long term, a diet that is adapted to deal with the problem of limited ability to digest disaccharides should be used (♦ Box: Follow-up diet options). Based on currently available research, restriction of lactose is not necessary. If symptoms continue to occur in the further course of the nutritional therapy, additional elimination of lactose could be implemented and integrated into the meal plan. It should be noted that polysaccharides such as starch can lead to symptoms due to the impaired isomaltase function and the release of disaccharides due to amylase.

The follow-up diet options presented in the box each have advantages and disadvantages in terms of their implementation, and these should be taken into account. In general, the concept chosen should always be adapted to the preferences and tolerance of the patient. Careful selection of the diet plan to be used is fundamental to the success of the nutritional intervention, and this requires incorporating the wishes of the patient. Key disadvantages of a Modified Atkins Diet (MAD) include limited compliance in ketogenic diets and the possibility of weight loss, which would be contraindicated in the case of NPC patients [20, 21]. However, it should be noted that the ketogenic aspect of the diet is not what is important for the treatment of NPC, but rather the reduction of critical carbohydrates with the aim of improving the gastrointestinal situation. Increasing carbohydrates up to the patient's level of tolerance could result in an acceptable and very feasible diet.

The targeted reduction of disaccharides and starch without implementing carbohydrate reduction and with simultaneous switching in favor of monosaccharides as the second option could result in undesirably high fluctuations in glucose levels. Increased fructose intake may represent an additional disadvantage. There is currently a debate on whether it may be associated with the development of metabolic and cardiovascular diseases [22]. However,

Category	Suitable	Unsuitable
Milk products	unsweetened milk products, or in the case of additional lactose intolerance: lactose-free products	sweetened milk products
Meat, game, poultry	not breaded, without flour, without added starch	sweetened sausages and sausages with flour, grains, or starch (e.g. liverwurst and teesausage spread), products with mayonnaise (added sugar!)
Fish	not breaded, without flour, without added starch	fish in sauces/marinades/dressings, ready-made salads, breaded fish products
Vegetables	2–3 portions/day, not breaded, without flour, without added starch, choose vegetables with a low sucrose and/or starch content	vegetables with a high sucrose and/or starch content (e.g. peas, beans, sweetcorn)
Fruit	1–2 portions/day, fresh, no added sugar, choose fruit with a low sucrose content (such as cherries, berries, kiwis, pears)	fruit with a high sucrose content (such as bananas, mandarins, mangoes, peaches)
Bread and other baked goods	types of breads in which no sugar is added in the manufacturing process; use wholemeal products as far as possible, bake cakes and other baked goods at home (replace half the required amount of sugar with monosaccharides as required)	sweetened breads and rolls, products usually found in shops such as cakes, baked goods, rusks, and biscuits
Cereal products	use only in small quantities (e.g. flour, semolina, rice, pasta); binding and gelling agents based on gelatin, agar agar, carrageenan, guar gum or locust bean gum are well suited	sugar, all sweet spreads (e.g. jam, honey), malt sugar, malt extract, maltodextrin, muesli and breakfast cereals with added sugar, raisins, cornflakes with sugar, Bircher muesli, cake mixes, sweetened infant food and mash
Confectionery	sweetener; sugar substitutes such as xylitol, lactitol, sorbitol, stevia in small quantities; sugar-free candies and chewing gum, glucose and glucose candies; chocolate prepared with fructose or sweetener	all confectionery with sucrose
Drinks	coffee, tea, mineral water, sugar-free soft drinks	all products with sugar, maltose, malt extract, or glucose syrup (e.g. soft drinks, fruit juices), malt drinks
Medications	sugar-free medicinal preparations	liquid preparations (such as cough syrup) and homeopathic remedies containing maltodextrin or sugar

Tab. 5: **Suitable and unsuitable foodstuffs for dietary treatment of gastrointestinal side effects during miglustat treatment for NPC** [Source: own template]

Foodstuff (100 g)	Carbohydrate (total, g)	Fructose (g)	Glucose (g)	Sucrose (g)	Starch (g)
Zucchini	2.3	1.1	1.0	0.1	0.5
Cauliflower	2.3	0.9	1.0	0.2	0.3
Spinach	0.7	0.2	0.2	0.2	0.2
Broccoli	2.7	0.9	0.9	0.4	0.1
Pumpkin	4.8	1.4	1.6	1.1	0.7
Kohlrabi	3.7	1.2	1.3	1.0	0.1
Parsnip	11.1	0.2	0.2	2.1	7.2
Carrot	6.9	0.8	0.8	5.1	0

Tab. 6: **Vegetables with low sucrose and starch content, based on 100 g edible quantity** [source: BLS 3.02]

all in all, depending on individual tolerance, an easy-to-implement nutritional therapy can be achieved by replacing and avoiding certain foods. Further studies with targeted interventions will be needed to determine whether the types of diet discussed here are also effective in the long-term.

Conclusion

The elimination of disaccharides in the daily diet of two patients with NPC led to complete halting of gastrointestinal side effects during treatment with miglustat. The intervention either increased or stabilized body weight compared to baseline, and it improved the health condition of the patients. The dietary approach did not impair micronutrient supply.
In the further course of the nutritional therapy, it would be possible to use an adapted form of MAD or a low-disaccharide, low-starch diet to prevent gastrointestinal symptoms after the transition to solid food intake. Based on current research, restriction of lactose intake is not necessary. Further research with a larger patient population will be needed in order to draw conclusions about the effects of the nutrient composition and options for follow-up diet presented here.

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Conflict of Interest
Tobias Fischer und Thorsten Marquardt declare no conflict of interest. Ulrike Och wrote brochures and chaired congresses for Dr. Schär and Vitaflo, received lecture fees by Nutricia and MetaX, and got refund of traveling expenses and participation fee by Biomarin.

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