Nutrition management of Niemann Pick disease type C: A case report

Rejane VIANA DOS SANTOS¹, Tamila DAS NEVES FERREIRA², Daniela OLIVEIRA DE ALMEIDA³,
Lilian BRITO DA SILVA FATAL⁴, Edilene Maria QUEIROZ ARAUJO⁵

¹Nucleus of Research and Extension in Nutritional Genomics and Metabolic Dysfunctions (GENUT), Life Sciences Department/University of the State of Bahia (UNEB), Salvador-BA, Brazil; ²University Hospital of Federal University of Sergipe, Aracaju-SE, Brazil; ³Interactive Process of Organs and Systems, Health Sciences Institute/Federal University of Bahia (UFBA), Salvador-BA, Brazil; ⁴Life Sciences Department/UNEB, Salvador-BA, Brazil; ⁵Coordinator of Nutrition Course and GENUT, Life Sciences Department/UNEB; Interactive Process of Organs and Systems, Health Sciences Institute/UFBA, Salvador-BA, Brazil
E-mail: rejaneviananutri@gmail.com

Objectives. We aim to report the clinical repercussions of a nutritional approach in a patient diagnosed with Niemann Pick disease type C (NPC) using miglustat as pharmacological therapy.

Case report. A 33-year-old woman diagnosed with NPC using miglustat was instructed to look for a dietary management at our nutrition service. Patient's symptoms were weight loss and important gastrointestinal alterations. Our nutritional prescription was a high-calorie and high-protein, lactose- and sucrose-free diet, as well as a daily supplementation of L-glutamine, probiotics, omega 3, and coenzyme Q10. After two months, the patient had weight gain and improvement in the intestinal health.

Conclusions. We found that nutritional prescription aided in the treatment of NPC and revealed that nutritional care represents an important strategy in the management of rare genetic diseases.

Key words: Niemann Pick type C disease, nutrition, rare diseases, miglustat, intestinal dysbiosis

Niemann Pick type C disease (NPC) is a rare genetic disorder with autosomal recessive pattern, characterized by fat deposition in some organs, with an estimated incidence of 1 per 120,000 live births (Cuisset et al. 2016). NPC is caused by a mutation in a glycolipid transporter, which executes intracellular mobilization of water-insoluble molecules, such as unesterified cholesterol. The encoded transporter is unstable, which leads to lipids' trafficking impairment. Thus, cholesterol accumulates within lysosomes, promoting various clinical manifestations (Bountouvi et al. 2017). Scientific data about the nutritional management of this disease are scarce. Therefore, this paper reports the case of a patient with

a dominant pattern of NPC undergoing clinical and nutritional care due to weight loss and gastrointestinal alterations after using miglustat.

This research was approved by the Research Ethics Committee of the University of the State of Bahia (protocol number: 25076819.4.0000.0057). Every procedure was conducted following the international ethical guidelines of the Declaration of Helsinki.

Case Report

A 33-year-old woman was referred to our nutrition clinic after a myriad of gastrointestinal alterations. She was diagnosed with NPC since her 29th

year, when developed physical impairments such as dysarthria, ataxia, dystonia, spasticity, and paresis of vertical gauze.

In the month prior to the nutrition appointment, she initiated a drug treatment with miglustat, which led her to gastrointestinal discomfort, distended abdomen, flatulence, abdominal pain, and increased intestinal rhythm with diarrheal stools (twice or thrice per day, Bristol stool scale type 6) (Bountouvi *et al.* 2017; Martinez and de Azevedo 2012), followed by clinically important weight loss.

The patient had undergone oral lactose tolerance test and other biochemical tests, and brought the following results: basal blood glucose at 0 min = 85 mg/dl, at 30 min = 90 mg/dl, at 60 min = 80 mg/dl (lactose intolerant); triglycerides = 116 mg/dl; total cholesterol = 115 mg/dl, high-density lipoprotein cholesterol (HDL-c) = 35 mg/dl, low-density lipoprotein cholesterol (LDL-c) = 97 mg/dl; aspartate transaminase = 22 U/L and alanine transaminase = 17 U/L. Despite the exacerbated production of cholesterol in NPC, the serum levels were unchanged, as they were retained in lysosomes. An abdominal ultrasound test diagnosed hepatosplenomegaly. A genotyping test identified mutation in the NPC1 gene.

During physical examination, she had a skinny body structure, mild alopecia, pale inner eyelid membranes, white tongue coating, brittle nails with vertical lines, and abdominal distension with tympanic sound. She reported muscle weakness in upper and lower limbs.

During food frequency questionnaire application, she reported high consumption of refined cereals, low intake of fiber and micronutrient as well as regular consumption of dairy products, sausages, and fried foods. Calculation of one 24-hour dietary recall showed a diet with a total energy value (TEV) of 966.02 kcal/day (17.56 kcal/kg of actual body), of

which 44.1% fat, 39.2% carbohydrates, and 0.82 g proteins represented the actual weight/day.

The anthropometric patient measures were: weight = 55 kg; usual weight before miglustat treatment = 57.1 kg; weight loss within a month after beginning miglustat treatment = 3.7% (mild to moderate weight loss); height = 1.68 m; body mass index = 19.4 kg/m² (eutrophic); arm circumference = 25.8 cm (P15*–P25, adequate muscle-mass and fat-mass); tricipital skin-fold thickness = 15 mm (P15, risk of fat-mass depletion); corrected arm muscle area = 28.91 cm² (P25–P50, adequate muscle-mass); waist circumference (WC) = 75.5 cm (adequate WC even with hepatosplenomegaly and abdominal distension). The prescribed nutritional treatment consisted of a dietary plan with the following composition: hypercaloric with 1.720 kcal (31 kcal/kg of actual weight/day) of TEV; hyperproteic with 20% of TEV (1.56 g/kg/day); normoglycidic (50% of TEV) and normolipidic (30% of TEV) with strict selection of fat sources. For the management of gastrointestinal disturbances and gut microbiota reestablishment, lactose and sucrose were excluded from her diet, and probiotics were added in her prescription. In addition, daily supplementation of coenzyme Q10 (CoQ10), 3g of omega-3 eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) (2:1 ratio, respectively) and 5 g of L-glutamine were also prescribed, as well as a complementary protein supplement (whey protein). Our goal was to reestablish intestinal microbiota balance, prompting patient's weight gain, and improving her nutritional status (Table 1).

After two months, she returned to the clinic with 1.2 kg of weight gain (current weight = 56.2 kg), WC = 74.3 cm (with decreased abdominal distension), and reported improvement on nail appearance (strong and resistant), skin (more hydrated), hair (alopecia reduction), and reduction of gastrointestinal symptoms.

Table 1
Anthropometric parameters according to patient's self-report, and measured before and after nutritional intervention

Anthropometric measures	Self-referred data	Clinical data before intervention	Clinical data after intervention
Body weight (kg)	57.1	55.0	56.2
Height (m)	1.68	1.68	1.68
BMI (kg/m ²)	20.6	19.4	19.91
Arm circumference (cm)		25.8	25.5
Triceps skin fold (mm)		15	15
Arm muscular area (cm ²)		28.91	27.91
Abdominal circumference (cm)		75.5	74.3

Abbreviations: BMI – body mass index.

Discussion

The clinical hallmark of NPC is the accumulation of unesterified cholesterol and glycosphingolipids within the cell. It mainly affects liver tissue, spleen, and brain, leading to visceral neurological/cognitive injuries (Bountouvi et al. 2017).

Miglustat is a pharmacological treatment, which acts directly on glucosylceramide synthase enzyme, blocking the production pathway of glycosphingolipids. However, it promotes depletion of disaccharidases as an adverse effect. Thus, gastrointestinal symptoms emerge, in addition, to weight impairment (Shayman and Larsen 2014).

Nutritional care in NPC is strongly important, aiming the use of nutrients that aid the prognosis, and minimizing adverse effects caused by the pharmacological treatment. Our approach was based on the Food Guidance for NPC Patients under miglustat treatment (Actelion Pharmaceuticals Portugal), as well as other interventions to optimize nutritional gains, diarrhea reduction, and patient's overall well-being.

The prescription of a high-protein and high-calorie diet aided in patient's weight gain as well as improved her muscular strength. Probiotics (*L. acidophilus*, *L. lactis*, *L. casei* and *B. bifidum* strains, 1 million each) and L-glutamine supplementation led to the reestablishment of gut microbiota. She reported improvement of neurological symptoms, which is likely due to CoQ10 and omega-3 supplementation. Studies have shown that CoQ10 has a role in mitochondrial electron transport and antioxidant actions, and its deficiency is associated with cellular oxidative stress and neurodegenerative diseases (Li et al. 2019; Nakamoto et al. 2018). Scientific data have shown promising results of vitamin E supplementation, due to its antioxidant action, through c-Abl/p73 pathway, which prevents the pro-apoptotic activation of neurons. Accordingly, there is a delay in neurodegeneration, and improvement in locomotor function and survival in model mice of NPC (Marin et al. 2014).

In lactose intolerance situation, saturated fatty acid and gases such as hydrogen, carbon dioxide, and methane are produced in intestinal lumen, causing abdominal discomfort, bloating, flatulence, and osmotic diarrhea (Araujo et al. 2019). In this case, the most appropriate nutritional recommendation for reducing the frequency and severity of intestinal disorders is to decrease carbohydrates intake, especially disaccharides, in a single meal. With this measure, an increase in diet tolerability may be achieved, which attenuates great impacts on weight loss (Belmatoug et al. 2011). In addition, the use of probiotics, *Saccharomyces boulardii*, also decreases the severity of gastrointestinal disorders, such as diarrhea, as it has been reported in a double-blind, placebo-controlled study (Remenova et al. 2015). Thus, the modulation of patient's gut biome had a positive contribution to digestive physiology, since it regulated immunological effects on intestinal mucosa, intestinal permeability, and vitamin production, enabling a suitable nutrient absorption (Saad 2006; Wagner et al. 2018). As expected, the patient had good clinical evolution with weight gain.

Conclusion

The nutritional management was decisive for the reestablishment and improvement of the patient's clinical condition. Despite literary scarcity, scrupulous care of the health professional is mandatory in the diagnosis as well as the planning and implementation of therapeutic strategies. The nutritionist aims the recovery of the patient's nutritional status and well-being, especially when it comes to rare diseases, such as NPC.

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