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RESEARCH REPORT

# Feeding Difficulties and Orofacial Myofunctional Disorder in Patients with Hepatic Glycogen Storage Diseases

**Chenia Caldeira Martinez · Tássia Tonon · Tatiéle Nalin · Lilia Farret Refosco · Carolina Fischinger Moura de Souza · Ida Vanessa Doederlein Schwartz**

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**Abstract** Hepatic glycogen storage diseases (GSDs) are inborn errors of metabolism whose dietary treatment involves uncooked cornstarch administration and restriction of simple carbohydrate intake. The prevalence of feeding difficulties (FDs) and orofacial myofunctional disorders (OMDs) in these patients is unknown. *Objective*: To ascertain the prevalence of FDs and OMDs in GSD. *Methods*: This was a cross-sectional, prospective study of 36 patients (19 males; median age, 12.0 years; range, 8.0–18.7 years) with confirmed diagnoses of GSD (type Ia = 22; Ib = 8; III = 2; IXa = 3; IXc = 1). All patients were being treated by medical geneticists and dietitians. Evaluation included a questionnaire for evaluation of feeding behavior, the orofacial myofunctional evaluation (AMIOFE), olfactory and taste performance (Sniffin' Sticks and Taste Strips tests), and facial anthropometry. *Results*: Nine (25%) patients had decreased olfactory perception, and four (11%) had decreased taste perception for all flavours. Eight patients (22.2%) had decreased perception for sour taste. Twenty-six patients (72.2%) had FD, and 18 (50%) had OMD. OMD was significantly associated with FD, tube feeding, selective intake, preference for fluid and semisolid foods, and mealtime stress ($p < 0.05$). Thirteen patients (36.1%) exhibited mouth or oronasal breathing, which was significantly associated with selective intake ($p = 0.011$) and not eating together with the rest of the family ($p = 0.041$). Lower swallowing and chewing scores were associated with FD and with specific issues related to eating behavior ($p < 0.05$). *Conclusion*: There is a high prevalence of FDs and OMDs in patients with GSD. Eating behavior, decreased taste and smell perception, and orofacial myofunctional issues are associated with GSD.

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C. C. Martinez (✉) · T. Tonon · T. Nalin · I. V. D. Schwartz
Post-graduate Program in Medicine: Medical Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil
e-mail: chenia.martinez@gmail.com

L. F. Refosco · C. F. M. de Souza · I. V. D. Schwartz
Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil

I. V. D. Schwartz
Department of Genetics, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

## Introduction

Hepatic glycogen storage diseases (GSDs) are inborn errors of glycogen metabolism. These conditions are divided into subtypes, depending on the enzyme defect involved (Wolfsdorf and Weinstein 2003; Walter et al. 2016). Phenotype depends on the disease subtype and extent of metabolic control, but major features include growth retardation, short stature, a doll-like face, hepatomegaly, hypoglycemia, hyperlactatemia, hypercholesterolemia, and hypertriglyceridemia (Chen and Kishnani 2012; Kishnani et al. 2014; Derks and Smit 2015).

Treatment can include restricted intake of simple carbohydrates (fructose, maltose, glucose, lactose, galactose), administration of uncooked cornstarch several times a day (including overnight, as some patients do not tolerate fasting for more than 3 h), and management of clinical and laboratory parameters (Weinstein and Wolfsdorf 2002; Chen and Kishnani 2012; Derks and Smit 2015). Sometimes, due to the dietary restrictions and continuous feeding

required, tube feeding is indicated to maintain normoglycemia and proper metabolic control (Rake et al. 2002; Weinstein and Wolfsdorf 2002; Flanagan et al. 2015).

Feeding difficulties (FDs) are common in childhood, affecting up to 50% of children regardless of sex or socioeconomic status. Causes include a variety of organic and behavioral issues, as well as the feeding style of the caregivers; specific features and severity vary widely (Carruth et al. 2004; Wright et al. 2007; Dunitz-Scheer et al. 2009; Mascola et al. 2010; Benjasuwantep et al. 2013; Edwards et al. 2015; Kerzner et al. 2015).

The main organic conditions associated with FDs are dysphagia; gastrointestinal, metabolic, and cardiorespiratory abnormalities; structural/mechanical abnormalities; orofacial myofunctional disorders (OMDs); growth failure; and tube feeding. Other issues that are also directly related include prolonged mealtimes, food refusal, mealtime stress, lack of autonomy to self-feed, lack of distractions to increase intake, difficulty in eating foods with different textures, and picky eating. FDs can cause significant nutritional and emotional problems in children and in their caregivers (Carruth et al. 2004; Wright et al. 2007; Dunitz-Scheer et al. 2009; Mascola et al. 2010; Benjasuwantep et al. 2013; Edwards et al. 2015; Kerzner et al. 2015).

Few studies have assessed the issue of OMD and FDs in patients with GSDs. This population is particularly susceptible to FDs, as both the disease and its treatment are associated with risk factors for the development of feeding disorders. Poor acceptance of dietary plans by patients and families is also a concern (Correia et al. 2008; Santos et al. 2014; Flanagan et al. 2015). Within this context, the present study aimed to investigate FDs, OMDs, and olfactory and gustatory perception in Brazilian patients with hepatic GSDs.

## Materials and Methods

### Sample

This was a cross-sectional, prospective study of 36 patients (19 males; median age, 12.0 years; range, 8.0–18.7 years) with confirmed diagnoses of GSD (type Ia, $n = 22$; Ib, $n = 8$; III, $n = 2$; IXa, $n = 3$; IXc, $n = 1$) who were being treated at Hospital de Clínicas de Porto Alegre, a referral center in Southern Brazil. Fifteen patients (41.7%) were being tube-fed, 12 (36.1%) through a gastrostomy. Three patients (8.3%) were on tube feeding due to severe food refusal, and five (13.8%) were fed either orally or by tube. Data were collected from 2015 to 2017. A convenience sampling strategy was used.

Due to similarities in clinical characteristics and treatment, GSD subtypes were pooled as "subtype I" (Ia and Ib) and "other subtypes" (III and IX). Treatment included follow-up by an interdisciplinary team (a medical geneticist specializing in inborn errors of metabolism, a specialized dietitian, nurse, and clinical psychologist), with visits every 3 months; control of clinical and laboratory parameters; dietary management; and group therapy. Individuals under the age of 5 were excluded by recommendation of the tests. The study was approved by the Institutional Review Board of the hospital where it was carried out (protocol no. 150072), and written informed consent was obtained from all individuals before participation.

### Procedures

Clinical information was collected from medical records and through a structured interview with the patient about FDs. To investigate dietary habits and feeding difficulties, a questionnaire of relevant items was constructed according to Edwards et al. (2015) and Kerzner et al. (2015); caregivers answered the questionnaire when patients were unable to understand the questions. Relevant behavioral signs and issues included selective intake, fear/aversion of feeding, prolonged mealtimes, mealtime stress (e.g., parents' and/or caregivers' insistence on offering food, constant resistance and/or refusal to feed, especially in childhood), preference for fluid/semisolid foods, and family eating habits (e.g., not eating together). Subjects were classified as having a "feeding difficulty" on the basis of the following three aspects: (1) self-report by patients/caregivers, (2) clinical evaluation by the researcher, and (3) presence of one or more of the aforementioned behaviors.

Clinical evaluations were performed on the same day by a trained speech–language pathologist with experience in administration of the study instruments, namely, (a) a validated protocol for investigation of OMD, the orofacial myofunctional evaluation with scores (AMIOFE) (De Felício and Ferreira 2008); (b) analysis of olfactory perception by the *Sniffin' Sticks* test (Hummel et al. 1997); and (c) Analysis of taste perception by the *Taste Strips* test (Mueller et al. 2003). This test evaluates four tastes (sweet, sour, salty, bitter), being possible to obtain the total score or the score of each flavor separately. For the present study, it were analyzed the total score and the sour taste, since sour taste is often present in foods restricted in the diet of patients with GSDs.

### Statistical Analysis

The chi-square, Fisher's exact, Mann–Whitney *U*, and Spearman correlation tests were used for nonparametric variables, and Poisson regression with robust variance to analyze risk factors by prevalence ratio (PR). The

Kolmogorov–Smirnov test was used to evaluate the assumption of normality. The significance level was set at 5% ($p \leq 0.05$).

## Results

Assessment of smell and taste perception was performed in 22 patients (61.1% of the sample), all aged ≥11 years, in accordance with the test recommendations. Regarding olfactory perception, the median score was 10.0 (8.8–11.2) points. Nine patients (40.9%) had median scores below the cutoff point, indicating hyposmia. For taste perception, the median score was 11.5 (10.0–14.0) points. Four patients (18.2%) had scores below the cutoff point for all flavors, suggesting hypogeusia. The scale for sourness alone ranges from 0 to 4 points. The sample median was 3.0 (0.8–3.0) points, with eight patients (36.4%) having a score indicative of decreased sour taste perception.

Variables related to the reduction of olfactory, gustatory, and sourness perception were compared to behavioral issues regarding food. Decreased olfactory perception was associated with selective intake ($p = 0.027$), while decreased sourness perception was associated with preference for fluid and/or semisolid foods ($p = 0.006$).

The prevalence of feeding issues (feeding behaviors or conditions that may impact on the child's feeding) and a comparison with the presence of FD are presented in Table 1. The overall prevalence of FD in this sample was 72.2% ($n = 26$). Since GSD I requires a more restrictive diet than other subtypes, the potential association between this subtype and FD needs to be investigated. In this study, we could not conduct a statistical comparison due to the discrepancy in sample size (30 participants with GSD I vs. 6 patients with other GSDs).

Findings related to feeding behavior were analyzed and compared to median scores in the orofacial myofunctional scale, specifically total, deglutition, and mastication scores (Table 2). The total orofacial myofunctional score correlated positively with age ($r = 0.493$, $p = 0.002$), suggesting that younger individuals had lower test scores.

Variables were analyzed by Poisson regression with robust variances to investigate risk factors for OMD, using prevalence ratios controlled by age. Preference for fluid/semisolid foods (PR = 10.29, 95% CI 1.4–75.1, $p = 0.021$) and selective intake (PR = 7.94, 95% CI 1.1–56.6, $p = 0.038$) were significant. This suggests that, even after controlling for age, these feeding issues are risk factors for OMD.

Table 3 presents an analysis of posture/appearance, mobility of orofacial structures, and orofacial functioning, stratified by age range (Table 3). Regarding stomatognathic functions, 1 patient presented with mouth breathing and 12 (33.33%) with oronasal-type breathing. Both breathing patterns were associated with selective intake ($p = 0.011$) and nonparticipation in family meals ($p = 0.014$). Mastication could not be assessed in three children due to lack of oral feeding secondary to complete food refusal. In these cases, the minimum score of one point was assigned, in accordance with test recommendations.

**Table 1** Hepatic glycogen storage disorders: feeding aspects and feeding difficulty

| | Sample prevalence ($n = 36$) | Feeding difficulty[a] | | |
|---|---|---|---|---|
| | *n* (%) | Presence of feeding difficulty ($n = 26$) | Absence of feeding difficulty ($n = 10$) | *$p$-value |
| *Tube feeding >1 year* | 15 (41.7%) | 13 (50.0%) | 2 (20.0%) | 0.142 |
| *Exclusive breastfeeding <6 months* | 25 (69.4%) | 21 (80.8%) | 4 (40.0%) | 0.039* |
| *Feeding behaviors and conditions* | | | | |
| Selective intake | 23 (63.9%) | 22 (84.6%) | 1 (10.0%) | <0.001* |
| Fear of feeding (or food aversion) | 11 (30.6%) | 11 (42.3%) | 0 (0.0%) | 0.016* |
| Preference for fluid/semisolid foods | 21 (58.3%) | 19 (73.1%) | 2 (20.0%) | 0.007* |
| Prolonged mealtimes | 18 (50.0%) | 14 (53.8%) | 4 (40.0%) | 0.360 |
| Not eating together with the family | 14 (38.8%) | 14 (100%) | 0 (0.0%) | 0.003* |
| Mealtime stress | 19 (52.8%) | 16 (61.5%) | 3 (30.0%) | 0.139 |
| Gastrointestinal conditions | 13 (36.1%) | 12 (46.2%) | 1 (10.0%) | 0.060 |

*Statistical significance by Fisher's Exact test to "feeding difficulty" ($p \leq 0.05$). Data presented by frequency (percentage)

[a] "Feeding difficulties" were determined on the basis of tree of these aspects: (1) self-reports by patients/family members, (2) clinical evaluation by the researcher, and (3) presence of one or more of the aforementioned behaviors

**Table 2** Hepatic glycogen storage disorders: comparison between orofacial myofunctional evaluation scores with feeding aspects ($n = 36$)

| | Scores of orofacial myofunctional evaluation | | | | | |
|---|---|---|---|---|---|---|
| | Total score | *p*-valor | Deglutition score | *p*-valor | Mastication score | *p*-valor |
| *Tube feeding >1 year* | 84.0 (76.0–88.0) | 0.012* | 11.0 (9.0–13.0) | 0.008* | 5.0 (2.0–6.9) | 0.077 |
| *Exclusive breastfeeding ≥6 months* | 87.0 (82.0–91.5) | 0.256 | 12.0 (11.0–14.0) | 0.728 | 5.0 (3.5–7.0) | 0.446 |
| *Feeding difficulty* | 84.5 (81.2–90.0) | 0.001* | 12.0 (10.5–13.0) | 0.001* | 4.5 (3.0–6.0) | 0.009* |
| Selective intake | 84.0 (79.0–89.0) | <0.001* | 12.0 (9.0–13.0) | 0.004* | 4.0 (2.0–6.0) | 0.001* |
| Fear of feeding (or food aversion) | 83.0 (69.0–90.0) | 0.010* | 11.0 (8.0–12.0) | 0.015* | 5.0 (1.0–6.0) | 0.282 |
| Preference for fluid/semisolid foods | 84.0 (77.5–87.0) | <0.001* | 11.0 (8.5–13.0) | <0.001* | 5.0 (3.0–6.0) | 0.051* |
| Prolonged mealtimes | 84.0 (80.5–90.2) | 0.038* | 12.5 (11.0–14.0) | 0.532 | 5.0 (2.7–7.0) | 0.322 |
| Not eating together with the family | 84.6 (76.5–89.2) | 0.019* | 12.0 (8.0–12.2) | 0.008* | 5.0 (1.7–6.0) | 0.088* |
| Mealtime stress | 84.0 (79.0–90.0) | 0.010* | 12.0 (9.0–13.0) | 0.058* | 5.0 (3.0–6.0) | 0.030* |
| Gastrointestinal conditions | 85.0 (84.0–98.2) | 0.339 | 12.0 (8.5–13.5) | 0.152 | 5.0 (4.0–6.5) | 0.690 |

*Statistical significance by Mann–Whitney test to "scores of orofacial myofunctional evaluation" ($p \leq 0.05$). Data presented by median (interquartile range)

**Table 3** Hepatic glycogen storage disorders: children and adults in the specific abilities of orofacial myofunctional test

| | | Data by age range | |
|---|---|---|---|
| | | Child ≤12 years old ($n = 22$) | Teenagers and adults >12 years old ($n = 14$) |
| | Reference score | Median (IQR) | Median (IQR) |
| Lips | | 3.0 (2.0–3.0) | 3.0 (3.0–3.0) |
| Mandible/maxilla | 3 | 2.0 (2.0–3.0) | 3.0 (2.0–3.0) |
| Cheeks | 3 | 2.0 (2.0–3.0) | 3.0 (2.0–3.0) |
| Face | 3 | 2.0 (2.0–3.0) | 2.5 (2.0–3.0) |
| Tongue | 3 | 3.0 (2.0–3.0) | 3.0 (2.0–3.0) |
| Palate | 3 | 3.0 (2.0–3.0) | 3.0 (2.8–3.0) |
| *Movements* | | | |
| Lips | 12 | 10.0 (9.8–11.3) | 11.0 (9.5–12.0) |
| Tongue | 18 | 17.0 (15.8–18.0) | 18.0 (16.8–18.0) |
| Jaw | 15 | 14.0 (12.0–15.0) | 15.0 (14.8–15.0) |
| Cheeks | 12 | 12.0 (10.8–12.0) | 12.0 (11.0–12.0) |
| *Functions* | | | |
| Breathing | 3 | 2.0 (2.0–3.0) | 3.0 (3.0–3.0) |
| Deglutition | 15 | 12.0 (11.0–13.0) | 14.5 (11.8–15.0) |
| Mastication | 10 | 5.0 (2.8–6.3) | 7.0 (4.0–7.0) |
| Total | ≥88 | 85.0 (81.3–90.3) | 91.5 (84.8–99.0) |

Data presented by median (IQR interquartile range)

## Discussion

This was the first study in the literature to include a speech–language pathology viewpoint in the investigation of orofacial myofunctional issues and feeding behavior, as well as evaluate the possible association of these issues with the senses of smell and taste, in a sample of patients with hepatic glycogen storage diseases. Our findings indicate that feeding difficulties and orofacial myofunctional disorders are prevalent in this population, which may be particularly susceptible to the development of stomatognathic abnormalities.

GSD Ia was the most prevalent subtype in our sample, which is consistent with the literature (Janecke et al. 2001; Chou et al. 2002). Alternative feeding routes were used in a substantial portion of patients, which is consistent with the

need for uninterrupted dietary treatment to prevent fatal hypoglycemia. It is also worth noting that three patients presented with complete refusal of oral feeding secondary to progressive food refusal. Although alternative feeding routes are a necessary resource for some patients with GSD (Rake et al. 2002), tube feeding is known to cause adverse events, including negative impact on the stomatognathic system, and hinder swallowing and feeding behavior (Dunitz-Scheer et al. 2009; Gomes et al. 2015).

The study participants exhibited reduced olfactory and taste perception, and we identified an association between this reduced perception and feeding issues. These findings are consistent with the literature on FDs (Dunitz-Scheer et al. 2009; Edwards et al. 2015; Evans et al. 2017). It is well known that varied sensory experiences in childhood feeding (olfactory, gustatory, and others) play an important role in promoting proper and pleasant eating habits. It is understood that, in GSDs, olfactory and taste perception may be limited by the lack of stimuli caused by the highly restrictive diet, particularly regarding fruits and some vegetables.

We also found a high prevalence of FDs in the sample, which suggests that individuals with GSD have a higher frequency of selective intake and fear of feeding when compared to children without these diseases. Benjasuwantep et al. (2013) reported a 15.4% prevalence of selective intake and 0.25% prevalence of fear of feeding in the general population. Kerzner et al. (2015) and Edwards et al. (2015) note that children with chronic diseases or behavioral issues tend to develop feeding difficulties. In their study of phenylketonuria, an inborn error of metabolism which also requires a restrictive diet for proper management, Evans et al. (2017) showed that neophobia is mainly caused by fear of eating foods that may be forbidden in the patient's diet.

The high frequency of negative eating situations and behaviors identified in this sample corroborates previous studies showing that gastrointestinal abnormalities, orofacial myofunctional disorders, and the use of alternative feeding routes are mechanical and structural aspects that frequently cause feeding difficulty. Family habits and unfavorable and stressful environments have also been described as behavioral factors that predispose to food refusal and selective intake (Dunitz-Scheer et al. 2009; Kerzner et al. 2015; Edwards et al. 2015). Benjasuwantep et al. (2013) reported that children with eating problems tend to eat at the table with their families less often and have prolonged feeding times.

Within this context, we identified that several participants in our sample did not eat meals as a family and found an association between GSD type I and feeding difficulty. These findings may be related to the high overall prevalence of feeding difficulty in the sample, as individuals with feeding problems often do not eat at the family table (Dunitz-Scheer et al. 2009; Benjasuwantep et al. 2013), as well as to the disease itself and its treatment, since patients with hepatic GSD need to eat at prescribed times, which may diverge from family mealtimes (Rake et al. 2002; Weinstein and Wolfsdorf 2002; Flanagan et al. 2015). In the case of GSD type I, dietary control is associated with even greater restrictions and need for even more frequent intake of uncooked cornstarch to maintain normoglycemia and prevent secondary metabolic disorders than in other GSD subtypes (Rake et al. 2002; Flanagan et al. 2015).

In the present sample, the youngest patients and those with feeding difficulties performed worse on the orofacial myofunctional test. This finding is consistent with previous studies describing that structural and mechanical abnormalities, such as OMDs, can cause feeding difficulties (mainly selective intake and food aversion). Refusal of solid or difficult-to-chew foods is usually due to changes in breathing, swallowing, and mastication patterns, as well as aversive behaviors due to gagging, odynophagia, and increased protective oral reflexes (Dunitz-Scheer et al. 2009; Kerzner et al. 2015; Edwards et al. 2015).

We conclude that there is a high prevalence of feeding difficulties and orofacial myofunctional disorders in Brazilian patients with hepatic GSD. Our results suggest that individuals with GSD I subtypes may be at higher risk of feeding disorders and orofacial myofunctional disorders compared to those with other GSD subtypes also requiring strict dietary management. This warrants further evaluation. Likewise, our suspicion of decreased olfactory and taste perception in these patients was confirmed, especially for sourness. Weaknesses of this study include the fact that no validated protocol was used to assess feeding behavior, the small sample size, and the single-center design, which will have influenced dietary treatment practices and the eating habits of patients.

Our results also indicate that individuals with hepatic GSD may be inordinately susceptible to orofacial myofunctional disorders and feeding difficulties, due to factors related to the disease itself, to its treatment, and to eating habits. We suggest that clinicians involved in the management of GSDs need to be alert for selective intake, food refusal, and difficulties in chewing and swallowing in childhood and adulthood, especially in children during the period of food introduction, and should refer patients with these issues to specialist professionals for evaluation and follow-up. Further research on this topic be conducted to confirm whether olfactory and taste perception are reduced in these patients and investigate possible causes for

these sensory impairments, as well as to support early identification of eating disorders and feeding difficulties and development of therapeutic interventions to address these issues.

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## Concise One Sentence About Manuscript

Prevalence of feeding difficulties and orofacial myofunctional disorders in patients with hepatic glycogen storage disease.

## General Rules

- *Details of the Contributions of Individual Authors*

  Chenia Caldeira Martinez: author took the lead in design project; acquisition, interpretation, and analysis of data; was responsible for the writing of manuscript.

  Tássia Tonon: contributed to the design of study; acquisition, interpretation, and analysis of data; revised the manuscript in order to approve the final version.

  Tatiéle Nalin and Lilia Farret Refosco: both coauthors contributed to the conception and design of study; interpretation and analysis of data; revised critically the article in order to approve the final version of this manuscript.

  Carolina Fischinger Moura de Souza and Ida Vanessa Doederlein Schwartz: both coauthors contributed to the idealization; conception and design of study; interpretation and analysis of data; revised critically the article in order to approve the final version of this manuscript.
- *A Competing Interest Statement*

  Chenia Caldeira Martinez, Tatiéle Nalin, Tássia Tonon, Lilia Farret Refosco, Carolina Fischinger Moura de Souza, and Ida Vanessa Doederlein Schwartz declare that they have no conflict of interest.
- *Details of Funding*

  Project funded by Fundo de Incentivo à Pesquisa e Eventos (FIPE) of Hospital de Clínicas de Porto Alegre.
- *Details of Ethics Approval*

  The study was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (protocol no. 150072).
- *A Patient Consent Statement*

  According to the project no. 150072 of Ethics Committee of Hospital de Clínicas de Porto Alegre, a written informed consent was obtained from all individuals before participation in the study.
- *Documentation of Approval from the Institutional Committee for Care and Use of Laboratory Animals (or Comparable Committee)*

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