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Safety issues associated with dietary management in patients with hepatic glycogen storage disease

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ABSTRACT

Introduction: Hepatic glycogen storage diseases (GSDs) are a group of inherited disorders of carbohydrate metabolism for which dietary management is the cornerstone. Safety and acute complications associated with dietary management have been poorly documented. We hypothesized that safety issues and complications associated with dietary management are prevalent amongst patients with these ultra-rare disorders.

Methods: A questionnaire was developed consisting of 40 questions and was distributed via eight GSD patient organizations from multiple countries. Respondents were (caregivers of) patients with self-reported hepatic GSD.

Results: 249 GSD patients from 26 countries responded with a median age of 14.8 years (range: 0.5–66.1). Although management was considered safe by 71% of patients, 51% reported at least one acute complication associated with dietary management, with a total number of 425 reported complications.

Most frequently reported causes were: not waking up by an alarm clock (n = 70), forgetting a meal (n = 57) and infections (n = 43). Most frequently reported complications were: hypoglycemia (n = 112), hospital admissions (n = 79) and drowsiness (n = 74). Most complications occurred before the age of 12 years (82%; 637/774 total number of reported events) and during night time (63%; 340/536). Only 61% (152/249) of the GSD patients reported using a written emergency protocol.

Conclusions: Safety issues and complications associated with dietary management are prevalently reported by (caregivers of) 249 GSD patients. A discrepancy has been observed between the patient's perspective on safety of dietary management and occurrence of complications as a result of dietary management.

1. Introduction

Hepatic glycogen storage diseases (GSDs) are a group of inherited disorders of carbohydrate metabolism resulting from an enzyme or transporter deficiency in the glycogen synthesis or breakdown. Clinical presentation is characterized by fasting hypoglycemia, failure to thrive, and hepatomegaly [1]. Dietary management is the cornerstone of therapy, which may include frequent feeds, continuous nocturnal gastric drip feeding (CNGDF) and/or uncooked cornstarch (UCCS). The introduction of dietary management has changed the prognosis of patients with several subtypes of GSDs from fatal into manageable diseases [2–5]. The general purpose/aim of dietary management in GSD

Abbreviations: ABGLICO, Associação Brasileira de Glicogenose; AGSD, Association for Glycogen Storage Disease; CGM, Continuous Glucose Monitoring; CNGDF, Continuous nocturnal gastric drip feeding; DM, Diabetes Mellitus; GSD, Glycogen Storage Disease; METc, Medical Ethical Committee (*translated*); n, number; N.R., Not responded; OMIM, Online Mendelian Inheritance in Man; PREMs, Patient Reported Experience Measures; PROMs, Patient Reported Outcome Measures; SHG Glykogenose, Selbsthilfegruppe Glykogenose Deutschland e.V; SAGSD, Scandinavian Association for Glycogen Storage Disease; VKS, Volwassen Kinderen en Stofwisselingsziekten; UCCS, Uncooked cornstarch; WMO, Medical Research Involving Human Subjects Act (*translated*)

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patients is to maintain normoglycemia, preventing secondary metabolic derangement and development of long-term complications, such as hepatocellular adenomas/carcinomas, (cardio) myopathy, renal failure and osteoporosis [6].

Despite improved dietary management for GSD patients, case reports have described fatal outcomes after technical and/or personal failures. Fernandes et al. has emphasized the necessity of a safety device in case of inadvertent placement of nasogastric tubes [3]. Both the European and American guidelines have acknowledged the importance of safety precautions, such as bed-wetting devices (to detect formula leakage), feeding pump alarms, tape, adapters, connectors and emergency protocols [6–8]. However. these previous studies have not been designed to systematically investigate dietary management associated safety issues.

Based on our experiences in our doctor's offices, we have hypothesized that safety issues and acute complications associated with dietary management are underreported and relatively common amongst GSD-patients. This information provides an extra dimension to discussions on reimbursement of medical devices and nursing support at home for (caregivers of) GSD-patients. Therefore, we aimed to assess the prevalence and the potential consequences of dietary complications and technical failures in patients with hepatic GSD.A questionnaire was developed and distributed with the support of eight international GSD patient organizations.

2. Methods

The Medical Ethical Committee (METc) of the University Medical Center Groningen stated that the Medical Research Involving Human Subjects Act (WMO) did not apply to this project and that an official review and approval of this study was not required (METc 2015/522).

2.1. Patients

Respondents were (caregivers of) patients with self-reported hepatic GSD. We excluded multiple entries by the same responder. GSD patients above the age of twelve years were invited to answer the questionnaire together with the caretaker/parent. Caretakers and/or parents were requested to fill in the questionnaire for patients below the age of twelve.

2.2. Questionnaire development

A focus group was composed consisting of health care providers, patients and carers, representing international patient organizations to draft, translate and distribute a SurveyMonkey® web-based questionnaire. The group included authors of this manuscript and the persons mentioned in the acknowledgements section. The questionnaire consisted of 40 questions on five pages in three distinctive segments: personal information, dietary management and complications (see supplementary material for the English version).

2.3. Questionnaire distribution

The final English version was translated by native speakers and distributed in the following languages: Dutch, English, French, German, Portuguese, and Spanish. Comments were translated via reverse translation. The questionnaire was distributed through social media by the following eight patient organizations: Association for Glycogen Storage Disease (AGSD, USA), Association for Glycogen Storage Disease – UK (AGSD-UK), Canadian Association for Glycogen Storage Disease (Canada), Glucolatino (Latin America), Associação Brasileira de Glicogenose (ABGLICO, Brazil), Selbsthilfegruppe Glykogenose Deutschland e.V (SHG Glykogenose, Germany), Scandinavian Association for Glycogen Storage Disease (SAGSD, Scandinavia) and Volwassen Kinderen en Stofwisselingsziekten (VKS, The Netherlands). The questionnaire was distributed on 15-03-2016 and closed on 25-07-2016, with a reminder sent on 10-07-2016.

2.4. Data analysis

In data analysis, acute complications were defined as either drowsiness and/or hypoglycemia. Severe complications were defined as those conditions, that would correspond with the definition of serious adverse events [9], including hospital admission, intensive care unit admission, seizures/epilepsy, coma and/or death.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows v23.0 (Armonk, NY: IBM Corp.) and Microsoft Excel v.14.0.4734.1000 for Windows (Microsoft Corp., Redmond, WA, USA). Based on the sample size, the Kolmogorov-Smirnov test was used to test for normality. Since the data was not normally distributed, non-parametric tests were performed to examine differences between groups. For differences between groups, the Chi-Square test or Kruskal-Wallis test was performed, where appropriate. Differences were considered statistically significant at $p < 0.05$.

3. Results

In total 249 GSD patients from 26 countries responded, whose general characteristics are presented in Table 1. Mean age was 14.8 years (range: 0.5–66.1), 64% (159/249; 1 non-responders) of the patients were diagnosed before one year of age. Although management was considered safe by 71% (178/249) of patients, 52% (n = 129) reported at least one acute complication associated with dietary management. A total number of 425 complications was reported, including 364 severe complications. In Table 2, the complications and safety issues associated with dietary treatment are stratified by GSD subtype.

Table 3 presents the frequence of reported complications associated with the dietary management on a monthly basis (referring to question 26). Most frequently reported causes were: not waking up by an alarm clock (n = 70), forgetting a meal (n = 57) and infections (n = 43). In question 30, of the 129 patients reporting complications, most frequently reported were: hypoglycemia (n = 112), hospital admissions (n = 79) and drowsiness (n = 74). Less frequent complications were: ambulance called (n = 57), seizures/epilepsy (n = 47), intensive care unit admissions (n = 39) and coma (n = 17). In Question 31, the patients were asked to report the complications and the corresponding age at which the complications occurred. Most complications occurred before the age of 12 years (82%; 637/774 total number of reported events) and during night time (63%; 340/536). Fig. 1 shows the different age groups and their corresponding number and type of complications.

Only 61% (152/249) of the GSD patients reported using a written emergency protocol during intercurrent illness. Interestingly, patients with an emergency protocol had statistically more complications than patients without an emergency protocol (chi-square; $p < 0.001$). In this study, 17% of the patients did not have a glucose meter and an additional 14% of the patients did not use it. Of patients, 47% actively set an alarm and 5% reported using a bed wetting device to detect detached continuous feeds.

In Question 33, the patients were asked ‘What was consequence of the severest complication?’. In total, 30% (43/142 total number of reported events) were managed at home, 46% required hospitalization, whereas intensive care unit admission and resuscitation were required in 18% and 5%, respectively.

Table 4 displays qualitative comments of (caregivers/parents of) GSD patients, illustrating the burden of the disease.