Original Article

Hepatic Glycogen Storage Diseases: Toward One Global Collaborative Network

Journal of Inborn Errors of Metabolism & Screening
2017, Volume 5: 1–4

DOI: 10.1177/2326409817733009
journals.sagepub.com/home/iem
SAGE

Terry G. J. Derks, MD, PhD[1], Antal Nemeth, MD, PhD[2], Katrin Adrian, MD, PhD[3], Henrik Arnell, MD, PhD[2], Ann Bech Roskjær, RD[4], Eva Beijer, MD[2], Sebastiaan te Boekhorst, BICT[5], Carina Heidenborg, RD[2], Marcus Landgren, MD ,PhD[6], Mikael Nilsson, RD[7], Domniki Papadopoulou, MD[7], Katalin Ross, RD[8], Elisabeth Sjöqvist, RD[7], U Stachelhaus-Theimer, MD[9], Ulrike Steuerwald, MD[10], Carl-Johan Törnhage, MD, PhD[11,12], and David A. Weinstein, MD, PhD[8]

Abstract

The third international meeting of the Scandinavian Association for Glycogen Storage Disease focused on hepatic glycogen storage disease and was organized for health-care professionals, patient representatives, and representatives from the industry. This report highlights dilemmas in dietary management, differences in monitoring strategies, and challenges with rare disease care, research, and patient participation.

Keywords

glycogen storage diseases, ketone bodies, fasting, dietary management

Introduction

The Scandinavian Association for Glycogen Storage Disease (SAGSD) was established in 2011 with a goal of improving care for children and adults with glycogen storage disease (GSD). The primary aim of the SAGSD is to facilitate interactions between families and health-care professionals to allow sharing of information regarding these rare conditions. The third biannual international SAGSD meeting was conducted in Ängelholm, Sweden on May 14 to 15, 2016. The meeting was attended by 88 participants (14 health-care professionals, 72 patient representatives, and 2 representatives from the industry) from 10 countries (eg, Sweden, Denmark, Norway, Faroe Islands, United States, the Netherlands, United Kingdom, Spain, Germany, and Russia). The meeting was financially supported by industry and patients (details are provided under "potential conflicts of interest"). This report summarizes the topics presented at this SAGSD meeting as well as discussions on controversies and challenges.

Hepatic GSD

The GSDs are a group of inherited metabolic disorders that result from a defect in any one of several enzymes required for

[1] Section of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[2] Department of Pediatric Gastroenterology, Hepatology and Nutrition, Karolinska University Hospital, Stockholm, Sweden
[3] Department of Pediatrics, The Queen Silvia Children's Hospital, Gothenburg, Sweden
[4] Division of Pediatric Nutrition, Department of Pediatrics, Juliane Marie Centre, Copenhagen University Hospital, Copenhagen, Denmark
[5] PatientConnect, Bilthoven, the Netherlands
[6] Scandinavian Association for Glycogen Storage Disease, Limhamn, Sweden
[7] Department of Pediatrics, Skåne University Hospital, Lund, Sweden
[8] Glycogen Storage Disease Program, University of Florida College of Medicine, Gainesville, FL, USA
[9] Selbsthilfegruppe Glykogenose Deutschland e.V., Marl, Germany
[10] National Hospital of the Faroe Islands, Tórshavn, Faroe Islands
[11] Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[12] Department of Pediatrics, Skaraborgs Hospital, Skövde, Sweden

Received January 09, 2017, and in revised form April 15, 2017. Accepted for publication April 25, 2017.

Corresponding Author:
Antal Nemeth, Department of Pediatric Gastroenterology, Hepatology and Nutrition, Karolinska University Hospital, Stockholm, Sweden.
Email: antal.nemeth@ki.se

either glycogen synthesis or glycogen degradation. The GSDs can be divided into those with hepatic involvement, which present as fasting intolerance (+/- hypoglycemia), and those which are associated with neuromuscular disease and weakness. Some of them can cause both hepatic and neuromuscular manifestations. The severity of the GSDs range from those that are fatal in infancy if untreated to mild disorders with a normal lifespan. The third SAGSD conference was devoted to the hepatic forms of the disease, with or without muscular problems (GSD 0, I, III, VI and IX), while it was decided that the purely muscular forms will not be included into the activities of the group.

The following lectures were given:

- Glycogen storage disease in a historical perspective (Antal Németh, Sweden)
- Glycogen storage disease I, III, VI, and IX (David Weinstein, United States)
- Gene therapy (David Weinstein, United States)
- Heterogeneity within GSD Ia and update on the International Studies on Glycogen Storage Disease I (ISGSD III) study (Terry Derks, the Netherlands)
- Extended release cornstarch therapy update (Katalin Ross, United States)
- Glycogen storage disease III and diet (Ulrike Steuerwald, Germany)
- The strength of a patient association (Ute Stachelhaus, Germany)
- The GSD App (Bas te Boekhorst, the Netherlands)
- The GSD journey: A patient perspective (Casper Clayton, Denmark)

While the first day was a combined conference with patients and health-care professionals, the second day was spent with working group discussions. A meeting of health-care professionals allowed discussion regarding differences in treatment and controversies in GSD management. A key overriding aim of the meeting was also to facilitate a fruitful collaboration between internationally known GSD centers of excellence (for instance, Gainesville and Groningen) and the smaller ones with more limited populations. The care for patients with GSD has evolved, but there has been a lack of consensus regarding how best to treat this population. The SAGSD conference allowed debate regarding the following topics as particular interest.

Dietary Management in Hepatic GSD

Restriction of Fructose, Galactose, and Sucrose

A healthy diet is paramount, but dietary management in patients with GSD is medical treatment instead of a food. Dietary management aims to maintain euglycemia and to prevent secondary metabolic perturbations and long-term complications as much as possible. There is limited experimental data to substantial restrictions of simple sugars, and the existing data are difficult to extrapolate to daily care for individual patients. In addition, there is a lot of personal experience, which includes the recognition of inter- and intra-GSD patient variations. One concern is the excessive intake of nonutilizable sugars leading to glycogen storage and production of lactate, triglycerides, and uric acid in GSD I.[1,2] Based on case reports[3-5] and expert opinion, hypertrophic cardiomyopathy may be reduced by a reduction of excessive sugar intake in patients with GSD IIIa. In general, excessive sugar intake increases hepatomegaly in all of the hepatic GSDs. While it is clear that some sugar restriction is needed,[1,6] complete restriction of these sugars can impact quality of life and nutrition. There remains no consensus regarding the diet in GSD, and formal studies are warranted possibly involving all of the teams.

Treatment in GSD

In some patients with GSD, there is a relatively small therapeutic window for dietary management. Undertreatment leads to hypoglycemia, but overtreatment causes excessive glycogen storage, relative hyperinsulinism, obesity, and metabolic instability. The notion of too much treatment is often not factored into treatment plans, and weight base dosing in adults contributes to overtreatment. While it is clear that both continuous feeds and cornstarch can work in nocturnal treatment, the choice needs to be defined by the comfort of the care team and the family wishes.[7]

Alternative Treatments

There is increasing evidence that extended release cornstarch can be beneficial in GSD Ia, III, VI, and IX.[8,9] Concerns were raised about use in GSD Ib since the therapy can exacerbate inflammatory bowel disease. While the ketogenic diet has been proposed, it has been associated with poor outcomes in GSD I. In GSD III, the ketogenic diet can improve the associated myopathy, but it can be associated with worsening of the liver inflammation and poor growth. Experiences with increased dietary fat (medium-chain triglycerides, MCT), Atkins, and ketogenic diets) in patients with GSD are based on case reports and expert opinion. Vitamin E appears to be universally supported for patients with GSD Ib, but more studies are needed regarding the use of MCT oil in this population.

Monitoring in Patients With Hepatic GSD

Guidelines for GSD types I[10,13] and III[11,12] include several biomedical parameters and targets. They do not explain in detail how monitoring could be practiced in daily clinical care and an individual patient base. Variations among meters (ie, glucose, lactate, and ketone meters) and availability of supplies impact on practices. In addition, there is no standardization regarding how titration of dietary therapy should be performed. Review of the practices among our institutions revealed significant variation across institutions. In the Karolinska University Hospital, microdialysis analysis of glucose and lactate has become standard in GSD Ia (Antal Nemeth, unpublished data). The distances in Scandinavia also impact on how monitoring is

performed. Annual hospital-based monitoring is used in the United States, with hourly metabolic profiles. Since 2010, the GSD team in Groningen has changed toward primarily a combination of outpatient checkup and home-based monitoring including continuous glucose monitoring systems. In summary, differences in monitoring of patients with GSD include the location of the patient (as inpatient but conducting normal activities of daily life), the sampling sites (blood, subcutaneous), and (frequency of) parameters to monitor and highly depend on the health-care provider resources. The application of telemedicine may allow real-time feedback as help to transition care toward the outpatient arena in the future. It will combine important information from patients with rare diseases (ie, GSD) and rare medical expertise in a bidirectional way. Last, telemedicine will improve shared care models and hence safety for patients with GSD.

Challenges With Rare Disease Care and Research

With rare diseases, international collaborations are critical. The professional hepatic GSD community has a history of international collaborations through the European Study on Glycogen Storage Disease I and the ISGSDI and ISGSDIII. Register studies like these are rare in the field of rare diseases and an important base for better understanding and predicting short- and long-term patient outcome. The traditional and competitive biomedical scientific world, however, harbors more conflicts of interest than we usually disclose. Physicians, scientists, industry, universities, hospitals, health-care insurances, and patient representatives all struggle with arbitrary definitions of success, and the rare disease population particularly struggles from the traditional system.

Rare disease research is limited by the small number of patients, and ideal studies can rarely be performed. Case reports or small cohort studies often are difficult to publish in journals with high impact factors, and some universities require submission to these elite journals. Many of these journals do not encourage immediate open-access policies, which is very disadvantageous for patients with rare disorders. Even with multination collaborations, randomized controlled trials can be difficult, and the field is therefore left with treatment dilemmas like previously outlined. The system of peer-review is especially difficult in an area in which very few professionals are working. When study results need to be reported, potential peer-reviewers are either collaborators or competing with the investigators reporting their work. The current situation requires a high level of ethics from both sides, but this does not always occur. In the end, publication bias limits the worldwide spreading of ideas and knowledge for patients with rare diseases. European Union politics will direct us to create European reference networks for groups of rare diseases. The networks need to develop a clear governance structure for knowledge sharing and care coordination across countries and new methods to collaborate and to judge and acknowledge physicians and scientists. However, the challenges with patient care and research for patients with ultrarare diseases ideally require a worldwide network. Involvement of other centers from the Americas, Asia, Africa, and Australia is crucial to share experience, and political systems should encourage such an approach. This is also indicated by the formulation of different guidelines worldwide.

Finally, researchers often silenced by nondisclosing agreements. Industry is not always forthcoming about negative results, and negative studies are usually not published. In the rare disease field, off-label use of products is common since research is limited, and it is critical for the centers to share the entirety of experience.

Improving Rare Disease Care

The GSD field like many of the rare diseases depends on leadership from patient organizations. These groups foster collaborations and sharing of information and often the parent organizations are responsible for communicating clinical advances. There is often resistance to these patient groups from health-care professionals. Doctors do not have time to attend meetings for every rare disease. As a result, only the most dedicated physicians attend, but other professionals resent that the experts present new information and findings directly to their patients. Finally, physicians need to learn to appreciate the patients themselves.

In the past, scientists and industry mostly determined research agendas, although patients and families often are the true experts in rare diseases. The James Lind Alliance (JLA) methodology embraces the expertise of patients, carers, and nonresearch active but experienced clinicians in shaping research agendas. The JLA is a non-profit-making initiative established in 2004 that developed Priority Setting Partnership (http://www.jla.nihr.ac.uk/). In general, by bringing together people with a disease and those who treat them, unanswered questions about existing treatments are first identified and then prioritized. The main focus is to agree the list of the top 10 priorities for future research that need to be promoted to key groups, including research funders, scientists, patients, and carers. In addition to the current list of more than 40 conditions, this methodology may be of value for the GSD community.

Next Steps

After Fulda (2000),[10] Milan (2010), Lyon (2012), and Heidelberg (2013), the next international GSD conference was organized in Groningen, the Netherlands, on June 15 to 17, 2017 (www.igsd2017.com). The program included dedicated time for network sessions and will include the following topics:

- Formation of a global GSD network, consisting of professionals, patients, and industrial partners.
- Discussions of clinical advisory boards from ongoing and future clinical trials.
- International guidelines.

- Web-based interactive platforms to facilitate case discussions, including patient collaboration around confirmed and suspected cases of hepatic GSD.
- Patient registries and biobanks.
- Examples how patients could participate. In the global GSD community, there are many well-educated patient representatives who could participate in the early phases of clinical trial protocol designs. Next, it could be suggested that these patients could become formal members of ethical committees which judge whether human research meets national and international laws. It is likely that the quality of their decision-making process and in the end the research would benefit by including patient's opinion.

The next biannual SAGSD meeting will be held on April 28 to 29, 2018, in Scandinavia.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Fernandes J, Koster JF, Grose WF, Sorgedrager N. Hepatic phosphorylase deficiency. Its differentiation from other hepatic glycogenoses. *Arch Dis Child*. 1974;49(3):186-191.
2. Fernandes J, Van de Kamer JH. Studies on the utilization of hexoses in liver glycogen disease. *Pediatrics*. 1965;35:470-477.
3.. Dagli AI, Zori RT, McCune H, Ivsic T, Maisenbacher MK, Weinstein DA. Reversal of glycogen storage disease type IIIa-related cardiomyopathy with modification of diet. *J Inher Metab Dis*. 2009;32 suppl 1:S103-S106.
4. Sentner CP, Caliskan K, Vletter WB, Smit GPA. Heart failure due to severe hypertrophic cardiomyopathy reversed by low calorie, high protein dietary adjustments in a glycogen storage disease type IIIa patient. *JIMD Rep*. 2012;5:13-16.
5. Valayannopulos V, Bajolle F, Arnoux J, et al. Successful treatment of severe cardiomyopathy in glycogen storage disease type III with D, L-3-hydroxybutyrate, ketogenic and high-protein diet. *Pediatr Res*. 2011;70(6):638-641.
6. Fernandes J, van de Kamer JH. Hexose and protein tolerance tests in children with liver glycogenosis caused by a deficiency of the debranching enzyme system. *Pediatrics*. 1968;41: 935-944.
7. Derks TG, Martens DH, Sentner CP, et al. Dietary treatment of glycogen storage disease type Ia: uncooked cornstarch and/or continuous nocturnal gastric drip-feeding? *Mol Genet Metab*. 2013;109(1):1-2.
8. Bhattacharya K, Orton RC, Qi X, et al. A novel starch for the treatment of glycogen storage diseases. *J Inher Metab Dis*. 2007; 30(3):350-357.
9. Correia CE, Bhattacharya K, Lee PJ, et al. Use of modified cornstarch therapy to extend fasting in glycogen storage disease types Ia and Ib. *Amer J Clin Nutr*. 2008;88(5):1272-1276.
10. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;16(11). e1:1-29.
11. Kishnani PS, Austin SL, Arn P, et al. Glycogen storage disease type III diagnosis and management guidelines. *Genet Med*. 2010; 12(7):446-463.
12. Phillips A. More questions: 10 years later. *Eur J Pediatr*. 2002; 161(suppl 1):102-105.
13. Rake JP, Visser G, Labrune P, Leonard JV, Ullrich K, Smit GP. Guidelines for management of glycogen storage disease type I—European Study on Glycogen Storage Disease Type I (ESGSD I). *Eur J Pediatr*. 2002;161(suppl 1): 112-119.