A generic emergency protocol for patients with inborn errors of metabolism causing fasting intolerance: a retrospective, single-center chart review of 128 patients

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Research

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Abstract

Background - Patients with inborn errors of metabolism causing fasting intolerance are at risk of acute metabolic decompensations. Disease specific emergency protocols are widely available, but long-term data on safety and efficacy outcomes are lacking. We hypothesized that a generic emergency protocol can be safe and effective in patients with inborn errors of metabolism causing fasting intolerance.

Results - We retrospectively evaluated our generic emergency protocol in 128 patients with a hepatic glycogen storage disease or fatty acid oxidation defect between February 1, 2014 and April 24, 2019. In total, 127 hospital admissions were documented in 54 out of 128 patients (42%). Hypoglycemia (glucose concentration <3.9 mmol/l) was reported in 15% of admissions. Hypoglycemia at admission was uncommon in patients with ketotic glycogen storage disease and verbal patients with a fatty acid oxidation defect. Convulsions, coma or death were not reported.

Conclusions - Generic emergency protocols can be safe and effective for home management by the caregivers and the first hour in-hospital management of metabolic emergencies in patients with hepatic glycogen storage disease and medium-chain Acyl CoA dehydrogenase deficiency.

Introduction

There is an extensive group of rare inborn errors of metabolism (IEM) characterized by fasting intolerance. Fasting intolerance can lead to acute life-threatening presentations, such as severe hypoglycemia, metabolic acidosis and eventually coma or death. After establishment of the diagnosis, it is important that such metabolic decompensations and emergencies are effectively prevented, risk situations are timely recognized, and that it is anticipated with prompt safe treatment (1). The episodes of metabolic emergencies are often triggered by catabolism, evoked by combinations of fever, decreased enteral intake and increased enteral losses by vomiting and/or diarrhea. To prevent catabolism and subsequent metabolic decompensation, the key initial measure in IEM emergency protocols is the promotion of anabolism (2–4).

IEM-specific emergency protocols are available at multiple online resources (5–7) and scientific publications, such as for urea cycle defects (8), maple syrup urine disease (9), organic acidemias (10), fatty acid oxidation defects (FAOD) (11), or incorporated in guidelines for glutaric aciduria type I (12) and subtypes of hepatic glycogen storage diseases (GSD) (13–17). These guidelines and emergency protocols are mostly based on expert opinions and follow-up studies are not available on safety and efficacy of emergency treatment. Furthermore, given the geographical distance between centers of expertise and IEM patients' home addresses, local or regional physicians are often the healthcare providers who will start initial emergency treatment. It is recognized that most pediatric residents feel to have insufficient knowledge to start emergency treatment of IEMs in the absence of expert advice or written protocols (18).

We hypothesized that a generic emergency protocol can be safe and effective in patients with IEMs causing fasting intolerance. In the last five years, IEM patients in our center received emergency letters based on a generic algorithm, instead of IEM-specific emergency protocols. This is a retrospective, observational, single-center chart review of the safety and efficacy of our generic emergency protocol in patients with hepatic GSD or FAOD.

Methods

The Medical Ethical Committee of the University Medical Center Groningen (UMCG) stated that the Medical Research Involving Human Subjects Act was not applicable in this study as it concerned retrospective, anonymous data collection of standardized care, therefore, official study approval by the Medical Ethical Committee was not required (METc 2019/119).

Since February 2014 we have replaced individualized, IEM-specific emergency letters by emergency letters based on the generic “Emergency protocol for children at risk for acute metabolic decompensation”. The protocol and template for a patient emergency letter are provided as additional file (see Additional file 1). In brief, the protocol describes two phases. Phase I is initiated by the caregivers or patients at home under the following circumstances: (1) more than one-time vomiting, or (2) a combination of (a) fever > 38.5°C, (b) decreased enteral intake and (c) increased enteral losses. Phase I prescribes a weight dependent dose of paracetamol to reduce fever according to The Netherlands pediatric formulary (19) and administration of the ‘emergency solution’. Before 2014, several of our IEM patients had reported emergency treatments in local hospitals, that were complicated by hypoglycemia after using oral rehydration salt solutions. Therefore, in our protocol we have ensured that total fluid maintenance requirements per 24 hours include glucose polymer enrichment, as described by Van Hove et. al. (4), with slight simplifications. Total carbohydrate prescriptions are based on experimental data using stable isotopes (20); the emergency solution provides 75 grams (15w/w%) and 110 grams (20w/w%) maltodextrin in 500 mL oral rehydration salt, for patients with body weights < 12 kg and > 12 kg, respectively. The protocol is updated when the body weight changed more than 10%. If phase I is not tolerated, phase II becomes applicable. For phase II, local physicians (pediatricians, internal medicine specialists) are asked to provide IEM patients direct access to the emergency or general department to ensure prompt enteral or parenteral carbohydrate administration. Local physicians are advised in the protocol to contact the metabolic consultant on call latest when the initial laboratory results are available, usually within one hour after hospital admission. This is where the emergency protocol can be changed into a personalized management, taking into account the specific IEM.

Clinical and laboratory data from emergency department visits and hospital admissions between February 1, 2014 and April 24, 2019 were retrieved from the electronic health record (EHR) system from the UMCG. Inclusion criteria were a confirmed diagnosis of hepatic GSD or FAOD, and the presence of an emergency letter based on our generic protocol. Excluded were patients for whom our center was not the primary responsible center in the entire healthcare chain, but we have served to provide medical expertise solely. Primary outcome measures were the number of admissions due to a metabolic emergency, the

percentage of patients with hypoglycemia at admissions and the occurrence of serious adverse events, here defined as intensive care unit (ICU) admission, coma, or death. Secondary outcome measures were neurological symptoms (convulsions, lethargy) and blood concentrations of creatine kinase (CK) and ammonia.

Study data were collected and managed using REDCap electronic data capture tools hosted at the UMCG (21). Hypoglycemia was conservatively defined as blood glucose concentrations < 3.9 mmol/L, based on glycemic thresholds for activation of counterregulatory systems (22).

Results

In total, 128 patients (50% males) with hepatic GSD or a FAOD were included. One patient was excluded from data analysis, because of severe comorbidities that complicated the interpretation of hospital admissions. Median age at implementation of the generic emergency protocol was 12 years (range: 0–50 years) and the total cohort represented 470 emergency protocol years. Patients with the following IEMs were included: medium-chain Acyl CoA dehydrogenase deficiency (MCADD) (n = 63, 49%), hepatic GSD (n = 59, 46%), multiple-chain Acyl CoA dehydrogenase deficiency (MADD) (n = 3, 2%), long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) (n = 2, 2%) and very-long-chain Acyl CoA dehydrogenase deficiency (VLCADD) (n = 1, 1%).

Table 1 presents an overview of the 127 hospital admissions documented in 54 out of 128 patients (42%). Hospital admission was considered unnecessary in eleven presentations at the emergency department representing seven individual patients (data not shown). Data on glucose concentrations at admission were available in 64% (81/127). Hypoglycemia was reported in 15% (19/127) of hospital admissions (Fig. 1). The majority of hypoglycemia's was reported in patients with GSDIa and Ib (Fig. 1A). When stratifying for age, we found that hypoglycemia occurred in all age groups in GSDI patients, but that hypoglycemia was uncommon in verbal FAOD patients (Fig. 1B). No convulsions, coma or death due to a metabolic decompensation were reported. One GSDIb patient died in the data collection period because of a severe dilated cardiomyopathy unrelated to metabolic decompensations. An ICU admission was documented for two GSDIa patients, to support safe monitoring in one adult patient, and because of the need for a central venous catheter in a one-year-old patient. The duration of ICU treatment was one day in both patients and no long-term complications due to these admissions were reported.

Acute rhabdomyolysis was reported in two patients with LCHADD (n = 1) and VLCADD (n = 1), with CK concentrations of 63,238 and 3,200 U/L, respectively. No hyperammonemia was documented. Lethargy was reported in patients with GSDIa (n = 2), GSDIb (n = 1), GSDXI (n = 1), MCADD (n = 4), LCHADD (n = 1) and VLCADD (n = 1). In three out of four MCADD patients in whom lethargy was documented, glucose concentrations were above 3.9 mmol/L.

Discussion

The prevention of acute metabolic decompensations by timely recognition of catabolism, prompt safe treatment and communication is pivotal for IEM patients with fasting intolerance. This is the first study that describes safety and efficacy outcome measures of emergency protocols in IEM patients. We demonstrate that a generic emergency protocol can be safe and effective for home management by the caregivers and the first hour in-hospital management of metabolic emergencies in patients with hepatic GSD and MCADD. In the recent international liver GSD priority setting partnership, management of sickness and emergency situations was prioritized amongst the top 11 research priorities for liver GSD (23).

Interestingly, in our cohort relatively few patients were hypoglycemic at hospital admission. Hypoglycemia was uncommon in ketotic GSD patients and verbal FAOD patients. This is remarkable because an important subset of the IEM patients has severe fasting intolerance with regular hypoglycemias in daily life (24). Importantly, the objective of our study justified a relatively conservative hypoglycemia definition of < 3.9 mmol/L, rather than 2.6 mmol/L as used in other studies (25). The preventive character of our emergency protocol and the relatively high initial carbohydrate intake - estimated based on the actual body weight (20)- aim to prevent catabolism to a maximum extent and to promptly reach out for further medical treatment, if needed. This approach likely has prevented hypoglycemias in many IEM patients with severe fasting intolerance.

Convulsions, coma, or death were not reported in the present cohort of 128 patients in the past 5 years. Nonetheless, hospital admissions were frequent among all studied IEMs. Although, newborn screening for FAOD has led to a significant reduction in deaths and serious adverse events (24), acute care utilization remains high in these patients compared to age-matched controls. In line with our study, a retrospective cohort study in patients with IEMs identified through newborn screening between 2006–2007 reported that 44% (27 out of 61) of patients with a FAOD had IEM-related acute care utilization during their first year of life (26). Another recent study from Canada reported that children with MCADD experienced on average 0.6 hospital admissions per year, from six to 12 months of age (27). Long-term data on hospital admissions in patients diagnosed with hepatic GSD is lacking, but results from an international questionnaire showed that hospital admission due to complications of dietary management are common (24). In the latter study, 61% of the respondents reported using a written emergency protocol. Nevertheless, it remains speculative how the implementation of emergency protocol affects acute care utilization in patients with IEM associated with fasting intolerance.

The recognition of catabolism and metabolic decompensation in patients with IEM is challenged by IEM-specific pathophysiology of fasting. For instance, in GSDI patients lactate can function as alternative energy substrate to glucose for the brain (28). As a consequence, patients may remain without clear neuroglycopenia related symptoms during hypoglycemia. In patients with FAOD, however, hypoglycemia is a relatively late finding of metabolic decompensation and often preceded by lethargy and vomiting (29). Indeed, in the present study we found that lethargy was reported in three out of four MCADD patients in whom glucose concentrations were above hypoglycemic cutoff values. Therefore, although

our protocol is generic, caregivers and patients instructions should be individualized, and education and clinical pathways are both crucial to optimize emergency care of IEM patients (30,31).

Potential weakness of this study is the retrospective design introducing selection bias and information bias. There is lack of interoperability and interconnectivity between different EHR systems. Hospital admissions and initial laboratory studies may not always have been communicated with our center or documented in the EHR system. However, it is unlikely that we have missed metabolic decompensations causing death, coma, convulsions and/or ICU admissions. In this study, we were not able to include a control group, theoretically IEM-specific emergency letters may be as effective. Furthermore, it is unknown how many hospital admissions have been prevented by starting phase I of the emergency protocol at home, and if the emergency solution was well tolerated. Finally, the number of patients included in this study with a FAOD other than MCADD was low, and safety and efficacy of generic emergency protocols for patients with IEMs of the intoxication type needs to be assessed. However, as prevention of catabolism is also key in intoxication type of inborn errors of metabolism, the generic emergency protocol with use of the carbohydrate solution can be used as well, with addition of disease specific remarks. Obviously, our generic emergency protocols are contraindicated in patients with a ketogenic or carbohydrate restricted diet.

The emergency letters are part of a shared care model, which uses the medical and communication competences of all stakeholders; the metabolic center of expertise, the local healthcare providers, the caregivers and the patients, who all share joint responsibility. We have recently digitalized our emergency protocol as part of the GSD Communication Platform; a telemedicine platform for patients with hepatic GSD (32). Future perspectives may include next digitalization steps to support national and international interconnectivity between EHR systems of different healthcare professionals, including rare disease registries and the European Reference Networks for Rare Hereditary Metabolic Disorders (33).

Conclusion

This first follow-up study on emergency protocols presents that a generic emergency protocol can be safe and effective for home management by the caregivers and the first hour in-hospital management of metabolic emergencies in patients with hepatic GSD and MCADD. Dissemination of emergency protocol methods and outcomes is crucial for further improvements, international consensus among healthcare providers and prospective research projects in patients with IEM associated with fasting intolerance.

Declarations

Ethics approval and consent to participate

The Medical Ethical Committee of the University Medical Center Groningen (UMCG) stated that the Medical Research Involving Human Subjects Act was not applicable in this study as it concerned

retrospective, anonymous data collection of standardized care, therefore, official study approval by the Medical Ethical Committee was not required (METc 2019/119).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there is no potential conflict of interest related to this work. There are no prior publications or submissions with any overlapping information, including studies and patients.

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Authors' contributions

IJH was involved in data collection, analyzed and interpreted the patient data and wrote the first draft of the manuscript. TA and FJW were involved in data collection and analyzed the patient data. CMAL is involved in care for patients with GSD and FAOD, and critically revised the manuscript. FB, MJF, ILR and ED are metabolic dieticians involved in GSD and FAOD patient care, they critically revised the manuscript. SCG and DM were involved in study design and critically revised the manuscript. FJS is responsible for the care of GSD and FAOD patients in the UMCG, was involved in study design and critically revised the manuscript. TGJ is responsible for the care of GSD and FAOD patients in the UMCG, initiated and designed the study, was involved in data collection, analysis and interpretation, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Abbreviations

creatine kinase, CK; electronic health record, EHR; fatty acid oxidation defects, FAOD; glycogen storage disease, GSD; intensive care unit, ICU; inborn error of metabolism, IEM; long-chain 3-hydroxyacyl-CoA

dehydrogenase deficiency, LCHADD; medium-chain Acyl CoA dehydrogenase deficiency, MCADD; multiple-chain Acyl CoA dehydrogenase deficiency, MADD; very-long-chain Acyl CoA dehydrogenase deficiency, VLCADD.

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Table

IEM	Total of patients, n	Total admissions, n	Unique patients with admission, n (%)[1]	Median of admissions per patient [range]	Median age[2], years [range]
GSDIa	23	25	8 (35%)	1 [0 – 10]	18 [1 – 39]
GSDIb	7	10	4 (57%)	1 [0 – 4]	13 [4 – 19]
GSDIIIa	8	7	3 (38%)	1 [0 – 3]	8 [6 – 11]
GSDIIIb	3	0	-	-	-
GSDVI	1	0	-	-	-
GSDIX	15	16	7 (47%)	1 [0 – 4]	3 [0 – 6]
GSDXI	2	1	1 (50%)	1 [0 – 1]	6 [NA]
MCADD	63	50	26 (41%)	1 [0 – 4]	3 [0 – 13]
MADD	3	14	2 (67%)	4 [0 – 7]	4 [0 – 21]
LCHADD	2	2	2 (100%)	2 [1 – 2]	4 [0 – 5]
VLCADD	1	1	1 (100%)	1 [NA]	4 [NA]
Total population	128	127	54 (42%)	1 [0 – 10]	8 [0 – 39]

Table 1. Overview of hospital admissions during metabolic decompensation in 128 patients with an IEM associated with fasting intolerance. Legend: [1], Number of unique patients divided by total number of patients with a specific IEM; [2], age at hospital admission.

Figures

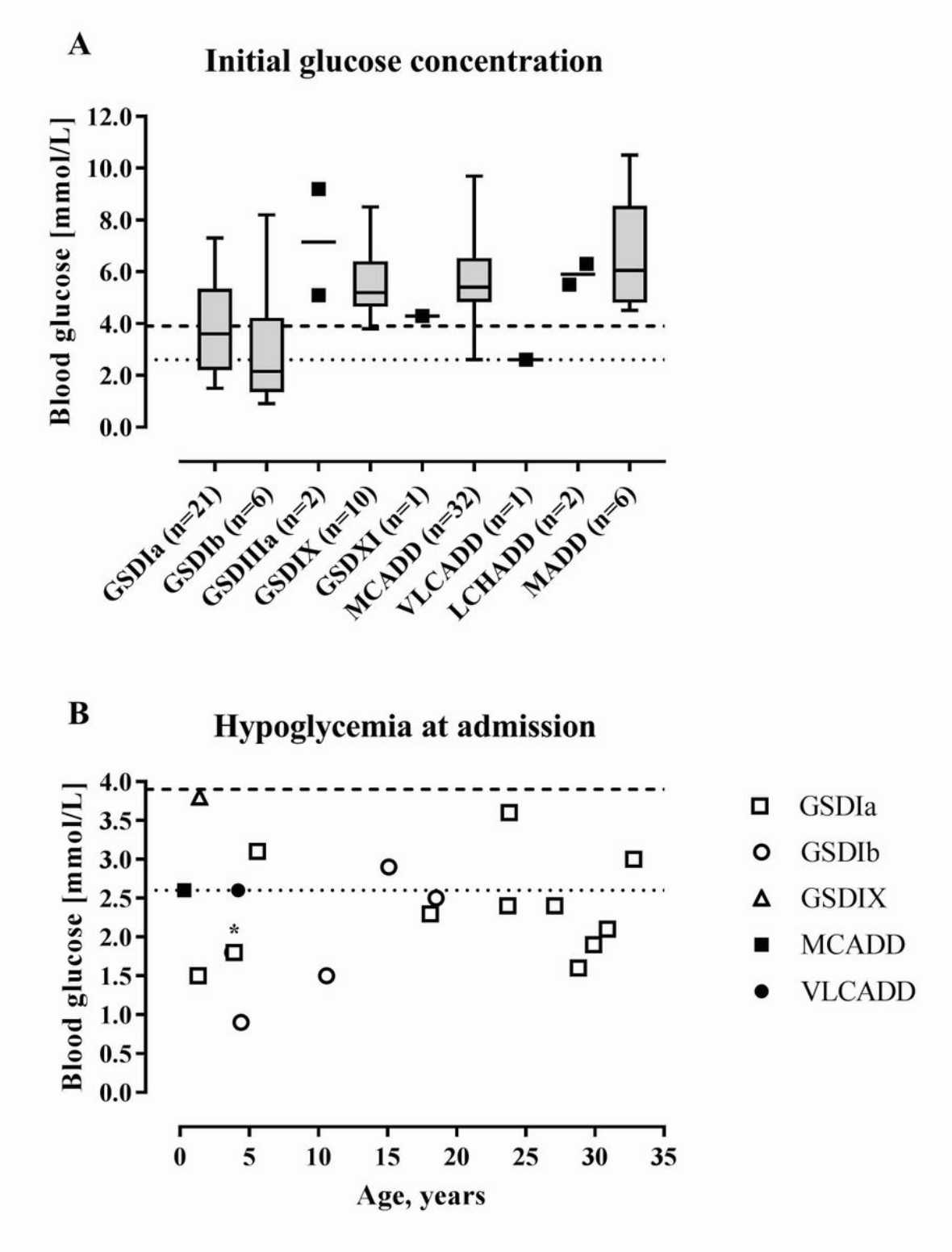

Figure 1

Blood glucose concentrations at hospital admission. A) Initial glucose concentrations at hospital admission per IEM (n=81). The boxes represent the 25th to 75th percentiles, the whiskers represent the range. B) Characteristics of hypoglycemic glucose concentrations at hospital admission (n=19). Dashed lines represent the cut-off values for hypoglycemia at 2.6 mmol/L (25) and 3.9 mmol/L (22), respectively.

*; data point represents two patients with a glucose concentration of 1.8 mmol/L at the age of 4 years with GSD type Ia and Ib.

Supplementary Files

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- Suppl.AEmergencyprotocolDutchandEnglishSubmission.pdf