JCN Open Access ORIGINAL ARTICLE

pISSN 1738-6586 / eISSN 2005-5013 / J Clin Neurol 2020;16(1):96-101 / https://doi.org/10.3988/jcn.2020.16.1.96

Clinical Implications of Ketosis in Children with Benign Convulsions with Mild Gastroenteritis

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Background and Purpose The pathophysiologic mechanisms underlying benign convulsions with mild gastroenteritis (CwG) in children remain unclear. We investigated the incidence of ketosis in CwG and whether this is related to seizures.

Methods This retrospective study included children aged from 6 months to 6 years who visited our emergency department and were diagnosed as CwG between June 2015 and December 2018. The clinical and laboratory data were analyzed for these cases. Ketosis and severe ketosis were defined as blood β-hydroxybutyrate levels of ≥0.6 and ≥4.5 mmol/L, respectively.

Results We enrolled 42 pediatric CwG patients aged 21.0±11.5 months (mean±SD) whose blood β-hydroxybutyrate level was 3.65±1.51 mmol/L. Ketosis was observed in 95.2% of these children, while 35.7% had severe ketosis. Compared to the non-severe-ketosis group (n=27), the severe-ketosis group (n=15) demonstrated significantly lower blood glucose levels (68.8 vs. 82.6 mg/dL, p=0.020) and sodium levels (134.2 vs. 135.6 mEq/L, p=0.018), and included a larger proportion of low-body-weight children (defined as adjusted weight <50th percentile for age and sex) (53.3% vs. 18.5%, p=0.019). However, the incidence of repetitive seizures (two or more during an illness period) did not differ between these groups. Moreover, severe ketosis was not associated with the risk of seizure recurrence in the emergency department.

Conclusions Children with CwG are in a state of considerable ketosis. Severe ketosis in CwG may be associated with low blood glucose and sodium levels but does not reduce seizure recurrence.

Key Words child, emergency department, gastroenteritis, ketosis, seizures.

INTRODUCTION

Benign convulsions with mild gastroenteritis (CwG) is regarded as a pediatric disorder involving situation-related seizures. These are defined as afebrile seizures accompanying mild gastroenteritis symptoms without moderate-to-severe dehydration or electrolyte imbalance in otherwise-healthy infants and young children.[1,2] CwG is occasionally encountered in the pediatric emergency department (ED) and needs to be differentiated from other disease entities such as meningoencephalitis and epilepsy.[3] Because CwG has been regarded as a transient benign condition with a good prognosis, hospitalization and tests involving the CSF, EEG, or neuroimaging are generally unnecessary.[1,4]

Investigating the characteristics of CwG might help to improve its assessment and management in the ED. Several studies have described clinical manifestations and laboratory findings for this condition.[2,5] However, to our knowledge no previous study has focused on ketosis onset in CwG. Ketosis is a metabolic state of increased ketone-body production, which can be measured via the β-hydroxybutyrate (BHB) levels in the blood.[6] Ketosis is frequently observed in young children with vomiting, diarrhea, poor oral intake, and moder-

Received June 28, 2019
Revised September 20, 2019
Accepted September 23, 2019

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ate-to-severe dehydration.[7,8] Ketone bodies can be used as an energy source for the brain, and ketosis seems to be associated with seizure reduction.[9] A ketogenic diet is effective in treating children with refractory epilepsy, although the precise underlying pathophysiology remains unknown.[9,10]

The aims of the present study were to determine the frequency of ketosis in children with CwG and determine the relationship between ketosis severity and gastroenteritis or seizures in these cases. We hypothesized that severe ketosis can reduce the seizure recurrence in the ED in pediatric CwG patients.

METHODS

Study design

This retrospective study included children aged from 6 months to 6 years who visited the pediatric ED of our tertiary-care university-affiliated hospital and were diagnosed as CwG between June 2015 and December 2018. Blood tests that included measuring BHB levels were performed in all subjects, while CSF tests and urine or stool multiplex reverse transcription (RT)-PCR assays to detect rotavirus, norovirus, adenovirus, or astrovirus were applied in a selective manner. Patients received adequate IV fluids and were observed for a minimum of 4 hours in the ED for possible seizure recurrence. Intramuscular or IV benzodiazepines were used in any children who showed seizure activity upon arrival or during the period of observation in the ED. All medical decisions including those related to the patient disposition were made by experienced pediatric emergency physicians in consultation with pediatric neurologists. Patient data were collected from electronic medical records. The Institutional Review Board of Asan Medical Center approved this study and waived the requirement for informed consent (IRB No. 2019-0201/11, February 2019).

Patients

We initially screened our hospital records for presumed CwG patients from among previously healthy young children who had presented to our ED with new-onset afebrile seizures accompanying mild gastroenteritis symptoms. We excluded any cases that had been transferred from another hospital, showed features of moderate-to-severe dehydration,[11] or had underlying neurodevelopmental problems, an accompanying fever on the date of seizure or during the period of ED observation (body temperature ≥38°C as measured using a tympanic thermometer), documented hypoglycemia (blood glucose ≤50 mg/dL), or suspected meningoencephalitis.

Data analysis

Patient data were categorized according to the general characteristics of the children (age, sex, and body weight), the clinical features of CwG (duration of gastroenteritis symptoms at the ED visit, type of seizures, first seizure duration, number of seizures before and after ED arrival, benzodiazepine usage in the ED, length of ED observation time, and admission to a ward), and laboratory data (venous blood BHB, glucose, sodium, pH, urine ketones, stool multiplex RT-PCR, and CSF analysis and cultures). Repetitive seizures were defined as two or more during an illness period, which included the period prior to ED arrival. Adjusted weights were calculated as the measured weights/0.97 based on an assumption of 3% (mild) dehydration, and the percentile values for age and sex were determined with reference to the 2017 Korean National Growth Charts for children and adolescents.[12] Ketosis and severe ketosis were defined as blood BHB levels of ≥0.6 and ≥4.5 mmol/L, respectively. These definitions were determined based on a previous report that seizure control was better when the blood BHB level was >4.0 mmol/L in children on a ketogenic diet.[13]

Statistical comparisons of clinical features and laboratory data between the severe-ketosis and non-severe-ketosis groups were made using the χ^2 test for categorical variables and the *t* test for continuous variables. Risk factors for seizure recurrence in the ED were detected using univariate logistic regression analysis. These analyses were performed using IBM SPSS Statistics for Windows (version 20.0, IBM Corp., Armonk, NY, USA). Probability values of $p<0.05$ were considered to indicate statistical significance.

RESULTS

Patient characteristics and ketosis

This study enrolled 42 children with CwG aged 21.0±11.5 months (mean±SD), of whom 24 (57.1%) were male. The gastroenteritis symptoms were considered to be mild in this cohort since they presented within 3 days of seizure onset in most of the children and diarrhea usually occurred less than three times daily. None of the children showed hyponatremia with a blood sodium ≤130 mEq/L or any other marked electrolyte imbalance. The most common seizures in this CwG population were of a generalized type (97.6%) and had a duration of shorter than 1 minute (45.2%). Repetitive seizures were observed in 19 patients (45.2%), including 13 cases (31.0%) who had at least 3 seizures.

The blood BHB level in the study cohort was 3.65±1.51 mmol/L. Ketosis was identified in 40 patients (95.2%), and was severe in 15 (35.7%) of these cases (Table 1). Urine ketones were detected in 36 of the 37 children who underwent

Table 1. Characteristics of the pediatric patients with benign convulsions with mild gastroenteritis analyzed in this study (n=42)

Characteristic	Value
Age, months	21.0±11.5
Male sex	24 (57.1)
Adjusted weight for age and sex*	
<50th percentile	13 (31.0)
≥50th percentile	29 (69.0)
Duration of gastroenteritis symptoms at ED visit, days	3.29±1.15
<4	30 (71.4)
≥4	12 (28.6)
Type of seizure	
Generalized	41 (97.6)
Nongeneralized	1 (2.4)
First seizure duration, minutes	
<1	19 (45.2)
1–4.9	14 (33.3)
≥5	9 (21.4)
Number of seizures	
1	23 (54.8)
2	6 (14.3)
≥3	13 (31.0)
Multiple seizures prior to ED arrival	7 (16.7)
Seizure recurrence in the ED	18 (42.9)
Benzodiazepine usage in the ED	17 (40.5)
Length of ED observation time, hours	8.78±4.74
Admission to a ward	11 (26.2)
Blood BHB, mmol/L	3.65±1.51
Mild ketosis (0.6–2.9)	11 (26.2)
Moderate ketosis (3.0–4.4)	14 (33.3)
Severe ketosis (≥4.5)	15 (35.7)
Positivity for urine ketones†	36/37 (97.2)
Blood glucose, mg/dL	77.7±18.8
Blood pH	7.34±0.09
Blood sodium, mEq/L	135.1±1.9

Data are n (%) or mean±SD values.
*Adjusted weights were calculated as the measured weight/0.97, †Urine ketone test was performed in 37 patents.
BHB: β-hydroxybutyrate, ED: emergency department.

urine tests, with 20 cases showing a score of 6+. Stool multiplex RT-PCR was performed in 15 patients and detected norovirus in 8 cases, adenovirus in 5, and astrovirus and rotavirus in 1 child each. CSF tests were performed in five patients, but the results were unremarkable.

Clinical and laboratory findings in the severe-ketosis group

The study cases were divided into severe-ketosis (n=15) and non-severe-ketosis (n=27) groups using a cutoff blood BHB level of 4.5 mmol/L. The clinical and laboratory findings were then compared between these groups. The severe-ketosis group included a significantly larger proportion of the low-body-weight children (defined as adjusted weight <50th percentile for age and sex): 53.3% vs. 18.5% (p=0.019). The laboratory data revealed that these severe-ketosis cases had a significantly lower blood glucose (68.8 vs. 82.6 mg/dL, p=0.020) and lower sodium level (134.2 vs. 135.6 mEq/L, p=0.018). However, a comparison of the clinical features between these two groups did not reveal any significant differences in ≥4 days of gastroenteritis symptoms at ED visit, repetitive seizures, benzodiazepine usage in the ED, or admission to a ward (Table 2).

Risk factors for seizure recurrence in the ED

The ED observation time was 8.78±4.74 hours, during which 18 (42.9%) of the study patients experienced seizure recurrence. Risk factor analysis revealed that risk of ED seizure recurrence was significant higher in the children who had experienced multiple seizures prior to their ED arrival [odds ratio (OR)=11.500, 95% CI=1.238–106.851, p=0.032]. However, no relationship was found between severe ketosis, a blood glucose level of <75 mg/dL, or a blood sodium level of <135 mEq/L, and the risk of seizure recurrence in the ED (Table 3).

DISCUSSION

This retrospective cohort study investigated the frequency of ketosis and its clinical implications in CwG pediatric patients in the ED. We hypothesized that severe ketosis can reduce seizure recurrence in these patients. A particularly interesting aspect of our findings is the suggestion that most cases of CwG are accompanied by a considerable level of ketosis despite the presence of only mild clinical symptoms of gastroenteritis. Contrary to our expectation, severe ketosis does not seems to reduce seizure recurrence in children with CwG, but the associations of severe ketosis with low blood glucose and sodium levels suggest that ketosis is the consequence of gastroenteritis. These findings may significantly contribute not only to the understanding of metabolic reactions in CwG but also to the acute management of this condition in the ED.

It seems to be appropriate to regard CwG patients as being in a state of considerable ketosis as a consequence of their gastroenteritis. Infants and young children with gastroenteritis occasionally present with ketosis or hypoglycemia due to poor oral intake, as well as hyponatremic dehydration with antidiuretic hormone release.[7,8,14,15] Several previous studies have focused on mild hyponatremia in CwG, but most have not found any significant incidence of this condition.[5,16] It is

Table 2. Comparison between the severe-ketosis and non-severe-ketosis groups

Characteristic	Severe-ketosis (*n*=15)	Non-severe-ketosis (*n*=27)	*p*
Age, months	21.4±9.6	20.7±12.7	0.854
Male sex	9 (60.0)	15 (55.6)	0.780
Adjusted weight <50th percentile for age and sex	8 (53.3)	5 (18.5)	0.019*
Duration of gastroenteritis symptoms at ED visit ≥4 days	4 (36.7)	8 (29.6)	1.000
Repetitive seizures	8 (53.3)	11 (40.7)	0.432
Multiple seizures prior to ED arrival	3 (20.0)	4 (14.8)	0.686
Seizure recurrence in the ED	8 (53.3)	10 (37.0)	0.307
Benzodiazepine usage in the ED	7 (46.7)	10 (37.0)	0.543
Admission to a ward	4 (26.7)	7 (25.9)	1.000
Blood BHB, mmol/L	5.07±0.47	2.86±1.29	<0.001*
Urine ketone score of 6+	8/13 (61.5)	12/24 (50.0)	0.501
Blood glucose, mg/dL	68.8±13.5	82.6±19.6	0.020*
Blood pH	7.31±0.08	7.35±0.09	0.203
Blood sodium, mEq/L	134.2±1.7	135.6±1.8	0.018*

Data are *n* (%) or mean±SD values.
*Statistical significance (p<0.05).
BHB: β-hydroxybutyrate, ED: emergency department.

Table 3. Risk factors for seizure recurrence in the ED

Characteristic	Value	*p*
Adjusted weight <50th percentile for age and sex	1.909 (0.508–7.172)	0.338
Duration of gastroenteritis symptoms at ED visit ≥4 days	0.934 (0.241–3.625)	0.921
Multiple seizures prior to ED arrival	11.500 (1.238–106.851)	0.032*
Severe ketosis, ≥4.5 mmol/L	1.943 (0.540–6.990)	0.309
Urine ketone score of 6+	0.920 (0.252–3.368)	0.900
Blood glucose <75 mg/dL	1.120 (0.326–3.847)	0.857
Blood sodium <135 mEq/L	0.891 (0.256–3.102)	0.856

Data are odds ratio (95% CI) values.
*Statistical significance (p<0.05).
ED: emergency department.

generally accepted that the dehydration induce by gastroenteritis is mild in CwG, and laboratory tests in these patients typically reveal no electrolyte imbalance.[4,17] The accompanying gastroenteritis in the children with CwG in the present cohort was also regarded as mild, with diarrhea usually occurring fewer than three times daily and a mean sodium level of 135.1 mEq/L, which is within the normal range. However, it is notable that ketosis was identified in 95.2% of the current CwG cases, and the mean blood BHB level in this cohort was elevated at 3.65 mmol/L. Moreover, 35.7% of the current patients showed severe ketosis (blood BHB ≥4.5 mmol/L) and had significantly lower blood glucose levels (68.8 vs. 82.6 mg/dL, p=0.020) and sodium levels (134.2 vs. 135.6 mEq/L, p=0.018) than the children with nonsevere ketosis. These findings suggest that severe ketosis is a metabolic response to poor oral intake and hyponatremia in children with CwG, perhaps indicating the importance of measuring blood BHB levels and adequately administering dextrose-containing fluids in these cases.

Another important finding of our present analysis was the association between a low body weight and severe ketosis. We calculated the percentile weights of the children after adjusting for the presumed presence of mild (3%) dehydration and the percentiles for age and sex in our study population. This analysis revealed that the proportion of children with a low body weight (adjusted weight <50th percentile) was larger in severe ketosis group than in the nonsevere ketosis group (53.3% vs. 18.5%, p=0.019). Although this may have been partially due to a higher level of dehydration in severe ketosis, lean children can be vulnerable to glucose depletion and thus more prone to severe ketosis. Similarly, idiopathic ketotic hypoglycemia, which is the most common cause of hypoglycemia in children, occurs frequently in children who have a low body mass index for their age, and it has been suggested that reduced muscle mass contributes to impaired gluconeogenesis.[18] Therefore, a common metabolic pathway leading to ketosis may be shared by idiopathic ketotic hypoglycemia and CwG. Furthermore, individual susceptibility

such as due to different responses to metabolic stimuli or a genetic predisposition presumably affects the occurrence and severity of ketosis in children with CwG.

The relationship between ketosis and seizure recurrence, particularly in the ED, appears to be unclear in children with CwG. Repetitive seizures (two or more during an illness period) were observed in 45.2% of the current CwG patients, and 42.9% of these children experienced seizure recurrence in the ED. As reported previously, repetitive seizures are a unique characteristic of CwG, with a reported prevalence of 33−75% among these patients.[19-21] The current results indicate that severe ketosis is not significantly associated with seizure recurrence in the ED in comparison with nonsevere ketosis (53.3% vs. 37.0%, p=0.307), or with the risk of such recurrence (OR=1.943, p=0.309). Although ketosis during a ketogenic diet achieves seizure reduction in children with refractory epilepsy, it is unknown whether elevated ketones directly inhibit seizures.[9] Moreover, the metabolic situation of CwG may differ from the ketosis of a ketogenic diet, which is purposefully induced by a high fat intake and is usually sustained for at least a few months. Thus, acute ketosis in CwG is probably not sufficient to overcome neuronal hyperexcitability, and this is a possible explanation for the present results. Multiple seizures prior to arrival at the ED were revealed by our analysis to be the only significant risk factor for seizure recurrence in the ED (OR=11.500, p=0.032). It is therefore necessary to pay close attention to adequate observation times and hospitalization in these children.

This study had several limitations of note, including its retrospective design and the inclusion of a relatively small sample from a single institute only. Moreover, appropriate control groups to define whether ketosis is a distinct feature of CwG or is found in gastroenteritis without seizures were not selected. Regarding seizure recurrence, the ED observation time varied in the present series, although it was at least 4 hours in all cases. This limited our outcome measurements. Well-designed prospective studies with appropriate controls and serial measurements of the blood BHB are needed to validate the current findings.

In conclusion, most children with CwG have accompanying ketosis that may be the consequence of gastroenteritis. However, no clear relationship exists between severe ketosis and seizure recurrence in these children. Further studies are needed to determine the role of ketosis in children with CwG. Upon presentation at the ED, children with CwG should be regarded as being in a state of considerable ketosis and so the adequate administration of dextrose-containing fluids might be necessary.

Author Contributions

Conceptualization: Mi-Sun Yum, Tae-Sung Ko. Data curation: Jeong-Min Ryu, Jong Seung Lee. Formal analysis: Jeong-Min Ryu, Jong Seung Lee. Investigation: Jeong-Min Ryu, Jong Seung Lee. Methodology: Mi-Sun Yum, Tae-Sung Ko. Project administration: Mi-Sun Yum, Tae-Sung Ko. Supervision: Mi-Sun Yum. Validation: Jeong-Yong Lee, Mi-Sun Yum. Visualization: Jeong-Yong Lee. Writing—original draft: Jeong-Yong Lee. Writing—review & editing: Jeong-Yong Lee, Jeong-Min Ryu, Jong Seung Lee, Tae-Sung Ko, Mi-Sun Yum.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Acknowledgements

The authors received no financial support for the research, authorship, and/or publication of this article.

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