



Serum Uric Acid as a Predictive Factor for Rotaviral or Noroviral Benign Convulsions with Mild Gastroenteritis

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Purpose: This study investigated the relationship between serum uric acid levels and benign convulsions with mild gastroenteritis (CwG) caused by rotavirus and norovirus.

Methods: This retrospective study identified 89 patients with CwG at Inha University Hospital from January 1999 to December 2019. We analyzed serum uric acid levels in patients with CwG and in patients with acute gastroenteritis without seizures according to the causative virus.

Results: Among the 2,790 patients with rotavirus or norovirus gastroenteritis, 89 patients (3.2%) were diagnosed with CwG. The serum uric acid levels were significantly higher in CwG patients than in acute gastroenteritis patients (8.20 ± 2.34 mg/dL vs. 5.44 ± 2.69 mg/dL, $P < 0.001$). When examined according to the virus type, serum uric acid levels were higher in the CwG group than in the acute gastroenteritis group in patients with rotavirus (8.05 ± 2.48 mg/dL vs. 5.48 ± 2.78 mg/dL) and norovirus (8.43 ± 2.13 mg/dL vs. 5.31 ± 2.36 mg/dL) infections ($P < 0.001$). However, there were no significant differences in uric acid levels between patients with CwG caused by rotavirus and those with CwG caused by norovirus.

Conclusion: Patients with CwG, caused either by rotavirus or norovirus, showed significantly higher serum uric acid levels than those with acute gastroenteritis without seizures. Elevated serum uric acid levels could be a useful indicator for diagnosing CwG.

Keywords: Seizures; Gastroenteritis; Rotavirus; Norovirus; Uric acid

Introduction

Convulsions are a common problem in children. Benign convulsion with mild gastroenteritis (CwG) was first reported in Japan in 1982 [1], and is defined as an afebrile convulsion accompanied by symptoms of gastroenteritis in a child without a previous history of neurological disease or electrolyte abnormalities, moderate to severe dehydration, or metabolic acidosis. Long-term prognosis is favorable without serious sequelae. Most cases of CwG have been described in patients with rotavirus infection

[2-4], but cases of CwG caused by norovirus have increased recently [2,5-8].

The diagnosis of CwG is generally made by confirming the presence of convulsions in a child with gastrointestinal symptoms. No specific biomarker for CwG has been identified to date, and multiple studies have evaluated changes in the laboratory results of CwG patients. Specifically, studies related to uric acid levels have been reported [9,10]. In this study, we evaluated the serum uric acid levels of CwG patients compared to those of patients with acute gastroenteritis without convulsions. Our goal was to

investigate the relationship between serum levels of uric acid and CwG and examine the differences in uric acid levels depending on the viral pathogen that caused the gastroenteritis (rotavirus or norovirus).

Materials and Methods

The study included infants and children under the age of 7 who were admitted for the treatment of gastroenteritis caused by rotavirus or norovirus at the Pediatric Department of Inha University Hospital between January 1999 and December 2019. CwG was defined as (1) recurrent or non-recurrent convulsive seizures without fever within 5 days from the first day of the onset of acute gastroenteritis symptoms in healthy children without underlying neurological diseases; (2) no evidence of moderate or severe dehydration of more than 5% due to gastroenteritis; (3) no acid-base imbalance and no abnormality in cerebrospinal fluid, serum electrolytes, or blood sugar; (4) no suspected encephalopathy or meningitis, based on neurological examination; and (5) good prognosis and treatment outcome [11]. Exclusion criteria were (1) developmental delay or neurological abnormality; (2) electrolyte or blood sugar abnormality; and (3) body temperature measured in the ear-drum or axillary region of 38.0°C or higher; and (4) neonate (under the age of 1 month).

A total of 2,790 patients were diagnosed with acute gastroenteritis caused by either rotavirus (2,100 cases) or norovirus (690 cases). The CwG group consisted of 50 patients with rotavirus enteritis and convulsions and 39 patients with norovirus enteritis and convulsions. The remaining 2,701 patients without convulsions were selected as the control group. To exclude patients with confirmed duplicate infection, the rotavirus-positive group included only patients with no viruses except for rotavirus and the norovirus-positive group included only patients with no viruses except for norovirus.

1. Methods and statistics

The medical records of patients hospitalized with non-febrile seizures associated with symptoms of acute gastroenteritis were retrospectively reviewed to identify (1) the cause of gastroenteritis, pathogenicity of convulsions after gastroenteritis; (2) blood test results at the time of admission (e.g., electrolyte imbalance, hypoglycemia, uric acid levels); and (3) the degree of dehydration. If additional blood tests were performed during hospitalization, the results were excluded from the survey. The causative gastroenteritis pathogens were identified through stool antigen tests for rotavirus and norovirus.

Rotavirus antigen detection tests for stool samples were con-

ducted using immunochromatography assay kits (SD BIOLINE® Rotavirus, Standard Diagnostics Inc., Yongin, Korea) until 2010; between 2011 and 2019 an enzyme immunoassay was used (RIDASCREEN® Rotavirus, R-Biopharm Aktiengesellschaft, Darmstadt, Germany). Rotavirus real-time reverse transcription-polymerase chain reaction (RT-PCR) was conducted using the Allplex GI-Virus Assay (Seegene, Seoul, Korea) since June 2014.

Statistical analyses were performed to compare the differences in serum uric acid levels among the CwG patient group with rotavirus infection, the CwG patient group with norovirus infection, and the control group. The receiver operating characteristics (ROC) analysis was performed to obtain the cut-off value for distinguishing CwG patients from acute gastroenteritis patients. All statistical analyses were conducted using SPSS version 19.0 (IBM Co., Armonk, NY, USA), and the t-test was used to determine statistical significance ($P < 0.05$).

This study was approved by the Institutional Review Board of the Inha University Hospital (IRB No. 2020-04-012). Written informed consent by the patients was waived due to a retrospective nature of our study.

Results

Among the 2,790 gastroenteritis cases, 2,100 cases were caused by rotavirus and 690 cases were caused by norovirus. Among the patients who had convulsions, 89 patients were diagnosed with CwG (male:female = 43:46); when categorized based on the type of the virus, 50 patients (male:female = 24:26) had CwG caused by rotavirus and 39 patients (male:female = 19:20) had CwG caused by norovirus. This corresponded to 2.38% rotavirus-positive patients and 5.65% norovirus-positive patients diagnosed with CwG, and the number of CwG cases caused by norovirus was 2.3 times higher than that caused by rotavirus ($P < 0.05$).

The ages, sex ratio, and uric acid levels in the patient and the control groups are presented in Table 1. The average uric acid level for all CwG patients was 8.20 ± 2.34 mg/dL (95% confidence interval [CI], 7.69 to 8.72), while that of acute gastroenteritis patients was 5.44 ± 2.69 mg/dL (95% CI, 5.34 to 5.54). When categorized by virus type, the uric acid level in rotavirus CwG group was 8.05 ± 2.48 mg/dL (95% CI, 7.34 to 8.77), while that of the rotavirus gastroenteritis group was 5.48 ± 2.78 mg/dL (95% CI, 5.36 to 5.60). The uric acid level in norovirus CwG group was 8.43 ± 2.13 mg/dL (95% CI, 7.67 to 9.19), while that of norovirus gastroenteritis group was 5.31 ± 2.36 mg/dL (95% CI, 5.12 to 5.49).

The uric acid level in CwG patients was measured to be higher than the normal range (3.4 to 7.9 mg/dL), while the uric acid level

Table 1. Demographic Characteristics of Patients with CwG and Acute Gastroenteritis

Characteristic	CwG	Acute gastroenteritis	P value
Total			
Male:female	43:46	1,534:1,167	0.112
Age at onset (mo)	20.43 (1–53)	19.75 (1–83)	<0.001
Serum uric acid (mg/dL)	8.20 ± 2.34	5.44 ± 2.69	<0.050
Rotavirus			
Male:female	24:26	1,160:890	0.226
Age at onset (mo)	22.84 (1–53)	13.71 (1–82)	<0.001
Serum uric acid (mg/dL)	8.05 ± 2.48	5.48 ± 2.78	<0.050
Norovirus			
Male:female	19:20	374:277	0.285
Age at onset (mo)	17.33 (4–32)	19.74 (1–83)	0.156
Serum uric acid (mg/dL)	8.43 ± 2.13	5.31 ± 2.36	<0.050

Values are presented as median (range) or mean ± standard deviation. CwG, convulsions with mild gastroenteritis.

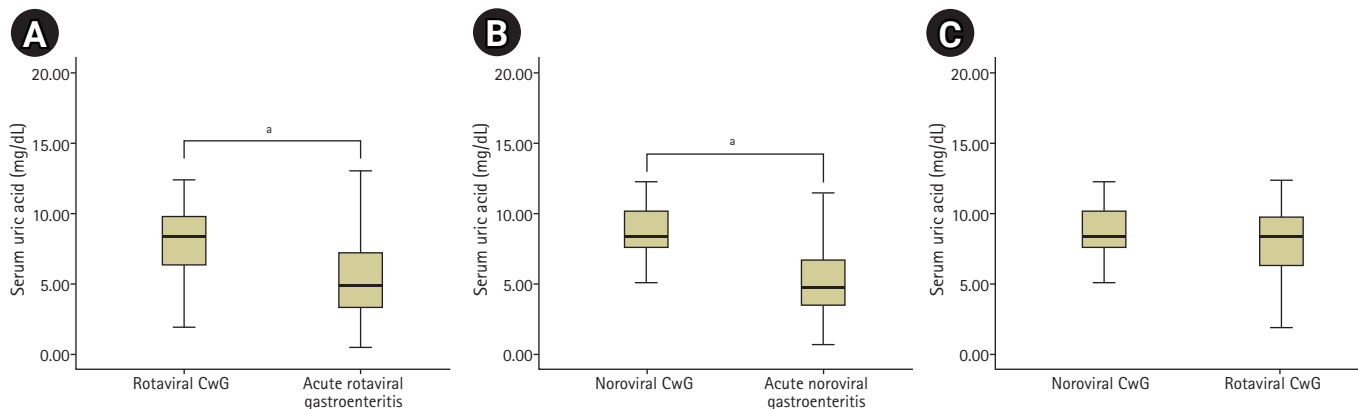


Fig. 1. Box plot comparing serum uric acid levels. (A) Rotaviral convulsions with mild gastroenteritis (CwG) and acute gastroenteritis. (B) Noroviral CwG and acute gastroenteritis. (C) Rotaviral CwG versus noroviral CwG. ^a $P < 0.05$.

in CwG patients was higher compared to that in the group with acute gastroenteritis without seizures ($P < 0.05$). However, when uric acid levels between the rotavirus CwG group and norovirus CwG group were compared, significant differences were not found between the groups ($P > 0.05$) (Fig. 1).

In ROC analysis, the optimal cut-off value of the serum uric acid level that can distinguish between CwG and acute gastroenteritis was 7.35 mg/dL; with a sensitivity of 70.7% and specificity of 77.7%. The area under the curve was 78.9% (95% CI, 74.5% to 83.3%) (Fig. 2).

Discussion

Patients with CwG have no abnormalities in the cerebrospinal fluid and on electroencephalography, and seizures do not recur after the resolution of gastroenteritis symptoms [2]. Long-term

anticonvulsant medications are rarely required, and the prognosis is very good. Recently, the range of ages for diagnosis has been widened from 6 months–3 years to 1 month–6 years. Cases of CwG have been predominantly reported in East Asian countries including Japan and Korea, and have been reported in Hong Kong and Taiwan. Although some studies have identified cases in Europe and the USA, these are rare, suggesting that regional or racial differences may affect the incidence of CwG [12].

The majority of CwG cases have been reported in patients with rotavirus infection [4,13–15], but gastroenteritis caused by norovirus is more common in winter months, which has led to an increased number of CwG reports caused by norovirus [6–8]. Some studies have reported that the incidence of norovirus-related CwG is higher than that of rotavirus-related CwG [5–8,16]. This finding is consistent with own observation that CwG accompanied by

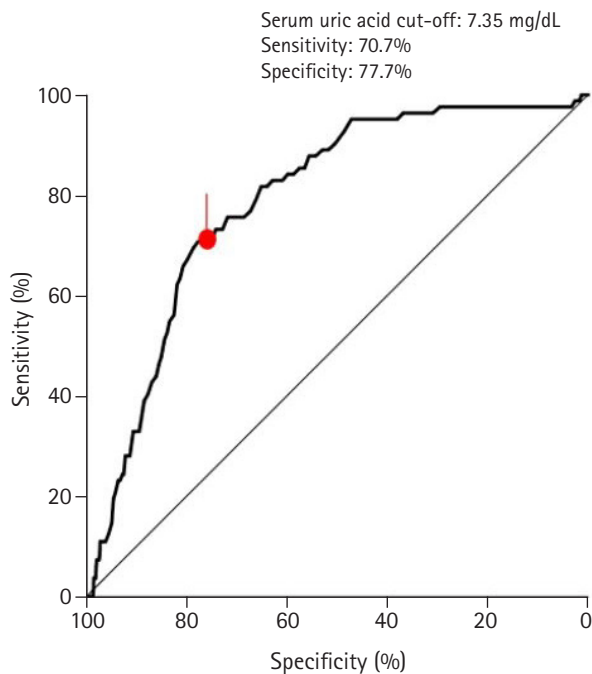


Fig. 2. Receiver operating characteristic curve of the capacity of serum uric acid levels to predict convulsions with mild gastroenteritis instead of acute gastroenteritis. The optimal cutoff value is indicated by a red dot.

norovirus infection accounted for 5.65% of all norovirus infections, while CwG accompanied by rotavirus infection accounted for 2.38% of all rotavirus infections. These differences may be because uptake of the rotavirus vaccine has resulted in a reduction in the number of gastroenteritis cases caused by rotavirus, or due to the increased accessibility of the norovirus test which has identified more cases of norovirus-related CwG [7,17].

The mechanism of seizure development in CwG patients in the absence of severe electrolyte imbalance or dehydration is not known. One possible explanation may be that children in this age group are undergoing a period of rapid growth and development of the central nervous system (CNS), and brain immaturity may have some effect on seizure development in CwG patients [18]. It was hypothesized that the rotavirus can invade the CNS through the bloodstream after penetrating the gastrointestinal tract and cause encephalitis, encephalopathy, or seizure. In fact, rotavirus RNA was detected by PCR in the cerebrospinal fluid of rotavirus CwG patients [19]. After invasion into the CNS, the rotavirus can stimulate the production of nonstructural protein (NSP4) that promotes seizure development by inducing neurotoxicity and neurotransmitter dysregulation. However, this hypothesis is controversial as not all cases of rotavirus CwG had evidence of rotavirus RNA in the cerebrospinal fluid. Another theory is that disruption of calcium homeostasis caused by NSP4 secretion after rotavirus

infection induces hypocalcemia which may play a significant role in seizure development [20]. However, research on the relationship between calcium homeostasis and rotavirus CwG is lacking, and further studies are required to explain the mechanism of hypocalcemia on seizure pathogenesis. Additionally, results suggesting that nitric oxide may be the cause of seizures in rotavirus CwG have been reported. Nitric oxide may have a role in the neuro-pathogenesis of brain inflammation. According to one study, nitric oxide levels were significantly high in both the serum and cerebrospinal fluid of the rotavirus-associated seizure patient group when compared with meningitis, encephalitis, and febrile seizure groups [21].

Taken together, the above evidence suggests that direct virus invasion, the increase in mediators such as NSP4, and the increase in nitric oxide are the main mechanisms to explain the etiology of seizures in rotavirus-associated CwG. However, other viruses have also been implicated in CwG including norovirus, which is known to be related to adenovirus, astrovirus, sapovirus, and coxsackievirus [13]. More research is necessary to identify the specific mechanisms whereby each of these viruses exerts its effect in CwG patients. In particular, a better understanding of the mechanism of seizures in CwG patients with norovirus is essential given the increasing prevalence of norovirus-associated CwG.

CwG is diagnosed clinically. Laboratory investigations, lumbar puncture, electroencephalography, magnetic resonance imaging, and other tests are not essential in diagnosing CwG. To date, few studies have evaluated the clinical utility of blood tests in diagnosing CwG or predicting patient prognosis.

No clear evidence has been found regarding the relationship between CwG and serum sodium levels. For example, while some studies have demonstrated an association of mild hyponatremia with CwG but not simple gastroenteritis [22], others failed to show a significant difference in sodium levels between groups [23-25]. Further, one study demonstrated that seizure duration was prolonged in patients with CwG with hyponatremia [26], but other studies showed no significant relationship between hyponatremia and seizure semiology, frequency, and duration [27].

Previous studies have also explored the effect of ketone bodies in CwG [28]. Lee et al. [28] found a significant association of ketosis with mild hyponatremia and low blood glucose levels in CwG patients, which was thought to be caused by the metabolic response to poor oral intake or hyponatremia in this group. However, there was no clear interaction between severe ketosis and seizure recurrence.

Recent studies have investigated the relationship between uric acid and CwG. Tsujita et al. [23] reported that blood tests from CwG patients had significantly high levels of uric acid. In a 2014

report, CwG patients showed significantly high serum uric acid levels (uric acid level ≥ 5.8 mg/dL in all patients in the CwG group), but only 44.7% of the patients in the control group showed hyperuricemia [10]. In the latest publication by Yoo et al. [9], found that the elevation of serum uric acid was not due to dehydration, nor to postictal phenomenon (Serum uric acid was not elevated in febrile seizure group in their study).

Consistent with previous studies, the total CwG group had a higher serum uric acid level than the simple gastroenteritis group, and this was maintained after further stratification into rotavirus and norovirus-associated CwG. However, when rotavirus CwG was compared with norovirus CwG, the serum uric acid levels between the groups did not show a significant difference. This finding demonstrates that hyperuricemia *per se* is insufficient to predict the viral pathogen responsible for CwG.

The results obtained in this study suggest that a serum uric acid level of ≥ 7.35 mg/dL may be a useful marker for predicting CwG in patients with gastroenteritis symptoms or seizure alone. Although the diagnosis of CwG cannot be made solely on the presence of a high serum uric acid level in acute gastroenteritis patients, being aware of this abnormal result may help clinicians better understand the pathophysiology of CwG and identify at-risk patients. Hyperuricemia is known to be related to gout, chronic metabolic diseases, Down syndrome, congenital heart disease, hemato-oncologic disorders, and metabolic syndrome in children, but the relationship between hyperuricemia and seizures has not yet been definitively proven. It has been reported that hyperuricemia may increase the secretion of tumor necrosis factor- α , which can cause seizure or endothelial dysfunction [29]. Studies in mice have also reported that elevated serum uric acid levels are associated with the occurrence of generalized seizures [30]. Additional research is needed to determine the relationship between hyperuricemia and seizures.

Uric acid levels change with growth [31,32]. Comparing the total CwG and acute gastroenteritis group, the result was that age at onset was higher in the CwG group. However, the age gap is not large enough to cause the difference in uric acid level to the extent identified in our study results. In addition, in the norovirus group, the age of onset of acute gastroenteritis was higher, although not statistically significant. Therefore, it seems difficult to conclude that age of onset caused a difference in uric acid levels between CwG and acute gastroenteritis groups.

This study has several strengths. First, our study was conducted using a large number of cases of CwG and acute gastroenteritis accumulated over 21 years at a single center. Second, we analyzed serum uric acid levels for each virus implicated in CwG. However, this study was a retrospective study, and therefore we were unable

to establish a clear causal relationship and temporal relationship between CwG and serum uric acid. In addition, there was no statistically significant difference in gender distribution between CwG and acute gastroenteritis group, and age at onset was not significantly different in norovirus group. It can be considered as a limitation that no control group has been established to correct this. Future prospective studies that address these limitations are warranted.

Serum uric acid measurements in this study were higher in CwG patients compared to simple acute gastroenteritis patients, but there was no difference in serum uric acid levels between rotavirus and norovirus CwG. These results strongly suggest that uric acid can be a predictive factor in the diagnosis of CwG. Therefore, it is important to measure uric acid levels in patients presenting with gastroenteritis associated with an afebrile seizure. In addition, a stool antigen test should be performed to confirm the causative virus.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Conceptualization: YSK. Data curation: GHL. Formal analysis: YL. Methodology: DHK and YSK. Project administration: YSK. Visualization: SYY. Writing-original draft: SYY and DHK. Writing-review&editing: YSK.

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