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 seizures. Elevated serum uric acid levels could be a useful indicator for diagnosing CwG.

Keywords: Seizures; Gastroenteritis; Rotavirus; Norovirus; Uric acid
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, axillary, or oral 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 conducted using immunochromatography assay kits (SD BIOLINE® Rotavirus, Standard Diagnostics Inc., Yongin, Korea) until 2010; between 2011 and 2019 an enzyme immunoassay was used (RIDA-SCREEN® Rotavirus, R-Biopharm Aktiengesellschaft, Darmstadt, Germany). Rotavirus real-time reverse transcription-polymerase chain reaction (RT-PCR) was conducted using the Allplex G1-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 $8.20 \pm 2.34$ mg/dL (95% confidence interval [CI], 7.69 to 8.72), while that of acute gastroenteritis patients was $5.44 \pm 2.69$ mg/dL (95% CI, 5.34 to 5.54). When categorized by virus type, the uric acid level in rotavirus CwG group was $8.05 \pm 2.48$ mg/dL (95% CI, 7.34 to 8.77), while that of the rotavirus gastroenteritis group was $5.48 \pm 2.78$ mg/dL (95% CI, 5.36 to 5.60). The uric acid level in norovirus CwG group was $8.43 \pm 2.13$ mg/dL (95% CI, 7.67 to 9.19), while that of norovirus gastroenteritis group was $5.31 \pm 2.36$ 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...
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

---

**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. *\(P<0.05\).*
Serum uric acid cut-off: 7.35 mg/dL
Sensitivity: 70.7%
Specificity: 77.7%

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, hematologic 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-a, 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.

ORCID

Si Yoon Yoo, https://orcid.org/0000-0003-3184-0750
Dong Hyun Kim, https://orcid.org/0000-0001-9883-0229
Young Se Kwon, https://orcid.org/0000-0003-4570-7037

Author contribution

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.

Acknowledgements

This study was supported by INHA University Research Grant.

References

1. Morooka K. Convulsions and mild diarrhea. Shonika 1982; 23:131-7.
2. Uemura N, Okumura A, Negoro T, Watanabe K. Clinical features of benign convulsions with mild gastroenteritis. Brain Dev 2002;24:745-9.
3. Narchi H. Benign afebrile cluster convulsions with gastroenteritis: an observational study. BMC Pediatr 2004;4:2.

4. Verrotti A, Moavero R, Vigevano F, Cantonetti L, Guerra A, Spezia E, et al. Long-term follow-up in children with benign convulsions associated with gastroenteritis. Eur J Paediatr Neurol 2014;18:572-7.

5. Kim BR, Choi GE, Kim YO, Kim MJ, Song ES, Woo YJ. Incidence and characteristics of norovirus-associated benign convulsions with mild gastroenteritis, in comparison with rotavirus ones. Brain Dev 2018;40:699-706.

6. Chan CM, Chan CW, Ma CK, Chan HB. Norovirus as cause of benign convulsion associated with gastro-enteritis. J Paediatr Child Health 2011;47:373-7.

7. Chen SY, Tsaï CN, Lai MW, Chen CY, Lin KL, Lin TY, et al. Norovirus infection as a cause of diarrhea-associated benign infantile seizures. Clin Infect Dis 2009;49:849-55.

8. Kim EJ, Lee MJ, Jang JY, Jeong DE, Kim SH. Norovirus is an important pathogen associated with benign convulsion with mild gastroenteritis in children. J Korean Child Neurol Soc 2015;23:39-44.

9. Yoo IH, Kim W, Cho J, Kim H, Lim BC, Hwang H, et al. Elevated serum uric acid in benign convulsions with mild gastroenteritis in children. J Clin Neurol 2019;15:496-501.

10. Chae SH, Rhee M, Kim YC, Kim SS. The relationship between serum uric acid level and benign convulsions with mild gastroenteritis. J Korean Child Neurol Soc 2014;22:191-4.

11. Komori H, Wada M, Eto M, Oki H, Aida K, Fujimoto T. Benign convulsions with mild gastroenteritis: a report of 10 recent cases detailing clinical varieties. Brain Dev 1995;17:334-7.

12. Castellazzi L, Principi N, Agostoni C, Esposito S. Benign convulsions in children with mild gastroenteritis. Eur J Paediatr Neurol 2016;20:690-5.

13. Kang B, Kwon YS. Benign convulsion with mild gastroenteritis. Korean J Pediatr 2014;57:304-9.

14. Verrotti A, Nanni G, Agostinelli S, Parisi P, Capovilla G, Beccaria F, et al. Benign convulsions associated with mild gastroenteritis: a multicenter clinical study. Epilepsia Res 2011;93:107-14.

15. Caraballo RH, Ganez L, Santos Cde L, Espeche A, Cersosimo R, Fejerman N. Benign infantile seizures with mild gastroenteritis: study of 22 patients. Seizure 2009;18:686-9.

16. Higuchi Y, Kubo T, Mitsuhashi T, Nakamura N, Yokota I, Komiyama O, et al. Clinical epidemiology and treatment of febrile and afebrile convulsions with mild gastroenteritis: a multicenter study. Pediatr Neurol 2017;67:78-84.

17. Ueda H, Tajiri H, Kimura S, Etani Y, Hosoi G, Maruyama T, et al. Clinical characteristics of seizures associated with viral gastroenteritis in children. Epilepsy Res 2015;109:146-54.

18. Verrotti A, Tocco AM, Coppola GG, Altabelli E, Chiarelli F. Afebrile benign convulsions with mild gastroenteritis: a new entity? Acta Neurol Scand 2009;120:73-9.

19. Liu B, Fujita Y, Arakawa C, Kohira R, Fuchigami T, Mugishima H, et al. Detection of rotavirus RNA and antigens in serum and cerebrospinal fluid samples from diarrheic children with seizures. Jpn J Infect Dis 2009;62:279-83.

20. Yeom JS, Kim YS, Park JS, Seo JH, Park ES, Lim JY, et al. Role of Ca2+ homeostasis disruption in rotavirus-associated seizures. J Child Neurol 2014;29:331-5.

21. Kawashima H, Inage Y, Oghara M, Kashiwagi Y, Takekuma K, Hoshika A, et al. Serum and cerebrospinal fluid nitrite/nitrate levels in patients with rotavirus gastroenteritis induced convulsion. Life Sci 2004;74:1397-405.

22. Motoyama M, Ichiyama T, Matsushige T, Kaijimoto M, Shiraishi M, Furukawa S. Clinical characteristics of benign convulsions with rotavirus gastroenteritis. J Child Neurol 2009;24:557-61.

23. Tsujiya Y, Matsumoto H, Nakamura Y, Nonoyama S. Analysis of the blood and serum biochemistry findings in patients demonstrating convulsion with mild gastroenteritis. No To Hattatsu 2011;43:282-4.

24. Kang B, Kim DH, Hong YJ, Son BK, Kim DW, Kwon YS. Comparison between febrile and afebrile seizures associated with mild rotavirus gastroenteritis. Seizure 2013;22:560-4.

25. Lloyd MB, Lloyd JC, Gesteland PH, Bale JF Jr. Rotavirus gastroenteritis and seizures in young children. Pediatr Neurol 2010;42:404-8.

26. Zifman E, Alehan F, Menascu S, Har-Gil M, Miller P, Saygi S, et al. Clinical characterization of gastroenteritis-related seizures in children: impact of fever and serum sodium levels. J Child Neurol 2011;26:1397-400.

27. Kim SS, Kim YC. Can serum sodium level affect seizure features of benign convulsions with mild gastroenteritis? J Korean Child Neurol Soc 2013;21:14-8.

28. Lee JY, Ryu JM, Lee JS, Ko TS, Yum MS. Clinical implications of ketosis in children with benign convulsions with mild gastroenteritis. J Clin Neurol 2020;16:96-101.

29. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. Kidney Int 2005;67:1739-42.

30. Thyrion L, Raedt R, Portelli J, van Loo P, Wadman WJ, Glorieux F, et al. Benign afebrile cluster convulsions with gastroenteritis: an observational study. BMC Pediatr 2014;14:283.

31. Kubota M. Hyperuricemia in children and adolescents: present knowledge and future directions. J Nutr Metab 2019;2019:3480718.
32. Rosini N, Cunha HP, Rosini RD, Machado MJ, da Silva EL. Serum uric acid in children and adolescents. J Bras Patol Med Lab 2018;54:21-7.