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Original Article

Clinical Epidemiology and Treatment of Febrile and Afebrile Convulsions With Mild Gastroenteritis: A Multicenter Study

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ABSTRACT

BACKGROUND: We investigated features and responses to treatment in patients with febrile and afebrile convulsions with mild gastroenteritis and characterized convulsions with rotavirus and norovirus gastroenteritis. **METHODS:** We conducted a prospective, observational study to evaluate patients with febrile and afebrile convulsions with mild gastroenteritis who were hospitalized between November 2011 and March 2014 at 13 facilities in the National Hospital Organization. We classified the patients into two groups: presence or absence of fever. We investigated the background,

Ethics Committee Approval: This study was approved by the ethics committee of the National Hospital Organization and each participating hospital. All procedures that were performed in studies involving human participants were in accordance with the 1964 Helsinki declaration, the 2003 Japanese Ethical Guidelines for Clinical Research, and their later amendments.

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clinical and laboratory characteristics, viral antigen in stool, and efficacy of anticonvulsant drugs. **RESULTS:** Of 126 patients enrolled in this study, 50 were febrile (Fc group) and 76 were afebrile (aFc group). A family history of febrile seizures was significantly more frequent in the Fc group than in the aFc group (28.0% vs 9.2%, $P = 0.005$). Clinical characteristics were similar between the rotavirus and norovirus groups, but fever was significantly more frequent in the rotavirus group (46.2% vs 8.3%, $P < 0.001$). Serum sodium levels were significantly negatively related to the number of seizures in the aFc group ($\beta = -0.13$; 95% confidence interval, −0.24, −0.03; $P = 0.01$). Carbamazepine was significantly more efficacious than diazepam suppositories in the aFc group (odds ratio = 49.3, 95% confidence interval, 2.35, 1037; $P = 0.01$). **CONCLUSION:** Febrile convulsions with mild gastroenteritis show characteristics of both febrile seizures and convulsions with mild gastroenteritis. Carbamazepine is optimal for convulsions with mild gastroenteritis. Clinical features of convulsions with rotavirus and norovirus gastroenteritis are similar, except for fever. Serum sodium levels may play a major role in the onset of convulsions with mild gastroenteritis.

Keywords: convulsions with mild gastroenteritis, febrile seizure, carbamazepine, rotavirus, norovirus

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Introduction

Convulsions with mild gastroenteritis (CwG) were first reported by Morooka et al. in 1982, and are recognized as a clinical entity.[1] CwG are defined as afebrile (less than 38°C), brief, and generalized seizures accompanying gastroenteritis without electrolyte abnormalities and dehydration in previously healthy children who have normal findings for laboratory data, cerebrospinal fluid, neuroimaging, and electroencephalography. Most seizures occur between ages six months and three years and often occur in clusters.[2,3]

However, in clinical practice, febrile CwG are experienced in some individuals because gastroenteritis is sometimes associated with fever. Furthermore, febrile seizures (FS) are the most common form of seizures that occur between ages 6 months and five years.[4] Therefore, distinguishing between febrile CwG and FS is not easy. Some studies have investigated the difference between febrile CwG and FS, but they were single-center studies with a small sample size.[5-7]

In Japan, a diazepam (DZP) suppository is frequently used for initial treatment of FS to prevent recurrent seizures during the same febrile illness.[8,9] DZP is considered as less efficacious than carbamazepine (CBZ) for CwG, but this efficacy has not been directly compared.[10-12] Furthermore, little has been reported on the treatment for febrile CwG.[7]

The pathogenesis of CwG is still unclear. Generally, electrolyte disturbance (especially hyponatremia) represents a frequent cause of afebrile seizures.[13] Some studies have reported that serum sodium levels are significantly lower in patients with CwG than in those with simple gastroenteritis.[12,14]

Rotavirus and norovirus are common causes of gastroenteritis in children.[15] Little is known about the distribution of causative organisms of CwG because rapid diagnosis of norovirus was not feasible until recently.[16] The difference in clinical presentation of seizures between rotavirus and norovirus has also not been determined.[7,16,17]

Therefore, this study aimed to investigate epidemiologic data, manifestation of seizures, examination findings, and efficacy of anticonvulsant drugs in patients with febrile and afebrile CwG (i.e., without severe dehydration). This study also aimed to characterize convulsions with rotavirus and norovirus gastroenteritis.

Materials and Methods

We conducted a prospective, observational study with 13 departments of pediatrics in the National Hospital Organization during 2011 to 2014. These hospitals are distributed nationwide and provide general and emergency pediatric services. We enrolled patients who had convulsions with gastrointestinal symptoms (vomiting or diarrhea) between November 2011 and March 2014. Moreover, patients who had convulsions without gastrointestinal symptoms and had a history of contact with someone with gastroenteritis were subjected to a viral antigen test on stool specimens obtained by glycerin enema. If the test was positive, they were enrolled. We did not conduct any sampling. The exclusion criteria were as follows: (1) electrolyte imbalance (serum sodium levels <125 or >150 mmol/L, corrected serum calcium levels <7.0 mg/dL [<1.75 mmol/L] or >12 mg/dL [>3.0 mmol/L]) and abnormal blood glucose levels (<40 mg/dL [<2.22 mmol/L] or >180 mg/dL [>9.99 mmol/L]) in a laboratory test at admission; (2) severe dehydration (>10% of body weight loss within 1 week before admission); (3) serious underlying medical condition, such as severe malnutrition, liver cirrhosis, heart failure, renal failure, or congenital malformation related to epilepsy; (4) receiving anticonvulsant drugs; and (5) age was less than three months or greater than six years.

For each patient, we reviewed background characteristics, past and family history of epileptic disease, history of rotavirus vaccination, fever (defined as body temperature ≥38°C), clinical manifestation of seizures (seizure type, number of seizures, period of cluster, longest duration of seizures, and period from the onset of gastroenteritis to the first seizure), and gastrointestinal symptoms (vomiting or diarrhea). Patients were classified into two groups: febrile patients (Fc group) and afebrile patients (aFc group). Blood samples were collected before treatment for measurement of various variables, including liver enzymes, lactate dehydrogenase (LDH) levels, serum electrolytes, C-reactive protein levels, white blood cell count, blood glucose levels, and venous blood gas. Rotavirus, norovirus, and adenovirus antigen detection tests in stool specimens were performed by using commercially available immunochromatographic kits as follows. For rotavirus, we used the Dipstick "Eiken" Rota (Eiken Chemical Co, Ltd, Tokyo, Japan) and ImmunoCard ST Rotavirus (Fujirebio, Inc, Tokyo, Japan). The sensitivity and specificity are 0.94 and 1.00, and 0.98 and 0.99, respectively. For adenovirus, we used the Dipstick "Eiken" Adeno (Eiken Chemical Co, Ltd). The sensitivity and specificity are 0.93 and 0.96. For rotavirus and adenovirus, we used the BD Rota/Adeno Examan stick (Nippon Becton Dickinson Co, Ltd, Tokyo, Japan), ImmunoCard SD Rota/Adeno (Fujirebio, Inc), and Rapidtesta Rota Adeno (Sekisui Medical Co, Ltd, Tokyo, Japan). The sensitivity and specificity for rotavirus are 0.95 and 0.95, 1.00 and 1.00, and 0.99 and 1.00, and those for adenovirus are 0.91 and 0.99, 0.97 and 1.00, and 0.94 and 0.96, respectively. For norovirus, we used the QuickNavi-Norovirus and QuickNavi-Norovirus 2 (Denka Seiken Co, Ltd, Niigata, Japan). The sensitivity and specificity are 0.82 and 0.97, and 0.92 and 0.98, respectively. Electroencephalography (EEG), cranial computed tomography (CT), magnetic resonance imaging (MRI), lumbar puncture, and stool