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Molecular epidemiology and clinical characteristics of norovirus gastroenteritis with seizures in children in Taiwan, 2006–2015

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Abstract

This study examined the characteristics of norovirus (NoV) gastroenteritis associated with convulsions in children and its molecular epidemiology. From July 2006 through December 2015, NoV infection was confirmed by the genome detection using reverse transcriptase polymerase chain reaction. Viral genotyping with strain validation was achieved using sequence analyses with Basic Local Alignment Search Tool genome identification. The patients' clinical features were assessed retrospectively, focusing on convulsive disorders. The diagnosis of encephalitis followed the International Encephalitis Consortium. Seizures occurred in 52 (20.9%) of 249 NoV infections. GII.4 Den_Haag_2006b (n = 22, 42.3%) and GII.4 Sydney 2012 (n = 10, 19.2%) were major variants correlated with convulsions. Patient with convulsions tend to have GII.4 genotype infection ($P < .001$), short vomiting (≤2 days) ($P < .001$), and no fever ($P = .002$). Compared to GII.4 Den_Haag_2006b, the GII.4 Sydney 2012-associated convulsions had similar manifestations except without significant winter preponderance ($P = .049$). The NoV infection with convulsions had less febrile course, specific genotype (GII.4) infections, and with shorter symptom of vomiting. Continuous surveillance is important for uncommon disease associated with emerging NoV strain infections. The prevention of NoV diseases requires the development of vaccines targeting highly virulent variants.

Abbreviations: AGE = acute gastroenteritis, CT = computed tomography, EEG = electroencephalography, MRI = magnetic resonance imaging, NoV = norovirus, RT-PCR = reverse transcriptase polymerase chain reaction.

Keywords: children, gastroenteritis, norovirus, seizures, Taiwan

1. Introduction

Norovirus (NoV) has replaced rotavirus as the leading cause of viral acute gastroenteritis (AGE) in humans worldwide after the launch of a rotavirus vaccine.[1–3] In addition to diarrheal disease, complications of NoV infections include convulsive disorders in children, particularly infants.[4–6] Infantile convulsions with mild gastroenteritis have been documented since 2000, and other than rotaviruses, small round-structured viruses (including NoVs) have also been found in the stools of patients with infantile benign convulsions.[7] The mechanism underlying the seizures remains undetermined and viremia has occasionally been documented in patients with seizures.[8]

Previously, we reported that specific genotypes of NoVs circulating in Taiwan are correlated with complications: the major NoV variant in 2006/2007, GII.4 Den_Haag_2006b, caused convulsions; the dominant subgenotype in winter 2008/09/10, GII.4 2010 (New Orleans), caused GI hemorrhage and abdominal pain or irritability.[9–11] Another dominant variant, GII.4 2012a (Sydney 2012), a new variant arising from a GII.e-GII.4 2010 recombination event, the predominant strain in 2011/2012 winter, caused a high fever and GI hemorrhage.[12] Multiple variants have circulated simultaneously since late 2011 in Taiwan.

This retrospective cohort study investigated the features of NoV-related gastroenteritis in Taiwan, focusing on the associated convulsions. We also examined the risk for convulsions based on the identification of circulating NoV strains by molecular epidemiology and correlations with clinical presentations.

2. Materials and methods

2.1. Ethics

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (CGMH103-5084A3 and 104-9820A3) and the participants or their guardians

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provided informed consent regarding the collection of specimens and clinical data. All methods used were performed in accordance with approved guidelines.

2.2. Patient enrolment and sample collection

Patients with a diagnosis of AGE hospitalized in the division of Paediatric Gastroenterology, Chang Gung Children's Hospital (CGCH) between July 2006 and December 2015 were selected for the identification of NoV infection irrespective of age, sex, ethnicity, and hospitalization ward. Fecal specimens were collected in a clean container within 3 days of hospitalization, excluding patients with major underlying diseases. NoV infection was confirmed by the detection of NoVs in the fecal specimens using reverse transcriptase polymerase chain reaction (RT-PCR). All patients with positive bacterial cultures for *Salmonella*, *Shigella*, and *Campylobacter* were excluded from the study.

A study program was introduced and followed for enrolled patients. The patients' symptoms were retrieved from the electronic medical records to determine how the clinicians addressed the patient-reported symptoms. Demographic and clinical data on disease timing were collected retrospectively from the medical records.

2.3. Clinical manifestations of NoV gastroenteritis with convulsion

Major AGE symptoms including vomiting and diarrhea frequency with duration were assessed. The level of dehydration was defined as mild if the patients had a slightly decreased urine output and a normal or slightly increased pulse rate, moderate if the patients had tachycardia at rest and dry mucous membranes, and severe if the patients had hypotension and cold, mottled skin.[13] Identified complications included hypoglycemia (sugar <70 mg/dL), electrolyte imbalance (hyponatremia, sodium <135 mmol/L; hypokalemia, potassium <3.5 mmol/L; or hypochloremia, chloride <98 mmol/L), hypotension (systolic blood pressure <70 mm Hg), and severe hyperthermia (body temperature >39°C). Convulsion characteristics were assessed including patterns of seizures, occurrence of status epilepticus, repetitive seizure attack within 24 hours after the 1st convulsion, with high fever or not, and associated electroencephalography (EEG), computed tomography (CT) or magnetic resonance imaging (MRI) examinations. The diagnosis of encephalitis followed the consensus statement of the International Encephalitis Consortium.[14]

2.4. Norovirus genome sequencing and genotyping

Viral nucleic acids were extracted from fecal samples using a QIAamp Viral RNA mini kit (QIAGEN, Hilden, Germany) according to the manufacturer's recommendations. The PCR primers and conditions used for determining NoV genotypes were previously described. The norovirus genomic DNA was amplified as previously described.[15] The cDNA products were cloned into pCR-XL-TOPO vector (Invitrogen, Carlsbad, CA), and the recombinant plasmid was transferred into competent *Escherichia coli* (TOPO XL PCR Cloning kit; Invitrogen). The NoV genomic RNA of different PCR products from the same specimen were used to reconstruct the near-full-length NoV genome using the Vector NTi software package (Invitrogen). Viral strains were identified by comparison with reference genome sequences of NoVs obtained from the National Centre for Biotechnology Information database (http://www.ncbi.nlm.nih.gov) using the Basic Local Alignment Search Tool. The near-full-length norovirus genome sequences were aligned using the MAFFT program with default parameters (http://www.ncbi.nlm.nih.gov/pubmed/23329690).

Comparison between the groups was performed with univariate analyses. Multivariate analyses were also conducted to identify the independent predictive factors and to eliminate confounding effects of convulsions. Continuous clinical data were analyzed using the Wilcoxon test and are expressed as the median (interquartile range [IQR]). Binary data were analyzed using the Chi-squared test. A P-value <.05 was considered to indicate statistical significance. All tests were performed using SAS ver. 8 for Windows (SAS Institute, Cary, NC).

3. Results

3.1. Norovirus gastroenteritis

Between 2006 and 2015, 1165 children with AGE were admitted to the Department of Paediatric Gastroenterology, Chang Gung Children's Hospital. Of these, 286 patients diagnosed with NoV gastroenteritis were eligible for the study. After excluding 31 patients with bacterial or viral coinfections and 6 with incomplete clinical information, our study included 249 patients (21.3%) with NoV infections (Fig. 1): 139 boys and 110 girls (male-to-female ratio, 1.25:1). The mean age of the patients was 25.8 (IQR 11–36) months with a median age of 17 months and age range of 1 month to 16.7 years. Most (212, 85.14%) of the children were under 5 years of age. The mean age of 879 non-NoV infections was 34.1 (IQR 14–42) months with a median age of 26 months.

3.2. Norovirus infections with convulsions

Fifty-two (20.9%) patients with NoV gastroenteritis experienced convulsions and none of them had a family history of epilepsy and the prevalence is significantly higher than that of patients with non-NoV gastroenteritis (3.98%) (P < .001). There were 24 boys and 28 girls with a mean age of 19.7 (IQR 15–25) months. Figure 2 shows the seasonal distribution of convulsion fraction with NoV-infected patients and non-NoV-infected patients. More than half patients (28, 52.8%) clustered in the NoVs infection outbreaks during the period from 2006 through 2007 especially in the winter of 2006. According to the viral detection ratio, there was no seasonal predilection of NoV-associated convulsions except in 2006 to 2007, with high fraction in winter season. No seasonal preponderance is found in convulsion fraction of non-NoV-infected patients.

The majority (38, 73.1%) of the patients experienced convulsions within 3 days after the onset of AGE symptoms. Mild, moderate, and severe dehydration were found in 19 (36.5%), 30 (57.7%), and 3 (5.8%) patients, respectively. Of the 52 patients, 5 had hyponatremia, 2 had hypokalemia, and 7 had hypoglycemia. Twenty-six patients (50%) experienced more than 1 convulsive episode within 24 hours after the 1st convulsion: 11, 7, 3, 2, and 3 patients had 2, 3, 4, 5, and >5 episodes, respectively (mean number of episodes, 3.3). In 4 patients, the 1st convulsion presented as status epilepticus. All convulsions were of the tonic–clonic type, except for 4 who had focal seizures with secondary generalization. More than half (29, 55.8%) of the patients had a fever, but only 6 (11.5%) experienced a body temperature >39°C during a seizure (i.e., a febrile seizure). Lumbar puncture was performed in 4 patients with focal neurologic signs. The cellular and biochemical analyses were negative and RT-PCR showed no NoV in the cerebrospinal fluid. Brain ultrasonography performed

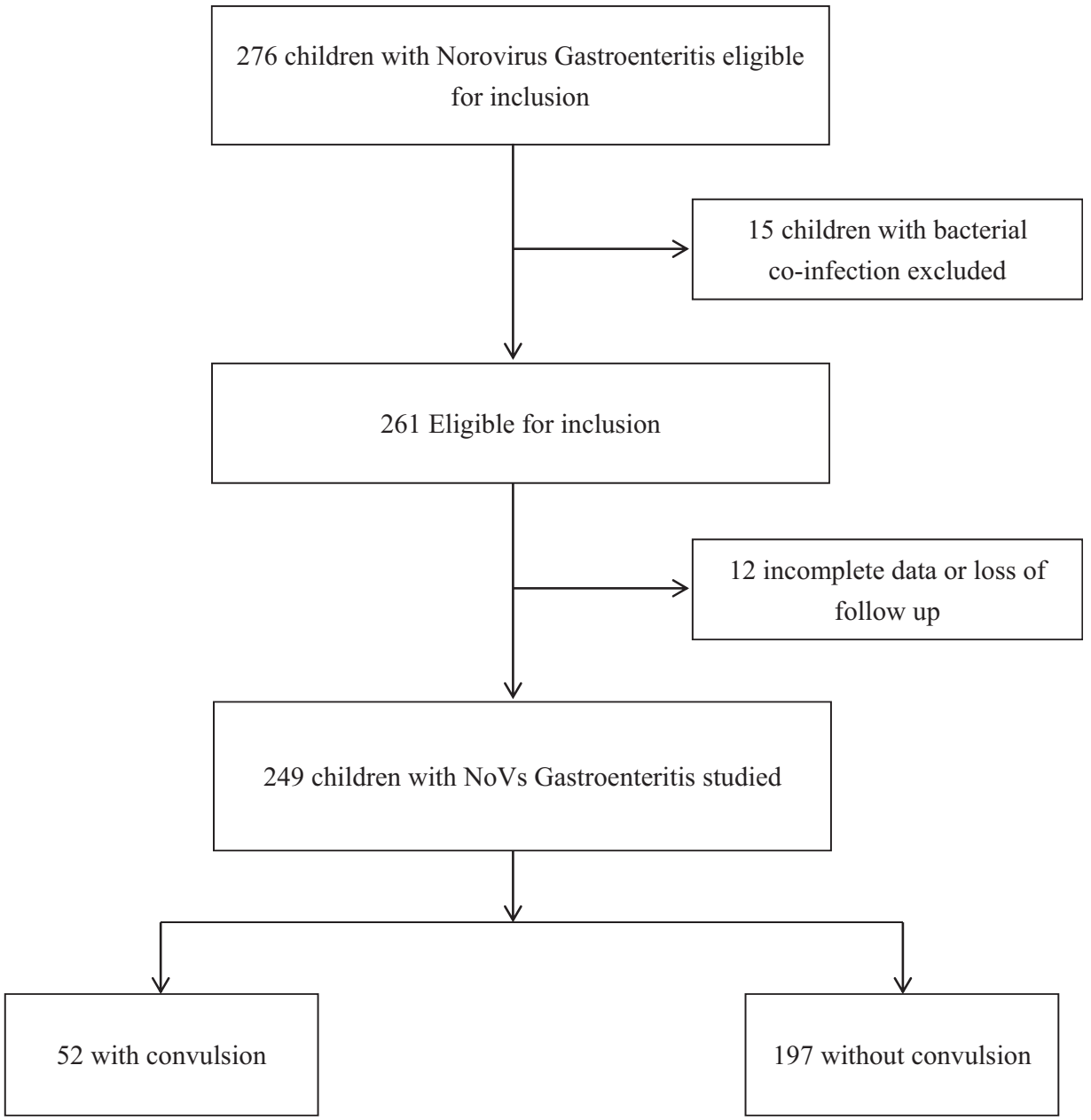

Figure 1. A study diagram for enrolled patients in the division of Paediatric Gastroenterology, CGCH between July 2006 and December 2015. A total of 249 patients with norovirus (NoV) infections after excluding 31 patients with bacterial or viral coinfections and 6 with incomplete clinical information.

in 15 patients showed brain edema in 1 child and no abnormalities in the remainder. EEG was performed in 29 patients in the acute stage of the infection, and 14 were found to have abnormal EEGs: 6 had cortical dysfunction, 4 had focal spikes, and 4 had epileptiform waves. Brain CT or MRI scans were obtained for 13 patients, including 2 who had both, and 6 had positive findings. Ultimately, 7 patients (3 boys, 4 girls) were diagnosed with probable encephalitis.

3.3. NoV gastroenteritis and the risk of convulsions

We compared NoV gastroenteritis with the demographic data and disease cohort results based on whether convulsions occurred (Table 1) based on multivariate analysis of patients with NoVs gastroenteritis with or without convulsions. Infection with no fever (odds ratio [OR], 3.17; $P = .002$) and GII.4 genotype infection (OR, 4.26; $P < .001$) were independent factors associated with the occurrence of convulsions whereas infection in winter (OR, 2.34; $P < .023$) showed no statistically significance after exclusion of confounding effects.

There was no correlation between the risk for convulsions and age ($P = .763$), sex ($P = .326$), the presence of hypoglycemia ($P = .461$), electrolyte imbalance ($P = .371$), or overall duration of AGE symptoms ($P = .106$). Regarding the AGE symptoms, we found that children to vomit last no longer than 2 days (OR, 7.19; $P < .001$) was the only independent predictor of convulsions, while the maximum frequency of vomiting (≤ 3 times/d; $P = .821$) and diarrhea (≤ 3 times/d; $P = .168$) and duration of diarrhea

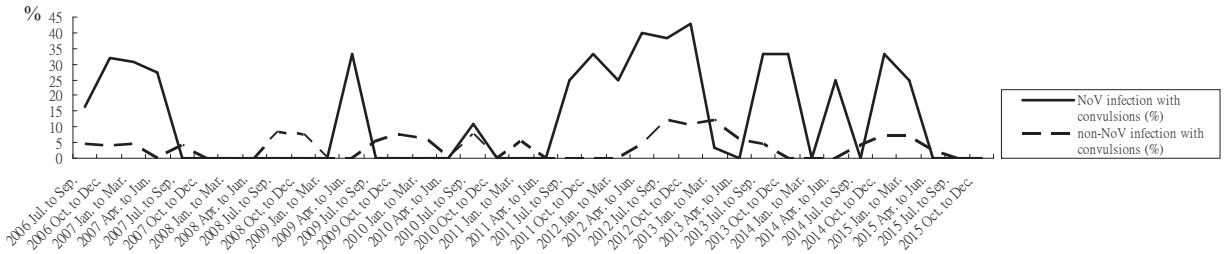

Figure 2. The seasonal distribution of convulsion fraction with norovirus (NoV)-infected patients and non-NoV-infected patients. This demonstrated that except in 2006 winter, with high convulsion fraction in winter season. No seasonal preponderance is found in convulsion fraction of non-NoV-infected patients.

(≤3 days; $P=.143$) were not significantly correlated with the convulsion risk.

3.4. Genotypes and variants of NoVs causing gastroenteritis associated with convulsions

Figure 3A shows the NoV genogroups and genotype distribution. During the study period, NoV GII.4 was the main cause of gastroenteritis (131 of 249, 53%) and GII.4 Den_Haag_2006b (53, 37%) and GII.4 Sydney 2012 (28, 20%) were the main GII.4 subtypes (variants). All 52 NoVs causing convulsions belonged to GII. Further genotyping classification identified 36 (69.2%) GII.4 variants, including the 2 major variants GII.4 Den_Haag_2006b (22, 42.3%) and GII.4 Sydney 2012 (10, 19.2%) and 2 GII.4 2012b, 1 GII.4 Hunter, and 1 GII.4 Bristol (Fig. 3B).

We compared the convulsions associated with NoV infections due the strains GII.4 Den_Haag_2006b and GII.4 Sydney (2012a) (Table 2). The occurrence of convulsions did not significantly differ (41.5% vs 35.7%; $P=.85$). Comparison of the demographic data and clinical manifestations showed no

Table 1

The clinical features of norovirus gastroenteritis with or without convulsions.

Characteristics	Patients group		
	Convulsion (n = 52)	Nonconvulsion (n = 197)	*P*-value
Age median (IQR), mo	18 (15–25)	16 (11–31)	.76
Sex, n (%)			
Boys	24 (46.1%)	106 (53.8%)	.326
Girls	28 (53.9%)	91 (46.2%)	
Fever status, n (%)			
No fever	25 (48.1%)	46 (23.4%)	.002
Mild fever	13 (25%)	94 (47.7%)	
High fever	14 (26.9%)	57 (28.9%)	
Duration of acute gastroenteritis gastroenteritis, d	5 (3–7)	6 (3–8)	
≤5	36 (69.2%)	112 (56.9%)	.106
>5	17 (3.8%)	85 (43.1%)	
Frequency of vomiting (times per day)	2 (1–3)	3 (1–4)	
≤3 times/d	38	147	.821
>3 times/d	14	50	
Duration of vomiting, d	2 (1–3)	2 (1–4)	
≤2	39	71	<.001
>2	13	126	
Frequency of diarrhea, times/d	3 (2–5)	4 (3–8)	
≤3	28	85	.168
>3	24	112	
Duration of diarrhea, d	4 (2–5)	5 (3–6)	
≤3	27	80	.143
>3	25	117	
Hypoglycemia, n (%)	7 (13.5%)	35 (17.8%)	.461
Electrolyte imbalance, n (%)	7 (13.5%)	37 (18.8%)	.371
Genotyping, n (%)			
GII.4	35 (67.3%)	75 (38.1%)	<.001
Non-GII.4	17 (32.7%)	122 (61.9%)	
Seasons, n (%)			
Winter	23 (44.2%)	48 (24.4%)	.023*
Nonwinter	29 (55.8%)	149 (75.6%)	
Family history of epilepsy, n (%)	1 (1.9%)	3 (1.5%)	.98
Final diagnosis of probable encephalitis	7 (13.4%)	0 (0)	NA

IQR = interquartile range, NA = nonassessed.

* No statistically significance after exclusion of confounding effects.

Table 2

Norovirus gastroenteritis with convulsions associated with different norovirus strains.

Characteristic no. (%)	GII.4 Den_Haag_2006b (n = 53)	GII.4 Sydney 2012 (n = 28)	*P*-value
Convulsions	22 (41.5%)	10 (35.7%)	.612
Age, median (IQR), mo	18 (15–24)	24 (15–30)	.722
Male-to-female ratio	12:10	3:7	.265
High fever (>39°C)	3 (13.6%)	3 (30%)	.346
Hypoglycemia	4 (18.2%)	1 (10%)	1.000
Electrolyte imbalance	3 (13.6%)	2 (20%)	.637
Recurrence within 24 h	15 (68.2%)	4 (40%)	.244
Seasonal distribution (winter season)	16 (72.7%)	3 (30%)	.049
Abnormal EEG report (examination no.)*	7 (12)	4 (7)	.76
Abnormal MRI or CT (examination no.)*	3 (6)	3 (5)	.21
Diagnosis of probable encephalitis	2 (3.8%)	3 (1.7%)	.334
Diagnosis of epilepsy	3 (5.7%)	4 (14.3%)	.227

CT = computed tomography, EEG = electroencephalography, IQR = interquartile range, MRI = magnetic resonance imaging.
* EEG and imaging studies were requested based on medical requirements.

differences in age (18 [15–24] vs 24 [15–30] months) ($P = .721$) and fever >38.5°C (30% vs 13.6%; $P = .346$). However, the frequency of convulsive episodes was significantly ($P = .03$) higher in females (70%) in those with GII.4 Sydney 2012 infections. There were no significant differences in acute complications such as hypoglycemia, electrolyte imbalance, or repetitive convulsions within 24 hours. The overall incidence of probable encephalitis as was the frequency of epilepsy was insignificant in convulsion caused by the 2 variants. Furthermore, convulsions caused by GII.4 Den_Haag_2006b NoVs were clustered predominantly in winter, unlike those caused by GII.4 Sydney NoVs ($P = .049$).

4. Discussion

The incidence of NoV gastroenteritis with seizures has been increasingly documented since the implementation of rotavirus vaccine, particularly in children hospitalized with AGE.[9,16–18] Our retrospective cohort study showed a significantly higher prevalence of convulsions in hospitalized children with NoV infections than non-NoV infections. NoV gastroenteritis causing convulsions tend to have GII.4 genotype infection, short vomiting (≤2 days), and no fever. No seasonal predilection of NoV-associated convulsions except in 2006 to 2007, with high fraction in winter season. Common presentations included convulsions within 3 days of the onset of AGE symptoms, mild or moderate dehydration, and more than 1 convulsive episode within 24 hours after the 1st convulsion. Seizures were uncommon in patients with a high fever (febrile seizures), electrolyte imbalance, or hypoglycemia. This differs from rotavirus infection, in which associated seizures are less frequent (59 of 755, 7.8%), more often febrile seizures (17 of 59, 28.8%), and in which no patients develop epilepsy during follow-up.[19] Furthermore, in our series, 14 of 52 (26.9%) patients had positive EEG findings and 6 of 13 (11.5%) had abnormal cranial CT or MRI results. Therefore, in such patients, EEG and imaging studies helped to diagnose encephalitis. By contrast, the seizures associated with rotavirus infection are relatively benign neurologically, and neurodiagnostic studies do not influence the management or outcome, with few exceptions.[20]

The rotavirus vaccination program has modulated the manifestations of rotavirus-associated seizures and has been effective at preventing febrile seizures in children up to 2 years of age.[21,22] In the future, seizures in infants associated with NoV infection will take more importance in viral disease in the postrotaviral vaccine era. We observed subsequent probable encephalitis in children with convulsions, although encephalitis related to NoV infection was rarely reported before 2010 and was primarily adult NoV-related encephalitis/encephalopathy, while NoV-associated encephalitis in children was 1st reported in 2015.[23,24]

In Taiwan, NoV genotype distribution is similar to the global epidemics with GII.4 predominance in recent 2 decades. GII.4 Den_Haag_2006b subtypes prevailed in the earlier decade and GII.4 Sydney 2012 in the latter decade.[25,26] Our study showed the highest prevalence of NoV gastroenteritis in 2011 to 2012 by GII.4 Sydney 2012, while the most common convulsion occurred in 2006 to 2007 infections by GII.4 Den_Haag_2006b. The overall increased role of NoVs in AGE might be associated with reduction of rotavirus infections in a long term after implementation of vaccine since 2006.[27] There is no significant clinical and demographic difference between convulsion caused by the 2 subtypes NoV except seasonal distribution. Although NoV gastroenteritis causing convulsions was more frequent in winter, the statistically significant conclusion is very likely due to confounding effects such as circulating strain difference. Many of the other years have much more patients with NoV detected, but surprisingly less convulsions than the 2006 October to December. This may be due to other factors such as the detection rate of NoV. Further study to explore air-temperature-associated epidemiology will be completed to test the robustness of seasonal factor.

Continuous surveillance is important to monitor changes in NoVs, which are capable of rapidly changing their antigenic epitopes.[28] This also makes it difficult to devise strategies for NoV prevention and for the human immune system to target NoVs. Like encephalitis, uncommon disease patterns caused by emerging NoV variants should be closely monitored as an important part of any universal surveillance system.

Our study had several limitations. First, we enrolled only hospitalized patients, who likely had more severe NoV infections. Second, the laboratory, EEG, and imaging studies were requested based on medical requirements, which might have underestimated the diagnosis of abnormality. Third, although most of the NoVs causing AGE with convulsion were genotyped, the viral strain was not validated in nearly one-third of the cases, which limits molecular epidemiology interpretations. Finally, the causes of some of the convulsions were still undetermined, although the majority of cases had benign presentations.

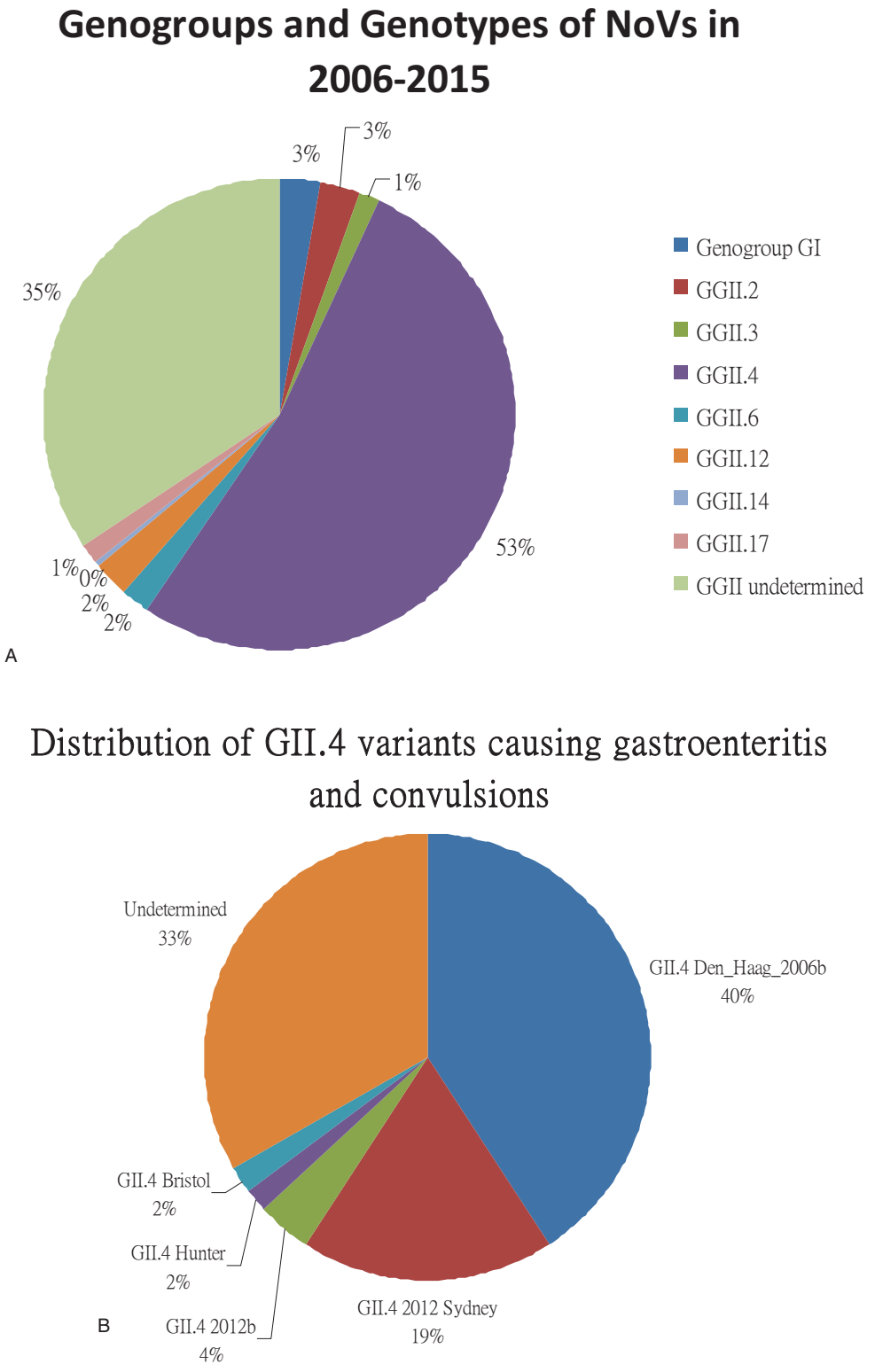

Figure 3. Genotypes and variants of norovirus (NoV) causing gastroenteritis and convulsions. The NoV genogroups and genotype distribution showed NoV GII.4 was the main cause of gastroenteritis (131 of 249, 53%) (A). GII.4 Den_Haag_2006b and GII.4 Sydney 2012 comprised the major of NoV GII.4 subtypes (variants) causing gastroenteritis and convulsions (B).

This study investigated the risk for seizure disorder and molecular epidemiology associated with NoV infections. Infantile convulsions are relatively common and there exists a possibility of subsequent encephalitis. NoV gastroenteritis with convulsions should be evaluated cautiously and the patients followed closely. The containment of NoV diseases depends on the development of vaccines targeting highly virulent variants.

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