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Aetiology and Prognosis of Encephalitis in Korean Children: A Retrospective Single-Centre Study, 2005–2020

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Purpose: Encephalitis is a heterogeneous syndrome that occurs in childhood and is not rare. However, epidemiological studies of encephalitis based on the International Encephalitis Consortium (ICS) and expert recommendations are lacking. We investigated the aetiology and prognosis of encephalitis in Korean children.

Materials and Methods: This retrospective study included children aged <19 years hospitalised for encephalitis at Severance Children's Hospital between 2005 and 2020. The 2013 ICS criteria were used to diagnose encephalitis, and causality was classified according to the site from which the specimen was obtained. Neurological sequelae were categorised using the modified Rankin Scale (mRS) score.

Results: In total, 551 children were included, with 7% classified as possible, 77% as probable, and 15% as proven cases. A cause was identified in 42% of the cases (n=222), with viruses being the most common (42%), followed by bacteria (38%) and autoimmune encephalitis (12%). In cases of proven/probable encephalitis (n=65), bacteria accounted for 52%, followed by viruses (25%) and autoimmune encephalitis (22%). In cases with a single pathogen, the anti-N-methyl-D-aspartate receptor autoantibody (n=14) was the most common, followed by Group B *streptococcus* (n=13), herpes simplex virus (n=11), enterovirus (n=4), and others. Approximately 37% of patients had severe sequelae (mRS score ≥3) at discharge, which decreased to 31% 6 months after discharge.

Conclusion: This large-scale study showed that autoimmune and infectious causes accounted for a significant proportion of encephalitis in Korean children. Further studies are needed to determine whether early targeted treatment following early diagnosis leads to a favourable prognosis in these populations.

Key Words: Encephalitis, aetiology, risk factor, prognosis

INTRODUCTION

Encephalitis is a clinical syndrome caused by the inflammation of the brain parenchyma. The number of reported encephalitis cases vary widely across studies, but the approximate incidence ranges from 0.1–12.6 per 100000 patient-years, with

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the exception of some endemic reports.[1,2] In particular, the annual incidence of encephalitis reported in Western industrialised countries is 10.5 per 100000 in children and greater than 2.2 per 100000 in adults, indicating that encephalitis exerts a greater burden on the paediatric population.[3]

Apart from the complexity in encephalitis diagnosis, more than 100 aetiologies of encephalitis have been reported. They can be broadly classified as infectious and non-infectious. Viruses such as herpes simplex virus (HSV), varicella-zoster virus (VZV), and enterovirus are relatively common compared to other bacteria, fungi, and parasites as infectious causes, and autoimmune encephalitis is representative of non-infectious causes. However, in most cases, the cause cannot be confirmed even through an extensive diagnostic work-up. In addition, even if a pathogen is detected in a patient with encephalitis, the causal relationship between the pathogen and the development of encephalitis cannot be confirmed in some cases owing to limitations in the site from which the specimen was obtained and the diagnostic method used.

To overcome these limitations, the International Encephalitis Consortium (ICS) and other experts have proposed recommendations for precise assessment of the diagnostic criteria for encephalitis, level of reliability, and causality of identified pathogens.[4,5] The epidemiology of encephalitis varies across countries and years. However, epidemiological studies of encephalitis based on these recommendations are lacking, except those conducted in the United States and some European countries. In three global prospective epidemiological studies on encephalitis, the proportion of unknown aetiology was 84% in California (1998–2005), 48% in France (2007), and 37% in the United Kingdom (2005–2006).[6-8] In particular, studies of encephalitis in Korean children are lacking. Two epidemiologic studies have been performed on paediatric encephalitis in Korea, but they did not apply the ICS criteria, had a small number of patients, and had a small proportion of patients with autoimmune encephalitis.[9,10] In the present study, we classified Korean paediatric encephalitis according to international recommendations and evaluated the causality of its aetiology. Furthermore, we studied the extent of encephalitis sequelae and the risk factors influencing them. This is the first study to investigate the aetiology and prognosis of paediatric encephalitis in Korea by applying the ICS criteria and modified Rankin Scale (mRS) score. This is the largest study of paediatric encephalitis in Korea to identify the significant proportion of patients with autoimmune encephalitis.

MATERIALS AND METHODS

Study design and population

This retrospective single-centre study was conducted between November 2005 and April 2020. Children aged <19 years and diagnosed with encephalitis at Severance Children's Hospital, Seoul, Korea were included. Data pertaining to children with the International Classification of Diseases-10 (ICD-10) diagnosis codes for encephalitis, encephalomyelitis, and/or acute demyelinating encephalomyelopathy were extracted through the Severance Clinical Research Analysis Portal, and the presence of encephalitis was determined through a medical chart review. The corresponding ICD-10 codes are listed in Supplementary Table 1 (only online). The exclusion criteria were as follows: 1) insufficient medical records; 2) error in ICD-10 code insertion; and 3) isolated spinal lesions, brain tumours, or metabolic disorders. The present study protocol was reviewed and approved by the Institutional Review Board of Severance Hospital (approval No. 2020-2617-001). Informed consent was submitted by all subjects when they were enrolled for the study.

Definitions and classification

We used the 2013 ICS criteria to diagnose encephalitis.[4] The ICS requires a change in consciousness lasting at least 24 h as the major criterion for encephalitis diagnosis. The minor criteria included the presence of fever within 72 hours of presentation, cerebrospinal fluid (CSF) pleocytosis, neuroimaging and electroencephalographic (EEG) changes consistent with encephalitis, seizures, and new onset of focal neurologic signs. According to the diagnostic requirements, occurrence of one major and two minor criteria was defined as 'possible' encephalitis, and one major and three or more minor criteria as 'probable/confirmed' encephalitis. To determine the causal relationship between pathogens and encephalitis, we used the hierarchy of diagnostic tests suggested by Granerod, et al.[5]; for example, a confirmed/probable aetiology was defined when a cause was confirmed in a central nervous system (CNS) specimen or a well-known antibody for autoimmune encephalitis was detected. 'Confirmed' means identification of the organism in the CNS (cerebral nerve system)±intrathecal specific immune response. Identification of the organisms from culture, polymerase chain reaction (PCR) or histology within the CNS tissue, and strong evidence of autoimmune encephalitis [e.g. anti-N-methyl-D-aspartate (NMDA) receptor/anti-GQ1b antibody/anti-myelin oligodendrocyte glycoprotein (MOG) antibody in CSF] are included. 'Probable A' means identification of the organisms in a sterile site±specific immune response (e.g. culture or PCR) obtained from blood, CSF, joint, pleural, or pericardial fluid. 'Probable B' means identification of carriage of the organism and evidence of a specific immune response (e.g. sputum culture, paranasal fluid culture). 'Possible' refers to evidence of organism carriage in non-sterile sites and no specific immune response [e.g. respiratory viral infection, mycoplasma antibody titer (1:640 or more), HSV, cytomegalovirus (CMV), VZV IgM-positive, stool PCR, autoimmune antibody positive except anti-NMDAR, anti-GQ1b, anti-MOG Ab] (Supplementary Fig. 1, only online). The degree of sequelae was determined using the mRS score at and 6 months after discharge. A good neurological outcome was defined as an mRS

score of 0–2, and a poor outcome as an mRS score of 3–6.[11] Detailed definitions and criteria for each variable are provided in Supplementary Table 2 (only online).

Data collection

We collected the data pertaining to demographic characteristics, such as age and sex at diagnosis, underlying disease, clinical symptoms, as well as laboratory, EEG, and neurological imaging findings through medical chart reviews. Laboratory data included the results of blood culture, CSF analysis through culture and PCR for viruses [HSV-1, HSV-2, Ebstein-barr virus (EBV), CMV, VZV, Japanese encephalitis virus, and enterovirus], serologic tests (HSV, VZV, EBV, measles, mumps, and mycoplasma), and multiplex real-time respiratory viruses panel (Anyplex™ II RV16 Detection, Seegene, Seoul, Korea). Histopathological findings in the brain tissue were also recorded. EEG findings were defined as abnormal if any of the following were evident: 1) epileptiform discharges, 2) spikes and background as focal slowing, or 3) slow and disorganised background. Abnormal brain magnetic resonance imaging (MRI) findings were defined as follows: 1) abnormal signal only in hippocampal or temporal lesions, 2) lesions not involving the hippocampus or temporal region, 3) lesions in both the hippocampus/temporal and other brain areas, and 4) diffuse brain atrophy. Finally, a paediatric neurologist reviewed the diagnostic test results, medical records, and clinical course of the patients to determine whether they met the criteria for encephalitis.

Statistical analysis

Continuous variables were expressed as means and standard deviations, and categorical variables were expressed as numbers and percentages. Numerical and categorical data were compared using the chi-squared test, analysis of variance, and McNemar's test (Bowker's test), as appropriate. To analyse paired categorical data, McNemar's test was used (e.g, analysis of the extent of sequelae at discharge and at 6 months after discharge in the same patients). Post-hoc analysis *p*-values were analysed using Bonferroni correction. Univariable logistic regression was performed to identify the risk factors for sequelae (mRS score ≥3) at discharge, and multivariable logistic regression on variables that were statistically significant was conducted. As a method of selecting independent variables in multivariable logistic regression, the authors included sex, age, comorbidities, symptoms and laboratory findings that were significant at $p<0.05$. Data pertaining to CSF protein levels were missing in several cases (n=176); therefore, it was excluded from the multivariable logistic regression. As variables related to each other may exist among significant variables in the univariable logistic regression, variable selection was conducted using the stepwise method, and the final model was created. The SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical analyses, and p-values<0.05 were considered statistically significant.

RESULTS

A total of 925 children diagnosed with encephalitis, encephalomyelitis or acute disseminated encephalomyelitis (ADEM) were identified for 14 years (Fig. 1). Among them, 203 were excluded due to insufficient medical records or data errors, and 171 were excluded as they did not meet the criteria for encephalitis. Finally, 551 patients with encephalitis were included in the analysis. The median age at diagnosis was 6.3 (range, 0–14) years, and the male sex accounted for 57% (n=313) of the study population. With respect to the occurrence of encephalitis by age, it presented most frequently around the age of 1 year, and then the frequency gradually decreased. Children under 5 years of age accounted for approximately half (50.3%) of all patients (Fig. 2A). The number of cases for each calendar year increased significantly for slope 2.2 [95% confidence interval (CI), 1.30–3.01] and reached a plateau after 2016 (Supplementary Fig. 2, only online). The overall number of cases of encephalitis was the highest during winter [28.4% (n=160)], followed by spring [25.0% (n=141)], summer [24.3% (n=137)], and autumn [22.2% (n=125)] (Fig. 2B). Approximately 61.4% (n=221) of patients had an underlying disease prior to the diagnosis of encephalitis. Notably, 22% of the patients did not have fever. Seizures were the most common symptom (74.2%), followed by focal neurological findings (67.9%), respiratory symptoms (43.4%), gastrointestinal symptoms (38.8%), and rashes (11.4%). CSF leucorrhoea was diagnosed in 45.5% (n=251) of the patients, and abnormal MRI findings were noted in 70.4% (n=388). Abnormal EEG findings were noted in 79.9% (n=440) of patients.

According to the 2013 ICS criteria, 15.4% (n=85) were proven, 77.1% (n=425) were probable, and 7.4% (n=41) were possible encephalitis cases (Fig. 1). Detailed demographic characteristics according to the ICS criteria for diagnosis of encephalitis are described in Table 1.

Aetiology of encephalitis

At least one aetiology was identified in 41.7% (n=230) of patients (Table 2).

Infectious encephalitis accounted for 36.7% (n=202) of patients

Viruses were the most common cause (41.3%), followed by bacteria (38.3%), combined pathogen (7.4%), and fungi or parasites (0.9%). Among the viruses, HSV was the most common [10.0% (n=23)], followed by enterovirus [6.5% (n=15)], EBV [5.7% (n=13)], and other viruses, while respiratory viruses, including influenza, accounted for 11.8% (n=27) of all patients. One case of Japanese encephalitis virus was also identified (in an unvaccinated foreign child). Among the bacteria, *Mycoplasma pneumoniae* was the most common [19.1% (n=44)], followed by Group B *Streptococcus* [7.8% (n=18)], *Pseudomonas aeruginosa* [2.2% (n=5)], and *Streptococcus pneumoniae*

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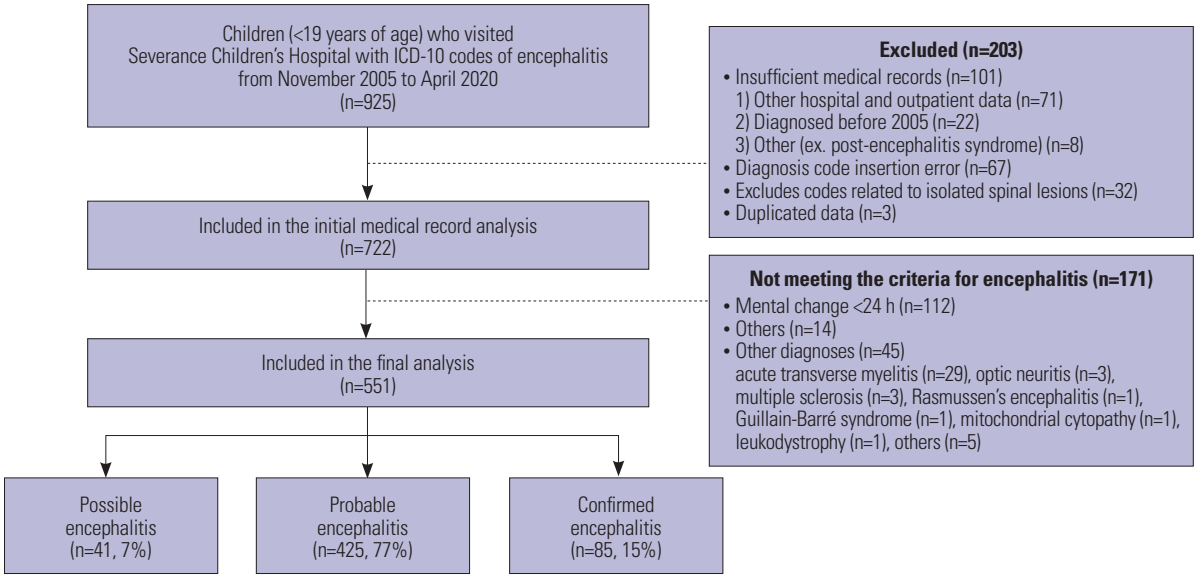

Fig. 1. Flowchart of selection of study population. ICD-10, International Classification of Diseases-10.

[1.7% (n=4)]. One case of *Mycobacterium tuberculosis* infection was confirmed.

Autoimmune encephalitis accounted for 5.1% (n=28) of patients

Among the autoimmune encephalitis cases, NMDA receptor encephalitis accounted for half [50% (n=14)] of the cases.

When the cause was identified in CNS specimens/tissues (n=64), bacteria were the most common [53.1% (n=34)], followed by viruses [25.0% (n=16)] and autoimmune encephalitis [21.9% (n=14)]. Among single pathogens, NDMA receptor autoimmune encephalitis was the most common [21.9% (n=14)], followed by Group B *Streptococcus* [20.3% (n=13)], HSV [17.2% (n=11)], and enteroviruses [6.3% (n=4)].

Notably, in infants younger than 1 year, bacteria were the most common cause, possibly Group B *Streptococcus*, and their occurrence was approximately twice as common as viruses. In the preschool age group of 3–8 years, viruses accounted for 41.6% of cases, followed by bacteria (39.3%), and the occurrence of autoimmune encephalitis increased slightly to 9.0% compared to that in younger children under 2 years of age. In school-aged children and adolescents older than 9 years, bacteria accounted for 33.9%, followed by viruses (28.8%) and fungi/parasites (3.4%). The presence of an autoimmune aetiology increased significantly to 30.5% in school-aged children and adolescents aged >9 years (Fig. 2C).

Sequelae at- and 6 months after discharge

Among 545 patients who had been followed up, up to 6 months after discharge, 129 patients (24%) recovered without any sequelae and 170 patients (31%) had mRS scores ≥3 sequelae causing moderate disability requiring some assistance (in some cases, assistance with walking) and severe disability requiring constant care and attention, bedriddenness, incontinence, and death. Fig. 3A shows whether there was a difference in the level of sequelae between discharge and 6 months. The occurrence of sequelae with mRS scores ≥3 was 36% at discharge, but it significantly decreased to 31% at 6 months after discharge (McNemar's test $p<0.0001$). In Fig. 3B, we analysed the extent of sequelae by recoding mRS (0–2) as good prognosis and mRS (3–6) as poor prognosis, and found significant results with a $p<0.0001$. A stratified analysis was performed to determine whether there were significant patient characteristics that influenced the prognosis, focusing on factors such as sex, age, underlying disease, symptoms, and laboratory findings in Table 3. The change in prognosis according to the characteristics of each case is shown in Supplementary Fig. 3 (only online).

Twelve deaths occurred due to encephalitis: two deaths related to Group B *Streptococcus* and *M. pneumoniae*, respectively, and one death each caused by *Pseudomonas aeruginosa*, EBV, and enterovirus (three cases unknown).

Risk factors for a poor outcome

In both univariable and multivariable analyses, 1) age <5 years, 2) occurrence of seizures, 3) focal neurological findings, and 4) abnormal findings on brain MRI were identified as significant risk factors for a poor outcome (mRS score ≥3) ($p<0.05$). CSF pleocytosis and abnormal EEG findings were not associated with a poor outcome.

For patients with mRS ≥3 at discharge, univariable logistic regression was performed to identify factors influencing symptom improvement. Factors associated with better prognosis in the stratified analysis were sex (female vs. male), age (10–14 years vs. 0–4 years), seizure (absent vs. present), and brain MRI abnormality (normal vs. abnormal). Males had a less favourable prognosis with an odds ratio (OR) (95% CI) 0.40 (0.18–

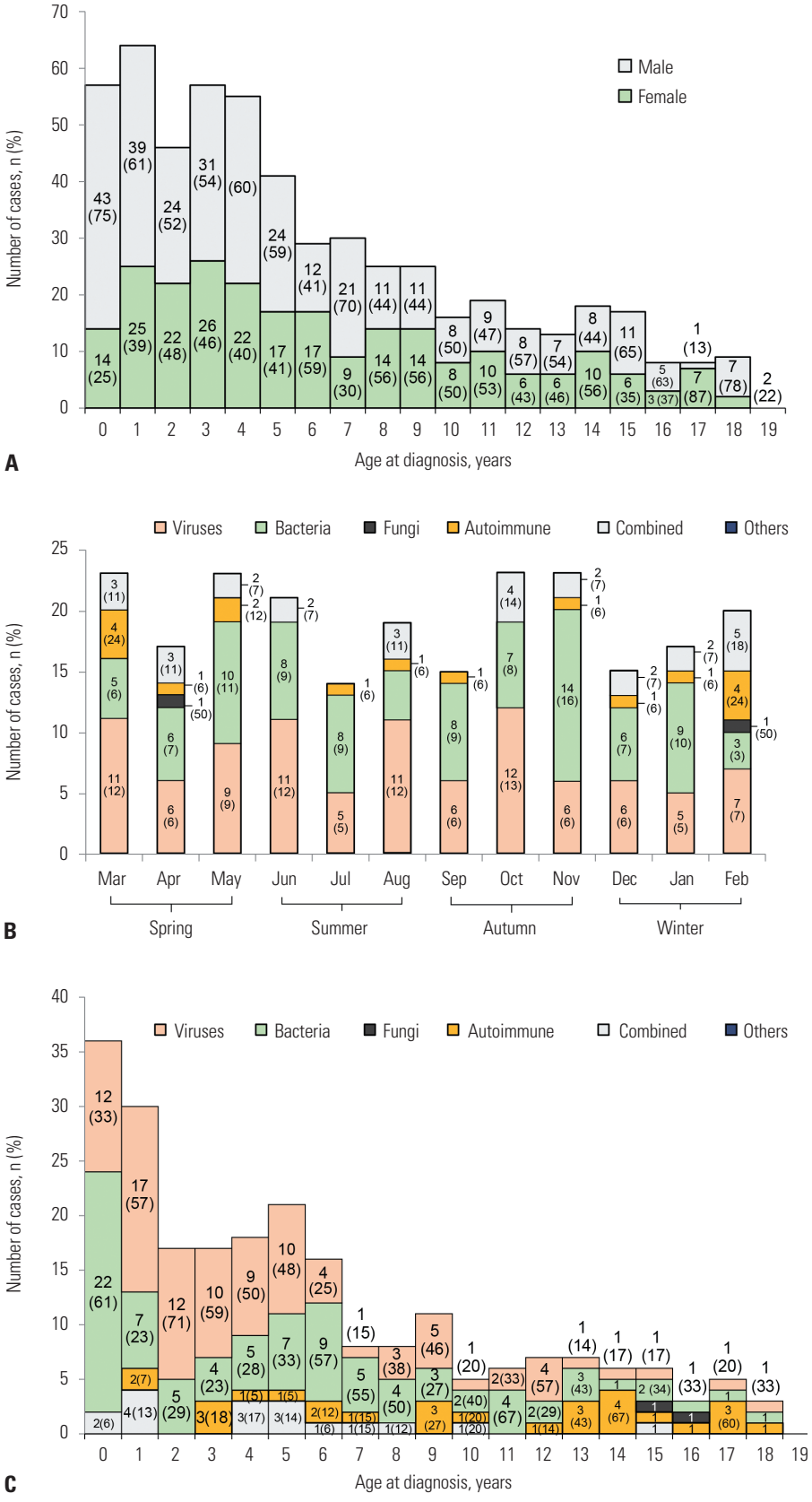

Fig. 2. Number of cases of encephalitis (A) by sex, (B) by aetiology and month, and (C) by aetiology and ages in which diagnosis was made. The x-axis of (A) and (C) represent the age at diagnosis of encephalitis, and the x-axis of (B) represents the month at diagnosis. Numbers in parentheses represent percentages.

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Table 1. Characteristics of Children with Encephalitis According to the 2013 International Encephalitis Consortium Diagnostic Criteria

Variable	Possible (1) (n=41)	Probable (2) (n=425)	Confirmed (3) (n=85)	*p* value	Post-hoc analysis, *p*		
					(1) vs. (2)	(1) vs. (3)	(2) vs. (3)
Sex, female	15 (36.6)	183 (43.1)	40 (47.1)	0.54	>0.99	0.80	>0.99
Age				0.0005	0.28	0.51	<0.0001
0–4 years	22 (53.7)	198 (46.6)	57 (67.1)				
5–9 years	10 (24.4)	132 (31.1)	9 (10.6)				
10–14 years	3 (7.3)	68 (16.0)	10 (11.8)				
15–19 years	6 (14.6)	27 (6.4)	9 (10.6)				
Underlying diseases							
Chronic lung diseases	1 (2.4)	16 (3.8)	7 (8.2)	0.15	>0.99	0.82	0.25
Cardiac diseases	1 (2.4)	17 (4.0)	9 (10.6)	0.03	>0.99	0.49	0.08
Neurologic diseases	10 (24.4)	60 (14.1)	15 (17.7)	0.18	0.24	>0.99	>0.99
Gastrointestinal diseases	1 (2.4)	9 (2.1)	1 (1.2)	0.83	>0.99	>0.99	>0.99
Genitourinary diseases	0 (0.0)	9 (2.1)	2 (2.4)	0.63	>0.99	>0.99	>0.99
Others	4 (9.8)	51 (12.0)	16 (18.8)	0.19	>0.99	0.58	0.27
Symptoms							
Focal neurological findings	17 (41.5)	301 (70.8)	56 (65.9)	0.0006	0.0003	0.03	>0.99
Seizures	20 (48.8)	322 (75.8)	67 (78.8)	0.0005	0.0006	0.002	>0.99
Fever	17 (41.5)	348 (81.9)	64 (75.3)	<0.0001	<0.0001	0.001	0.48
Rash	5 (12.2)	43 (10.1)	15 (17.7)	0.14	>0.99	>0.99	0.14
Respiratory	13 (31.7)	189 (44.5)	37 (43.5)	0.29	0.35	0.61	>0.99
Gastrointestinal	18 (43.9)	166 (39.1)	30 (35.3)	0.64	>0.99	>0.99	>0.99
Laboratory findings							
CSF leucocyte count >5/high-power field	5 (17.9)	197 (69.6)	49 (79.0)	<0.0001	<0.0001	<0.0001	0.41
CSF protein level (mg/L)	37.2±46.3	75.7±171.7	173.2±390.9	0.003	>0.99	0.02	0.01
Abnormal findings on brain magnetic resonance imaging	10 (37.0)	315 (78.0)	63 (79.8)	<0.0001	<0.0001	<0.0001	>0.99
Abnormal findings on electroencephalography	13 (38.2)	360 (88.2)	67 (87.0)	<0.0001	<0.0001	<0.0001	>0.99
C-reactive protein level (mg/L)	12.0±26.3	11.2±26.0	30.4±67.5	0.0004	>0.99	0.05	0.0002
Number of minor criteria for Encephalitis				<0.0001	<0.0001	<0.0001	0.01
2	41 (100)	1 (0.2)	4 (4.7)				
3	0 (0.0)	79 (18.6)	16 (18.8)				
4	0 (0.0)	164 (38.6)	25 (29.4)				
5	0 (0.0)	138 (32.5)	30 (35.3)				
6	0 (0.0)	43 (10.1)	10 (11.8)				

CSF, cerebral spinal fluid.

0.88) compared to females, and patients aged 10–14 years had a more favourable prognosis with an OR (95% CI) 3.06 (1.02–9.17) compared to those aged 0–4 years. Patients with seizures had a less favourable prognosis with an OR (95% CI) 0.26 (0.11–0.58) compared to those without seizures, and patients with abnormal brain MRI had a less favourable prognosis with an OR (95% CI) 0.33 (0.18–0.88). Among the variables that were significant in univariable logistic regression (e.g. sex male, age 10–14 years, seizure, abnormal findings on brain MRI, C-reactive protein), subgroups were created for each categorical variable and McNemar's test was performed.

McNemar's test showed a significant improvement in prognosis in females but a non-significant improvement in prognosis in males. The improvement in prognosis was significant in the 0–4 year age group, and the improvement in prognosis was not significant in the 5 years and above age group. The improvement in prognosis was significant in both the no seizure and seizure groups. The improvement in prognosis was not significant in the group with normal brain MRI, but it was significant in the group with abnormal brain MRI (Supplementary Fig. 3, only online).

DISCUSSION

To the best of our knowledge, this is the largest study to investigate the aetiology and sequelae of encephalitis in Korean children. Our results showed that both infectious and autoimmune causes account for a significant proportion of encephalitis cases in Korean children. In addition, approximately 36% of patients

Table 2. Aetiology of Encephalitis in Korean Children (in All and CNS Specimens)

Aetiology	Frequency	Percentage
All specimens		
Infectious	202	87.8
Virus	95	41.3
Herpes simplex virus	23	10.0
Respiratory viruses except influenza virus	16	7.0
Enterovirus	15	6.5
Epstein-Barr virus	13	5.7
Influenza virus	11	4.8
Rubella, Parvovirus	6	2.6
Norovirus, Rotavirus	5	2.2
Varicella zoster virus	4	1.7
Human herpesvirus-6 (Roseola)	1	0.4
Japanese encephalitis virus	1	0.4
Bacteria	88	38.3
Mycoplasma pneumoniae	44	19.1
Gram positive bacteria*	30	13.0
Gram negative bacteria†	12	5.2
Mycobacterium tuberculosis	1	0.4
Anaerobic bacteria‡	1	0.4
Fungus/parasite	2	0.9
Candida	1	0.4
Toxoplasma	1	0.4
Combined	17	7.4
Non-infectious	28	12.2
Autoimmune	28	12.2
NMDA receptor	14	6.1
Others§	6	2.6
Anti-myelin oligodendrocyte glycoprotein antibody	4	1.7
Thyroid antibodies¶	3	1.3
Human ganglioside Q1b antibody	1	0.4
Only CNS/CSF specimens		
Infectious	50	78.1
Virus	16	25.0
Herpes simplex virus	11	17.2
Enterovirus	4	6.3
Japanese encephalitis virus	1	1.6
Bacteria	34	53.1
Gram positive bacteria	28	43.7
Gram negative bacteria	4	6.2
Mycobacterium tuberculosis	1	1.6
Others	1	1.6
Non-infectious	14	21.9
Autoimmune	14	21.9
NMDA receptor	14	21.9

CNS, central nervous system; NMDA, anti-N-methyl-D-aspartate; CSF, cerebrospinal fluid.
*Gram-positive bacteria include *Streptococcus agalactiae* (n=18), *Streptococcus pneumoniae* (n=4), *Corynebacterium striatum* (n=2), *Listeria monocytogenes* (n=2), *Bacillus cereus* (n=1), methicillin-resistant *Staphylococcus aureus* (n=1), *Streptococcus intermedius* (n=1), and *Streptococcus mitis* (n=1); †Gram-negative bacteria include *Pseudomonas aeruginosa* (n=5), *Escherichia coli* (n=3), *Haemophilus influenzae type b* (n=2), *Achromobacter xylosoxidans* (n=1), and *Neisseria meningitidis* (n=1); ‡Anaerobic bacteria include *Clostridioides difficile* (n=1); §Autoimmune antibodies include anti-SS-A/Ro (n=3), anti-cardiolipin (n=2), and anti-nuclear antibodies (n=1); ¶Thyroid antibodies include anti-thyroid peroxidase antibody (n=2), anti-thyroid microsomal antibody (n=1), and anti-thyroglobulin antibody (n=1).

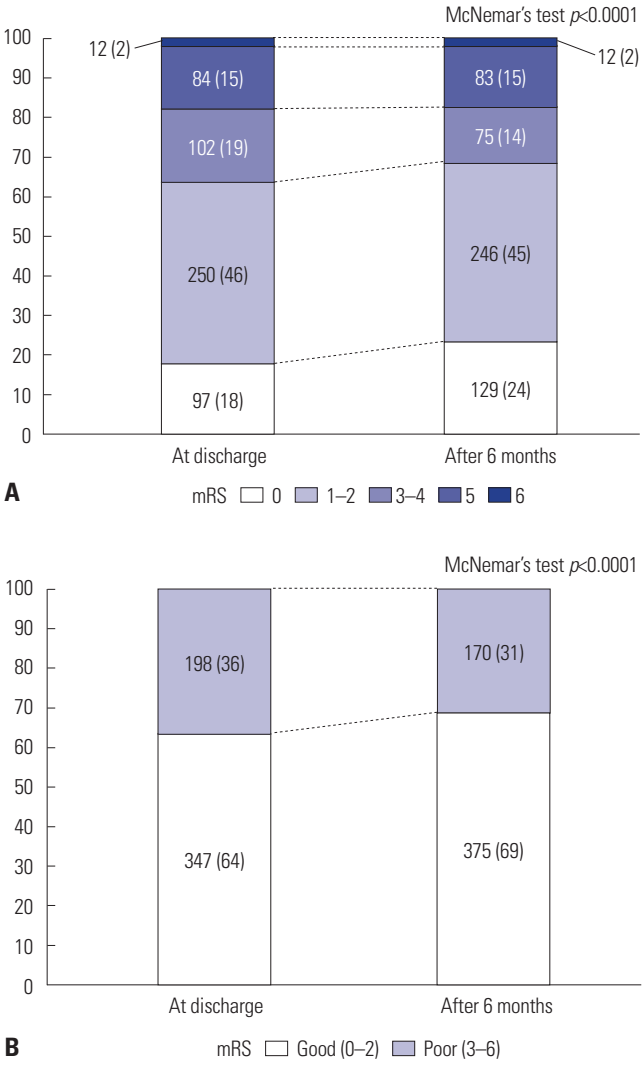

Fig. 3. Change in the severity of sequelae at and 6 months after discharge. (A) shows the modified Rankin Scale (mRS) score, and (B) shows the occurrence of mRS scores <3. Numbers in parentheses represent percentages.

had severe sequelae (mRS scores ≥3) at discharge, but some improvement was observed 6 months after discharge.

The cause of encephalitis was identified in 41.4% of patients in this study, which is comparable to the range of 16%–63% reported in previous prospective studies.[5-7] It was not as high (11.5%) when limited to CNS specimens; however, the California Encephalitis Project, the largest prospective encephalitis study, reported 16% of aetiology-identified cases when the causality level of encephalitis was limited to only probable/confirmed cases.[6] These low detection rates may be influenced by factors such as the timing of CSF/CNS evaluation, prior medication use (especially antimicrobials/immune modulators), low CSF pathogen titres, and poorly enforced assessment for rare pathogens due to the low probability of detection and insufficient sample volume. To overcome this problem, increasing efforts have been directed in recent years to identify the causes of encephalitis using metagenomic next-generation sequenc-

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Table 3. Risk Factors for Poor Prognosis (Modified Rankin Scale Score ≥3 at Discharge)

Variable	Univariable		Multivariable	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Sex, male (ref: female)	0.86 (0.61–1.22)	0.40	0.85 (0.57-1.28)	0.44
Age				
0–4 years	Ref		Ref	
5–9 years	0.54 (0.35–0.82)	0.004	0.56 (0.35–0.90)	0.02
10–14 years	0.42 (0.24–0.74)	0.003	0.52 (0.28–0.95)	0.04
15–19 years	0.44 (0.22–0.92)	0.03	0.37 (0.16–0.86)	0.02
Underlying diseases				
Chronic lung diseases	0.74 (0.30–1.80)	0.51	0.51 (0.16-1.68)	0.27
Cardiac diseases	1.03 (0.46–2.30)	0.94	1.13 (0.37-3.40)	0.83
Neurologic diseases	0.89 (0.55–1.45)	0.65	0.72 (0.38-1.36)	0.31
Gastrointestinal diseases	0.65 (0.17–2.49)	0.53	1.09 (0.19-6.06)	0.93
Genitourinary diseases	1.50 (0.45–4.96)	0.51	1.01 (0.25-3.99)	0.99
Endocrinologic diseases	1.47 (0.44–4.89)	0.53	1.16 (0.22-6.10)	0.86
Others	1.43 (0.86–2.36)	0.17	1.44 (0.77-2.71)	0.25
Symptoms				
Focal neurological findings	3.033 (1.994–4.614)	<0.0001	3.21 (1.98–5.19)	<0.001
Seizures	1.69 (1.11–2.58)	0.01	2.02 (1.27–3.23)	0.003
Fever	1.25 (0.82–1.92)	0.30		
Rash	0.80 (0.45–1.39)	0.42		
Respiratory	1.20 (0.84–1.70)	0.32		
Gastrologic	0.67 (0.47–0.97)	0.03	0.74 (0.49-1.12)	0.15
Laboratory findings				
CSF leucocyte count >5/high power field	0.99 (0.62–1.58)	0.96		
CSF protein level (mg/L)	1.003 (1.001–1.01)	0.003		
Abnormal findings on brain magnetic resonance imaging	3.56 (2.13–5.93)	<0.0001	3.20 (1.87–5.46)	<0.001
Abnormal findings on electroencephalography	1.26 (0.76–2.10)	0.37		
C-reactive protein level (mg/L)	1.002 (0.997–1.01)	0.43		
Number of minor criteria for Encephalitis				
2	Ref			
3	2.29 (0.86–6.06)	0.10		
4	3.69 (1.49–9.15)	0.01		
5	5.57 (2.24–13.83)	0.0002		
6	6.42 (2.33–17.67)	0.0003		
Encephalitis, diagnosis				
Possible	Ref			
Probable	5.57 (1.95–15.92)	0.001		
Proven	6.94 (2.27–21.23)	0.001		
Aetiology, probable/confirmed				
Virus	Ref			
Bacteria	1.47 (0.81–2.70)	0.21		
Fungus	2.03 (0.12–33.59)	0.62		
Combined	0.85 (0.27–2.62)	0.77		
Autoimmune	1.20 (0.49–2.92)	0.69		
Others				

OR, odds ratio; CI, confidence interval; ref, reference; CSF, cerebrospinal fluid.

ing.[12-14] In particular, Wilson, et al.[15] reported in a prospective study that an additional infectious aetiology could be identified in 22% (13/58) of 208 encephalitis patients that could not be detected by conventional methods. Therefore, the future introduction of such diagnostic methods can greatly contribute to the exploration of the causes of encephalitis in Korean children.

Although a high-level causal relationship cannot be ascertained, pathogens identified in respiratory and/or gastrointestinal specimens or serological tests may act directly or indirectly as causes or triggers of encephalitis. In particular, the possibility of direct cerebral parenchymal infection by the pathogen itself and the development of encephalitis through systemic immune-mediated responses or thromboembolic manifestations triggered by the infection have been reported for *Mycoplasma pneumoniae*.[16,17] Similarly, the association between other systemic infections and the occurrence of encephalitis needs to be considered thoroughly. In addition to the relatively common causative agents, it is necessary to test for rare causative agents, such as arbovirus, rickettsia, and Bartonella, based on travel and medical histories. We previously reported that during the early phase of the COVID-19 pandemic in Korea from 2020 to 2021, when stringent non-pharmaceutical interventions (NPIs) were implemented, the incidence of encephalitis was reduced by 66%–72% in children aged 0–9 years.[18] During the same NPIs period, the incidence of community-acquired respiratory viral infections in Korea had also decreased by 8%–25%.[19] This supports the hypothesis that community-acquired infections may be a critical cause or trigger of encephalitis. However, as these studies focused mainly on temporal relationships, establishment of causality is difficult. In addition, follow-up studies are needed to determine if cases of encephalitis surged coincidentally with an increase in community-acquired infections after the lifting of NPIs in the post-COVID-19 pandemic period.[20]

Notably, autoimmune encephalitis accounted for a significant proportion, specifically 12%–22% of all causes. A single-centre study conducted by Park, et al.[9] in 2014 on paediatric encephalitis in Korea showed that autoimmune encephalitis accounted for a lower proportion of cases (3%). This may have been an underestimation since autoimmune encephalitis was not actively investigated in Korea at that time. In international studies, after the first report of anti-NMDA receptor encephalitis, a representative form of autoimmune encephalitis, a British study in 2007 reported that autoimmune encephalitis accounted for about 7% of all causes of encephalitis.[8] Subsequent prospective studies, such as the California Encephalitis Project, found that autoimmune encephalitis accounts for a higher proportion of cases compared to any other viral aetiology.[21] Therefore, active suspicion and testing for autoimmune encephalitis are necessary in Korean children with encephalitis.[21,22]

In 2007, Wang, et al.[23] reported focal neurological deficits, multiple seizures, and EEG and MRI abnormalities as prognostic factors; in 2015, Sutter, et al.[24] found EEG findings to be a strong prognostic factor in encephalitis. In 2015, Singh, et al.[25] reported that in patients older than 65 years of age, CSF pleocytosis was strongly associated with poor outcomes in viral encephalitis; however, MRI abnormalities were not associated with prognosis. In 2017, Kim, et al.[10] reported that focal and/or lateralised abnormalities on EEG were predictive factors of viral encephalitis. In this study, younger age and occurrence of seizures, focal neurological deficits, and MRI abnormalities were poor prognostic factors, whereas EEG findings and CSF abnormalities were not significant prognostic factors.

Another strength of this study is the observation of improvements in activity in paediatric patients with encephalitis who were expected to have severe long-term sequelae. We observed a decrease in the proportion of patients with severe sequelae from 36% to 31%, with an improvement of approximately 13.9% when patients were assessed sequentially at and 6 months after discharge. This result is similar to the prevalence of complications and mortality at discharge reported in previous domestic paediatric patients with encephalitis (31%).[9] Early rehabilitation treatment results in functional gains in these patients; therefore, active rehabilitation should be considered even during hospitalisation.[26,27] Behavioural disorders and attention deficit disorder are common complications of encephalitis, and careful psychiatric evaluation of paediatric patients with encephalitis is warranted. Furthermore, in patients with autoimmune encephalitis, which is known to have a poor prognosis, early aggressive immunomodulatory therapy may affect the prognosis.[28,29] Therefore, proactive diagnostic efforts should be emphasised even at initial presentation of patients with encephalitis.

This study has some limitations. First, this was a retrospective study from a single-centre tertiary hospital, and has a possibility of selection bias. Therefore, our data may not be representative of the entire paediatric population in Korea. A single-centre study conducted by Park, et al.[9] in 2014 with 199 cases during the 13-year study period on paediatric encephalitis in Korea showed that specific pathogens were proven in only 32 patients (25%) from 128 infectious encephalitis. Among 185 patients who had been followed up, 127 cases (68.6%) recovered without sequela and 50 cases (27%) with sequelae. Eight cases (4.3%), including six with infectious encephalitis, one with ADEM, and the other with Reye syndrome, expired. One hundred 17 (58.8%) patients were male, with a mean age of onset of 6.8±4.9 years (1 day–18 years). Herpetic encephalitis was the most common with 9 (4.5%) cases, followed by seven cases of enteroviral encephalitis and 6 cases of tuberculous encephalitis. There were 6 (3.0%) cases of autoimmune encephalitis with autoimmune antibodies identified. Five had antinuclear antibody and one had NMDA-R antibodies. Seizure (OR 4.68, $p \leq 0.001$), pleocytosis (OR 0.43, $p=0.023$), and EEG abnormalities (OR 3.54, $p=0.011$) were statistically associated with poor prognosis in univariable regression. Multivariate regression of statistically significant variables analysis showed that seizures (OR 4.17, $p=0.007$) and EEG abnormalities (OR 3.37, $p=0.037$) were associated with poor prognosis.[9] Second, not all patients

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with suspected paediatric encephalitis underwent the same comprehensive diagnostic tests. In some cases, CSF could not be evaluated due to the patient's critical condition. Especially in cases of autoimmune encephalitis, its occurrence may have been underestimated in the early years (until 2014) of the study period owing to the lack of diagnostic tests and clinician awareness. Recently, anti-IgLON5 antibodies, which cause parasomnia, bulbar palsy, and progressive supranuclear palsy-like syndrome, are being tested in addition to the existing anti-synaptic antibody assays. Third, the presence of a single aetiology for encephalitis was diverse and uncommon in this study; therefore, subgroup analyses, such as causal or prognostic analyses based on MRI or EEG findings, could not be performed. Finally, excluded cases were those treated in other hospitals or countries, and had no data on laboratory findings, symptoms, or prognosis. Electronic medical records prior to 2005 had insufficient data. Causes identified included HSV encephalitis, Group B *streptococcus* meningoencephalitis, tuberous meningoencephalitis, anti-MOG Ab autoimmune encephalitis, and ADEM. In many cases, patients visited Severance Children's Hospital for rehabilitation or additional clinical care. In particular, 19 out of 101 cases were identified as having a poor prognosis with an mRS score ≥3, mainly due to poor treatment outcome or prognosis, such as cerebral palsy, hemiplegia, quadriparesis, intensive care unit cases, coma, or brain death.

Nevertheless, this large-scale study has the strength of evaluating the aetiology of paediatric encephalitis in Korea according to international criteria. Both autoimmune and infectious causes account for a significant proportion of paediatric encephalitis in Korean patients. In addition, approximately one-third of the patients with encephalitis have severe long-term sequelae. Further research is needed to determine whether early diagnosis of the cause of encephalitis in these children, followed by targeted treatment, can improve the prognosis.

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