Pediatric Neurology 146 (2023) 44–49

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Incidence of Pediatric Acute Disseminated Encephalomyelitis During the Coronavirus Disease 2019 Pandemic in South Korea

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ARTICLE INFO

Article history:
Received 1 September 2022
Accepted 12 June 2023
Available online 17 June 2023

Keywords:
Acute disseminated encephalomyelitis
Epidemiology
SARS-CoV-2
Coronavirus disease 2019
Acute respiratory virus

ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder of the central nervous system that is usually triggered by infections. We aimed to determine the temporal trends in the incidence of ADEM before and during the pandemic and their correlation with viral epidemiology.

Methods: We conducted a nationwide, population-based, retrospective, ADEM cohort study by using the Health Insurance Review and Assessment Service database. New-onset ADEM was defined as a patient (age <19 years) who was hospitalized with a diagnostic code of G04.0, G36.8, and G36.9 and a prescription of intravenous methylprednisolone. The National Infectious Disease Surveillance System was used to collect the nationwide viral epidemics.

Results: A total of 185 new-onset pediatric ADEM cases were included. The mean patient age was 7.0 ± 4.9 years. The incidence of ADEM was 0.34 to 0.48 of 100,000 persons per year before the pandemic, which dropped to 0.22 of 100,000 persons per year during the first pandemic year. The risk of ADEM occurrence was approximately 1.74% higher during the prepandemic years compared with the first pandemic year (odds ratio = 1.017, $P = 0.009$). There was a weak positive correlation between acute respiratory viral infection and ADEM incidence ($r = 0.28$, $P = 0.03$).

Conclusion: This study demonstrates how infection control during the early coronavirus disease 2019 (COVID-19) pandemic influenced the incidence of ADEM. The low incidence of ADEM in the early COVID-19 pandemic may be related to the decline in acute respiratory viral infections, which are potential triggers of ADEM.

Introduction

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system, characterized by acute or subacute onset of multifocal neurological deficits and encephalopathy.[1] ADEM is more common in children younger than 10 years than in adults, and it mostly occurs one to two weeks after an infection or rarely after vaccination.[2] Although a specific etiology has not been identified, approximately 70% to 80% of patients have recently had an upper respiratory tract infection, measles, mumps, rubella, Epstein-Barr virus, cytomegalovirus, influenza virus, or herpes simplex virus.[3] The pathogenesis of ADEM is still not completely understood, but it may be explained as a T cell-mediated response against myelin oligodendrocyte proteins via a mechanism of molecular mimicry.[3] In response to the outbreak of coronavirus disease 2019 (COVID-19), the Korean Disease Control and Prevention Agency (KDCA) implemented non-pharmaceutical interventions (NPIs), including social distancing, mask wearing, and sanitization, to suppress the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Various

Funding: This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIT) (grant number: 2021R1A2C1013206). The funders had no role in the study design and conduct of the study or in the decision to prepare and submit the manuscript for publication.

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https://doi.org/10.1016/j.pediatrneurol.2023.06.009

TABLE 1.
Characteristics of Patients With ADEM

Demographics and Clinical Features	2016	2017	2018	2019	2020
ADEM cases, n	49	40	33	43	20
Age, years (mean ± S.D.)	7.3 ± 5.1	6.3 ± 4.3	6.3 ± 5.2	6.9 ± 5.0	8.9 ± 4.8
Male:female, n	30:19	17:23	23:10	18:25	7:13
Length of hospital stay, days (mean ± S.D.)	22.6 ± 28.2	14.3 ± 13.9	15.2 ± 12.0	14.4 ± 9.3	11.9 ± 6.5
ICU care, n (%)	11 (22.4)	7 (17.5)	9 (27.3)	7 (16.3)	1 (5.0)
Invasive mechanical ventilation during illness, n (%)	6 (12.2)	4 (10.0)	3 (9.1)	2 (4.7)	0 (0.0)

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
ICU = Intensive care unit

infections, such as those caused by viruses in the respiratory and gastrointestinal systems, were significantly reduced during the NPI period.[4,5]

The neurological manifestations of COVID-19 include cerebrovascular disorders, seizures, headaches, dizziness, and olfactory or gustatory dysfunction.[6,7] ADEM has also been reported as a neurological complication of SARS-CoV-2 infection, but most published reports were of single cases or small case series and mostly in older patients.[8,9]

In this study, we designed a nationwide retrospective ADEM cohort study to assess the incidence of pediatric ADEM before and during the COVID-19 outbreak. The primary aim of our study was to compare the incidence of ADEM between the prepandemic years (2016 to 2019) and the first pandemic year (2020). The secondary aim was to analyze the correlation between various viral infections and the incidence of ADEM by using the epidemiology of viral infections.

Methods

Data sources

We conducted a nationwide, population-based, retrospective, ADEM cohort study by using the Health Insurance Review and Assessment Service (HIRA) database (Dataset No. M20210210108). The HIRA database consists of claims of approximately 98% of the Korean population (nearly 50 million individuals) and includes demographic data, diagnoses, prescriptions, procedures, and medical costs. Diagnostic codes are assigned based on the Korean Classification of Diseases, seventh revision, which is a modified version of the International Classification of Diseases, 10th Revision.

For the epidemiology of infectious diseases, we used the national statistics from the National Infectious Disease Surveillance System operated by the KDCA. This surveillance system was established to demonstrate the nationwide trends and patterns of notifiable infectious diseases since 2001.[10] In this system, notifiable infectious data with identified pathogens were collected from more than 200 sentinel surveillance health care centers in Korea. However, these data do not contain detailed information of each individual case. The KDCA data are accessible to the public on the infectious disease portal web site (https://www.kdca.go.kr/npt) and can be used without concern about copyright. We collected antigen or polymerase chain reaction-confirmed cases of acute respiratory viruses, enterovirus, norovirus, and rotavirus. In this study, respiratory syncytial virus, rhinovirus, parainfluenza virus, human bocavirus, human metapneumovirus, human coronavirus, and adenovirus were considered as acute respiratory viruses. Influenza-like illness was defined as confirmed influenza cases as well as those with fever of ≥38°C and symptom of acute respiratory infection according to the World Health Organization global influenza surveillance standards.[11]

TABLE 2.
Incidence of Pediatric ADEM in South Korea

Year	Total Number of ADEM Cases, n	Incidence Per 100,000 Persons (95% CI)	Odds Ratio (95% CI)	
2016	49	0.48 (0.36-0.66)	1.02 (1.01-1.04)*	
2017	40	0.40 (0.29-0.56)	1.02 (1.00-1.03)	
2018	33	0.34 (0.24-0.49)	1.01 (0.99-1.03)	
2019	43	0.46 (0.34-0.63)	1.02 (1.00-1.04)*	
2020	20	0.22 (0.15-0.35)	Reference	1.017* Reference

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
CI = Confidence interval
*P value < 0.05.

Study population

ADEM cases from January 1, 2016, to December 31, 2020, were collected from the HIRA database. Pediatric ADEM was defined as hospitalization of an individual (age <19 years) with an International Classification of Diseases, 10th Revision, diagnostic code for ADEM (G04.0, G36.8, and G36.9) with a prescription of intravenous (IV) methylprednisolone for at least one day. We excluded individuals with claim data for ADEM (G04.0, G36.8, and G36.9) and other encephalitis (G04.8 and G04.9) from January 1, 2015, to December 31, 2015, to confirm that all ADEM cases were new-onset cases.

Statistical analysis

The annual incidence of ADEM per 100,000 persons was calculated as the number of new-onset ADEM cases in each year divided by the annual midyear population obtained from the Korean Statistical Information Service. We compared the incidence of ADEM in each year as categorical variables by using a general linear model. Odds ratios calculated for the risk of ADEM occurrence in each year were compared with that in 2020. Student t test was used to determine the statistical significance between pairs of annual incidences. We used time series analysis and locally weighted scatterplot smoothing (LOWESS) to visualize trends in the occurrence of ADEM and viral epidemics. We constructed a model to predict the incidence of ADEM after the COVID-19 outbreak based on the actual incidence before the COVID-19 outbreak by using an autoregressive integrated moving average (ARIMA) model. The actual incidences and model predictions were visually examined to determine whether the observed incidences after the COVID-19 outbreak were within the 95% confidence

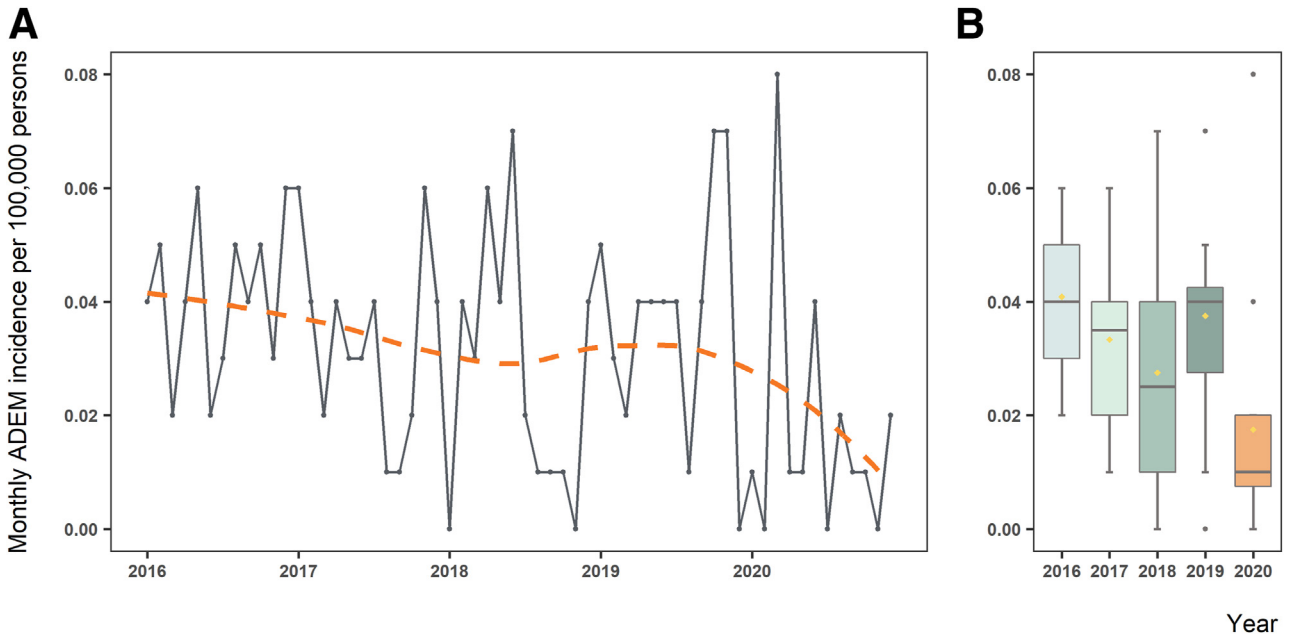

FIGURE 1. (A) Time series analysis of the monthly incidence of acute disseminated encephalomyelitis (ADEM) and locally weighted scatterplot smoothing (dotted orange line) showing the trend from 2016 to 2020. (B) Box plots representing the monthly incidence of ADEM in each year. The color version of this figure is available in the online edition.

intervals of the predicted values. Correlation analysis between viral pathogens and the incidence of ADEM was performed using Pearson correlation analysis. Correlation coefficients were calculated to measure the strength of the relationship between viral pathogens and the incidence of ADEM. *P* value <0.05 was considered statistically significant. Statistical analyses were performed using R version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) and SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics

This study was approved by the institutional review board of Chung-Ang University Hospital (IRB No. 2102-002-19352), and the requirement for informed consent was waived owing to the anonymized nature of information from the database.

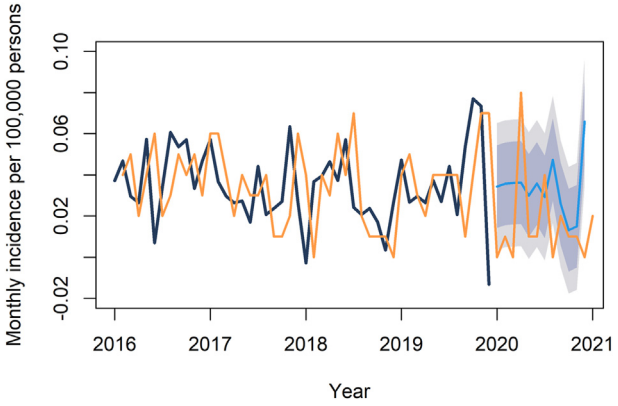

FIGURE 2. The actual monthly incidence of acute disseminated encephalomyelitis (orange line), the incidence fitted by removing a seasonal variation from the actual incidence in prepandemic years (black line), and the incidence predicted with an autoregressive integrated moving average model in the first pandemic year (blue line). The light and dark blue shaded areas represent the 80% and 95% confidence intervals, respectively, of the predicted incidence during the pandemic. The color version of this figure is available in the online edition.

Data availability

Individual-level data from the HIRA database are accessed only by authorized users. The full, anonymized dataset is available upon request from the corresponding author.

Results

Incidences of pediatric ADEM

In total, 185 patients with new-onset ADEM were identified (Table 1). The mean age was 7.0 ± 4.9 years. Of the 185 patients, 35 (18.9%) were admitted to the intensive care unit, and 15 (8.1%) required invasive mechanical ventilation during their illness. Compared with the prepandemic years (from 2016 to 2019), the proportion of patients requiring intensive care unit care or invasive mechanical ventilation was lower during the pandemic.

The annual incidence of ADEM before the pandemic was 0.34 to 0.48 cases per 100,000 persons; however, it dropped to 0.22 cases per 100,000 persons during the pandemic (Table 2). Compared with the first pandemic year (2020), the risk of ADEM occurrence was approximately 1.74% higher during the prepandemic years (2016 to 2019) (odds ratio = 1.017, $P = 0.009$). Time series analysis with LOWESS based on the monthly incidence of ADEM also demonstrated a lower incidence of ADEM during the pandemic (Fig 1). There were no seasonal variations in the incidence of ADEM before and during the pandemic. The actual monthly incidence of ADEM during the pandemic was lower than that predicted by the ARIMA model, except in March and June (Fig 2).

Correlation between viral infections and the incidence of ADEM

In the time series, remarkable seasonal peaks of viral infections were observed in prepandemic years (Fig. 3). However, the incidence of viral infections was significantly diminished in the first pandemic year and the seasonal variation disappeared. The LOWESS also demonstrated the decreasing trend of viral infections in the first pandemic year (Fig 3). The incidence of ADEM was

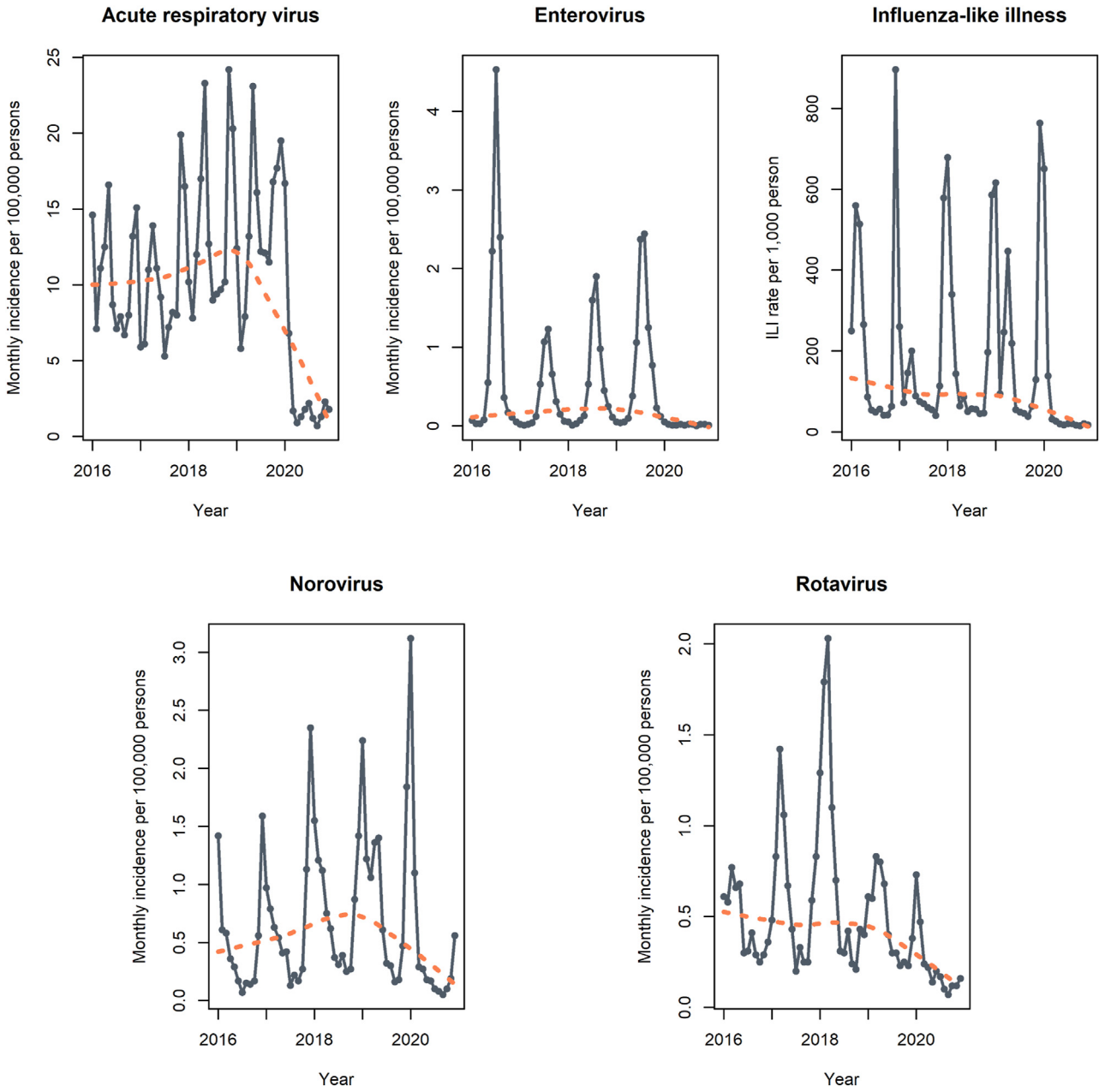

FIGURE 3. Monthly incidence of acute respiratory virus, enterovirus, norovirus, and rotavirus infection and influenza-like illness from the National Infectious Disease Surveillance System. The color version of this figure is available in the online edition.

positively correlated with acute respiratory virus infection ($r = 0.28$, $P = 0.03$) (Fig 4) but not with enterovirus, norovirus, or rotavirus infections or influenzalike illness.

Discussion

Although many viral pathogens, including SARS-CoV-2, have been implicated in ADEM, there are limited data on how viral epidemics influence the incidence of ADEM. We compared the incidence of pediatric ADEM before and during the COVID-19 pandemic using a nationwide database. Our study demonstrates how infection control influenced the incidence of ADEM during the early COVID-19 pandemic. The annual incidence of ADEM before the pandemic in our study is comparable with other nationwide incidences, such as that in Japan from 2005 to 2007 (0.4 per 100,000 children),[12] the United States from 2006 to 2014 (0.5 per 100,000 children),[13] and Denmark from 1977 to 2015 (0.5 per 100,000 children).[14] Few studies have been conducted to validate algorithms derived from administrative databases to predict the incidence of ADEM.[15] We defined ADEM as hospitalization with a diagnostic code of ADEM and at least one day of prescription of IV methylprednisolone; accordingly, the incidences of ADEM during the prepandemic years were comparable with those in the above-mentioned studies. When we applied this operational definition to the first pandemic year, we discovered that the incidence of ADEM was lower.

ADEM and acute hemorrhagic leukoencephalitis (AHLE) have both been reported in patients after SARS-CoV-2 infection.[8,9,16] In a systematic review of 46 cases of ADEM and AHLE, Manzano et al. reported that most patients with post-COVID-19 ADEM and AHLE

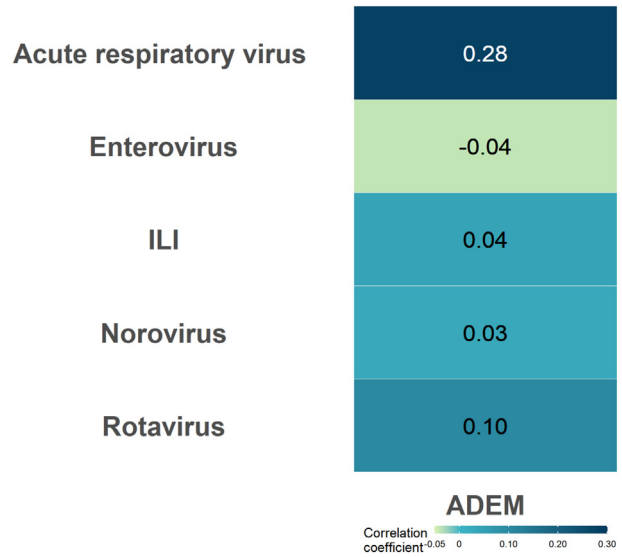

FIGURE 4. Heat map presenting correlations between various viral pathogens and the incidence of ADEM. ADEM, acute disseminated encephalomyelitis; ILI, influenza-like illness. The color version of this figure is available in the online edition.

were adults and that post-COVID-19 cases had a higher rate of hemorrhage on neuroimaging and higher morbidity and mortality rates than pre-COVID-19 cases.[16] They postulated that post-COVID-19 ADEM/AHLE may be a unique entity that is more likely in adults but cautioned that the higher incidence among adults might have been caused by publication bias, preferentially reporting adult cases, which are generally less common. Our study did not include adult cases of ADEM/AHLE and SARS-CoV-2 results were masked; nonetheless, the absolute number of pediatric ADEM cases did not increase and the clinical severity did not worsen in the first pandemic year compared with those in prepandemic years.

Our study supports the hypothesis that ADEM is triggered by a preceding infection, especially an acute respiratory virus infection. Although the pathogenesis of ADEM has not been fully elucidated, it is currently understood as a transient autoimmune phenomenon that is commonly triggered by infection.[3,17] There are two main hypotheses regarding the pathogenesis of ADEM. One hypothesis is that the antibodies respond to myelin oligodendrocyte glycoproteins through molecular mimicry.[18] The other is that a virus causes self-sensitization of reactive T cells against myelin oligodendrocyte glycoproteins.[19] In the past, pathogens such as measles and rubella were probably the main causes of ADEM; however, in the post-vaccination era, nonspecific upper respiratory infections are the most frequently reported etiology of ADEM.[20] The trigger of ADEM is difficult to identify because of the latency between the infection and the onset of neurological symptoms. Adenovirus and parainfluenza infections reportedly precede the neurological symptoms of ADEM.[21,22] Seasonal variation in the incidence of ADEM (it is more common in spring and winter) also suggests that antecedent infections can trigger ADEM.[12,23-25] We observed a clear seasonal distribution of viral infections before the pandemic; however, we did not observe the same seasonal variation in the incidence of ADEM. Overall actual incidences of ADEM were lower than those predicted by the ARIMA model, whereas the actual incidences of ADEM in March and June 2020 were higher than the predicted incidences. This finding may be explained by the small number of monthly ADEM cases and the lack of seasonal variation.

Our study has several limitations. First, ADEM cases were defined according to diagnostic codes and prescription records rather than the diagnostic criteria of the International Pediatric Multiple Sclerosis Study Group.[26] Individual clinical features of ADEM, including the onset of encephalopathy, lumbar puncture results, and radiological features of brain images, were unavailable because of the nature of the administrative database. Therefore, there are several considerations regarding the working definitions used in this study. During the COVID-19 pandemic, there has been a significant change in health care utilization, including hospitalization and outpatient and emergency visits. Nonhospitalized patients with ADEM were not included according to this definition. However, because the neurological symptoms of ADEM are severe, we believe that the impact of health care utilization on new-onset ADEM is minimal. We defined patients with ADEM as those requiring IV steroids. According to this working definition, we could miss some self-resolved ADEM cases; however, we reanalyzed with a definition of ADEM solely based on the diagnostic codes without the prescription of IV steroids and obtained consistent results. In addition, we did not include patients who received IV immunoglobulin or therapeutic plasma exchange as the initial treatment. These are alternative treatment options; however, they are not covered by the national health insurance as initial therapy and we could not identify them from the HIRA database. Second, we used the nationwide epidemiology of viral infections from the official national surveillance system and did not isolate the viruses from individual specimens. Therefore, these results cannot be used to establish a causal relationship between viral infections and ADEM. We found a weak correlation between acute respiratory virus infections and ADEM incidence suggesting there could be no linear relationship between these two variables. Third, NPIs and school closures in Korea during the study period contributed to the lower prevalence of COVID-19 in children in Korea than the prevalence in children in other countries.[27] Through further studies using the data from 2021 to 2022, when the number of patients with COVID-19 dramatically increased in Korea, we may obtain additional information about the impact of COVID-19 on the incidence of ADEM. Conversely, we did not verify how the epidemiology of pediatric ADEM changed based on shifts in viral infections as the NPIs were discontinued. Last, we could not analyze data according to the SARS-CoV-2 test results as these were considered confidential information and not disclosed at the time of analysis.

Conclusions

This nationwide, retrospective cohort study of pediatric ADEM demonstrated that the incidence of ADEM decreased in South Korea during the first year of the COVID-19 pandemic. The incidence of ADEM may be influenced by the epidemiology of acute respiratory virus infections, which are potential triggering factors for ADEM. Further studies on the impact of COVID-19 or other viral epidemics on the incidence and clinical severity of pediatric ADEM are warranted.

Declaration of Competing Interest

None of the authors has conflicts of interest to disclose.

Acknowledgments

We would like to thank Eun-Hye Kim and Mi Ryoung Yoon for their valuable assistance with data management and statistical analysis.

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