Temporal Trends of Pediatric Hospitalizations with Acute Disseminated Encephalomyelitis in the United States: An Analysis from 2006 to 2014 using National Inpatient Sample

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Objective To determine the temporal trends in the epidemiology of acute disseminated encephalomyelitis (ADEM) and hospitalization outcomes in the US from 2006 through 2014.

Study design Pediatric (≤18 years of age) hospitalizations with ADEM discharge diagnosis were identified from the National (Nationwide) Inpatient Sample (NIS) for years 2006 through 2014. Trends in the incidence of ADEM with respect to age, sex, race, and region were examined. Outcomes of ADEM in terms of mortality, length of stay (LOS), cost of hospitalization, and seasonal variation were analyzed. NIS includes sampling weight. These weights were used to generate national estimates. *P* value of < .05 was considered significant.

Results Overall incidence of ADEM associated pediatric hospitalizations from 2006 through 2014 was 0.5 per 100 000 population. Between 2006 through 2008 and 2012 through 2014, the incidence of ADEM increased from 0.4 to 0.6 per 100 000 (*P*-trend <.001). Black and Hispanic children had a significantly increased incidence of ADEM during the study period (0.2-0.5 per 100 000 population). There was no sex preponderance and 67% of ADEM hospitalizations were in patients <9 years old. From 2006 through 2008 to 2012 through 2014 (1.1%-1.5%; *P*-trend 0.07) and median LOS (4.8-5.5 days; P_{trend} = .3) remained stable. However, median inflation adjusted cost increased from $11 594 in 2006 through 2008 to $16 193 in 2012 through 2014 (P_{trend} = .002).

Conclusion In this large nationwide cohort of ADEM hospitalizations, the incidence of ADEM increased during the study period. Mortality and LOS have remained stable over time, but inflation adjusted cost of hospitalizations increased. *(J Pediatr 2019;206:26-32).*

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder of the central nervous system that predominantly affects children, usually following an infection.[1,2] ADEM typically is monophasic in course, with acute or subacute onset of multifocal neurologic deficits with encephalopathy.[3,4] In the pre-vaccination era, ADEM commonly followed childhood infections such as measles, smallpox, and chickenpox, often leading to significant mortality and neurologic sequelae.[5] The advent of effective immunizations and improved vaccine formulations have led to a decrease in the incidence of ADEM. Despite this downward trend, ADEM is among the most common demyelinating disorders of childhood.[6] ADEM most often is reported to follow a nonspecific upper respiratory tract infection of a variety of viral and bacterial etiologies.[7,8]

ADEM presents as a diagnostic challenge and is associated with 1%-3% mortality.[9-12] There are no specific biomarkers or confirmatory tests, and the presenting symptoms and signs overlap with multiple sclerosis, central nervous system infections, and other autoimmune diseases. Diagnosis typically depends upon a high level of clinical suspicion and can be confirmed by clinical and radiologic signs. Cerebrospinal fluid may show evidence of inflammation in form of pleocytosis and/or increased protein concentration, but cerebrospinal fluid can be normal.[1,13] Although previous studies have assessed clinical features of ADEM, difficulties with diagnosis have led to a paucity of information regarding the epidemiology and management of ADEM.

ADEM	Acute disseminated encephalomyelitis
HCUP	Healthcare Cost and Utilization Project
LOS	Length of stay
MRI	Magnetic resonance imaging
NIS	National (Nationwide) Inpatient Sample

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The purpose of the present study was to investigate the trends in incidence, resource utilization, and outcomes of pediatric patients hospitalized with ADEM in the US.

Methods

National (Nationwide) Inpatient Sample (NIS) databases from the years 2006-2014 were used to derive our study population. NIS is one of a family of databases and software tools developed for the Healthcare Cost and Utilization Project (HCUP) that is sponsored by Agency for Healthcare Research and Quality.[14] NIS database contains inpatient data including clinical and resource use information derived from billing data submitted by hospitals to statewide data organizations across US. The 2014 NIS contained data from 44 states and District of Columbia representing more than 96% of the US population. The unit of analysis for NIS is inpatient stays and not individual patients. Each hospitalization in this database is deidentified and recorded as a unique entry with 1 primary discharge diagnosis, <30 secondary diagnoses along with <15 procedural codes during that hospitalization. Because NIS contains deidentified data it was exempted from Institutional Review Board approval. The NIS large sample size enables analyses of rare conditions, uncommon treatments, and special patient populations. NIS previously has been used to study trends in hospitalization in the neonatal, pediatric, and adult population.[15-17]

Study Population

We queried NIS database from the years 2006-2014 and extracted all pediatric hospitalization (age ≤18 years). To limit double counting, hospitalizations that resulted in transfer to a skilled nursing facility, intermediate care facility, another type of facility, and short-term hospital were excluded using the 'DISPUNIFORM' variable.[18] ADEM related hospitalizations were identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code 323.61 in any of the diagnosis fields.

Definition of Variable

We studied encounter level and hospital level baseline characteristics for our study population. Encounter related information such as age in years (0-4, 5-9, 10-14, 15-18), sex, race, median household income as per zip code (<$36 000, $36 000-$44 999, >$45 000), primary payer (Medicare/Medicaid, private insurance, other), and hospital level characteristics such as hospital location and teaching status (rural, urban nonteaching, and urban teaching), hospital bed size (small, medium, and large), and hospital region (Northeast, Midwest, South, and West) were studied. NIS contains data on total charges for each hospital discharge in the database. We utilized HCUP cost-to-charge files to estimate the cost of resource use for inpatient hospitalization. Costs reflect the actual expenses incurred during the inpatient stay.[19] Adjusted cost for each year was calculated in terms of the 2014 cost after adjusting for inflation according to the latest consumer price index data released by US government.[20] This enabled us to standardize the costs over the study period.

Statistical Analyses

We analyzed the baseline characteristics of the study population. For continuous variables, median and IQR were reported. For categorical variables, percentages were reported. We compared the baseline characteristics of both groups to ensure estimate differences using the χ^2 test, Student t test, Wilcoxon rank-sum test, and survey regression depending on the distributions of the variables. NIS includes weights to produce national estimates. These sampling weights are calculated by stratifying the NIS hospitals on variables that were used for creating the sample.[21] Each discharge abstract was assigned a weight in the form of DISCWT: variable. When weighted discharge data are applied to unweighted NIS data, they represent all inpatient discharges from community hospitals in the US. NIS database underwent changes in its sampling strategy starting in 2012. To account for these changes, TRENDWT was used for trend analysis.[21] NIS is a complex survey design in which discharges are clustered within the hospitals. SURVEY procedures were used to account for clustering. For trend analysis, χ^2 test of trend for proportions was used using the Cochrane Armitage test.[22] Survey regression was used for continuous variables such as length of stay (LOS).[23] The annual incidence of ADEM was estimated using the number of ADEM hospitalizations for numerator and corresponding subgroup population derived from the Center for Disease Control and Prevention's wide-ranging online data for epidemiologic research database as denominator. Population estimates in these online databases are bridged-race population estimates produced by the US Census Bureau in collaboration with the National Center for Health Statistics.[24] SAS v 9.4 (SAS Institute Inc, Cary, North Carolina) was utilized for analyses. *P* value of <.05 was considered significant.

Results

We identified a total of 55 667 114 pediatric hospitalizations within the NIS between 2006 and 2014 of which 3319 had an ADEM diagnosis with *International Classification of Diseases, Ninth Revision, Clinical Modification* code 323.61. Of the total ADEM cases identified, ADEM was the primary diagnosis in 73 cases and the secondary diagnosis in 3246 cases. The overall incidence of ADEM for the study period was 0.5 per 100 000 children/year. **Table I** describes the baseline and demographic characteristics of children hospitalized with ADEM. In summary, 67% were in the 0-9 years age group, 52% were male, 41% were of white race, 94% had private (52%) or public health insurance (Medicare/Medicaid) (42%). Children with ADEM were more likely to be hospitalized in a large (65%), urban teaching hospital (93%) in the South census region (38%) of the US. Household income was distributed across income quartiles.

Table II shows the rates of ADEM-associated hospitalizations per 100 000 children according to age group, sex, race, and region. The incidence of ADEM increased from 0.4 to 0.6 per 100 000 children/year from 2006-2008 to 2012-014 (P_{trend} <.0001) across the US. There was significant variation both between and within geographic regions in the incidence of

Table I. Baseline characteristics of ADEM hospitalizations

	2006-2008	2009-2011	2012-2014	Total	*P* value
ADEM (unweighted)	183	247	259	689	
ADEM (weighted)*	847	1176	1295	3319	
Age (median)	6	7	5	6	.5
(IQR, 25th percentile - 75th percentile)	(2.8-10.7)	(2.7-11.1)	(2.2-11.0)	(2.5-10.9)	
Age, y (%)					<.0001
0-4	32.9	33.7	39.4	35.7	
5-9	32.3	33.1	29.3	31.4	
10-14	21.7	24.6	18.9	21.6	
15-18	13.1	8.6	12.4	11.2	
Sex (%)					.003
Male	51.8	55.0	48.3	51.6	
Female	47.6	44.7	51.7	48.2	
Missing	0	0	0	0	
Race (%)					<.0001
White	44.6	44.0	36.3	41.2	
Black	8.2	11.9	15.1	12.2	
Hispanic	12.0	19.8	20.5	18.1	
Others	11.9	7.0	13.5	10.8	
Missing	23.4	17.3	14.7	17.8	
Median household income category for zip code (%)					<.0001
0-25th percentile	25.3	25.4	23.6	24.7	
26-50th percentile	19.3	21.4	21.2	20.8	
51-75th percentile	21.1	31.8	27.8	27.5	
76-100th percentile	31.4	21.3	23.9	24.9	
Missing	2.9	0.0	3.5	2.1	
Payment (%)					.01
Private	54.3	53.7	49.4	52.2	
Medicare/Medicaid	39.8	39.1	45.2	41.6	
Others	6.0	7.2	5.4	6.2	
Hospital characteristics					
Hospital location and teaching status (%)					<.0001
Rural	1.2	2.6	0.0	1.2	
Urban nonteaching	7.5	5.7	2.3	4.8	
Urban teaching	91.3	90.1	97.7	93.4	
Hospital region (%)					<.0001
Northeast	28.4	12.2	11.6	16.1	
Midwest	19.0	24.0	22.8	22.2	
South	38.9	35.4	40.9	38.5	
West	13.7	28.5	24.7	23.2	
Bed size (%)					<.0001
Small	18.4	9.0	14.3	13.5	
Medium	11.3	23.3	25.9	21.3	
Large	70.2	66.1	59.9	64.7	

*NIS includes sampling weight. These weights were used to generate national estimates.

ADEM. Overall, both male and female children were equally affected with an incidence of 0.5 per 100 000 children/year and there was a significant increase in ADEM incidence for both sexes during the study period. Except for the Northeast, which experienced a decline, all other regions experienced a significant increase in ADEM incidence during the study period.

Overall incidence of ADEM-associated hospitalizations over the study period was 0.5 per 100 000 children/year. The ADEM-associated hospitalization rate has increased from 0.4 per 100 000 children/year in 2006-2008 to 0.6 per 100,000 children/year in 2012-2014 ($P_{trend} = < .0001$). The incidence of ADEM was inversely related to age, decreasing from 0.7 per 100 000 children/year in hospitalizations of children aged 0-4 years to 0.2 per 100 000 children/year in the 15- to 18-year-old age group. There was variation in ADEM incidence over time within and between age groups. All age groups experienced a significant increase in ADEM incidence from 2006-2008 to 2012-2014, with the highest increase occurring in children aged 0-4 years (0.5-0.9 per 100 000 children/year; P_{trend} <.0001). The age distribution of ADEM hospitalizations did not change over the study period. **Figure 1** describes the proportions of ADEM-associated hospitalizations by age in years and shows peak incidence of ADEM-associated hospitalizations in children aged 2 years.

From 2006-2008 to 2012-2014, there was significant upward trend in ADEM hospitalizations per 100 000 among black children (0.2-0.5; P_{trend}<.0001), Hispanic children (0.2-0.5; P_{trend}<.0001), and children from other races (0.6-0.7; P_{trend}<.002). There was no change among white children over time during the study period. The seasonal variations for ADEM-associated hospitalizations are shown in **Figure 2**. Almost one-third of hospitalizations occurred during the spring (30.2%), whereas the lowest hospitalizations were observed during the summer (16.7%).

Table III (available at www.jpeds.com) demonstrates in-hospital outcomes for the study population. From 2006 to 2014,

Table II. Incidence of Acute Disseminated Encephalomyelitis (ADEM) per 100 000 with standard error by age, sex, race/ethnicity, and hospital region

	2006-2008	2009-2011	2012-2014	Total	*P*-trend
Total	0.4 ± 0.05	0.5 ± 0.06	0.6 ± 0.02	0.5 ± 0.03	<.0001
Sex					
Male	0.4 ± 0.06	0.5 ± 0.07	0.5 ± 0.02	0.5 ± 0.03	<.0001
Female	0.4 ± 0.04	0.5 ± 0.05	0.6 ± 0.02	0.5 ± 0.02	<.0001
Age, y					
0-4	0.5 ± 0.07	0.7 ± 0.07	0.9 ± 0.04	0.7 ± 0.03	<.0001
5-9	0.5 ± 0.07	0.6 ± 0.08	0.6 ± 0.02	0.6 ± 0.03	<.0001
10-14	0.3 ± 0.06	0.5 ± 0.08	0.4 ± 0.01	0.4 ± 0.04	.009
15-18	0.2 ± 0.02	0.2 ± 0.04	0.3 ± 0.01	0.2 ± 0.01	<.0001
Race/Ethnicity					
White	0.2 ± 0.03	0.3 ± 0.04	0.3 ± 0.01	0.3 ± 0.02	.1
Black	0.2 ± 0.02	0.4 ± 0.05	0.5 ± 0.03	0.3 ± 0.02	<.0001
Hispanic	0.2 ± 0.04	0.4 ± 0.09	0.5 ± 0.02	0.4 ± 0.03	<.0001
Others	0.6 ± 0.12	0.5 ± 0.08	1.0 ± 0.06	0.7 ± 0.04	.002
Region					
Northeast	0.6 ± 0.15	0.4 ± 0.07	0.4 ± 0.03	0.5 ± 0.05	.002
Midwest	0.3 ± 0.10	0.6 ± 0.16	0.6 ± 0.04	0.5 ± 0.08	<.0001
South	0.4 ± 0.08	0.5 ± 0.08	0.6 ± 0.03	0.5 ± 0.03	<.0001
West	0.2 ± 0.06	0.6 ± 0.13	0.6 ± 0.05	0.5 ± 0.04	<.0001

the overall mortality rate for ADEM-associated hospitalizations in the pediatric population was 1.7%. In-hospital mortality increased from 1.1% in 2006-2008 to 1.5% in 2012-2014, but this trend was not statistically significant (P_{trend} = .07). LOS in hospital over the study period increased from 4.8 days to 5.5 days, but this also was not statistically significant (P_{trend} = .3). The median inflation-adjusted cost of care increased significantly over the study period by 40% from $11 594 to $16 193 ($P_{trend}$ = .002) per hospitalization.

Discussion

In this analysis using the NIS, a large nationally representative database of inpatient hospitalizations in the US, we have demonstrated upward trends in the incidence of ADEM-associated pediatric hospitalizations in the US from 2006 to 2014. Upward trends of incidence were seen across all age groups with peak incidence at age 2 years. Increased incidence also was seen in black and Hispanic children, and across all regions of the US except the Northeast. Seasonal variation was observed, with highest incidence in the spring and lowest incidence in the summer. Concurrent with the upward trends in ADEM incidence, the cost of hospitalization showed an upward trend, but mortality and median LOS remained unchanged during the study period. Our nationally representative study extends the breadth of currently existing literature on pediatric ADEM hospitalizations.

The overall incidence of ADEM in our study, 0.5 per 100 000 children/year, is comparable with the nationwide incidence of 0.4 in Japan[25] and 0.5 in Denmark[26] but higher than the incidences of 0.2 in Canada in children <18 years of age,[6] 0.007 in Germany in children <16 years of age,[1] and 0.32 in the Jiangsu Province of China.[27] Variations in the incidence of ADEM likely result from differences in the demographics of the populations studied, the study methodology, and the different criteria used for the diagnosis of ADEM. For example, a study conducted in 2004 in San Diego found a mean incidence of 0.4 per 100 000 children/year <20 years of age using acute neurologic abnormalities and imaging evidence of demyelination as inclusion criteria.[28] Banwell et al note in their study examining the incidence of demyelinating conditions in Canadian children that if the same ADEM diagnostic criteria used for the San Diego study had been applied to their study cohort, it would have yielded an incidence of 0.7 rather than 0.2 per 100 000 children/year.[6] The study by Leake et al showed that compared with 1991-1997, overall incidence of ADEM in San Diego more than quadrupled during 1998-2000.[28]

The present study also demonstrated upward trends in the overall incidence of ADEM-associated pediatric hospitalizations in the US during the study period (0.4 per 100 000 children/year in 2006-2008 to 0.6 per 100 000 children/year in 2012-2014). The reason for this upward trend in

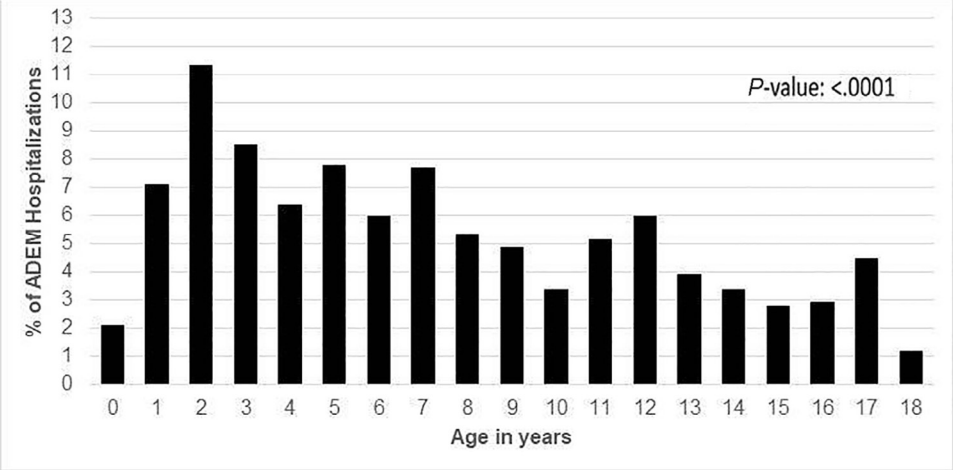

Figure 1. Proportion of ADEM hospitalizations by age.

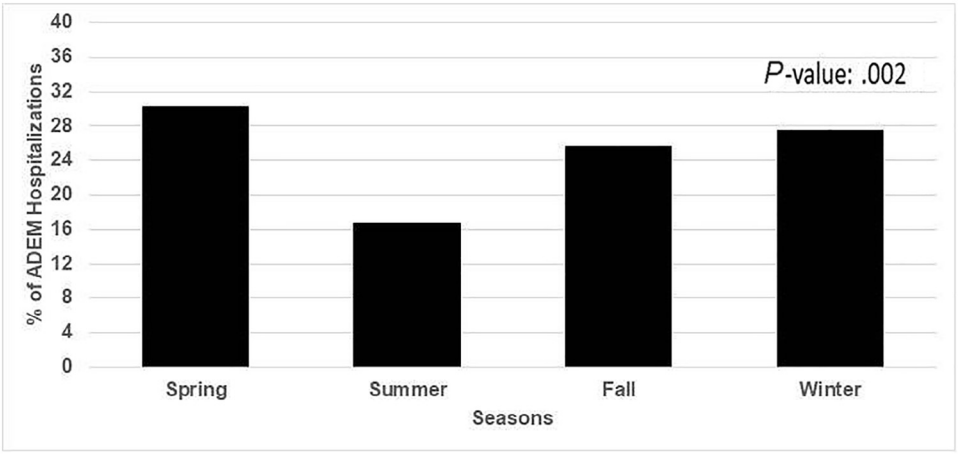

Figure 2. Proportion of ADEM hospitalizations by season.

incidence is not clear based on the previously published studies, but it could be related to the publication of clear diagnostic definitions published in 2007[29] and revised later in 2013,[30] as well as increased availability of imaging modalities such as magnetic resonance imaging (MRI). In addition, the availability of MRI with higher strength magnets since the year 2000 may have allowed for the increased identification of demyelination.[31] In spite of these plausible reasons, it is uncertain whether the increase in ADEM incidence is real or representative of the natural cycle of the disorder.

Several epidemiologic studies have described the sex-specific and race-specific incidence rates of ADEM in the US. Previous studies have found no sex predominance in ADEM,[28,32,33] which is consistent with our findings, although some pediatric cohort studies described a male predominance.[1,34-36] We found a higher incidence of ADEM among the 0-4 year age group. This finding differs from other studies, which described mean age of presentation ranging from 5 to 8 years of age.[13,35,37] These studies were based in different geographic locations and time frames and, thus, population level differences could possibly explain differences in incidence of ADEM among different age groups. In addition, the incidence of upper respiratory tract infections is highest among children <5 years of age,[38-40] likely due to immunologic naivete. Several studies have also shown that >70% of ADEM cases are preceded by infections such as upper respiratory tract infections.[10,13,41] In addition, children suffering from other types of encephalitis also can mimic ADEM, making diagnosis difficult. These factors possibly could explain higher incidence of ADEM in <5 years of age in our study. Further studies are needed to assess the differences in incidence among different age groups.

Seasonal distribution of ADEM described in previous studies showed higher incidence in winter and spring with lowest incidence in summer.[6,28,34] Our findings were consistent with these studies. This seasonal variation may be explained by higher incidence of viral infections during the winter and spring months.[38,41,42] Racial/ethnic disparities in children's health and healthcare exist,[39] and we are not aware of any previous studies that specifically examined race as a variable in the incidence of ADEM. Black and Hispanic children and other races had a higher incidence of ADEM-associated hospitalizations compared with white children in the present study. There were also upward trends in the incidence of ADEM-associated hospitalizations in children of non-white race over the study period. Because ADEM is a postinfectious autoimmune disease, this finding compatible with the increased rate of hospitalization for viral infections in black and Hispanic children.[40] Interestingly, a study performed in Southern California between 2004 and 2009 found that the incidence of acquired pediatric demyelinating syndromes of the central nervous system in a multi-ethnic cohort was higher in black children and those of the Pacific Island ancestry compared with white children. This suggests that apart from environmental factors such as infections, there could be genetic predisposition to ADEM.[43]

Our study provides insight into resource utilization for children with ADEM. The overall median LOS was 5.2 days, and there were no significant trends during the study period. The median LOS of 5.2 days (IQR, 3.3-8.1) is comparable with the 6 days reported by a previous study from New York[34] and 8 days from California[28]; most patients in these 3 studies were treated with corticosteroids. Khurana et al reported LOS of 30 days in a case series of 13 patients[44] of which 6 patients showed poor response to corticosteroids and intravenous immunoglobin therapy and subsequently underwent plasmapheresis. Thus, difference in severity and aggressiveness of ADEM and treatments may account for the varying LOS among studies. The median inflation-adjusted cost of care increased significantly over the study period by 40% from 2006-2008 to 2012-2014. The reason for this increase is unclear but may be related to variations in management and use of intensive care facilities for the care of children with ADEM.[9] Development of clinical pathways and protocols are worthy of study to determine standardization of care and reduction in hospital cost.

Overall, previous reports suggest that pediatric ADEM carries a long-term favorable prognosis with complete recovery in most

patients.[1,2,34] However, in-hospital mortality rates of 1%-3% have been reported recently.[9-12] In the present study, overall in-hospital mortality in the US was 1.7%, which is comparable with the rate of 1.4% reported by Press et al in a retrospective cohort study of children aged >30 days to 18 years hospitalized with a diagnosis of ADEM in the Pediatric Health Information System, a national administrative and billing database from 48 tertiary children's hospitals in the US.[9] There were no trends in the in-hospital mortality in spite of the upward trends in the incidence of pediatric ADEM hospitalizations. This could be attributed to the finding that >90% of the hospitalizations were in urban teaching hospitals. These teaching hospitals are more likely to have pediatric neurologists,[45] pediatric critical care resources,[46] and ready access to pediatric MRI for prompt diagnosis and management of ADEM.

The current study has limitations. Large databases such as the NIS are susceptible to coding errors, omissions, and duplications. However, the HCUP has instituted mechanisms to ensure the validity of the data in NIS.[47] In addition, ADEM is a major discharge diagnosis and more likely to be coded correctly because this it is related to reimbursement. The NIS database has no data on clinical factors such as preceding illnesses, vaccinations prior to onset of ADEM, lumbar puncture results, MRI brain results, and other diagnostic tests. Cases were not subjected to diagnostic criteria. The data used in our study were discharge diagnoses rather than for individual patients. Exclusion of patients transferred to rehabilitation and other facilities could have led to missing cases of ADEM. We cannot analyze readmissions, and data on some patients may be represented more than once for any given year. The NIS database does not include follow-up information, so we were unable to study the long-term outcomes of ADEM-associated hospitalizations. Often demyelinating disorders have overlapping presentations; other studies cite ADEM cases that are later classified as multiple sclerosis cases, and this may have occurred in our study sample as well. Such cases coded as ADEM could not be confirmed, due to the nature of the NIS database.

The NIS database is uniquely equipped to capture ADEM cases across the country. This is because part of the clinical manifestations of ADEM is encephalopathy, patients usually are treated on an inpatient basis and because the NIS is the largest inpatient care database in the US, it is likely to include the vast majority of ADEM cases in the US. Thus, our findings are nationally representative. Further studies are needed to better delineate the etiologies for rising incidence, hospital cost and seasonal variation of ADEM in children. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table III. ADEM in hospital outcomes

	ADEM in-hospital outcomes				
	2006-2008	2009-2011	2012-2014	Total	*P* value
In hospital mortality (%)	1.1	2.4	1.5	1.7	.07
Median cost of care ($)	11 594	13 904	16 193	13 944	.002
(IQR)	(7649-18 968)	(7894-23 756)	(9670-29 007)	(8169-24 628)	
Median LOS (d)	4.8	5.1	5.5	5.2	.3
(IQR)	(3.0-7.8)	(3.5-8.0)	(3.4-8.4)	(3.3-8.1)	