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Original Article

Incidence of acute disseminated encephalomyelitis in the Jiangsu province of China, 2008–2011

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Abstract

Background: It is important to have an estimate of the incidence of acute disseminated encephalomyelitis (ADEM) because the incidence of ADEM is unknown and the outcomes undefined in China.

Objectives: This study attempts to describe ADEM incidence in large Chinese populations located in four geographically different and moderately distant areas of the same province.

Methods: A retrospective investigation was conducted with ADEM patients in Nanjing, Nantong, Yancheng and Xuzhou. The survey was carried out in regions that might have received patients meeting the case definition of ADEM provided by the International Pediatric MS Study Group from 2008 to 2011. A total of 125 hospitals were included and 412 patients were identified through the hospital information systems (HIS).

Results: The incidence of ADEM was 0.32/100,000/year. There are two peaks on the age-specific ADEM rates curve. One is 0.77/100,000/year among 0- to 9-year-olds, the other is 0.45/100,000/year in those aged 50–59 years. The incidence rate found for ADEM in males was 0.34/100,000/year, and in females was 0.29/100,000/year. The highest incidence rate was in Nanjing (0.40/100,000/year).

Conclusions: The average annual incidence of ADEM was 0.32/100,000/year. The peak age of onset was 50–59 years old and 0–9 years old. The incidence among males was insignificantly higher than that among females. There was no significant difference in incidence by seasonal variation.

Keywords: Epidemiology, acute disseminated encephalomyelitis, incidence, China

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Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated central nervous system (CNS) disorder.[1] It is characterized by an acute encephalopathy with polyfocal neurological deficits. In the absence of specific biological markers the diagnosis of ADEM is still based on clinical features and magnetic resonance imaging (MRI) evidence of widespread demyelination, after ruling out other possible explanations for an acute encephalopathy.[2] In 2007 the International Pediatric Multiple Sclerosis (MS) Study Group proposed a consensus definition for ADEM for application in research and clinical settings.[3] The pathogenesis of ADEM is not fully known, but adhesion molecules, chemokines, matrix metalloproteinase, and other cell factors can play important roles in its occurrence and development.[4]

Formerly, ADEM occurred particularly often in children with measles. However, the disease most often follows a nondescript viral or even bacterial infectious illness. Many identifiable infections have been associated with ADEM, such as measles, mumps, rubella, coxsackie, coronavirus, herpes, influenza A and B, hepatitis A and B, human T-lymphotropic virus-1, human immunodeficiency virus, dengue virus, or smallpox.[5] In addition to a known association with infections, vaccinations (e.g. rabies, smallpox or measles vaccines) have also been suggested to increase the risk of ADEM.[6] There have been many recent studies showing no long-term association between vaccinations and ADEM.[7]

In recent years, the Expanded Program on Immunization (EPI) has been carried out in China. The type and number of vaccines administered to residents were expanded. The probability of having an abnormal reaction such as ADEM to vaccines is small, but the occurrences of such reactions increased

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Table 1. Age-, sex- and place-related variations in ADEM incidence.

Variable	Number of cases	Population	Incidence × 100,000	Relative risk (RR)	
				Point	95% CI
Sex					
Males	225	66,124,494	0.34	1.14	0.93–1.40
Females	187	64,095,329	0.29	1.00	–
Age groups					
0–9 years	87	11,328,184	0.77	3.94	1.44–10.77
10–19 years	52	17,034,024	0.31	2.29	0.83–6.36
20–29 years	52	20,863,214	0.25	1.91	0.69–5.28
30–39 years	33	21,385,242	0.16	1.19	0.42–3.36
40–49 years	29	19,815,233	0.15	1.86	0.64–5.39
50–59 years	75	16,713,559	0.45	2.90	1.06–7.92
60–69 years	55	12,584,837	0.43	2.80	1.00–7.84
70–79 years	25	7,068,874	0.36	2.61	0.90–7.59
>80 years	4	3,426,655	0.12	1.00	–
Population					
Nanjing	117	29,116,289	0.40	1.49	1.12–2.00
Nantong	104	30,610,147	0.34	1.16	0.86–1.57
Yancheng	81	32,288,440	0.25	0.82	0.60–1.14
Xuzhou	109	38,204,947	0.29	1.00	–

Deviance = 118.22; degrees of freedom = 59. ADEM: acute disseminated encephalomyelitis; CI: confidence interval; RR: risk ratio.

after the EPI, causing widespread public concern. This may reduce public confidence in vaccines. When evaluating the risk of vaccines leading to ADEM or when judging whether ADEM has a causal association with vaccination, epidemiological features and population-level baseline incidence rates, in addition to clinical characteristics and disease diagnosis, must be assessed. A firm measure of the incidence of ADEM is increasingly important.

ADEM is an uncommon illness and hence epidemiologic studies are complicated by small case series from limited centers. Worldwide distribution of ADEM is still unknown.[5] This study attempts to describe ADEM incidence in a selection of large Chinese populations located in four geographically different and moderately distant areas of the same province.

Materials and methods

Medical and pediatric services

In China, most people receive medical technology and specialized neurological care provided by public hospitals. In general, patients who are suspected of having ADEM are taken to the hospital as emergencies, and soon after, a neurologist will be invited to take care of them. Patients younger than 16 years old who are affected by neurological diseases are usually taken to pediatric hospitals.

Study population

ADEM cases were selected from January 1, 2008 to December 31, 2011. The surveyed areas were Nanjing, Nantong, Yancheng and Xuzhou, which are four cities in Jiangsu province in China. Both urban and rural populations were involved in each city. Gender-specific and age-specific population numbers from 2008 to 2011 were from the local Bureau of Statistics. The population denominator ruled out the migratory labor population, which does not officially reside in these cities. The populations involved in this research and the geographical locations of the four cities are shown in Table 1 and Figure 1.

Case selection

Cases from all hospitals that may have admitted ADEM patients were searched and reviewed through the hospital information systems (HIS). Cases were identified by the 10th revision of the International Classification of Diseases (ICD-10) diagnostic

Figure 1. Geographical location of Jiangsu province in China (1 = Jiangsu) and the study areas in Jiangsu. (2 = Xuzhou; 3 = Yancheng; 4 = Nanjing; 5 = Nantong.).

codes (G04.001, G04.002, G04.051, G04.903, G04.912). In these hospitals, any departments that might have received patients meeting the case definition were involved, including neurology, pediatrics, internal medicine, and inpatient wards. Relevant information was extracted from HIS.

ADEM cases were confirmed by neurologists from clinical data, such as clinical manifestations, electroencephalograph (EEG), computed tomography (CT), MRI, and cerebrospinal fluid (CSF) examinations. The consensus definitions of ADEM that were proposed by the International Pediatric MS Study Group were used: A first clinical event with a presumed inflammatory or demyelinating cause, with acute or subacute onset that affects multifocal areas of the CNS. The clinical presentation must be polysymptomatic and must include encephalopathy. Event should be followed by improvement, either clinically, on MRI, or both, but there may be residual deficits. No history of a clinical episode with features of a prior demyelinating event. No other etiologies can explain the event. New or fluctuating symptoms, signs, or MRI findings occurring within three months of the inciting ADEM event are considered part of the acute event. Neuroimaging shows focal or multifocal lesion(s), predominantly involving white matter, without radiologic evidence of previous destructive white matter changes.[8]

Some of the cases were from foreign cities. They were excluded from the numerator because these cases would affect the accuracy of local incidence assessment. The Poisson model was used to calculate the point values and 95% confidence intervals (CIs) of the rate ratio (RR) for sex, age and place. The research protocol was approved by the institutional review board of the Jiangsu Provincial Center for Disease Control and Prevention (JSCDC). All analyses were conducted in 2012.

Results

In all, 125 hospitals and 4,652,355 records in the four cities were surveyed. From these records, 471 ADEM cases were found in the study population. Among these 471 cases, 59 cases were ruled out owing to residence outside of the geographical areas of study. A total of 412 cases were involved in the incidence calculation. The incidence was 0.32 cases per 100,000 person-years.

Variation with age

Age- and sex-specific incidences of ADEM are shown in Figure 2, and the corresponding age-specific RRs, controlling for the effect of sex and location, are shown in Table 1. For both sexes, there are two peaks on the age-specific ADEM rates curve. One is 0.77/100,000/year among children (0–9 years), the other is 0.45/100,000/year in 50–59-year-olds. There are lower incidences in adults (40–49 years) and the highest age group of ≥80 years. One is 0.15/100,000/year, the other is 0.12/100,000/year. For females, there is a higher incidence in the age group of 20–29 years than that of 10–19 years.

Sex variation

The incidence rate found for ADEM in males was 0.34/100,000/year, which is higher than that in females (0.29/100,000/year) (Table 1). The sex differential did not prove to be statistically significant. There is a sharper age-specific incidence curve in males than in females (Figure 2).

Geographical variation

The variations in incidence by location, adjusted for age and sex, were 1.60-fold. The incidence rate in Nanjing was 0.40/100,000/year, with the highest RR (1.40, 95% CI 1.04–1.89). Yancheng was 0.25/100,000/year, with the lowest RR (0.84, 95% CI 0.60–1.17). The incidence difference for females, which was 2.1-fold, was more notable (Figure 3).

Seasonal variation

New cases of ADEM occurred in each month throughout the whole year. The highest risk of acquiring ADEM for males was in February and, for females, was in April and November (Figure 4(a)). The highest incidences were seen for young populations (under 40 years) in March and older populations in April (Figure 4(b)). There was no significant difference in incidence by seasonal variation.

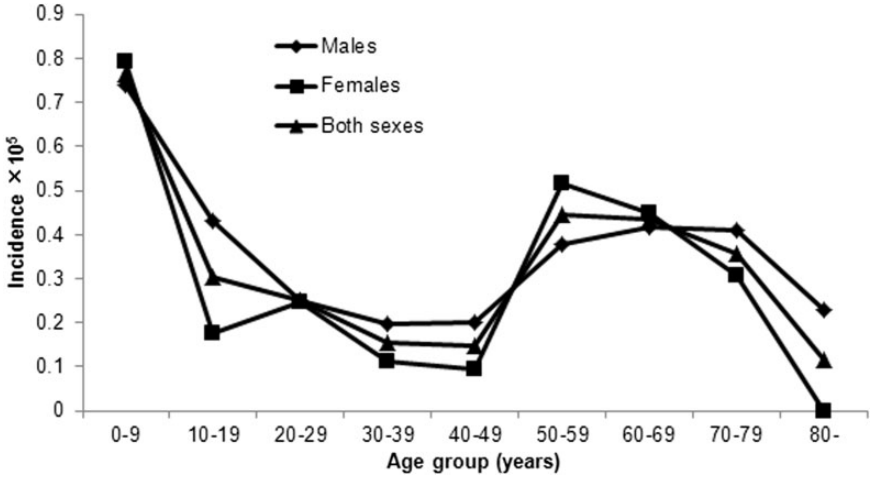

Figure 2. Age- and sex-specific acute disseminated encephalomyelitis (ADEM) incidence between 2008 and 2011.

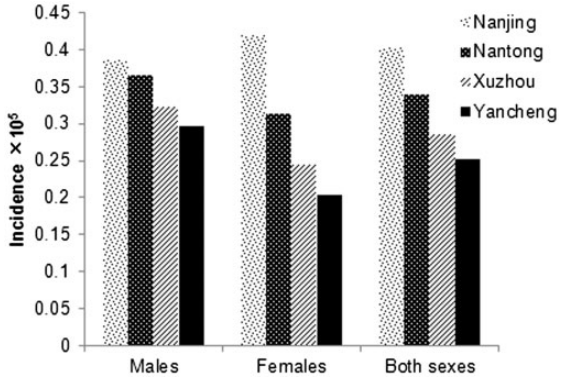

Figure 3. Sex-specific acute disseminated encephalomyelitis (ADEM) incidence in Nanjing, Nantong, Xuzhou and Yancheng, China.

Discussion

This study was the first large-scale investigation of ADEM incidence in Jiangsu province in China, and it could help us to understand the baseline ADEM incidence in Jiangsu. This study found that incidence rates in four cities within Jiangsu province were 0.32/100,000/year, which is much higher than that in Germans between 1997 and 1999 (0.07/100,000/year),[9] lower than that in San Diego County (California, USA) among people <20 years between 1991 and 2000 (0.4/100,000/year),[10] lower than that in Thailand between 1997 and 2006 (4.1/100,000/year),[11] lower than that reported by Noorbakhsh et al. (0.4/100,000/year–0.8/100,000/year)[12] and similar to that in Nanchang (China).[13] These results may indicate that the differences in the incidence of ADEM among countries could be in favor of environmental factors, race factors or climate factors triggering the disease. Some of the variation in incidence is due to the different definitions of ADEM that were used in all of the studies and the different types of cases that were captured.

Reportedly, ADEM can occur at any age, with higher frequency in children than adults. Predominant age of occurrence in children is 5–8 years,[6,14–17] or mainly in children and young people.[18] Pohl et al. reported that the incidence rate of ADEM was 0.09/100,000/year among children less than 10 years old and 0.03/100,000/year among children 10–15 years old in Germany.[9] In Canada, children with ADEM were more likely to be younger than 10 years.[19] Previous studies on ADEM have focused on children but rarely on adults. Our study found that the highest incidence rate was among individuals 0–9 years old (0.77/100,000/year), and the incidence decreased with the increase of age among people less than 50 years old. But the incidence increased among people 50–59 years old (0.45/100,000/year), followed by individuals 60–69 years old (0.43/100,000/year). Senile ADEM, which attracts much of our attention, has rarely been reported.[20] It is probably due to: (1) differences between the elderly and young people in susceptibility or immune response to infectious agents, and (2) lack of sensitive tools to examine patients before the widespread use of MRI.[21]

Some studies have reported no gender predominance in children.[10,13,22] Pohl et al. reported that the female-to-male ratio was balanced up to the age of

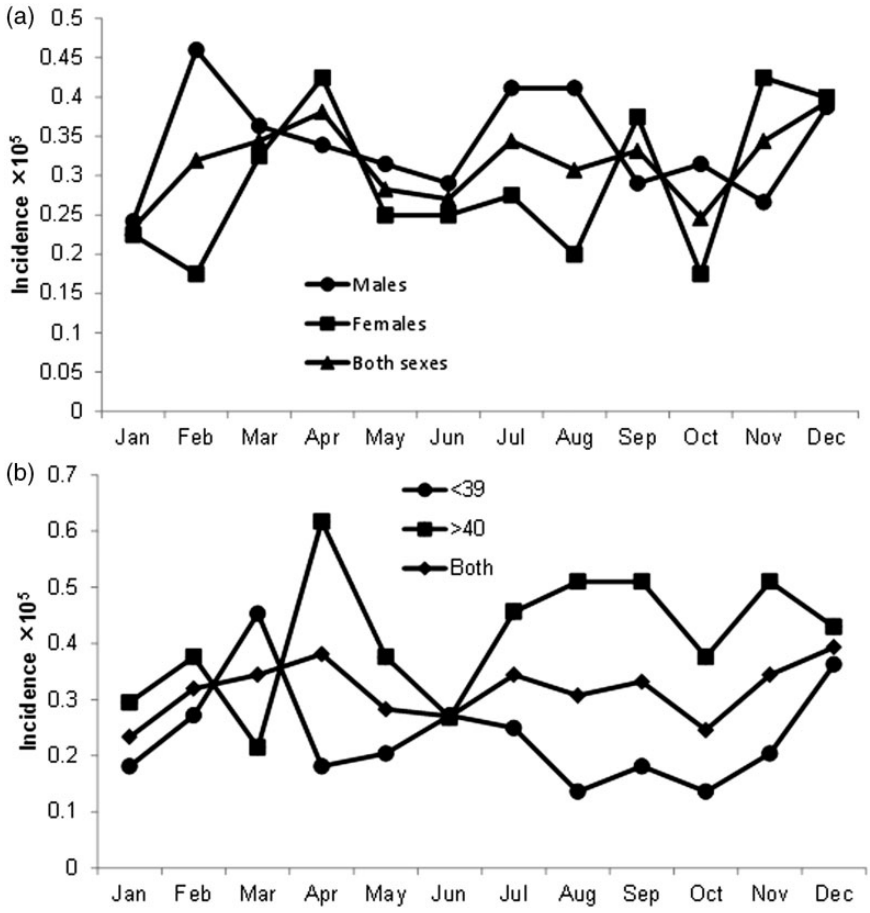

Figure 4. (a) Monthly distribution of sex-specific acute disseminated encephalomyelitis (ADEM) incidence. (b) Monthly distribution of ADEM incidence of individuals aged less than 39 years and older than 40 years.

13 years, and more than twice as many girls than boys were reported in the 14- to 15-year-old group of children in Germany.[9] Our study found that males had an insignificantly higher risk of ADEM; the male/female ratio was 1.17. This frequency distribution has also been observed by others.[15,23] A male-to-female incidence ratio that changes with advanced age may suggest differential referral, detection, or access to a neurologist. Generally, older women and men with neural disorders may be differentially referred from their households or homes to hospitals.

When comparing geographical variations of the incidence of ADEM in Jiangsu, we found that the incidences from the highest to the lowest were in Nanjing, Nantong, Xuzhou and Yancheng. Such a result may be related to the level of social and economic development. Concerning the level of social and economic development, Nanjing has the highest level of social and economic development, followed by Nantong and Xuzhou, and Yancheng has the lowest level. In richer areas, there is more access to health care, more doctors, more neurologists, more beds, better medical conditions, better medical equipment and perhaps a lower rate of misdiagnosis.

An absence of seasonal variation in ADEM incidence was also found in Nanchang,[13] another city in central China. This conclusion is different from San Diego,[10] Buffalo (New York, USA)[23] and the United Kingdom,[22] where ADEM occurs more frequently in the spring and in the winter. ADEM is thought to be triggered by a nonspecific preceding infection in more than 70% of cases.[14,22,23] A number of infectious agents, such as influenza, rubella, measles, mumps, herpes, varicella, simplex virus, Epstein-Barr virus (EBV), hepatitis viruses, coxsackieviruses, legionella, mycoplasma, Campylobacter, streptococcus, and rickettsia, have been implicated in ADEM.[23] The lack of obvious seasonal variation in incidence may be

because the infections found most frequently to trigger this disease occur in different seasons around the globe.

The concern that vaccinations could induce a small increased risk of ADEM remains controversial. A recent nested case-control study showed no longer-term association of vaccines with ADEM. The short-term increase in risk intimates that vaccines may accelerate the transition from subclinical to overt autoimmunity in cases with existing disease.[7] The relationship is not reviewed in current series. It would be pleasing if a cohort study on the association between vaccines and ADEM were carried out.

Our study has several limitations. Some cases may have not been to the hospital or have been admitted to hospitals in regions outside of the surveyed areas and, as a result, the incidence would have been underestimated. The incidence rates found by retrospective studies produced slightly lower incidence rates than prospective studies. This may also contribute to an underestimate of the incidence. The duration of this survey was too short to discover long-term trends in the incidence of ADEM.

Our findings provide a rough estimate of baseline AEDM incidence in four large populations in parts of Jiangsu province in China and provide useful information for potential epidemiological surveillance of ADEM, which will be carried out in the near future. Our findings also provide information for further studies assessing the effects of potential risk factors, such as immunizations or infections. It would be satisfactory if future investigators carry out studies for a longer period of time to ensure the discovery of a long-term trend in the incidence rate of ADEM.

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Conflict of interest

None declared.

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