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Vaccination-associated acute disseminated encephalomyelitis

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ABSTRACT

While the basic definition of vaccination-associated acute disseminated encephalomyelitis (ADEM) is relatively clear and easily understandable, it is often difficult to diagnose ADEM based on clinical findings alone. ADEM is actually a heterogeneous clinical syndrome that can be approximately characterized by encephalomyelitis with multiple inflammatory demyelination, autoimmune causes, and relationship with a preceding infection or vaccination. The differential diagnosis of ADEM should exclude the possibility of infectious or other autoimmune encephalitis. The occurrence of vaccination-associated ADEM is influenced by several factors including the health and ethnic status of the vaccinated individual, vaccine components, and environment. Cases suspected of vaccination-associated ADEM should be analyzed cautiously from multi-disciplinary perspectives.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a monophasic demyelinating encephalomyelitis that is presumably caused by an autoreactive immune response in the central nervous system (CNS). ADEM is considered to be associated with antecedent infection and vaccination. Vaccination-associated ADEM is rare and accounts for less than 5% of total ADEM [1–4]. Cases of paralysis associated with vaccination were initially reported following the realization of Jenner's vaccination for smallpox. Thereafter, the first case of paralysis related to Pasteur's vaccine for rabies was reported in 1888 [5]. Since then, numerous cases of vaccination-associated ADEM have been reported, including ADEM-like phenomena after vaccination for preventing specific diseases such as Alzheimer's disease [6].

2. How is ADEM clinically diagnosed?

The basic definition of ADEM includes (1) encephalomyelitis with multiple inflammatory demyelination (2) caused by an autoimmune response (3) that develops in the period following infection or vaccination. This definition is well supported by the widely-used animal model, experimental autoimmune encephalomyelitis [7]. Yet, ADEM can be difficult to diagnose based on clinical findings. At present, there are 2 main sets of clinical criteria for ADEM: the criteria for vaccination-associated ADEM proposed by the Brighton Collaboration Encephalitis Working Group and criteria for pediatric ADEM proposed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG).

2.1. Brighton Collaboration Encephalitis Working Group case definition

The Brighton Collaboration Encephalitis Working Group proposed a case definition of ADEM with 3 levels of certainty [8]. ADEM level 1 includes a pathological diagnosis or fulfillment of the following 3 conditions: presentation with focal or multifocal signs and symptoms related to CNS lesions, characteristic magnetic resonance imaging (MRI) abnormalities, and a monophasic course. ADEM level 2 is defined as fulfillment of the following 2 conditions: presentation with focal or multifocal signs and symptoms related to CNS lesions and characteristic abnormalities on MRI. ADEM level 3 is defined as presentation with focal or multifocal signs and symptoms related to CNS lesions. As per these definitions, a case should not be classified as ADEM in the presence of apparent infection, inconsistent MRI or pathological findings, or relapse within 3 months. Many cases of vaccination-associated ADEM have been classified and analyzed using this definition [9].

2.2. IPMSSG definition

In 2007, the IPMSSG proposed a definition of pediatric ADEM for the purpose of diagnosing MS early after the first demyelinating

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; IPMSSG, International Pediatric Multiple Sclerosis Study Group; MRI, magnetic resonance imaging.

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event. These criteria define pediatric ADEM as the first acute or subacute clinical event with multifocal lesions in the CNS presumably caused by inflammation or demyelination [10]. Additionally, children with ADEM are polysymptomatic and present with encephalopathy; alterations in behavior and consciousness. Clinical changes within 3 months after onset constitute a single episode. The IPMSSG revised its definition of pediatric ADEM in 2012 to include typical abnormalities on MRI in the acute phase without the appearance of new symptoms or MRI abnormalities after 3 months of the incident ADEM [11].

3. The diagnosis of ADEM based on clinical findings

While the ADEM criteria are readily applied to patients with suspected ADEM, it is often difficult to definitively diagnose ADEM based on clinical findings alone because of its similarity to infectious and other autoimmune encephalitis. The following is an example of clinical presentation of mistaken cases of ADEM.

Case presentation

A 10-year-old boy presented with high fever and headache for 3 days and was admitted to the hospital. The next day, he showed mild conscious disturbance. Laboratory studies revealed pleocytosis in the cerebrospinal fluid and MRI showed multiple lesions in the bilateral thalami and left frontal lobe (Fig. 1). The patient was diagnosed with ADEM tentatively and treated with high-dose methyl-prednisolone. However, the therapeutic effect was insufficient. Hence, we tested specific antibodies for Japanese encephalitis virus despite very low incidence of Japanese encephalitis in Japan because the patient was found not to have received the vaccine. Later, the patient was re-diagnosed with Japanese encephalitis based on elevations in specific antibodies for Japanese encephalitis.

In the above case, encephalitis with multiple lesions led to an initial misdiagnosis of ADEM; however, it was difficult to exclude infectious encephalitis by routine blood or CSF routine examination or MRI in the early stage.

Several factors can complicate the diagnosis of ADEM. First, most patients with suspected ADEM do not undergo a brain biopsy, precluding the possibility of pathological confirmation. Instead, inflammatory demyelination is identified with a combination of MRI and laboratory findings. Yet, it is often difficult to distinguish demyelinating lesions from structural deficits, ischemia, edema, or other inflammation on MRI. Second, it is difficult to determine whether inflammatory demyelination is caused by an autoimmune response or an immune response to infectious agents. Both of the diagnostic criteria for ADEM require the exclusion of infectious disease as a possible diagnosis. Infectious diseases must be deliberately excluded by examination of specific antigens, DNA or RNA, and antibodies. Third, it is difficult to draw an association between antecedent infection or vaccination and encephalomyelitis based on the temporal relationship between ADEM onset and prior infection or vaccination. Most previous studies of ADEM investigated previous events within 1 month of onset; however, there is no consensus on the acceptable duration between an antecedent event and ADEM onset. Finally, it is not possible to know whether a present demyelinating event is monophasic or multiphasic.

It is necessary to keep in mind that ADEM is a heterogeneous clinical syndrome that can be approximately characterized by encephalomyelitis with multiple inflammatory demyelination, autoimmune causes, and relationship with a preceding infection or vaccination. A critical obstacle to the accurate diagnosis of ADEM is a lack of ADEM-specific laboratory and neuroimaging markers.

4. Epidemiology of ADEM

The reported annual incidence of pediatric ADEM is 0.07–0.64/100,000 children (Table 1) [1–4,12–17]. The variability in this reported incidence is partially attributed to the difficulty of accurately diagnosing ADEM as mentioned above, but it suggests that pediatric ADEM is influenced by geographic, ethnic, and/or genetic factors. Population-based studies of patients with ADEM in Asian countries have indicated a relatively high incidence of pediatric ADEM. A nationwide survey in Japan reported that the annual incidence of pediatric ADEM was 0.40/100,000 [16], and multicenter studies in Fukuoka, Japan and Nanchang, China demonstrated incidences of 0.64/100,000 [15] and 0.47/100,000 [4], respectively. Population-based studies performed in the United States have showed similar or slightly lower incidences of pediatric ADEM (0.40/100,000 in San Diego [2] and 0.30/100,000 in Southern California [13]). In contrast, other studies have reported lower annual incidence of pediatric ADEM: 0.20/100,000 in Canada [1],

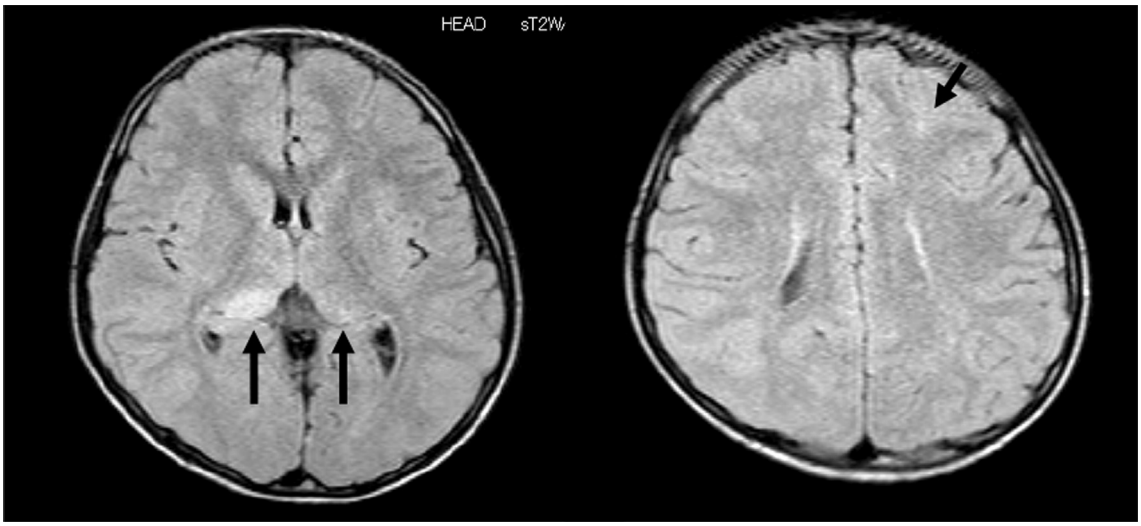

Fig. 1. Magnetic resonance imaging findings for the presented case. A fluid-attenuated inverse recovery image showing asymmetrical bilateral lesions of thalami and single small lesion in the juxtacortical white matter of the left frontal lobe (arrows).

Table 1
Overview of epidemiolgic features of ADEM from population- based studies.

Studies for ADEM	Country	Surveillance style				Estimated annual incidence of ADEM, (/ 100,000 children)	Demographic features of ADEM children for survey				
		Region	Period	Diagnostic criteria	Age group		Number	Male gender, %	Mean age at onset, years	Antecedent infection, %	Antecedent vaccination, %
Torisu H et al. [15]	Japan	Fukuoka prefecture	1998–2003	Others	Under 16	0.64	26	69	5.7	73	15
Yamamaguchi Y et al. [16]	Japan	Nationwide	2005–2007	2007 IPMSSG	Under 16	0.40	66	67	5.5	62	18
Leake JA et al. [2]	USA	San Diego county	1991–2000	Others	Under 20	0.40	42	57	6.5	93 within 21 days	5
Xong C et al. [4]	China	Nanching	2008–2010	2007 IPMSSG	All age	0.31	47	51	33.4	32 within 2 months	0
Absoud M et al. [14]	UK	Nationwide	2009–2010	2007 IPMSSG	Under 16	0.31	40	60	5.3	ND	ND
Langer-Gould A et al. [13]	USA	Southern California	2004–2009	Others	Under 19	0.30	15	47	5.6	ND	ND
Banwell B et al. [1]	Canada	Nationwide	2004–2007	2007 IPMSSG	Under 18	0.20	49	56	7.7	ND	4 in all ADS
Ketelslegers IA et al. [3]	Netherland	Nationwide	2007–2010	Others	Under 18	0.16[#]	21	48	3.9	48	5
Gudbjornsson BT et al. [17]	Iceland	Nationwide	1990–2009	2007 IPMSSG	Under 18	0.13	2	50	3–5 and 15–17 years	ND	ND
Pohl D et al. [12]	Germany	Nationwide	1997–1999	Others	Under 18	0.07	28	57	6.6	ND	ND

ND: not described, IPMSSG: International pediatric multiple sclerosis study group, ADS: acquired demyelinating syndrome.
[#] : Polysymptomatic acquired demyelinating syndrome with encephalopathy.

0.16/100,000 in the Netherlands [3], 0.16/100,000 in Iceland [17], and 0.07/100,000 in Germany [12].

Whereas most previous studies of pediatric ADEM including a study in China have indicated little-to-no sex preference, studies in Japan have demonstrated high male predilection for ADEM of almost 70% (Table 1) [16].

The age range of onset for pediatric ADEM extends from infancy to adolescence, with the most frequent age of onset around 5–7 years in most countries (Table 1) [1–4,12–17]. This finding suggests that ADEM tends to develop at an age when children are still acquiring sufficient immunity against common infections.

5. Factors influencing vaccination-associated ADEM

At present, vaccines are assumed to cause ADEM at a rate of almost 1–2 cases per 1 million vaccinations. Vaccination-associated ADEM can potentially occur as the result of an immune response to vaccine components, and this response can be influenced by the target infectious agents of the vaccine, individual immune response characteristics of the vaccinated person, the type and the amount of chemical adjuvant used in the vaccine, and other factors. Vaccination-associated ADEM is not thought to be caused by contaminating animal neural components in vaccine products, although early cases of ADEM were associated with the use of neural tissue in some vaccine components. According to the annual reports of adverse events associated with vaccination in Japan [18], the incidence of ADEM following Japanese encephalitis vaccination did not vary in accordance with the use of neural tissues in vaccine components (as opposed to vaccines produced using cell culture). Moreover, animal neural components have been largely eliminated from current vaccine formulations as a result of the popularization of *in vitro* methods.

The incidence of vaccination-associated ADEM does vary across different kinds of vaccines. Vaccines commonly associated with ADEM include measles, varicella zoster, rubella, small pox, and influenza. Post-marketing studies on vaccine adverse events from 1994 to 2004 in Japan revealed that ADEM developed at a rate of 7 cases per 67.2 million vaccinations: 0 cases per 3.64 million measles vaccinations, 1 case per 4.0 million rubella vaccinations, 1 case per 1.53 million mumps vaccinations, 2 cases per 9.45 million Japanese encephalitis virus vaccinations, 3 cases per 38.02 million influenza vaccinations, and 0 cases per 10.56 million diphtheria/pertussis/tetanus vaccinations [19].

Vaccination-associated ADEM also appears to be influenced by geographic, ethnic, and genetic factors. Previous studies found that up to 5% of children diagnosed with ADEM had received vaccination within 1 month of onset [1–4], whereas this percentage was as high as 15–18% in Japanese studies [15,16]. These studies did not highlight specific vaccines associated with ADEM: the Japanese studies reported ADEM associated with the influenza vaccine; combination vaccine for measles and rubella; combination vaccine for diphtheria, pertussis, and tetanus; poliovirus vaccine; rubella vaccine; Japanese encephalitis vaccine; and hepatitis B vaccine. Similarly, the Canadian nationwide study reported ADEM associated with the hepatitis B vaccine; influenza vaccine; measles, mumps, and rubella vaccine; human papillomavirus vaccine; pertussis vaccine; and combination vaccine for diphtheria, pertussis, and tetanus [1]. There were no definite differences in ADEM-associated vaccines between Japan and other countries.

The type of immunization program and individual differences likely influence vaccination-associated ADEM. A study of ADEM based on vaccine adverse event reporting systems in the United States and Europe (the EudraVigilance post-authorization module) analyzed 404 ADEM cases reported between 2005 and 2012 and revealed fluctuations in the number of vaccination-associated ADEM (most frequently associated with seasonal influenza and human papilloma virus vaccines) during the survey period [20]. Specifically, there was a decrease in the number of reported ADEM cases after 2010 related to a reduction in the number of reports associated with human papilloma virus, diphtheria, pertussis, tetanus, polio, and *Haemophillus* influentiae type B vaccines. Additionally, this study revealed that different vaccines were associated with ADEM across different age groups. In children <5 years of age, ADEM was most commonly associated with the measles, mumps, and rubella vaccine; pneumococcal conjugate vaccine;

diphtheria vaccine; pertussis vaccine; and tetanus vaccine. In contrast, ADEM was associated with vaccination against human papilloma virus in children and adolescents (6–17 years), and the seasonal influenza vaccine in adults.

6. Conclusion

While the basic definition of vaccination-associated ADEM are relatively clear and easily understandable, it is often difficult to diagnose ADEM based on clinical findings alone because of a lack of ADEM-specific laboratory and neuroimaging markers. The differential diagnosis of ADEM should exclude the possibility of infectious or other autoimmune encephalitis. The occurrence of vaccination-associated ADEM is influenced by several factors including the health and ethnic status of the vaccinated individual, vaccine components, and environment. Cases suspected of vaccination-associated ADEM should be analyzed cautiously from multi-disciplinary perspectives.

7. Declarations of interest

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