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Case Reports

Acute Disseminated Encephalomyelitis Following *Streptococcus Pneumoniae* Meningoencephalitis

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Abstract Acute disseminated encephalomyelitis (ADEM) is an autoimmune demyelinating disease of the central nervous system. We report a 4-year-old girl who suffered from acute meningoencephalitis caused by *Streptococcus pneumoniae* (*S. pneumoniae*). After 8 days of treatment by sensitive antibiotics, the cerebrospinal fluid (CSF) cell count, blood count and the serum level of C-reactive protein recovered quickly, while the level of CSF protein was still high, with continuous coma and fever. Magnetic resonance imaging indicated multifocal changes in the brain parenchyma, mainly in white matter, with bithalamic involvement. The CSF IgG index increased, oligoclonal bands were positive. After high-dose intravenous methylprednisolone and intravenous immunoglobulin were given, the patient came around, with normal CSF results and body temperature. Within a few months the patient recovered completely and there were no relapses during nearly 3 years of follow-up. To our knowledge, this may be the first report of ADEM following *S. pneumoniae* meningoencephalitis in children.

Key words Acute disseminated encephalomyelitis (ADEM); *Streptococcus pneumoniae*

Introduction

Acute disseminated encephalomyelitis (ADEM) is an autoimmune disease characterised by an inflammatory reaction and demyelination in the central nervous system (CNS) that usually develops following acute viral infection, vaccination or organ transplantation.[1-3] It may also occur after bacterial infection, such as Legionella, Campylobacter, *Borrelia burgdorferi, Rickettsia rickettsii, Leptospira, Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.[1,3] There were 3 cases of adult ADEM following *Streptococcus pneumoniae* (*S. pneumoniae*) meningoencephalitis reported.[4-6] *S. pneumoniae* is the main pathogens of bacterial pneumonia and meningitis in children. To our knowledge, there was no report of ADEM following *S. pneumoniae* infection confirmed in children. We report on a patient diagnosed as ADEM following *S. pneumoniae* meningoencephalitis.

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Case Report

A 4-year-old girl with cough, fever, partial seizures and coma was admitted to the Children's Hospital, Zhejiang University School of Medicine on 7th May 2009. One week before admission, she suffered from cough, without fever and seizures. Three days later, she has a fever, the body temperature ranged from 38 to 39 centi-degree. Meanwhile, the cough increased, accompanied with headache and vomit. Two days before admission, intermittent clonic jerks of the left limbs presented, duration of the seizures was 5 to 6 minutes. At first, the consciousness between two seizures was normal, one day before admission, she was in a coma. Four days before, she was treated with ceftriaxone mannitol and diazepam in local hospital, but she was

transferred to our hospital due to aggravation. The neurodevelopmental outcome before the event was normal. She had no fever and rash for two months, and she had not been vaccinated for one year. She had never received pneumococcal vaccine. Brain computer tomography (CT) of the local hospital showed no obvious lesions.

On admission, the patient was in a coma and high fever, meningeal irritation signs and bilateral Babinski signs were all positive, with hypertonia and intermittent partial seizure. The diameter of the pupils was 3-4 mm, with slow light reflex. Mechanical ventilation was used due to severe respiratory distress. Meropenem and Linezolid were administered, mannitol, dexamethasone (0.4 mg/kg for 3 days) and carbamazepine were also given. After admission, blood count showed leucocyte 9.4 x 10^9/L, neutrophilic 92.4%, and the serum level of C-reactive protein (CRP) was more than 160 mg/L. Chest X-ray showed pneumonia of the right upper lung. Lumbar puncture was performed (Table 1). Meropenem was changed to ceftriaxone according to the cerebrospinal fluid (CSF) smear results next day. Two days later, *S. pneumoniae* was cultured from the CSF (Table 1). The blood culture result was negative.

Four days after admission, the patient was free from partial seizures and weaned from mechanical ventilation, blood count and the serum level of CRP were normal, with improved CSF results (Table 1). But her consciousness disturbance, low-grade fever and hypertonia were continued. CT indicated several low-density lesions in the bilateral frontal and parietal lobe, the boundary of gray and white matter was obscure, and no leptomeningeal and intraparenchymal contrast enhancement was observed. An electroencephalogram showed middle diffuse theta-delta activity, predominantly on the frontal region.

Eight days after admission, brain magnetic resonance imaging (MRI) revealed bilateral widespread changes on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences in the cerebrum and the cerebellum with obscure boundary, especially white matter in the top of bilateral cerebral ventricles and centrum semiovale (Figure 1), the thalami were involved (Figure 2). Magnetic resonance angiography (MRA) was normal, the serologic test results of enterovirus, herpes simplex virus (type 1 and type 2), cytomegalovirus, hepatitis virus (A, B, C, D and E), HIV, Epstein-Barr virus, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were all negative.

Based on the clinical manifestations and MRI results, the diagnosis of ADEM following *S. pneumoniae* meningoencephalitis was suspected. Lumbar puncture was performed again (Table 1), the CSF IgG index increased and oligoclonal bands were positive. Antibiotics were continued, 20 mg/kg.d methylprednisolone for 5 days and 2 g/kg intravenous immunoglobulin were given.

After 9 days of immunotherapy, the patient recovered from the coma, fever and hypertonia completely, meanwhile, the CSF results was in normal range (Table 1). The lesions in MRI was significantly reduced (Figure 1). The intravenous methylprednisolone regimen was changed to a regimen of oral prednisone 10 mg/d for 2 weeks, and then to 5 mg/d for 2 weeks. Six months later, MRI showed slight demyelination changes and cerebral atrophy (Figure 1). Followed up nearly 3 years, there was no recurrence.

Discussion

ADEM is a rare disease lack of strict diagnostic criteria, thus, the morbidity in the population is not precisely known. The estimated morbidity is 0.8 /100,000 per year.[7] A study conducted in San Diego County, CA, estimated the mean incidence rate of ADEM as 0.4/100,000 per year among persons less than 20 years old.[7] The morbidity in a population of children aged less than 15 years is 0.64/100,000 per year in Fukuoka Prefecture, Japan.[8] The morbidity of ADEM in different regions, races and ages is different.

Table 1 The cerebrospinal fluid results

Time	Leucocyte (10^6/L)	Neutrophilic (%)	Glucose (mmol/L)	Chlorides (mmol/L)	Protein (mg/L)	Smear	Culture
Day 0	6250	90	1.06	103.5	4544.1	G^+ coccobacteria	*Streptococcs pneumoniae*
Day 4	32	–	3.82	107.1	1304.6	Negative	Negative
Day 8	36	–	2.64	106.3	1532.9	Negative	Negative
Day 17	2	–	2.81	115.9	401.7	Negative	Negative

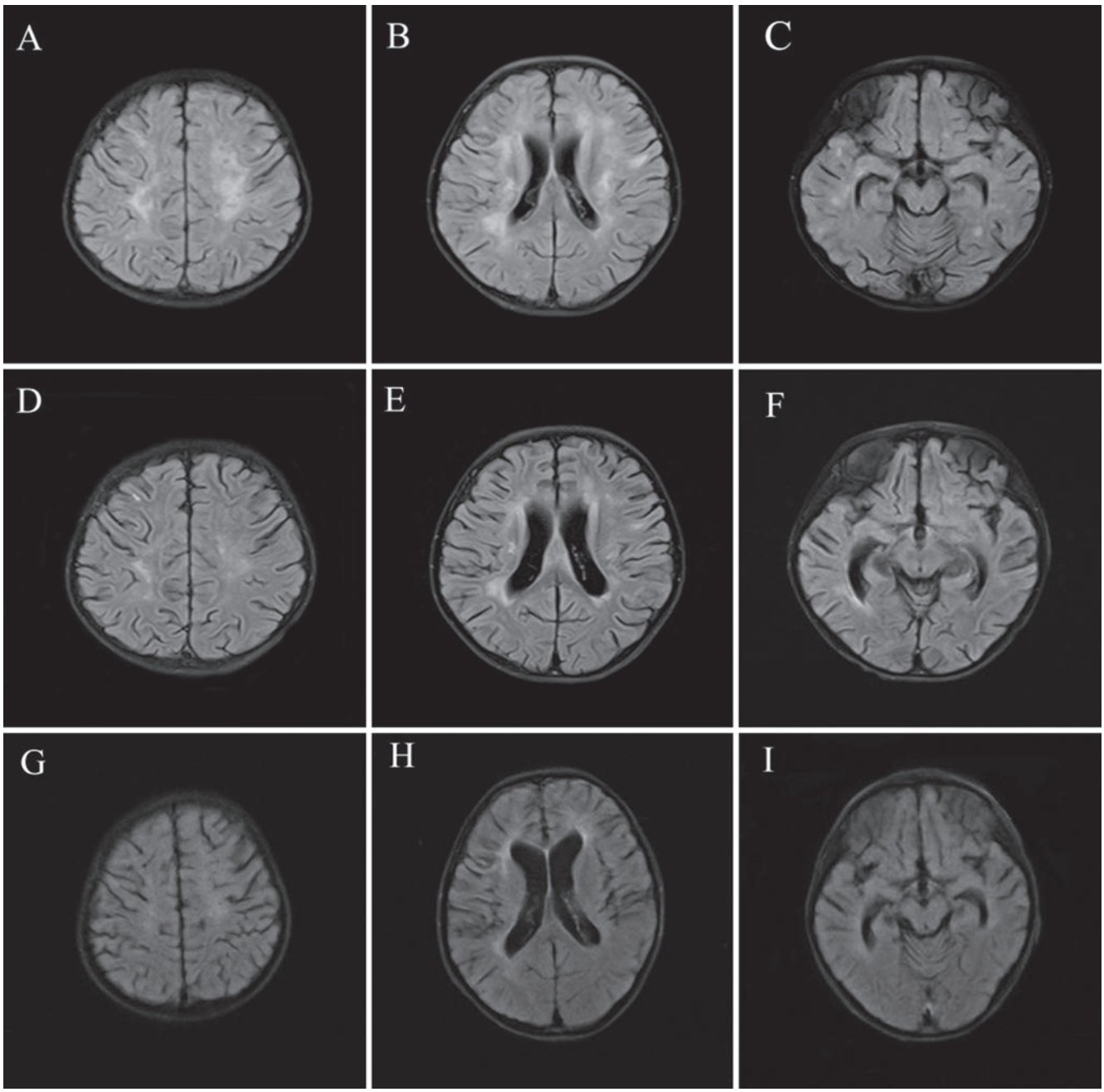

Figure 1 Magnetic resonance imaging (MRI) results in the brain. Before the immunotherapy, bilateral widespread changes in fluid-attenuated inversion recovery (FLAIR) sequences in the cerebrum, especially white matter in the top of bilateral cerebral ventricles and centrum semiovale, the boundary of the lesions were obscure (A, B and C). After 9 days of immunotherapy, the foci of abnormal signal in FLAIR sequences were remarkably reduced in number and size (D, E and F). Six months later, MRI showed mild cerebral atrophy, expanded ventricles and slight demyelination in the horns of lateral ventricles and centrum semiovale (G, H and I).

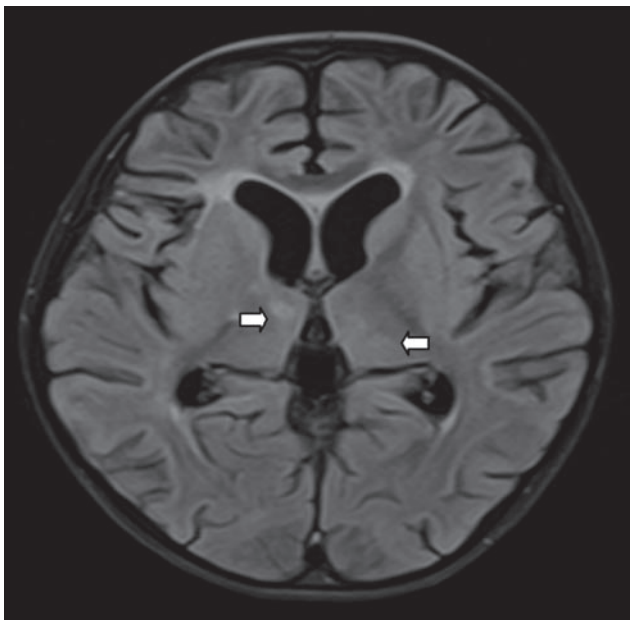

Figure 2 High-intensity signal in bilateral thalami in fluid-attenuated inversion recovery (FLAIR) sequences.

The main pathogens of post-infective ADEM are viruses, including influenza virus, enterovirus, measles, mumps, HIV, rubella virus, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis virus (A and C) and coxsackievirus, et al.[1-3,9] The incidence rate of ADEM following a wild-type measles encephalitis, rubella virus and varicella-zoster virus is 1/1000, 1/10000 and 1/20000, respectively.[1,9] Incidence of ADEM following other viral infections is unknown.[9] There were case report of ADEM after bacterial infection, such as Legionella, Campylobacter, B*orrelia burgdorferi, Leptospira, Rickettsia rickettsii, Mycoplasma pneumoniae and Chlamydia pneumoniae*.[1,3] Ten patients diagnosed as ADEM after Group A beta-hemolytic streptococcus infection were reported, but it was not very precise.[10] There were 3 cases of adult ADEM following *S. pneumoniae* meningoencephalitis reported,[4-6] but all of which were short of long-term follow-up.

It is widely accepted that viral infection or vaccination induce to inflammatory reaction of para-venules in the CNS by molecular mimicry mechanism. Some peptides of viral protein or vaccine are similar to the structures of myelin basic protein or lipid protein. The sensitized T- lymphocytes by the peptides attache to vascular endothelial cell in the help of adherence factor through blood circulation. Permeability of blood-brain barrier increases because of released inflammatory factors, and the sensitized T-lymphocytes can pass through more easily. Then chemotactic factors recruit many kinds of lymphocytes to the CNS and immune impairment outbreak.[1,2] Other hypotheses assumed that the virus would activate or suppress some clones of T-cells.[2] Another speculation implied that it could be a change of the immunological status after a past or occult bacterial infection or organ transplantation which was responsible for the ADEM.[2] ADEM also was found a significant association with the class II alleles, such as HLA-DRB1-01, HLA-DRB-03, HLA-DRB1-1501, HLA-DRB5-0101, HLA-DQB1-0602-1501 and DRDI-1503.[11-13] We presume the pathogenesis of ADEM following *S. pneumoniae* meningoencephalitis is similar to ADEM after viral infection. The antigens of *S. pneumoniae* cross-react with myelin components and in a secondary manner induce a hyper-allergic reaction, leading to ADEM. Maybe the changed immunological status due to *S. pneumoniae* infection was responsible for the disease.

The diagnosis of ADEM is difficult to confirm, because definite laboratory method, or even markers suggesting ADEM have not been established.[1,2] MRI abnormalities are most frequently identified on T2-weighted and FLAIR sequences as patchy, poorly marginated areas of increased signal intensity. Lesions in ADEM are typically large, multiple, and asymmetric. They typically involve the subcortical and central white matter and cortical gray-white junction of both cerebral hemispheres, cerebellum, brainstem, and spinal cord. The gray matter of the thalami and basal ganglia are frequently involved, typically in a symmetric pattern. The periventricular white matter is also frequently involved. Lesions confined to the corpus callosum are less common.[3] Though MRI is the most widely applied diagnostic tool for ADEM, but no MRI criteria have been identified specific for ADEM.[1-3,14] Recently, magnetic resonance spectroscopy and proton magnetic resonance spectroscopy seem to be of great diagnostic value.[1,15,16] It is widely accepted that follow-up MRI scans help establish or confirm a diagnosis of ADEM, the interval should not be shorter than 6 months.[1]

Focal parenchymal abnormalities in *S. pneumoniae* meningoencephalitis in children may attribute to cerebral infarctions or cerebritis. It is hypothesized that inflammation and thrombosis may be caused either by the accumulation of large numbers of inflammatory cells between the endothelium and internal elastic lamina of small arteries and arterioles or by direct invasion of blood vessel walls by organisms.[17] In this case, MRA was normal, MRI displayed diffuse lesions in the brain parenchyma, which was not located in some artery supplied area. There was no

softening lesion found in MRI 6 months later and oligoclonal bands were positive. So cerebral infarction and cerebritis was not likely. Meanwhile, no encephalomalacia was observed during the follow-up, suggesting less possibility of necrotising cytotoxic edema. Only slight demyelinating changes and cerebral atrophy were found in MRI 6 months later, which may happen in 25 to 53% of patients suffered from ADEM.[3]

Oligoclonal bands are more frequent in multiple sclerosis (MS),[1,2] the median frequency in childhood cases of ADEM was 12.5%.[1] The sudden, multifocal clinical onset and the extensive, asymmetric lesions in MRI, with bithalamic involvement, as well as the absence of relapses after nearly 3 years, made the diagnosis of MS unlikely.

This patient was definitely suffering from pneumococcal meningoencephalitis in the early stage, but subsequently it was complicated by the development of ADEM. After the MRI was scanned, the diagnosis of ADEM was suspected. But the diagnosis was not just based on the brain MRI, the CSF findings (including the CSF IgG index and oligoclonal bands) would also help. Aside from routine serial MRI scan in CNS infection, the effectiveness of immunotherapy and long-term follow-up were crucial in the diagnosis.

References

1. Menge T, Hemmer B, Nessler S, et al. Acute Disseminated Encephalomyelitis an update. Arch Neurol 2005;62:1673-80.
2. Wender M. Acute disseminated encephalomyelitis (ADEM). J Neuroimmunol 2011;231:92-9.
3. Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007;68:S23-36.
4. Ueda M, Kanamori A, Mihara T, Hara H, Mutoh T. A case of acute disseminated encephalomyelitis (ADEM) following treatment for pneumococcal meningoencephalitis [Article in Japanese]. Rinsho Shinkeiqaku 2009;49:96-9.
5. Kureshiro J, Kuzumoto Y, Aomatsu H, Kusunoki S. Acute meningoencephalitis caused by Streptococcus pneumoniae, mimicking acute disseminated encephalomyelitis [Article in Japanese]. Risho Shinkeiqaku 2008;48:255-8.
6. Ohnishi H, Sawayama Y, Ariyama I, Yamaji K, Furusyo N, Hayashi J. Acute disseminated encephalomyelitis (ADEM) onset during meningitis and sepsis [Article in Japanese]. Kansenshoqaku Zasshi 2007;81:577-81.
7. Leake JA, Albani S, Kao AS, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J 2004;23:756-64.
8. Torisu H, Kira R, Ishizaki Y, et al. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 2010; 32:454-62.
9. Tselis A, Lisak R. Acute disseminated encephalomyelitis. In: Antel J, Birnbaum G, Hartung HP, Vincent A (Eds.). Clinical Neuroimmunology 2005. Oxford:Oxford University Press 2005, pp. 147-71.
10. Dale RC, Church AJ, Cardoso F, et al. Poststreptococcal acute disseminated encephalomyelitis with basal ganglia involvement and autoreactive antibasal ganglia antibodies. Ann Neurol 2001; 50: 588-95.
11. Alves-Leon SV, Veluttini-Pimentel ML, Gouveia ME, et al. Acute disseminated encephalomyelitis: clinical features, HLA DRB1*1501, HLA DRB1*1503, HLA DQA1*0102, HLA DQB1*0602, and HLA DPA1*0301 allelic association study. Arq Neuropsiquiatr 2009;67:643-51.
12. Idrissova ZhR, Boldyreva MN, Dekonenko EP, et al. Acute disseminated encephalomyelitis in children: clinical features and HLA-DR linkage. Eur J Neurol 2003;10:537-46.
13. Oh HH, Kwon SH, Kim CW, et al. Molecular analysis of HLA class II-associated susceptibility to neuroinflammatory diseases in Korean children. J Korean Med Sci 2004;19:426-30.
14. Erazo-Torricelli R. Acute disseminated encephalomyelitis in children. Rev Neurol 2006; 42:S75-82.
15. Ben Sira L, Miller E, Artzi M, Fattal-Valewski A, Constantini S, Ben Bashat D. 1H-MRS for the diagnosis of acute disseminated encephalomyelitis: insight into the acute-disease stage. Pediatr Radiol 2010;40:106-13.
16. Mader I, Wolff M, Nagele T, Niemann G, Grodd W, Kuker W. MRI and proton MR spectroscopy in acute disseminated encephalomyelitis. Childs Nerv Syst 2005;21:566-72.
17. Jorens PG, Parizel PM, Wojciechowski M, et al. Streptococcus pneumoniae meningoencephalitis with unusual and widespread white matter lesions. Eur J Paediatr Neurol 2008;12:127-32.