Acute Disseminated Encephalomyelitis in Siriraj Hospital: Clinical Manifestations and Short Term Outcome

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Objective: *To describe clinical manifestations, neuroimaging findings, and clinical outcomes in children with acute disseminated encephalomyelitis (ADEM).*
Material and Method: *Children with a diagnosis of ADEM who were less than 15 years of age at Siriraj Hospital between January 2002 and December 2008 were retrospectively reviewed. Clinical symptoms and signs as well as cerebrospinal fluid analysis, neuroimaging findings and clinical outcomes were extracted from medical records using a standard form.*
Results: *During the present study period, 14 children were diagnosed with ADEM. Median age was 7.2 years (range, 1.25-13 years). The most common presenting symptoms were decreased mental status (93%), weakness (71%), and fever (50%). Cranial MRI was abnormal in all patients. All but one patient received high dose intravenous methylprednisolone and a course of tapered oral prednisolone. After a mean follow-up period of 28.6 $\pm$ 19.8 months, 13 patients were classified as monophasic ADEM and one progressed to have multiple sclerosis. Eleven patients recovered completely while one was left with mild hemiparesis and the other two (one with final diagnosis of MS) with severe psycho-neurological disturbances.*
Conclusion: *There are no specific symptoms and signs in children with ADEM. Multifocal neurological deficits along with encephalopathy and abnormal MRI findings lead to correct diagnosis. Treatment with corticosteroid may improve clinical outcomes. Some children may progress to MS. Long-term clinical and neuroimaging studies in these children are needed.*

Keywords: *Acute disseminated encephalomyelitis, Children, Thailand*

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Acute disseminated encephalomyelitis (ADEM) is an autoimmune mediated disease that causes inflammatory demyelinating lesions of the central nervous system (CNS)[1]. ADEM occurs more common in children than adults. Patients usually present with encephalopathy and multifocal neurological deficits[2-7]. Fever and decreased mental status are common and resemble clinical pictures of encephalitis. It is commonly preceded by viral infections or vaccination.

In an epidemiologic study, the incidence of ADEM in patients less than 20 years of age was 0.4/100,000/year[4]. Diagnosis of ADEM is made on the ground of clinical manifestations and radiographic findings since currently there is no specific biologic marker for this disease. Different terms and definitions were used in the literature to describe patients with ADEM[2-6,8]. In 1997, the International Pediatric Multiple Sclerosis Study Group (IPMS) proposed definitions of acquired CNS demyelinating diseases including ADEM and its variants[1]. Several studies used this criteria in their study[7,9]. In the present report, the authors describe the demographic data, clinical manifestations, laboratory and neuroimaging findings and short-term outcomes of these patients in Siriraj Hospital compared to other studies.

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Material and Method

The present study was approved by Siriraj Institutional Review Board (IRB). All patients with a diagnosis of ADEM who were admitted to Siriraj Hospital, Bangkok, Thailand, between January 2002 and December 2008 were retrospectively reviewed. Demographic data, clinical manifestations, physical examinations, laboratory findings, neuroimaging

findings, types of treatment and clinical outcomes from medical records were extracted using a standardized form.

Diagnosis of ADEM is made by using definition of ADEM proposed by the IPMS which includes a first clinical event with 1) encephalopathy that is defined by behavioral changes or altered consciousness and 2) multifocal neurological deficits 3) focal or multifocal hyperintense lesions predominantly involve white matter of the CNS 4) no history of previous clinical or radiographic evidences of demyelinating episodes[1]. Relapsing CNS demyelinating episodes are further classified as recurrent ADEM or relapsing ADEM. Cranial computed tomography (CCT) with contrast was done in some cases. All patients had cerebrospinal fluid (CSF) analysis and cranial magnetic resonance image (CMRI) performed (1.5 Tesla). CMRI generally included axial T1- and T2-weighted image, fluid attenuated inversion recovery images (FLAIR) and MRI with gadolinium. A neuroradiologist (PC) who was blinded to patients' clinical manifestations and outcomes reviewed the neuroimaging findings.

All children were followed-up and any changes in neurological symptoms were documented. Follow-up CMRI was performed in some cases. By December 2009, all patients were evaluated for their final types of ADEM or other demyelinating disease and neurological outcomes using modified Rankin score (mRS)[10] (Table 1).

Results

During the present study period, 15 patients were diagnosed with ADEM. One patient was excluded, because the patient had no encephalopathy at the time of presentation and was reclassified as clinical isolated syndrome (CIS). Fourteen patients fulfilled the diagnostic criteria of ADEM. Median age was 7.2 years (range, 1.25-13 years) while 10/14 of the patients (71%) were 3 to 10 years of age. Nine patients were male. Predisposing factors were found in eight patients (57%), six patients with non-specific upper respiratory infections or febrile illnesses, one with varicella infection and one after Japanese encephalitis vaccine. All developed neurological symptoms within 28 days (range, 5 to 28 days) after antecedent infection or vaccination. The clinical presenting symptoms and signs are shown in Table 2. Initial diagnoses include encephalitis in eight patients, three with stroke and one of each with cerebellar ataxia, brain tumor and transverse myelitis.

All patients had encephalopathy (13 with decreased mental status ranges from lethargy to coma, and one with behavioral change). Six patients had weakness (4 with hemiparesis and two with paraplegia).

Cerebrospinal fluid analysis was obtained in all patients and was normal in five (36%) patients. CSF abnormalities were pleocytosis (> 5 cell/mm^3) in nine patients (64%) (range, 10 to 92) and mildly elevated protein (> 40 mg/dL) in seven patients (50%) (range,

Table 1. Modified Rankin Scale[10]

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities but able to look after own affairs without assistance
3	Moderate disability; requiring some help but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention

Table 2. Clinical manifestations of in 14 patients with ADEM

Symptoms and signs	No. of patients (%)
Clinical presenting symptoms	
Altered mental status	
Decreased mental status	13 (93)
Behavioral changes	1 (7)
Fever	7 (50)
Weakness	6 (43)
Hemiparesis	4 (29)
Paraplegia	2 (14)
Ataxia	4 (29)
Headache	3 (21)
Seizure	2 (14)
Neurological signs	
Pyramidal tract signs	6 (43)
Cranial nerve	3 (21)
Cerebellar signs	3 (21)
Meningeal irritation sign	2 (14)
Spinal cord signs	2 (14)
Optic neuritis (bilateral)	1 (7)

42 to 100). None had positive bacterial culture. CSF oligoclonal band was not performed in all patients.

CCT were obtained in 11 patients, of which 10 (91%) showed multifocal hypodensity of cerebral white matter or at the cerebellar hemispheres. CMRI were performed in all patients. The results of MRI findings are shown in Table 3. Eight patients (57%) had both supratentorial and infratentorial areas, 4 (29%) at supratentorial only, and two (14%) at infratentorial only. Most children have bilaterally, asymmetry, poorly marginated, hyperintense areas on T2-weighted and FLAIR images. Deep gray matter including basal ganglia and thalamic involvements were seen in 10 patients (71%); five at basal ganglia only, three with thalamus and basal ganglia, and two at thalamus only. Spinal MRI was obtained only in those with spinal cord symptoms and signs and was abnormal in two out of two patients.

All patients received supportive care and anti-epileptic drugs whenever indicated. All patients but one received intravenous methylprednisolone at a dose of 30 mg/kg/day (maximum 1 gram) for three days followed by four to six weeks of oral corticosteroid. One received intravenous immunoglobulin because of no improvement after intravenous corticosteroid. Two received intravenous acyclovir, one for possible herpes simplex infection, and the other with varicella infection.

Table 3. Laboratory and neuroimaging findings in 14 patients with ADEM

Laboratory result	No. with findings/ No. tested (%)
Cerebrospinal fluid analysis	
Normal	5/14 (36)
Pleocytosis	9/14 (64)
Elevated protein	7/14 (50)
Cranial computed tomography	
Abnormal	10/11 (91)
Cranial magnetic resonance imaging	
Abnormal	14/14 (100)
White matter	11/14 (79)
Subcortical	11/14 (79)
Corpus callosum	3/14 (21)
Gray matter	10/14 (71)
Cortical/juxtacortical	10/14 (71)
Deep gray matter	10/14 (71)
Brain stem	6/14 (43)
Cerebellum	5/14 (35)
Gadolinium enhancement	4/14 (29)
Spinal magnetic resonance imaging	
Abnormal	2/2 (100)

Two patients had a recurrent attack with new symptoms and new lesions on CMRI findings at six weeks and seven weeks after initial onset. These two patients had no further demyelinating attack on follow-up MRI and recovered completely. One patient had further demyelinating lesions at eight weeks and 12 months after initial onset. This patient was finally diagnosed with multiple sclerosis.

The mean follow-up period was 28.6 $\pm$ 19.8 months (range 2-60 months). None died during the follow-up. Eleven patients recovered completely and were able to live a normal life with a mRS of 0-1. One patient was left with mild hemiparesis with mRS of 2. Two patients (including one patient with MS) had moderately severe neuro-psychological disturbance with mRS of 4 and 5, respectively. Repeat CMRI was done in nine patients (most within 4-6 months after the clinical onset) and eight showed improvement and no new lesions. One patient had further demyelinating lesions and finally diagnosed with MS. By the end of the present study, 13 patients (93%) were classified as monophasic ADEM and one (7%) with MS.

Discussion

The authors report 14 cases of ADEM in Siriraj Hospital over a 7-year period. In the present study, 10/14 patients aged ranged from 3 to 10 years and the median age of 7.2 years, which is similar to other studies[2-4,7]. Male predominate in the authors' series were also reported in other reports[3-5,11]. Antecedent infections or vaccinations were found in 57%.

All children had encephalopathy. Fever and weakness were the next most common presenting symptoms. A combination of encephalopathy and fever or weakness was the reason why 11/14 patients were diagnosed as encephalitis (8 patients) or stroke (3 patients) initially. Other presenting symptoms were seizure and cerebella ataxia. Clinical manifestations and neurological findings are not different from previous studies[2-7,9,11,12].

Diagnosis of ADEM is based on clinical manifestations and neuroimaging studies since there is no specific biologic marker. CSF studies may be normal, mild pleocytosis or mildly elevated protein. In the present study, cranial CCT was abnormal in 10/11 (91%) but most showed nonspecific, faint, multifocal, and hypodensity at either cerebral hemispheres or cerebellar hemispheres. These nonspecific findings

along with clinical symptoms raised the clinical suspicious of ADEM and then CMRI were obtained. CMRI is a very sensitive neuroimaging study to diagnose this condition. T2-weighted image and FLAIR of CMRI show multiple, bilaterally but asymmetry of hyperintense areas most commonly at either at the cortical/juxtacortical or subcortical areas of the cerebral hemispheres. The lesions could also be found at the brain stem, cerebellum, and spinal cord. Involvement of corpus callosum was found in 29% in one study[2] and galidonium enhancement was found around 30%[2,3] comparable to the present study. Several studies found that there was no correlation between patients' symptoms and the location of lesions on CMRI[4,11]. In the present study, the findings of CMRI were not different from the previous studies[2-7,9,11,12]. Diagnoses of ADEM were made with certain after typical MRI findings.

Although there is no standard therapy for ADEM, corticosteroids are the most common used medication. Several studies showed rapid improvement in most patients[3-5]. Most authors suggest a high dose of intravenous methylprednisolone at 10-30 mg/kg/day (maximum 1 gram/day) or dexamethasone 1 mg/kg/day for three to five days and generally followed by a 4- or 6-week course of tapering with oral corticosteroid. All of the present patients but one received intravenous methylprednisolone and a course of tapered oral corticosteroids. One patient received IVIG as she did not respond well to corticosteroid. One patient recovered completely when the CMRI was obtained and received no treatment. Full recovery after treatment was found in 50-90% of the patients. In the present study, 11/14 (79%) recovered completely. Spontaneous recovery from ADEM did occur but patients with significant neurological deficits or showing deterioration should be treated with corticosteroid[2].

ADEM is classically thought to be a monophasic autoimmune disease. However, recurrent attacks of CNS demyelination either in the form of recurrent, multiphasic ADEM or MS have been reported varied from 5 to 24%, which may partly be due to the variations of definition of ADEM used in their studies and the mean follow-up period[2,3,13-15]. Moreover, when recurrence of ADEM occurred, different definition of recurrence and cut-off duration whether the new symptoms were the same acute or different episodes were used[2,3,5,6,8]. In 2007, IPMS group proposed diagnostic criteria for CNS demyelination in children[1]. When encephalopathy is a strict diagnostic criteria, recurrent form of ADEM or progression to MS is reported in less than 10%[9]. In the present study, two patients had new symptoms and new lesions on MRI findings. These new episodes occurred within three months after the initial ADEM onset, thus, according to IPMS criteria; these patients were classified as monophasic ADEM. The other one had two further non-ADEM demyelinating lesions and MS was diagnosed (according to IPMS criteria) at the end of the study. This is different from one cohort study in Thai children that showed three out of 16 patients (19%) developed MS[7]. This is probably due to shorter duration of follow-up in the present study. Another study found a relapse rate of 18% at a mean follow-up of five years and five months. They did not further classify into multiphasic ADEM or MS, however[12]. Patients with atypical for ADEM or those with a diagnosis of CIS, the risk of subsequent MS may be as high as 46%[9]. One large cohort study showed an increased risk of recurrence was associated with optic neuritis, family history of CNS inflammatory deymyelination, Barkhof multiple sclerosis criteria on MRI and no neurological sequelae after first attack[12]. The number of patients in the present study is too small and follow-up period is too short to find any risk factors to predict progression of MS in patients with ADEM. These patients should be followed-up in a long term since MS may develop in years after ADEM onset[14].

In conclusion, the present study demonstrates that clinical outcomes in children with ADEM are favorable. CMRI should be an investigation of choice when ADEM is suspected. Treatment with corticosteroid may improve the outcomes in these patients. Prognosis in the majority of the patients is favorable. One patient developed MS during the present study period. The best way to distinguish ADEM from MS is long-term clinical and neuroimaging follow-up in these patients.

Potential conflicts of interest

None.

References

1. Krupp LB, Banwell B, Tenembaum S. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007; 68 (16 Suppl 2): S7-12.
2. Hynson JL, Kornberg AJ, Coleman LT, Shield L, Harvey AS, Kean MJ. Clinical and neuroradiologic features of acute disseminated encephalomyelitis in children. Neurology 2001; 56: 1308-12.

3. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. Neurology 2002; 59: 1224-31.
4. Leake JA, Albani S, Kao AS, Senac MO, Billman GF, Nespeca MP, et al. Acute disseminated encephalomyelitis in childhood: epidemiologic, clinical and laboratory features. Pediatr Infect Dis J 2004; 23: 756-64.
5. Singhi PD, Ray M, Singhi S, Kumar KN. Acute disseminated encephalomyelitis in North Indian children: clinical profile and follow-up. J Child Neurol 2006; 21: 851-7.
6. Weng WC, Peng SS, Lee WT, Fan PC, Chien YH, Du JC, et al. Acute disseminated encephalomyelitis in children: one medical center experience. Acta Paediatr Taiwan 2006; 47: 67-71.
7. Visudtibhan A, Tuntiyathorn L, Vaewpanich J, Sukjit P, Khongkatithum C, Thampratankul L, et al. Acute disseminated encephalomyelitis: a 10-year cohort study in Thai children. Eur J Paediatr Neurol 2010; 14: 513-8.
8. Mikaeloff Y, Suissa S, Vallee L, Lubetzki C, Ponsot G, Confavreux C, et al. First episode of acute CNS inflammatory demyelination in childhood: prognostic factors for multiple sclerosis and disability. J Pediatr 2004; 144: 246-52.
9. Dale RC, Pillai SC. Early relapse risk after a first CNS inflammatory demyelination episode: examining international consensus definitions. Dev Med Child Neurol 2007; 49: 887-93.
10. Huybrechts KF, Caro JJ, Xenakis JJ, Vemmos KN. The prognostic value of the modified Rankin Scale score for long-term survival after first-ever stroke. Results from the Athens Stroke Registry. Cerebrovasc Dis 2008; 26: 381-7.
11. Khurana DS, Melvin JJ, Kothare SV, Valencia I, Hardison HH, Yum S, et al. Acute disseminated encephalomyelitis in children: discordant neurologic and neuroimaging abnormalities and response to plasmapheresis. Pediatrics 2005; 116: 431-6.
12. Mikaeloff Y, Caridade G, Husson B, Suissa S, Tardieu M. Acute disseminated encephalomyelitis cohort study: prognostic factors for relapse. Eur J Paediatr Neurol 2007; 11: 90-5.
13. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics 2002; 110: e21.
14. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000; 123 (Pt 12): 2407-22.
15. Cohen O, Steiner-Birmanns B, Biran I, Abramsky O, Honigman S, Steiner I. Recurrence of acute disseminated encephalomyelitis at the previously affected brain site. Arch Neurol 2001; 58: 797-801.

Acute disseminated encephalomyelitis (ADEM) ในเด็ก: อาการทางคลินิกและผลการรักษาในระยะสั้น

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วัตถุประสงค์: *เพื่อศึกษาอาการและอาการแสดงทางคลินิก ผลการตรวจภาพวินิจฉัยระบบประสาท และผลการรักษาของโรค acute disseminated encephalomyelitis (ADEM) ในผู้ป่วยเด็กที่เข้ารับการรักษาที่ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล*

วัสดุและวิธีการ: *เป็นการศึกษาเชิงพรรณนา โดยการทบทวนเวชระเบียนของผู้ป่วยที่มีอายุน้อยกว่า 15 ปี ที่ได้รับการวินิจฉัยว่าเป็นโรค ADEM ระหว่างเดือนมกราคม พ.ศ. 2545 ถึง ธันวาคม พ.ศ. 2551 โดยบันทึกอาการแสดงทั่วไปและทางระบบประสาท ผลการตรวจน้ำไขสันหลัง การตรวจภาพวินิจฉัยระบบประสาท และการติดตามอาการทางคลินิก รวมถึงการวินิจฉัยขั้นสุดท้ายของผู้ป่วย*

ผลการศึกษา: *ในระยะเวลาที่ทำการศึกษามีผู้ป่วย 14 ราย ได้รับการวินิจฉัยว่ามีโรค ADEM มีอายุระหว่าง 1 ปี จนถึง 13 ปี อาการที่นำผู้ป่วยมาพบแพทย์มากที่สุดคือ การเปลี่ยนแปลงของระดับการรู้สึกตัว อาการอ่อนแรงของแขนและขา และไข้ การตรวจคลื่นแม่เหล็กไฟฟ้าของสมองผิดปกติในผู้ป่วยทุกราย ผู้ป่วย 13 ราย ได้รับการรักษาด้วยสเตียรอยด์ในขนาดสูง หลังจากการติดตามผู้ป่วยเป็นระยะเวลา 28.6 $\pm$ 19.8 เดือน พบว่าผู้ป่วย 13 ราย ได้รับการวินิจฉัยขั้นสุดท้ายว่าเป็น monophasic ADEM และ ผู้ป่วย 1 ราย เป็นโรคปลอกประสาทเสื่อม (multiple sclerosis) ผู้ป่วย 11 ราย หายจากโรคอย่างสมบูรณ์ และอีก 3 รายมีอาการทางระบบประสาทหลงเหลืออยู่*

สรุป: *โรค ADEM ไม่มีอาการหรืออาการแสดงที่จำเพาะ ผู้ป่วยที่มีอาการทางระบบประสาทหลายตำแหน่งที่มีการเปลี่ยนแปลงของระดับการรู้สึกตัวควรนึกถึงโรคนี้ และควรได้รับการตรวจภาพวินิจฉัยระบบประสาทโดยเฉพาะอย่างยิ่งด้วยคลื่นแม่เหล็กไฟฟ้าของสมองและไขสันหลัง การรักษาด้วยยาสเตียรอยด์ในขนาดสูงอาจจะช่วยให้อาการของผู้ป่วยดีขึ้น ผู้ป่วยเหล่านี้จำเป็นต้องได้รับการติดตามในระยะยาว เนื่องจากผู้ป่วยอาจจะมีอาการของโรคเกิดขึ้นซ้ำซึ่งจะมีแนวทางการรักษาที่แตกต่างไปจากโรคนี้*