

# Acute disseminated encephalomyelitis in children

## *A descriptive study in Tehran, Iran*

Noorbakhsh Samileh, MD, Tonekaboni Hassan, MD.

### ABSTRACT

**Objective:** To determine the frequency, etiology (viral infection or vaccination), presenting signs and symptoms, response to therapy, complication and course of acute disseminated encephalomyelitis (ADEM) in our hospitals.

**Methods:** A 2-year retrospective, descriptive, chart review of children with final diagnosis of ADEM in 2 hospitals (Hazrat Rasool and Mofid in Tehran, Iran during 2000-2002) were carried out. The diagnosis is based upon clinical presentation, physical examination and ruling out of other disease (imaging, laboratories and so forth) of expert pediatric neurologists. Acute disseminated encephalomyelitis was documented in all cases by characteristics MRI changes included inflammation and demyelination in subcortical or periventricular regions.

**Results:** Acute disseminated encephalomyelitis were diagnosed in 15 patients. More than half of patients were between 9-14 years old. It was rare in 1-5 years old children. It had an abrupt onset, preceding infection/vaccination with no gender differences. Approximately 46.4% of cases had a recent upper respiratory tract illness. Varicella zoster virus infection, urinary tract infection, and mycoplasma pneumoniae were observed. Presentation signs included ataxia, decreased consciousness, fever plus nausea/vomiting, cranial nerve involvement, dysarthric speech, convulsion, hemiparesis, paresthesia, meningismus, and headache. We identified inflammation and demyelination in subcortical than periventricular lesions by magnetic resonance imaging. Prognosis was excellent with low mortality rate (6.6%).

**Conclusion:** Acute disseminated encephalomyelitis is common in our children, possibly because of the high prevalence of causative infections. Due to advances in control of traditional exanthematous diseases such as measles, rubella and so forth, most cases of ADEM in this study followed non-specific upper respiratory infections. Differentiation of ADEM from a single episode of multiple sclerosis is difficult. Diagnosis of multiple sclerosis should be carried out if new symptoms and signs or imaging abnormalities appear, more than 3 months after the onset of clinical symptoms in ADEM cases.

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*From the Department of Pediatric Infectious Disease (Samileh), Hazrat Rasool General Hospital, Iran University of Medical Sciences and the Department of Pediatric Neurology (Hassan), Shabid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran.*

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*Address correspondence and reprint request to: Dr. Samile Noorbakhsh, Research Center of Pediatric Infectious Diseases, Iran University of Medical Sciences, Hazrat Rasool Hospital, Niayesh Ave, Satarkhan Street, Tehran 14455, Islamic Republic of Iran. Tel. +98 (21) 66525328. Fax. +98 (21) 66517118. E-mail: Samileh\_noorbakhsh@yahoo.com*

Acute disseminated encephalomyelitis (ADEM) is an acute autoimmune mediated disease characterized by rapid onset of multifocal neurological deficits.<sup>1-3</sup> Acute disseminated encephalomyelitis is thought to be a T cell mediated response to myelin basic protein, triggered by antigens.<sup>4,5</sup> Acute disseminated encephalomyelitis frequently preceded by an acute viral infection<sup>6-11</sup> or vaccination.<sup>2-5</sup> The exact incidence of ADEM is not known. It is more common in children because of higher frequency of immunization and exposure to antigens. In the past, ADEM followed infections (measles, smallpox, and chickenpox) was associated with significant mortality and morbidity in developing countries.<sup>1-3</sup> Because of significant advances in infectious disease control, ADEM in developed countries is now seen most frequently after non-specific upper respiratory tract infections and the etiological agent remains unknown.<sup>11-15</sup> Viral infections associated with ADEM include measles, mumps, rubella, varicella-zoster, Epstein Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, and coxsackie virus.<sup>1,2,5-7</sup> Other bacterial infections such as *Borrelia burgdorferi*, *Leptospira*, and Group A beta-hemolytic correlating with encephalomyelitis or polyneuritis.<sup>8-12</sup> The main bacterial infection, which has been implicated with the occurrence of ADEM is mycoplasma.<sup>10</sup> An incidence rate of one per 25,000 vaccinations occurred with duck embryo antirabies vaccine.<sup>3</sup> Currently, post-immunisation encephalomyelitis is most commonly associated with measles, mumps, and rubella vaccinations.<sup>1-3</sup> The incidence is

1-2 per million for live measles vaccine immunizations, which is significantly lower than that for post-infectious encephalomyelitis from measles itself.<sup>1,2</sup> The hallmark of clinical features of ADEM is the development of a focal or multifocal neurological disorder.<sup>13-18</sup> Systemic symptoms such as fever, malaise, myalgias, headache, nausea, and vomiting often precede the neurological symptoms of ADEM.<sup>1,2,19,20</sup> The onset of the central nervous system disorder is rapid. Initial clinical features include encephalopathy ranging from lethargy to coma. Other clinical features include bilateral optic neuritis, visual field defects, aphasia, motor and sensory deficits; meningismus; ataxia, and varied movement disorders. and psychosis. Focal or generalized form of seizure may occur in severe cases, especially in the acute hemorrhagic form of ADEM. Optic neuritis is often bilateral and transverse myelopathy is often complete.<sup>1,20</sup> Young adults and children are most commonly affected. The rate of prior infection was lower in adult patients.<sup>19</sup> Most adult patients present clinically in a fashion similar to that of children, except that there is a relatively infrequent occurrence of headache, fever and meningismus, and a higher frequency of sensory deficits. Optic neuritis is also infrequent in adult ADEM.<sup>1,2,19</sup> It results from a transient autoimmune response against myelin or other autoantigens. The hallmark of the pathological findings are very similar to the post-infectious encephalomyelitis. It is the areas of perivenous demyelination and infiltration of lymphocytes and macrophages. Although post-infectious encephalomyelitis typically involves the white matter, lesions in grey matter have also been seen. Basal ganglia, thalamus, and even cortical grey matter may be involved. The pathological findings described in ADEM are very similar to the experimental allergic encephalomyelitis (EAE). Acute hemorrhagic leukoencephalitis is a more severe and frequently fatal hyperacute variant of ADEM. The most important distinguishing feature of acute hemorrhagic leukoencephalitis and HEAE (from ADEM and EAE respectively) is necrotizing vasculitis of venules.<sup>1-3,19,20</sup> Magnetic resonance imaging is the neuroimaging study of choice for establishing the diagnosis and for following the course of the disease.<sup>1-3,19,20</sup> Most patients with ADEM improve with methylprednisolone. If that fails, immunoglobulins, plasmapheresis, or cytotoxic drugs can be given.<sup>13-18</sup> Acute disseminated encephalomyelitis has a favorable long term prognosis. Recovery can begin within days, but more frequently occurs over the weeks or months.<sup>1,2,20</sup> The mortality varies between 10% and 30%, with complete recovery in 50%. Poor prognosis is correlated with severity and abruptness of onset of the clinical syndrome. In the case series after rabies vaccine, a mortality of 18% was recorded. Measles virus associated ADEM may carry a worse prognosis than

vaccine associated disease.<sup>1,2,19,20</sup> Acute disseminated encephalomyelitis and multiple sclerosis are parts of the same spectrum of inflammatory demyelinating conditions. Both have similar clinical presentation, cerebrospinal fluid analysis, histopathological and neuroimaging appearance. Recent literature suggests that a significant proportion of patients with ADEM will later develop multiple sclerosis. Diagnosis of multiple sclerosis should be carried out if new symptoms and signs or imaging abnormalities appear, more than 3 months after the onset of clinical symptoms in ADEM cases. Follow up experience from developing countries does not support this view.<sup>1-3,20</sup> In India and other developing countries ADEM is a common neurological condition, possibly because of the high prevalence of causative infections. However, the reasons for the low occurrence of multiple sclerosis are not known.<sup>2,3</sup> The true incidence of ADEM in Iran is unknown. Antecedent events (exanthematous fevers and other viral infection), which predispose to ADEM, are still prevalent. The goal of study is to report frequency, etiology (viral infection or vaccination), presenting signs and symptoms; response to therapy, complication and course of ADEM cases in our patients.

**Methods.** A 2-years retrospective, descriptive study in 2 educational and referral hospitals (Hazrat Rasool and Mofid) in Tehran, Iran during 2000-2002 were carried out. In this chart review study, we selected all children aged <15 years which had finally diagnosis of ADEM. The diagnosis of ADEM based on clinical presentation, physical examination and ruling out other diseases and ADEM documented by characteristic changes (periventricular inflammation and demyelination) in MRI.

**Results.** Fifteen cases were identified (8 males and 7 females) and the mean age was  $4.83 \pm 3.93$  years, range: 14 years. Most of the patients aged between 11-14 years (33%); 9-11 years (26%); 6-8 years (26%); 1-2 years (15%); no cases aged between 2-5 years. Sixteen patients (88%) presented in either winter or spring. Seven cases (46.4%) had URI and common cold in previous 2 weeks. Previous vaccination was positive in 2 cases (13.6%). Varicella zoster virus infection in the last week was positive in at least one case. Two cases had previous UTI infection. Six (40 %) children had no any previous URI or vaccination. Despite microbiologic testing, a definite diagnosis was established only in one child with Mycoplasma pneumonia (specific IgM). The most common sign of presentation was ataxia (60 %); altered consciousness (60 %), fever and nausea/vomiting (46%). Cranial nerve involvement (33%); dysarthric speech (26%); convulsion (20%); hemiparesis (20%);

paresthesia (13%); meningismus (13%) headache (6%). There was not any gender predilection of ADEM in patients Ataxia and meningismus had seen only in male (100%); fever was most frequent in female (70%). Other signs not differed between 2 sexes. Ataxia as the first presentation signs of ADEM were more common in patients between 7-12 years (66%) versus (30%) in 1-6 years old patients. Loss of consciousness was more common in patients <6 years (66%) versus 33% in patients >6 years old. No significant difference between age groups were seen depend upon other signs of presentation. Cerebrospinal fluid abnormalities occurred in 70% of ADEM cases. Brain magnetic resonance imaging identified: subcortical white matter (93%), cerebral cortex lesion (80%), periventricular white matter (59%), brainstem, and deep gray matter (47%) of patients. Twelve patients (80%) treated with corticosteroids, 3 cases with intravenous immunoglobulins. Most of the patients responded well. One patient died (6.5%). Other patients survived. Long-term neurologic sequelae (convulsion and hemiparesis) were observed in 3 patients (20%) in follow up studies.

**Discussion.** Results of present study suggests an infectious cause for ADEM in our country. Most cases of ADEM is seen after nonspecific difficult-to-diagnose winter/spring upper respiratory virus. Only one case of VZV infection developed ADEM. Also, previous urinary tract infection was observed in 2 cases, and it had not reported yet in another studies. Our results are similar to a recent study in children from Taiwan, causative agents from those of traditional exanthematous diseases to nonspecific respiratory infections.<sup>1</sup> One study in India reported specific viral infections and Semple antirabies vaccination together accounted for 56.2% of antecedent events.<sup>2</sup> The new Castle experience indicates that approximately one per 1000 children with exanthematous fevers develop ADEM.<sup>1,2</sup> Most ADEM cases in the present study were in age ranged 9-14 years. This high frequency is due to higher exposure to respiratory infection and antigens. Acute disseminated encephalomyelitis was rare in 1-5 years old children. Both gender were affected with equal frequency in this study like other studies,<sup>1,4</sup> it opposed to female preponderance in MS.<sup>1,20</sup> The clinical characteristic features of the present study include ataxia 60 % and altered consciousness 60%. The frequency of ataxia (60%) is closer to other studies<sup>2</sup> but only in one case followed by varicella-zoster infection. Altered consciousness observed in 60% of cases with good prognosis, but without a previous rash history. There were no similarity with other studies in which the encephalitic symptoms may precede or simultaneously

or follow the rash.<sup>3,4</sup> We observed hemiparesis and paresthesia in 33% of our patients (without previous measles, rubella and mumps infection). All of them had good prognosis. It opposed to previous studies in which hemiplegic form (following measles, rubella and mumps infection and vaccination) reported with poor prognosis.<sup>1-5</sup> Cranial nerve involvement (33%); dysarthric speech (26%); convulsion (20%); were more frequent in our patients. But meningismus (13%) and headache (6%) was rare. Probably, it is due to the higher age of our patients (9-14 year) compare with other studies.<sup>1-4,20</sup> Acute hemorrhagic encephalopathy was rare disorder<sup>15,20</sup> and occurred in one case who died. In previous studies<sup>2,4,5</sup> stiff neck, hemiplegia or other focal sings reported equal frequency in both gender. It was opposed to female preponderance for impaired consciousness in the present study. Ataxia and meningismus had seen only in male (100%). Fever was most frequent in female (70%). Other signs not differed between 2 sexes. Ataxia as the first presentation sign in ADEM, was more common (66%) in patients between 7-12 years versus (30%) in 1-6 years old patients. In contrast, loss of consciousness was more common in patients <6 years (66%) versus (33%) in patients more  $\geq$ 6 years. No significant difference between age groups. Cerebrospinal fluid abnormalities such as other studies<sup>1-3,20</sup> was frequent and occurred in 70% of cases. Magnetic resonance imaging identified periventricular inflammation and demyelination in 60% of patients. Subcortical white matter (93%) and cerebral cortex involvement (80%) was more frequent than periventricular lesions. Deep gray matter and brain stem involved in 47% of patients. Prognosis for survival and outcome was excellent in our patients. Mortality rate was rare (6.6%) in apposed to mortality rate (10-25%) reported in other studies.<sup>15,20</sup> Only one patient died on the second day of admission, other patients survived. Three patients (20%) had long-term neurologic sequelae.

In conclusion, ADEM is a common neurological condition, possibly due to high prevalence of causative infections in our country. It frequently preceded by a non-specific winter/spring upper respiratory virus. Because of significant advances in infectious disease control, ADEM in Iran (such as as other developing countries) was considered a changing trend.<sup>1,4</sup> Higher incidence of ADEM in older age (9-14 year) may be due to higher frequency of exposure to respiratory infections and antigens. Most cases had an abrupt onset and MRI identified inflammation and demyelination in subcortical than periventricular lesions. In this study, the prognosis is excellent with low mortality rate (6.6%). We agree with other experts that it is difficult to differentiate ADEM from a single episode of MS.

Since multiple sclerosis has low incidence in Iranian children, probably ADEM is not a part of the MS spectrum in our patients.

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