Acute disseminated encephalomyelitis: an evaluation of 15 cases in childhood

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SUMMARY: İncecik F, Hergüner MÖ, Altunbaşak Ş. Acute disseminated encephalomyelitis: an evaluation of 15 cases in childhood. Turk J Pediatr 2013; 55: 253-259.

To describe our experience with acute disseminated encephalomyelitis (ADEM) and the relationships between the clinical course, magnetic resonance imaging (MRI) findings and treatment, a retrospective record review was conducted of 15 children who were admitted with the diagnosis of ADEM during the period 2004–2010. Their ages ranged between 2 and 13 years. Patients presented most often with ataxia (53.3%) and secondly with weakness and headache (46.6%). Myelitis was determined in two patients. Five patients were treated with high-dose intravenous (IV) methylprednisolone followed by oral prednisolone, seven patients were treated with oral prednisolone, one patient was treated with plasmapheresis with IV immunoglobulin (Ig), and one patient was treated with IVIg. We observed recurrence in one patient. ADEM is a demyelinating disorder that is being diagnosed increasingly more as MRI studies are performed more frequently in patients with acute encephalopathy. Early diagnosis and therapy might improve the outcome.

Key words: acute disseminated encephalomyelitis, magnetic resonance imaging, clinical, children.

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating, autoimmune, monophasic, and polysymptomatic disorder of the central nervous system (CNS) white matter[1]. The pathogenesis is unclear, but it is thought to be immune-mediated, because in up to three-fourths of the cases, it follows an antecedent infection or immunization[2].

No definitive biomarkers for ADEM are currently available, and the diagnosis rests heavily on the clinical and magnetic resonance imaging (MRI) characteristics and the absence of clinical or laboratory findings of other disorders.

In general, the clinical presentation of ADEM may be very heterogeneous. However, a combination of altered consciousness or behavior and multifocal neurological deficits, especially in close relation to an infection, should raise the clinician's suspicion to consider ADEM in the differential diagnosis.

High-dose intravenous methylprednisolone (MP), dexamethasone, intravenous immunoglobulin (IVIg), and plasmapheresis have all been used in the treatment of ADEM[3]. The prognosis is favorable, with most children making a full recovery[4]. Although ADEM is classically described as a monophasic disorder, several studies have described relapses.

The present report analyzes the different clinical presentations, response to treatment and outcome in a series of 15 patients with ADEM.

Material and Methods

Fifteen cases with ADEM followed in the Child Neurology Department from 2004 to 2010 were reevaluated. The clinical findings and laboratory and imaging results of the patients were reviewed.

The diagnosis of ADEM was based on the International Pediatric MS Study Group classification[5]: a first clinical event with a polysymptomatic encephalopathy with acute or subacute onset, showing focal or multifocal hyperintense lesions predominantly affecting

the CNS with white matter changes should be present, and there should be no history of a previous clinical episode with features of a demyelinating event. If a patient had a current demyelinating event fulfilling the diagnostic criteria for ADEM, occurring at least three months after the initial ADEM event and at least four weeks after completing steroid therapy, the diagnosis of recurrent ADEM was made. Finally, multiphasic ADEM referred to one or more ADEM relapses, including encephalopathy and multifocal deficits, but involving new areas of the CNS on MRI and neurologic examinations.

All of the cases were reevaluated with neurological examination, biochemical analysis, serologic tests for bacterial and viral infections (measles, mumps, rubella, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and Mycoplasma pneumoniae), cerebrospinal fluid (CSF) examination, and cranial and spinal imaging with 1.5 Tesla MRI. Patients were followed for at least three months. In those patients who developed flaccid paralysis of the lower limbs, a possible accompanying radiculoneuropathy was also suspected; therefore, these patients also underwent nerve conduction studies.

The diagnosis was made in each case by a consultant pediatric neurologist.

Results

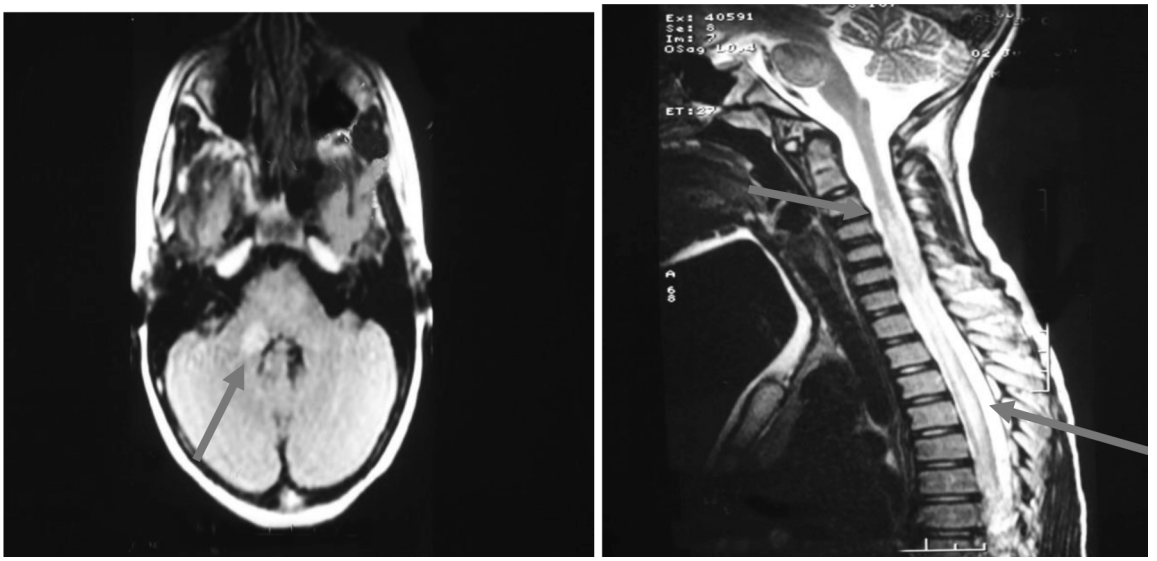
Of the 15 children, 9 were male and 6 were female. The mean age at presentation was 89.3±36.1 months (range: 2-13 years). Preceding infections (upper respiratory tract infection) were determined in 53.3% of the cases. There was no history of vaccination or other infection. The mean interval between the preceding infection and the symptoms of encephalomyelitis was 7 days.

The most common presenting symptoms were: ataxia in 53.3%, altered consciousness, weakness, and headache in 46.6%, and fever in 40% of the patients. Neurological examination revealed pyramidal motor signs such as hemiparesis (33.3%), brisk deep tendon reflexes and pathological reflexes (73.3%), cranial nerve involvement (20%), dysarthria (20%), disturbance of micturition (13.3%), diplopia (13.3%), and nystagmus (6.6%). In two patients, spinal cord involvement was also diagnosed (Table I).

Laboratory investigations revealed leukocytosis in 53.3% of the cases. Serologic tests were negative for cytomegalovirus, measles, mumps, rubella, Epstein-Barr virus, herpes simplex virus, and *M. pneumoniae*. CSF examination was performed in 12 cases. Ten patients had normal CSF examination, and two patients had mild CSF lymphocytosis. Oligoclonal bands were also found to be negative. Cranial MRI was performed in all cases, and spinal MRI was performed in two cases who had sphincter dysfunction and distal weakness. On cerebral MRI T2-weighted images and FLAIR sequences, multiple symmetrical high signal areas were detected in the basal ganglia, thalamus, cortical white-gray matter junction and subcortical white matter, and brainstem (Fig. 1). On spinal MRI, T2 hyperintense lesions were detected beginning from the cervical 4 level throughout the medulla spinalis in one patient (Fig. 2), and in another patient, there

Table I. Clinical Symptoms and Signs of the Patients

Clinical symptoms and signs	n (%)
Ataxia	53.3
Altered consciousness	46.6
Headache	46.6
Weakness	46.6
Fever	40
Hemiparesis	33.3
Pyramidal sign	73.3
Cranial nerve involvement	20
Dysarthria	20
Disturbance in micturition	13.3
Diplopia	13.3
Nystagmus	6.6
Spinal cord involvement	13.3



Figs. 1,2. A 13-year-old girl with acute disseminated encephalomyelitis with spinal cord involvement at the first presentation. 1. Axial FLAIR image of the cerebrum showing hyperintensity of the cerebellar pedincule. 2. Sagittal T2 image of the spine showing T2 hyperintensity in the cervicothoracic spinal cord.

were lesions beginning from thoracic 10 level throughout the medulla spinalis. They also had CNS findings on the cerebral MRI.

Steroid treatment, IVIg, or plasmapheresis with IVIg was given to all patients. In seven patients, steroid was administered as oral prednisolone 1 mg/kg/day for 4 weeks. In five patients, high-dose IV MP 30 mg/kg per day for 3-5 days followed by oral prednisolone at a dose of 1-2 mg/kg/day with tapering over 4-6 weeks was given; one of them also received IVIg therapy at the dose of 400 mg/kg/day for 5 days consecutively. Among the last three patients, one received only IVIg for 5 days; one received IV MP followed by prednisolone plus IVIg and plasmapheresis; and one received IV MP followed by oral prednisolone plus IVIg. The demographic details, presenting features, imaging findings, treatments, and outcomes are shown in Table II. One of the patients had multiphasic ADEM with new clinical symptoms and new lesions on MRI 11 months after the first attack.

Discussion

Acute disseminated encephalomyelitis (ADEM) is usually a monophasic inflammatory demyelinating disease of the CNS defined by a polysymptomatic presentation and encephalopathy. It is often seen 7–14 days following a viral infection or immunization[6]. There may be prodromal findings such as fever, malaise, headache, nausea, and vomiting. The clinical features are determined by the distribution of lesions in the CNS. Multifocal neurological signs such as hemiparesis, bilateral upper motor neuron signs, cerebellar ataxia, cranial nerve palsies, dysarthria, seizures, and disturbances in micturition may be seen[7].

There are no pathognomonic clinical or laboratory findings for ADEM. The CSF is usually normal, but may show lymphocytic pleocytosis and mild elevation of protein. Other markers such as oligoclonal bands, IgG or myelin basic protein (MBP) are sometimes detectable, but not diagnostic[7]. The electroencephalogram (EEG) often shows non-specific features of an encephalopathic process, and visual evoked potential (VEP) responses may be delayed. In the absence of specific biologic markers, the diagnosis of ADEM is based on the clinical and radiologic features. Cerebral MRI shows high signal lesions of the same age on T2-weighted images in the subcortical white matter, with or without involvement of the cerebellum, gray matter and spinal cord[7,8].

Presentation and clinical course can be quite variable because of the distribution of lesions in the CNS[9,10]. Tosun et al.[9] reported 12 patients who presented weakness and fever (50%), loss of consciousness and seizures (33.3%), vomiting (25%), and headache (16.6%). In

Table II. The Demographic Details, Clinic Features, Treatments and Outcomes

No	Sex	Age	Presenting features	Neurological examination	Radiological findings	Treatment	Follow-up	Outcome
1	F	7.5	Fever, headache, encephalopathy	Hyperreflexia, bilateral extensor plantars	Left frontoparietal white matter	MP 3 days P 4 weeks	3 months	Normal
2	M	6.5	Ataxia, dysarthria	Ataxia, hyperreflexia	Periventricular white matter	P 6 weeks	12 months	Epilepsy
3	M	11	Ataxia, seizure, weakness	Left hemiparesis, ataxia VII cranial nerve palsy	Right parietoccipital area	P 6 weeks	6 months	Hemiparesis
4	M	8	Ataxia, headache	Ataxia, hyperreflexia	Basal ganglia	P 4 weeks	4 months	Normal
5	M	9.5	Ataxia, headache	Ataxia, dysmetria, hyperreflexia	Brainstem, parietal area	P 6 weeks	24 months	Normal
6	F	2	Fever, encephalopathy	Right hemiparesis	Periventricular white matter	MP 3 days P 4 weeks	3 months	Normal
7	M	3	Loss of vision	VI cranial nerve palsy	Bilateral frontal and occipital area	P 6 weeks	24 months	Normal
8	M	6	Headache, encephalopathy	Hyperreflexia	Right parietoccipital area	IVIG	6 months	Normal
9	M	3.5	Ataxia	Ataxia	Brainstem, frontotemporal area	P 4 weeks	18 months	Normal
10	M	10	Ataxia, headache weakness, encephalopathy	Right hemiparesis	Basal ganglia, frontoparietal area	MP 3 days P 4 weeks	4 months	Normal
11	M	8	Weakness urinary retention	Paraparesis	Cortical and subcortical area Thoracic, lumbar areas of medulla spinalis	MP 3 days P 4 weeks IVIG	5 months	Normal
12	F	7.5	Ataxia, headache fever	Ataxia, dysmetria bilateral extensor plantars	Parietoccipital area	MP 3 days P 4 weeks	6 months	Normal
13	F	8	Weakness, urinary retention	Paraparesis	Frontoparietal area,cerebellum Cervical, thoracic, lumbar areas plasmapheresis of medulla spinalis	MP 3 days P 4 weeks IVIG	3 months	Normal

14	F	8.5	Fever, ataxia, weakness, seizure	Left hemiparesis	Basal ganglia, thalamus subcortical white matter	P 4 weeks	3 months	Normal
15	F	13	Headache, fever weakness, vomiting	Right hemiparesis	Basal ganglia, thalamus frontotemporal area	MP 3 days P 4 weeks	18 months	Recurrence at the 11th month after MP and 6 weeks P

IVIG: Intravenous immunoglobulin. MP: Intravenous methylprednisolone. P: Oral prednisolone.

another series, Gupte et al.[10] reported the most common presenting symptoms as ataxia, loss of vision, and headache. Anlar et al.[11] reported 46 patients with common symptoms and signs pertaining to the motor system and consciousness. Krishnakumar et al.[12] reported a case of ADEM presenting as a depressive episode in a child. In our patients, the most common clinical features were ataxia, headache, altered consciousness, weakness, and fever. The other symptoms were dysarthria, disturbance in micturition, diplopia, and nystagmus. In previous literature, spinal cord involvement was reported in 3-25% of cases[6]. Cord lesions were significantly more longitudinally extensive in ADEM than acute transverse myelitis. This may be a reflection of lesion load, which is often large in ADEM. We established ADEM with spinal cord involvement in two patients who presented with flaccid quadriparesis.

Rarely, acute hemorrhagic leukoencephalitis, acute hemorrhagic encephalitis and acute necrotizing hemorrhagic leukoencephalitis are considered hyperacute subforms of ADEM, and were observed in 2% of patients[13]. Lesions on MRI tend to be large, with perilesional edema and mass effect.

Neither pathognomonic nor disease-specific clinical presentations can be defined, and the diagnosis has to be made by exclusion of a number of likely differential diagnoses such as CNS infections, vascular plus inflammatory diseases and inherited encephalopathies[13]. The first priority should be to rule out an acute viral or bacterial infection of the CNS, and a gadolinium-enhanced MRI of the brain and spinal cord and lumbar puncture should be performed. In the absence of clear evidence of an infectious cause, the neuroimaging findings should define the regional distribution of the demyelinating-inflammatory process. The most important and most common differential diagnosis with regard to therapeutic options and prognosis is multiple sclerosis (MS). ADEM is considered a monophasic disease, but up to one-third of patients will have relapses in the future. ADEM is more likely than MS if the patient has a preceding illness, fever, headache, polysymptomatic presentation, encephalopathy, or blood pleocytosis. MS is more likely if unilateral optic neuritis is present or if ocular lesions are present on MRI[14].

We could not identify specific viral agents with serologic tests in our cases. Oligoclonal bands in serial CSF examinations can suggest MS and may help to distinguish these two conditions, but it is not specific for ADEM and MS[9]. Tenembaum et al.[13] reported their pediatric series of 84 children with ADEM for whom CSF samples were analyzed, and none of them showed oligoclonal bands. In our patients, oligoclonal bands were tested in 10 cases, and were absent.

In the treatment of ADEM, dexamethasone and high-dose IV MP have also been used[7,11]. In addition, IVIg and plasmapheresis have been reported to be effective, particularly in patients who do not respond to steroids[15]. It has been described as practical to use high-dose IV MP 20 mg/kg per day for 3–5 days followed by oral prednisolone commencing at 2 mg/kg per day, with tapering over 4–6 weeks. We administered oral prednisolone in seven patients; high-dose IV MP followed by oral prednisolone in five patients; IVIg in one patient; IV MP followed by oral prednisolone plus IVIg and plasmapheresis in one patient with spinal cord involvement; and MP followed by oral prednisolone plus IVIg treatment in one patient.

The outcome of ADEM is generally good, with 57-89% of children making a full recovery[6,16,17]. In our group, one child had epileptic seizures requiring antiepileptic drug treatment, one child had headache and behavioral problems, and one child had left hemiparesis on remission. The other patients recovered completely. Only one patient had multiphasic ADEM. In another report, complete recovery was detected in 71% of the patients, and 33% of patients had relapses[11].

In conclusion, a combination of acute encephalopathy and polysymptomatic neurologic findings, especially in close relation to an infection, should alert the clinicians to consider ADEM. The widespread availability of MRI means that more cases are now being recognized. Early diagnosis and prompt treatment of ADEM will probably reduce morbidity. It should not be forgotten that cases can be repeated.

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