Pediatrics & Therapeutics
ISSN: 2161-0665

Elhassanien et al., Pediat Therapeut 2013, 3:1
DOI: 10.4172/2161-0665.1000139

Research Article Open Access

Acute Demyelinating Encephalomyelitis (ADEM): Clinical Characteristics and Outcome

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Abstract

Background: ADEM, although relatively uncommon, is probably under-recognized.

Objectives: To spotlight on the clinical profile and therapeutic outcome of children with ADEM.

Methods: This is a prospective study of patients with ADEM who were admitted to the Pediatric Departments in Aladan and Alfarawanya Hospitals in Kuwait, from January 2009 to January 2011. Clinical, microbiological, radiological and therapeutic data were analyzed.

Results: Of 48 patients presented with acute neurological symptoms and signs, 21 patients fulfilled criteria for ADEM. 80.95% of cases were presenting in winter and spring, 57% of patients had a history of upper respiratory tract illness. The commonest presentations were motor deficits, convulsions followed by altered conscious. CSF virology studies showed Herpes Simplex Virus (HSV) and Epstein-Barr virus (EBV) in 3 patients whereas nasal and nasopharyngeal swab showed evidence of influenza H1N1 virus in 1 patient. Brain MRI was performed in all patients and revealed multiple hyperintense supratentorial brain lesions on T2/FLAIR images. 85.7% of patients had cortical and/or subcortical white matter lesions which were bilateral and asymmetric in location and size.

Most of the patients were treated with steroids alone, 3 patients received high-dose intravenous methylprednisolone and 6 patients received both steroids and intravenous immunoglobulin.

Keywords: Acute Demyelinating Encephalomyelitis (ADEM); Children; Acute neurological insult; Viral infection; Post vaccination

Introduction

Acute Disseminated Encephalomyelitis (ADEM) is a monophasic acute nonvasculitic inflammatory demyelinating disorder of the central nervous system characterized by diffuse neurologic signs and symptoms coupled with evidence of multifocal lesions of demyelination on neuroimaging. It is first described in the early 18th century as uncommon presentation of measles and small pox. Little is known about incidence throughout the world but in USA it may be approximately 1.5–3/100,000. ADEM is more common in the winter months and 80% of childhood cases occur in first decade of life [1-2]. McAlpine in 1931 [3] described 3 sets of patients with ADEM: 1) postvaccination, 2) after infectious fevers and 3) spontaneous. A number of recent reports of ADEM in children have confirmed the observations of McAlpine [4,5].

The imaging studies are the cornerstone in confirming the diagnosis of ADAM using CT and the more sensitive MRI for disclosure of extent and number of lesions [6,7]. Others including EEG, CSF and virology studies also help in diagnosis. Several articles suggested that improved outcome of ADEM was attributable mainly to the use of intravenous gamma globulin, steroids and other immunosuppressive therapies [8,9].

The objective of the present study is to clarify ADEM with an emphasis on the relationship of clinical features, microbiology, neuroimaging, and treatment to clinical outcome in 21 Kuwaiti children with ADEM.

Materials and Methods

Patients and methods

-**Design:** Prospective study

-**Period:** January 2009 to January 2011.

-**Place:** Aladan and Alfarawanya hospitals, Kuwait,

-**Inclusion criteria:** Patients presented with acute onset of neurologic neurological signs and symptoms together with brain MRI evidence of multifocal, hyperintense lesions on T2-weighted images.

-**Exclusion criteria:** Any chronic neurological lesions, patients with MRI not with evidences of ADEM as transverse myelitis, Guillain-Barre syndrome etc.

This is a prospective study of the patients with ADEM who were admitted to the pediatric departments in Aladan and Alfarawanya hospitals, Kuwait, from January 2009 to January 2011.

During the period of the study, any patient presented with acute neurological symptoms and signs and fulfilled the above mentioned criteria were subjected to thorough clinical history taking, complete physical and neurological examinations. All studied children were subjected to complete blood count, liver function tests, renal function tests, blood culture and sensitivity, creatinine phosphokinase and cold agglutinin. Cerebrospinal fluid (CSF) examination had performed for all the patients within the first 24 hours of admission. CSF examination

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Received November 15, 2012; **Accepted** December 26, 2012; **Published** December 28, 2012

Citation: Elhassanien AF, Alghiaty HAA, Zakaeria M (2013) Acute Demyelinating Encephalomyelitis (ADEM): Clinical Characteristics and Outcome. Pediat Therapeut 3:139. doi:10.4172/2161-0665.1000139

included biochemistry, gram stain, cytology, latex agglutination, culture and sensitivity for bacteria and virology studies. Polymerase chain reaction (PCR) tests for enteroviruses, herpes simplex virus (HSV), Epstein-Barr virus (EBV), and Mycoplasma pneumoniae were done from pharyngeal and nasopharyngeal swabs, blood and CSF. Whereas enzyme-linked immunosorbent assay (ELISA) for rotavirus (in stool if there was concurrent history of diarrhea) and immunoglobulin G (IgG) and IgM antibody tests for viruses and Mycoplasma pneumoniae. In the case of antibody titers, IgM-specific antibody levels, and rising IgG-specific antibody levels were considered significant.

Brain computerized tomography (CT) and magnetic resonance imaging (MRI) scans were performed for all patients. Spinal MRI scans of the cervical, thoracic and lumbar cord were performed for 13 patients who had spinal related neurological symptoms. Clinical follow-up of all patients after discharge from hospital with brain and spinal MRI scans for the degree of improvement, appearance of new lesions, and enhancement. The first follow-up visits were after 3 month of the presentation.

The diagnosis of ADEM was based on the acute onset of neurologic neurological signs and symptoms together with brain MRI evidence of multifocal, hyperintense lesions on T2-weighted images.

Variable	N (%)
Age at onset Years Range (Mean)	 2-12 (7.5)
Sex Male Female	 12 (57.1) 9 (42.9)
Seasonal clustering Winter-spring Summer Late fall	 17 (80.9) 1 (4.8) 3 (14.3)
pH of preceding infections None URTI Age Vaccination	 6 (28.6) 12 (57.1) 2 (9.5) 1 (4.8)
Systemic signs and symptoms Fever Nausea and vomiting Headache Neck stiffness	 9 (42.9) 4 (19.04) 6 (23.8) 2 (9.5)
Neurological symptoms and signs Neurological deficit Ataxia Hemiparesis Paraparesis Monoparesis Convulsion Focal Generalized Eye signs/symptoms Eye ache and visual disturbances Oculomotor nerve palsy Impairment of consciousness Urinary symptoms Sensory deficits	 9 (42.9) 4 (19) 2 (9.5) 1 (4.8) 2 (9.5) 6 (23.8) 2 (9.5) 4 (19.04) 3 (14.3) 1 (4.8) 2 (9.5) 3 (14.3) 1 (4.8) 2 (9.5)
Duration of stay in hospital	7-31 days (14.3 days)
Treatment Steroid alone Oral prednisone Intravenous methylprednisolone Steroid with IVGG	 15 (71.4) 12 (57.1) 3 (14.3) 6 (28.6)
Outcome No neurological residual deficits Neurological residual deficits Gait disturbances Paraparesis Hemiparesis	 16 (76.2) 5 (23.8) 3 (14.3) 1 (4.7) 1 (4.7)

Table 1: Demographic and clinical characteristics of the study population.

Variable	Range (mean)
TLCs	3200-29200 cells/mm^3 (11300)
CSF Cells Protein Sugar Gram stain Latex agglutination Bacterial culture and sensitivity	 0-1400 cell/mm^3 (50.6) 45-2200 mg/dL (89.7 mg/dL) 10-57 mg/dL (34 mg/dL) Negative Negative Negative
Viral studies by PCR CSF HSV EBV Enterovirus Measles Pharyngeal and nasopharyngeal swabs Enterovirus Mycoplasma EBV Influenza H1N1	 2 1 0 0 0 2 0 1
Viral studies by ELISA Stool Rota virus Blood Mycoplasma EBV RSV Entero virus Mumps Measles	 0 1 0 0 0 0 0

Table 2: Initial laboratory studies in 21 patients with ADEM.

Statistical Analysis

Demographic data, clinical symptoms and signs, laboratory results, CT and MRI findings, and treatment response were tabulated. SPSS program version 16 was used to analyze data.

Results

During the period of the study 48 patients (26 males and 22 females) were presented with acute neurological symptoms and signs, among them 21 patients (12 male and 9 female) fulfilled the diagnostic criteria for ADEM. The demographic and clinical characteristics of our patients are summarized in table 1.

The patients' age ranged from 2 years to 12 years with a mean of 7.5 years. The patients showed a seasonal distribution with 80.95% (17 of 21) presenting in winter and spring (December to May). Only 1 case (4.8%) occurred in summer and 3 (14.3%) in late fall. 57% of patients (12 of 21) had a history of upper respiratory tract illness mostly in 4 weeks before presentation. One patient had history of measles, mumps and rubella (MMR) vaccine and 2 patients had history of acute gastroenteritis.

The most common presentation was motor deficits (as ataxia, paraparesis, hemiparesis, and monoparesis). Fewer patients were presented with convulsions (either generalized or, focal or even status epilepticus) and altered consciousness. Only one patient was presented with eye aches and visual disturbances and urinary symptoms as transient retention of urine. Two patients presented with oculomotor nerve palsy and sensory deficit.

Table 2 showed the laboratory features of our patients. The white blood cell (WBC) count ranged from 3200 to 29200/mm^3 with a mean

of 11300 cells/mm^3. CSF evidence of inflammation (either pleocytosis or elevated protein) was present in 16 patients (76.2%). The CSF leucocytes count ranged from 0 to 1400 with a mean of 50.6 cells/mm^3. The CSF protein ranged from 45 mg/dL to 2200 mg/dL with a mean of 89.7 mg/dL. CSF glucose concentrations were normal in all patients. None of the bacterial cultures were positive.

Viruses were identified in only 4 patients. Among twelve patients with respiratory secretions whom obtained for fluorescent antibody testing, one was positive for influenza H1N1. A definite microbiologic diagnosis of HSV and EBV were established in CSF samples of 3 patients (2 for HSV and 1 for EBV). A possible diagnosis of M. pneumoniae disease was made in 2 patients with a history of upper respiratory tract symptoms. Fifteen patients did not have any microbiologic diagnosis.

Electroencephalograms were performed in 13 patients, 3 of them showed generalized slowing, and 2 showed focal discharges.

Neuroimaging

Brain CT scan revealed lesions in only 1 patient who had scattered supratentorial mild hypodensities in the subcortical white matter and no associated mass effect. These lesions were bilateral and asymmetric.

Brain MRI was performed in all patients with T1, T2, FLAIR, and gadolinium-enhanced T1 images. MRI findings are summarized in table 3. All patients had multiple hyperintense supratentorial brain lesions on T2/FLAIR images. A total of 232 lesions were seen in the brain (mean: 11.2 per patient; range: 4–48). Most lesions were mostly less than 1 cm in but in some cases were up to 2 cm in diameter.

Eighteen patients (85.7%) had cortical and/or subcortical white matter lesions which were bilateral and asymmetric in location and size. In 3 patients, predominantly unilateral involvement of the cortical gray and subcortical white matter was noted. As regards lobar location, 47.6% of these hyperintense lesions were frontal, followed by parietal (23.8%), temporal (19.1%), and occipital (9.5%). Lesions were detected in the cerebral cortex in 76.1%, in subcortical white matter in 90.5%, in periventricular white matter in 61.9%, in deep gray matter (basal ganglia or thalamus) in 47.6%, and in brainstem in 38.1% of patients. All Spinal MRI scans were normal.

Follow-up MRI scan was performed in all our patients at 3 month after discharge from the hospital and may be repeated up to 2 years after discharge from hospital according to the neurological status of the patient. In only 1 of 21 patients the MRI did not return to normal, whereas the other 20 patients MRI scan findings were improved both in number and in size of lesions.

One patient had urinary retention at 9 months from the initial presentation. A repeat MRI showed complete disappearance of previous lesions, but 3 new lesions appeared in different locations. This patient had no other neurological deficits and these new lesions disappeared on follow-up MRI scan 18 months from the initial lesion. Another patient had a repeat MRI scan at 18 months because of continuing seizures. This patient had new hyperintense lesions on T2 FLAIR in the cortical gray matter of the contralateral side with mild encephalomalacia in the right temporal lobe. However, a putative diagnosis of multiple sclerosis (MS) remains a consideration in both of the patients.

Location of hyperintense lesions on T2/FLAIR	No. of patients (%)	No. of lesions per patient (mean (range))
Bilateral Unilateral	18 (85.7) 3 (14.3)	
No of lesions (range, mean)	4-48 (11.2)	
Size of lesions (range, mean)	2-20 mm (9.3)	
Frontal lobe Parietal lobe Temporal lobe Occipital lobe	10 (47.6) 5 (23.8) 4 (19.1) 2 (9.5)	0–23 (7) 0–19 (2.9) 0-5 (1.4) 0-5 (1.1)
Site Cortical grey matter Subcortical white matter Periventricular white matter Deep gray matter Brain stem Cerebellum Corpus callosum (Splenium)	 16 (76.1) 19 (90.5) 13 (61.9) 10 (47.6) 8 (38.1) 0 (0) 0 (0%)	 0-28 (5.1) 0-42 (6.3) 0-15 (2.4) 0-2 (0–2) 0–2 (0.3) 0-6 (1.2) 0

Table 3: Initial T1, T2/FLAIR MRI Findings in 21 Patients with ADEM.

Hospital course

Patients stayed in the hospital for a duration ranged from 7 days to 31 days with a mean of 14.3 days. Eighteen patients had maximum neurological deficits on admission. Three patients deteriorated during the first week of hospitalization. None was ventilated.

Treatment

Treatment regimens were decided according the clinical findings and severity of presentation. Fifteen patients (71.4%) were treated with steroids alone. 12 patients received prednisone at 2 mg/kg/d for 7 days and tapered over 10 days. 3 patients received high-dose intravenous methylprednisolone of 20 mg/kg/d within the first week of hospitalization for 5 days and tapered over 4 weeks. None of the patients on steroid regimens experienced any adverse effects from steroids. Six patients received both steroids and intravenous immunoglobulin (IVIG) at 400 mg/kg/d for 5 days. Antibiotics were given to all our patients, and acyclovir was given to 11 patients. One patient received ganciclovir for EBV infection. Treatment was continued until the throat secretions were negative for EBV by PCR. Anticonvulsants were administered to any patient who had seizures during the course of their illnesses and only one of them required long-term anticonvulsant medication.

Outcome

At discharge all patients were completely conscious but only 5 patients had mild neurologic deficits (3 patients with gait disturbances, 1 patient with paraparesis and 1 patient with resolving hemiparesis). Sixteen patients did not have any neurological deficits at the time of discharge from the hospital.

All our patients had been seen on follow-up. The duration of follow-up ranged between 12 months and 24 months. Of the five patients who had neurological deficits at discharge, three of them were functioning normally without any deficits within the first 3-month follow-up and the other 2 patients had residual gait problems which improved completely within 6-month follow-up. Only one patient had transient urine retention without other neurological defects 9 month after initial presentation and his follow-up MRI showed complete disappearance of previous lesions, but 3 new lesions appeared in different locations. One patient had continuing seizures and needed anticonvulsant medication. His initial MRI scan showed unilateral lesions. Follow-up MRI scans showed mild encephalomalacia in the right temporal lobe and new hyperintense lesions on T2 FLAIR in the contralateral cortical gray matter. However, he did not have any new neurologic deficits.

Discussion

Twenty one cases of ADEM were identified during a 2-year period

in a two general hospital. Our study showed a seasonal distribution of cases as 80.9% of cases occurred in winter and spring seasons, suggesting an infectious cause that is also reported in 3 other studies from USA, United Kingdom and Australia [4,10,11]. In these 3 studies, a nonspecific infectious disease preceded the onset of ADEM in >70% of cases, which is also close to our study in 61.9% of cases.

Many infectious agents, as mumps, rubella, influenza, measles, varicella, HSV, EBV, Coxsackievirus, Mycoplasma, Campylobacter, streptococcus, legionella, and rickettsia, have been implicated in ADEM. Despite vigorous attempts to identify microbial pathogens in the present study, only six patients were identified to have infectious agents (2 with HSV, 1 with EBV, 1 with influenza virus type H1N1 and 2 with Mycoplasma). The failure to identify microbiological agent suggests that the inciting agent or agents are unusual or cannot be recovered by standard laboratory procedures.

The list of potential winter/spring respiratory pathogens includes influenza, respiratory syncytial virus, and corona virus, but only influenza H1N1 is associated with the winter/spring respiratory illness pattern observed in the present report. Corona virus is the most difficult to detect in standard virus laboratories. Corona virus has the ability to induce CNS demyelination in humans and animals [12,13].

No Rota virus isolated from any of our patients, however, one report described the role of rotavirus in ADEM in 2 children with rotavirus diarrhea [14].

A minority of children initially presenting with clinical and neuroimaging features of ADEM may subsequently be considered as having multiple sclerosis (MS). ADEM by definition is a monophasic illness; any clinical or radiological recurrences beyond the first few months of the initial illness, MS should be considered. Two patients (9.5%) in the present study were suspected to have MS because of the recurrence. Distinction between ADEM and MS at initial presentation cannot be made, although some clinical, radiologic and even biochemical features may point toward one or the other diagnosis [10,15]. Establishing the diagnosis of MS may require prolonged follow-up as the second attack of MS may occurs over a period of months to several years [16]. So, clinical and radiological (MRI scan) follow-up of children with ADEM beyond the first few months may help in the early diagnosis of MS as the early treatment of MS has been shown to prevent the progression of the disease [17].

The present study also confirmed the overall good outcome observed in the American, British and Australian reports [10-12]. One hundred percent of children survived ADEM in our study and 76.2% of children were neurologically normal on discharge from the hospital and the other 23.8% were completely neurologically free within the 12 month follow-up (Table 1). In addition, relapses occurred in only 9.5% of the patients. And there was no relation between relapse and weaning of steroid that had happened in the American study [10]. Although high-dose steroid therapy was used in only 14.3% of the children in the present report, whereas 21%, 74% and 88% of children received high-dose steroids in the American, British and Australian studies respectively. Although there were differences in treatment, but neurologic outcome, relapse rates, and MRI findings at follow-up were similar. However our study and the other 3 studies [4,10,11] were designed to evaluate therapy, so it is difficult to assess the actual benefits of steroid therapy in ADEM.

Conclusion

The present study demonstrated that ADEM in children occurs in winter/spring and closely follows an upper respiratory tract illness. MRI studies demonstrate asymmetric lesions in the cortical and subcortical white matter of the brain. Initial lesions may persist and new lesions may appear during the immediate recovery period. Clinical outcome, in general, is favorable regardless of therapy.

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