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Pattern and Outcome of Acute Disseminated Encephalomyelitis (ADEM)

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is an immune disease marked by widespread of inflammation in the brain and spinal cord. ADEM typically damages myelin, causing destruction of white matter. It often occurs following a viral infection or vaccination. Its symptoms are similar to multiple sclerosis (MS) and are considered part of the multiple sclerosis borderline diseases.

Patients and Methods: This is an observational prospective study done in Bab Al-Shariah University Hospital in period between 31th of December 2017 to 30th of December 2018 on children from birth to 18 years old who were having definite ADEM by neuroradiological study of the brain (MRI brain) presented to the Neuropediatric outpatients clinic or inpatients of Pediatric Department during the period of the study. Those with history suggestive of definite perinatal asphyxia or with other congenital malformation of neurological system were not involved in our study.

Results: We found that the most common clinical features of ADEM in our community are fever, disturbed conscious level (DCL), motor system weakness and convulsions, and the most valuable tool in diagnosis is brain MRI. These findings are very important in the diagnosis, management and counseling of patients with ADEM.

Conclusion: ADEM is an area of active research especially in the field of imaging where there is a rapid development. In future we may have better diagnostic and therapeutic options for ADEM.

Keywords: Multiple sclerosis, acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an immune mediated disease of the brain. It usually occurs following a viral infection but may occur following vaccination, bacterial or parasitic infection, or even appear spontaneously. As it involves autoimmune demyelination, it is similar to multiple sclerosis, and is considered part of the multiple sclerosis borderline diseases **(1).**

The incidence rate is about 8 per 1,000,000 people per year. Although it can occur in all ages, most reported cases are in children and adolescents, with the average age around 5 to 8 years old. The mortality rate may be as high as 5%, however full recovery is seen in 50 to 75% of cases with increase in survival rates up to 70 to 90% with figures including minor residual disability as well. The average time to recover is one to six months **(2).**

ADEM produces multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter. Usually the lesions are found in the subcortical and central white matter and cortical gray-white junction of both cerebral hemispheres, cerebellum, brainstem, and spinal cord, but periventricular white matter and gray matter of the cortex, thalami and basal ganglia may also be involved. When there is recurrence of more than one demyelinating episode, it is called recurrent disseminated encephalomyelitis or multiphasic disseminated encephalomyelitis (MDEM) **(3).**

Neurologic deficits develop 3–6 weeks following an antecedent event. The onset can be abrupt or may happen over a period of several days. Prodromal illness may precede the neurologic symptoms. ADEM can affect any part of the neuraxis and thus the clinical presentation is variable and usually polysymptomatic: altered mental status, pyramidal dysfunction, cerebellar ataxia, brainstem syndromes, optic neuritis, myelitis, and rarely myeloradiculopathy and extrapyramidal syndromes. Seizures are common, may be focal or generalized. Encephalitic illness is more common in

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children younger than 3 years. Rarely ADEM may present with features of intracranial space occupying lesion [(1)].

Platelet counts are increased in a substantial number of children with ADEM. Sedimentation rates are occasionally mildly increased. Cerebrospinal fluid (CSF) is abnormal in about two-thirds of patients and shows a moderate pleocytosis with increased proteins. The CT scan low-density abnormalities are found in more than half of childhood or adolescent ADEM cases, but this technique is less sensitive than MRI for the disclosure of extent and number of lesions [(1)].

Magnetic resonance imaging (MRI) is the imaging of choice to demonstrate white matter lesion in ADEM. A recent study in children suggested the presence of any 2 of the MRI features: (1) absence of bilateral diffuse pattern; (2) presence of black holes; and (3) presence of 2 or more periventricular lesions help to differentiate MS from ADEM. The sensitivity and specificity of these criteria was 81% and 95% respectively. A study done to compare the MRI pattern of lesions, which could help to differentiate ADEM from MS found the following characteristics: solitary lesion, unilateral large lesion, cortical lesions, and subcortical grey matter (basal ganglia and thalamus) affection. Other studies suggested that bilateral thalamic lesion may be diagnostic of ADEM [(4)].

AIM OF THE WORK

The objectives of this study were performing a clinical analysis and reviewing the data of 36 children having ADEM considering the clinical presentation and neuro-radiological findings (MRI Brain), with special consideration for the presence of convulsions and disturbed conscious level (DCL). In addition we analysed neuro-developmental outcome and IQ status.

PATIENTS AND METHODS

Study Design: Observational cross sectional hospital-based cohort study.

Place of the study: Inpatient, Emergency Department and Pediatrics neurology clinics of Pediatric Department, Bab Al-Shariah University Hospital.

Study Period: one year (from 31-12-2017 to 30-12-2018).

Patients: All children (36 cases) from birth to 18 years old who fulfilled the criteria for diagnosis of acute disseminated encephalomyelitis were included in this study.

Methods of the study: Detailed clinical data of the patients were observationally collected with special reference to:

Complete medical history with special attention to: Antenatal, perinatal and postnatal history. Developmental history. Onset of the disease. The presenting symptoms focusing on nervous system as disturbed conscious level, convulsions, abnormal movements, motor symptoms, sensory symptoms, sphincteric symptoms, abnormal behavior. Family history of any neurological problems. Types, frequency of seizures, duration and response to treatment.

Physical examination: Focusing on neurological system as conscious level, mental status, and abnormal features. Developmental assessment. Motor, sensory, sphincteric examination.

Investigations: Cerebrospinal fluid examination (CSF). Magnetic resonance imaging of the brain (MRI). Complete blood count (CBC). IQ: Stanford Benit test (version 4).

The study was approved by the Ethics Board of Al-Azhar University.

Statistical analysis:

Clinical, neuro-radiological, MRI for the brain, CSF and IQ data were entered into the SPSS 10, software package for descriptive statistics. Results of the study were expressed as mean with standard deviation and range, for continuous variables and as percentages for discrete variable.

According to Stanford -Binet Intelligence Scale, IQ was done to the studied cases.

RESULTS

Table (1) Age and sex distribution of studied population.

Characteristics	Number (%)	P value
Age		
Less than 12 months	2 (5.5%)	
1-4 years	14 (38.89%)	
5-8 years	16 (44.44%)	
9-12 years	2 (5.56%)	0.009
More than 12 years	2 (5.56%)	
Gender		
Male	20 (55.56%)	0.25
Female	16 (44.44%)	

Table (1): Neurological examination of studied population

Characteristics	Number (%)
GCS	
Less than 6	4 (11.11%)
6-10	18 (50.00%)
11-14	14 (38.89%)
Limb affection	
Free	10 (27.78%)
Monoparesis	2 (5.56%)
Hemiparesis	12 (33.33%)
Quadriparesis	12 (33.33%)
Muscle tone	
Normal	10 (27.78%)
Flaccid	16 (44.44%)
Spastic	10 (27.78%)
Reflexes	
Normal	8 (22.22%)
Hyporeflexia	2 (5.56%)
Hyperreflexia	26 (72.22%)
Sphincteric affection	
No	14 (38.89%)
Yes	22 (61.11%)

Table (2): Treatment of studied population

Characteristics	Summary statistics
Steroid treatment started at	
The first day of symptoms	8 (22.22%)
First week (excluding the first day)	22 (61.11%)
After one week of symptoms	6 (16.67%)
Immunoglobulin started at	
The first week of symptoms	10 (27.78%)
After one week of symptoms	8 (22.22%)
Not received	18 (50.00%)

Table (3): Platelet count and CSF finding of studied population.

Characteristics	Summary statistics
Platelet count	
150000 – 450000	16 (44.44%)
More than 450	20 (55.56%)
CSF	
Done	30 (83.33%)
Not done	6 (16.67%)
CSF protein (if CSF was done)	
20-40	16 (53.33%)
40-60	10 (33.33%)
60-80	4 (13.33%)
CSF glucose	
More than 2/3 serum glucose	26 (86.67%)
Less than 2/3 serum glucose	4 (13.33%)
CSF cell count	
Less than 5	22 (73.33%)
From 5-100	8 (26.67%)
Type of CSF cellularity	
Lymphocytes	22 (73.33%)
Polymorphs	8 (26.67%)

Table (4): Criteria of the studied population according to MRI brain.

Characteristics	Summary statistics
MRI pattern	
Subcortical	10 (27.78%)
Central white matter	6 (16.67%)
Cortical gray white junction	2 (5.56%)
Widespread	18 (50.00%)
Size of demyelination patches	
Less than 5 mm to 5 mm	2 (5.56%)
From 5 mm to 5 cm	30 (83.33%)
More than 5 cm	4 (11.11%)
Distribution of demyelination	
Bilateral	36 (100%)

Table (5): Evaluation of studied population after 3 and 6 months

Characteristics	After 3 months	After 6 months	P value
GCS			
11-14	6 (18.79%)	4 (12.50%)	1.00
15	26 (81.25)	28 (87.50%)	
IQ finding			
Profound MR (<19)	2 (6.25%)	2 (6.25%)	0.34
Sever MR (20-35)	2 (6.25%)	0	
Moderate MR (36-49)	6 (18.75%)	0	
Mild MR (50-69)	4 (12.50%)	8 (25.00%)	
Below average (70-89)	16 (50.00%)	16 (50.00%)	
Super average (110-119)	2 (6.25%)	6 (18.75%)	
Limb affection			
Free	22 (68.75%)	24 (75.00%)	0.91
Hemiparesis	8 (25.00%)	6 (18.75%)	
Quadriparesis	2 (6.25%)	2 (6.25%)	
Muscle tone			
Normal	22 (58.75%)	24 (75.00%)	1.00
Spastic	10 (31.25%)	8 (25.00%)	
Reflexes			
Normal	22 (48.75%)	24 (75.00%)	1.00
Hyperreflexia	10 (31.25%)	8 (25.00%)	
Sphincteric affection			
No	24 (55.00%)	30 (93.75%)	0.33
Yes	8 (25.00%)	2 (6.25%)	
Convulsion			
No	20 (62.50%)	24 (75.00%)	0.45
Yes	12 (37.50%)	8 (25.00%)	
Type of seizures if present			
Partial	2 (16.67%)	2 (25.00%)	0.68
Generalized	8 (66.67%)	6 (75.00%)	
Multiple	2 (16.67%)	0	
Frequency of seizures if present			
Not frequent			
Frequent	10 (83.33%)	8 (100%)	1.00
	2 (16.67%)	0	

DISCUSSION

Acute disseminated encephalomyelitis (ADEM) is an inflammatory, demyelinating, immune-mediated disorder common in the pediatric population. It is often associated with viral or bacterial infection or it may occur as rare post vaccination complication. It is characterized by an inflammatory reaction and demyelination of the central nervous system (CNS), with pathological changes occurring typically around small veins **(5).**

ADEM typically has a monophasic course with a favorable prognosis. Multiphasic forms have been reported, resulting in diagnostic difficulties in distinguishing these cases from multiple sclerosis. In addition, many inflammatory disorders may have a similar presentation with frequent occurrence of encephalopathy and should be considered in the differential diagnosis of acute disseminated encephalomyelitis **(6).**

The present study performed a clinical analysis and prospectively collected the data of 36 children having ADEM. They were subjected to complete neurological examination, investigations including; magnetic resonance imaging (MRI) of the brain, cerebrospinal fluid analysis (CSF), IQ examination according to **Stanford–Binet** Intelligence Scale, with a special consideration to neurological manifestations (e.g., the presence of disturbed conscious level, convulsions and its characteristic, motor system affection, autonomic disturbance and analysis of the neuro development status).

The age of studied populations ranged between 11 months and 14 years old. The mean age incidence was 5.5± 0.9 years old which was slightly higher than that of Pavone et al., study which was 3.6 years old**.** The male to female ratio was (1.25:1). This ratio was close to the study of Pavone et al., study where it was (1.4:1) **(7).**

The most prominent prodroma of ADEM was fever, there was history of symptoms suggesting acute viral or bacterial infection in 72.22% of cases, while those who didn't preceded by definite acute infection were five cases, and no case had history of proceeded vaccination prior to illness. This findings was close to Jayakrishnan et al., study as an acute febrile illness preceded the onset of neurological symptoms in 9 (64%) children. Among them, five (36%) had upper respiratory tract infection and four (27%) had non-specific fever. No preceding illness could be identified in five (36%) children **(8).**

The most common neurological complaint in our study was disturbed level of consciousness, which was detected in 30 children, followed by convulsions. While paresis and limb weakness was the complaint of two cases. Most patients had multiple complaints like DCL and convulsions or DCL and paresis. This was close to Tenembaum et al., study as patients who had acute hemiparesis were (76%), unilateral or bilateral long tract signs (85%), and changes in mental state (69%) were the most prominent presenting features **(9).**

By general examination of studied population, there was no characteristic finding except of fever. All cases were feverish at time of presentation, half of them suffered from low grade fever with trans rectal temperature ranging from (37.5°C to 38.5°C) and other half was having trans rectal temperature ranging from (38.5°C to 39.5°C). This was close to Pavone et al., study where 88% of patients were presented with fever **(7).** In our study, two cases had marked hepatosplenomegaly as he was suffering from lymphoma.

During neurologic examination, Glasgow coma scale evaluation of cases (GCS) revealed that 18 cases had GCS from 6 to 10, while 14 cases had GCS ranging from 11 to 14. Motor system affection was prominent as 12 cases had quadriparesis and other 12 cases had hemiparesis. Sphincteric affection was found in 61.11% of cases. So, 72.22% of cases had pyramidal tract affection which was close to Sundar et al, study where patients shown pyramidal signs (77.7%), acute hemiplegia (76%), ataxia (31%), myelitis (24%), bowel/bladder abnormalities (65.5%) and impairment of speech in (5%) **(10).**

Convulsions in our study were found in 30 cases. Those convulsions were generalized in 22 cases, multiple types of seizures in 6 cases and partial seizures in two cases. This was close to Tenembaum et al., study where generalized convulsions were the main feature and other types of seizures were also present. Seizures were frequent (occurring daily up to 5 times/day) in 16 cases, very frequent (more than 5 per day) in 10 cases, two cases suffered from status epileptics and not frequent (not daily convulsions) in two cases also. The response of seizures in our study to anticonvulsants was partial in 18 cases, good in 10 cases and two cases only had poor response. Seizures occurred in Weng et al., study were less than us, as it occurred in 10 cases (50%). but only one child developed epilepsy in follow-up **(11, 12).**

Thrombocytosis was found in 20 cases. This was in agreement with Sundar et al., study(10). Fifteen cases were subjected to cerebrospinal fluid analysis (CSF), it showed that 8 cases had CSF proteins ranging from (20-40mg/dl) and five cases had CSF proteins ranging from (40-60mg/dl). CSF glucose was normal in 86.67% of cases, while it was less than 2/3 serum glucose in two cases only. CSF cells count was normal in 22 cases and mild increase was noticed in eight cases. The cells were lymphocytes in 22 cases and polymorph nuclear leucocytes in eight cases. This agrees with Alper et al.**,** study as mild to moderate increase in CSF proteins was found. Another study done by Rezai et al., **(13)** showed that cerebrospinal fluid changes often included increased CSF pressure, raised protein and lymphocytic pleocytosis. In the study done by Govender et al., it showed that CSF are usually abnormal (in > 67% of cases), typically showing

a moderate pleocytosis with an elevated protein content [6, 14].

Magnetic resonance imaging of the brain (MRI) for all patients showed multiple foci of increased signal intensity on T2 and FLAIR images within the cerebral white matter. The demyelination patches were widespread in 18 cases, mainly subcortical in 10 cases. The size of those demyelination patches was from 5 mm to 5 cm in 30 cases (83.33%) and the distribution of demyelination patches was typically bilateral in all cases. This was constant with Sundar et al., study as subcortical and periventricular white matter involvement were the most frequent patterns seen. Thalamic and cortical grey matter involvement was also noted in 3.4 % and 20.6 % subjects respectively. Cortical grey matter, basal ganglia and thalamic involvement is a distinct feature of ADEM, while the same is exceedingly rare in MS [10].

In this study, 22 cases received corticosteroids at the first week of symptoms, eight cases only received corticosteroids at the first day of symptoms and six cases didn't receive corticosteroids until the first week had passed. These results were close to Sundar et al., study where the time interval in this study between the first symptom and initiation of treatment, ranged from 1 day to 3 months. Thirteen patients (44.8%) presented and were treated within 1 week of onset, 11 patients received treatment only between 10- 42 days after disease onset that was too late than our study. In Sundar et al., study, treatment with intravenous steroids was initiated in 25 patients (86.2%). Steroids act as immune suppressants leading to slowing of demyelination [10].

As regard immunoglobulin; it was given to cases that had poor response to high dose intravenous corticosteroids, some cases didn't receive it. Only 10 cases received immunoglobulin at the first week of symptoms, eight cases received it after the first week and 18 cases didn't receive immunoglobulin at all. This finding was more than Panicker et al., study as additional treatment with intravenous immune globulin was necessary in (13.33%) of patients [15].

After the course of treatment had finished, 16 cases (44.44%) completely cured, the other 16 cases (44.44%) developed neurological deficit (motor deficit or convulsions). Death was the fate of four cases, two of them died due to respiratory failure following aspiration pneumonia and the others had central respiratory suppression. These results were close but less than Menge et al., study as in follow up, approximately 60% of children has no neurologic deficits compared to 44.44% of our patients. This study also reports a mortality rate less than our study as it was 5% of cases compared to 11.12 % [16].

Follow up of the studied population showed that conscious level was markedly improved after 3 months, 26 cases (72.22%) were fully conscious, while six cases had conscious level ranging from (11-14 GCS). After 6 months another two cases gained its conscious level to make the total number of improved patients 28 case (87.50%) while four cases remained with disturbed conscious level (11-14 GCS). This agrees with Anlar et al., study of 39 children with 12 months' follow-up, 71 % recovered completely [17].

Motor system follows up after 3 months revealed that 22 cases became totally free (68.75%), eight cases had hemiparesis and two cases had quadriparesis. These cases showed more improvement after 6 months: It was found that (75%) of cases became totally free (18.75%) cases had hemiparesis and two cases had quadriparesis. This was close to Tenembaum et al., study, where motor deficits persist in 30% of cases and included paraparesis, hemiparesis and ataxia [12].

Convulsions were persisted after 3 months in 37.50% of cases. Convulsions were generalized in eight cases, focal in two cases and another two cases suffered multiple type convulsions. The seizures were not frequent in ten cases and frequent in another two cases. After 6 months; 24 cases were free from convulsions, while eight cases were still suffering from it. Seizures were generalized in six cases and focal in two cases (16.67%). It was the same as Panicker et al., study as persisting complaints included motor signs in 22.9 % (n=15) and bladder symptoms in 8 % of cases (n=5). None of the patients developed recurrence of neurological symptoms during the period of study [15].

CONCLUSION

ADEM is an area of active research especially in the field of imaging and there is a rapid development. In future we may have better diagnostic and therapeutic options for ADEM.

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