

Pattern and Outcome of Acute Disseminated Encephalomyelitis (ADEM) in Children: Experience in a Tertiary Center, Upper EgyptAbdelrahim Abdrabou Sadek¹, Mostafa Ashry Mohamed², Ashraf Abou-Taleb², Marwa Ibrahim Mohammed³

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Abstract

Introduction: Acute disseminated encephalomyelitis (ADEM) is an immune mediated disease of the brain. Although it occurs in all ages, most reported cases are in children and adolescents. The aims of this study were to study the clinical pattern and outcome of ADEM in children in a tertiary center in Upper Egypt and to determine the effect of combined use of steroids and IVIg on outcome.

Methods: This observational study was carried out from January 2014 through December 2014 in the Pediatric Department of Sohag University Hospital (Egypt). All children diagnosed as ADEM during a one year period were included in this study. The treatments used were IV methylprednisolone followed by oral prednisone taper and intravenous immunoglobulin for severe cases. All studied cases were followed up and reevaluated at three months and six months. We used SPSS version 10 and Chi Square, Spearman's test and t-test for data analysis.

Results: Eighteen children were included in this study (10 males and 8 females), the average age was 5.5 ± 0.9 years. Prodroma was found in 72.22% of the cases while the main complaint was encephalopathy (83.33%) followed by seizures (11.11%). The neurological findings were convulsions in 83.33%, quadriplegia (33.33%), hemiparesis (33.33%), bladder involvement (both retention and incontinence) in 61.11%, and cranial nerve affection (11.11%). Demyelination patches were multifocal in 50%, mainly subcortical in 27.78%. Intelligence quotient (IQ) assessment after 6 months follow up showed that 50% were below average, 25% had mild MR while neurological evaluation showed that 75% of our patients were completely cured. The predictors of better outcome were; children related to the age group (1-4 years) ($p = 0.01$), children with higher GCS (6-14) ($p = 0.01$), and children who received steroids on the first day of symptoms and intravenous immunoglobulin in the first week ($p = 0.03$).

Conclusion: The clinical pattern of acute disseminated encephalomyelitis is variable, and a disturbed level of consciousness was the most common presentation. The outcome is generally favorable although motor deficit and cognitive impairment were reported. The combined use of steroids and IVIg has substantial effect on the outcome in children with ADEM.

Keywords: Acute disseminated encephalomyelitis, ADEM, Egypt

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune mediated disease of the brain. It occurs following a viral infection but may appear following vaccination, bacterial or parasitic infection (1). It occurs in all ages, with an average age of around 5 to 8 years old. Full recovery is seen in 50 to 75% of cases. The estimated mortality rate may be as high as 5% (2). The inflammatory lesions are found in the subcortical and central white matter and cortical gray-white junction of cerebral hemispheres, cerebellum, brainstem, and spinal cord (3). When the patient suffers more than one demyelinating episode, it is called recurrent disseminated encephalomyelitis or multiphasic

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disseminated encephalomyelitis (MDEM) (4). The clinical presentation is polysymptomatic: altered mental status, pyramidal dysfunction, acute hemiparesis, cerebellar ataxia, brainstem syndromes, optic neuritis, and myelitis. Seizures can be focal or generalized and encephalitic illness is more common in children younger than 3 years (1, 5-7). The accepted first-line treatment is high doses of intravenous corticosteroids, such as methylprednisolone, followed by 3-6 weeks of gradually lowered oral doses of prednisolone (8). Other anti-inflammatory and immunosuppressive therapies have beneficial effects; plasmapheresis, high doses of intravenous immunoglobulin (IVIg), mitoxantrone and cyclophosphamide (9). A review of IVIg treatment of ADEM found that 70% of children showed complete recovery after treatment with IVIg, or IVIg plus corticosteroids (10). Residual deficits estimated to remain in about 8 to 30% of cases, ranging from mild clumsiness to hemiparesis (7). Patients with ADEM showed cognitive deficits even when there was minimal physical disability (11). Few studies were conducted addressing pattern and outcome of ADEM in children in Upper Egypt, so this work was aimed at clarifying this subject and exploring the effect of steroids and IVIg on outcome.

2. Material and Methods

2.1. Study design and research ethics

This is an observational hospital based study, carried out in the Pediatric department at Sohag University Hospital, Egypt, during a one year period from January 2014 through December 2014. All children from one month to 18 years who fulfilled criteria for ADEM diagnosis were eligible, and informed consent of parents of children was taken in addition to approval of the Faculty of Medicine, Sohag University Ethics Committee. The work has been carried out in accordance with The Code of Ethics of The World Medical Association (Declaration of Helsinki) for experiments on humans.

2.2. Data collection and statistical Methods

The diagnosis of ADEM is based on clinical features (acute neurologic abnormalities), and radiological evidence of demyelination as proposed by the International Pediatric Multiple Sclerosis Study Group (12). All children were admitted to the Pediatric Department, Sohag University Hospital. Magnetic resonance imaging of the brain (MRI) was carried out for all patients as a diagnostic modality for ADEM. We used multiplanar MRI system (1.5 tesla), and sagittal T1 weighted, coronal T2 weighted, axial diffusion weighted, T1 weighted, and Flair sequences were applied. All studied patients were subjected 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 (types, and response to treatment), along with abnormal movements, motor symptoms, sensory symptoms, sphincteric symptoms, abnormal behavior, and family history of any neurological problems. Full clinical examination; general, systematic, and detailed neurological examinations (conscious level, mental status, and abnormal features, motor, sensory, and sphincteric examination) were carried out for all patients. Complete blood counts were carried out for all patients (by Abbott Cell Dyn Ruby analyzer, Abbott Diagnostic, Abbott Park, IL, USA) while cerebrospinal fluid (CSF) analysis (physical, chemical, and cytological aspects by Cobas c 311 analyzer, Roche Diagnostics, Germany) for only 15 patients. The treatment protocol was intravenous methylprednisolone 30 mg/kg/d for 3 consecutive days followed by oral prednisone taper over one month and severe cases received also IVIg 400mg/kg/ d for five days. Developmental evaluation, and IQ assessments using Stanford Binet Intelligence Scales (4th edition) (13, 14) were carried out for all remaining children in the study group at three months and six months after the acute attack. Data were analyzed by SPSS version 10 (SPSS Inc., Chicago, Illinois, USA). Results of the study were expressed as mean, standard deviation, and range, for continuous variables and as percentages for discrete variable. Chi Square, Spearman's test and t-test were employed for inferential statistical analysis. The probability of less than 0.05 was used as a cut off point for all significant tests.

3. Results

Eighteen children [10 males (55.56%) / 8 females (44.44%)] diagnosed as ADEM were recruited, their ages ranged between 11 months and 14 years with average age of 5.5 ± 0.9 years. Encephalopathy was the main complaint in 15 cases (83.33%) followed by convulsions in two cases (11.11%). Prodromal events (history suggestive of viral or bacterial infection) reported in 13 cases (72.22%). Neurological findings showed nine cases (50%) had Glasgow Coma Scale (GCS) from 6 to 10, while seven cases (38.89%) had GCS ranging from 11 to 14; six cases (33.33%) had quadriparesis, six cases (33.33%) had hemiparesis, two cases (11.11%) had cranial nerve affection. Bladder involvement (both retention and incontinence) was found in 11 cases (61.11%) (Table 1). Fifteen cases (83.33%) developed convulsions which were generalized in 11 cases (73.33%), multiple types (20 %), and the response of seizures to anticonvulsants was partial in nine cases (60 %) (Table 1). Eleven cases (61.11%) received

corticosteroids at first week of symptoms, and four cases (22.22%) received corticosteroids at first day of symptoms. Furthermore immunoglobulin was received at first week of symptoms in five cases (27.78%), after first week in four cases (22.22%) (Table 2). Thrombocytosis was found in 10 cases (55.56%), while CSF analysis was carried out in fifteen cases, the majority of them (8 cases / 53.33%) had CSF proteins ranging from (20-40mg/dl), furthermore CSF cell count was normal (less than 5 cells /mm³) in 11 cases (73.33%) and mild pleocytosis was noted in four cases (26.67%) (Table 3).

Table 1. Neurological evaluation of studied cases

Characteristics		n (%)
GSC score	<6	2 (11.11)
	6-10	9 (50)
	11-14	7 (38.89)
Convulsions	Yes	15 (83.33)
	No	3 (16.67)
Type of seizures (if present)	Generalized	11 (73.33)
	Multiple	3 (20.00)
	Partial	1 (6.67)
Response of seizures to anticonvulsants	Partial	9 (60.00)
	Good	5 (33.33)
	Poor (status epilepticus)	1 (6.67)
Limb affection	Hemiparesis	6 (33.33)
	Quadriparesis	6 (33.33)
	Normal	5 (27.78)
	Monoparesis	1 (5.56)
Muscle tone	Spastic	8 (44.44)
	Flaccid	5 (27.78)
	Normal	5 (27.78)
Reflexes	Hyperreflexia	13 (72.22)
	Normal	4 (22.22)
	Hyporeflexia	1 (5.56)
Sphencteric affection	Yes	11 (61.11)
	No	7 (38.89)

Table 2. Treatment of studied cases

Characteristics		n (%)
Steroid treatment started at:	The first day of symptoms	4 (22.22)
	First week (excluding the first day)	11 (61.11)
	After one week of symptoms	3 (16.67)
Immunoglobulin started at:	The first week of symptoms	5 (27.78)
	After one week of symptoms	4 (22.22)
	Not received	9 (50.00)

Table 3. Platelet count and CSF finding of studied group

Characteristics		n (%)
Platelet count	150,000 – 450,000 / mcL	8 (44.44)
	More than 450,000 /mcL	10 (55.56)
CSF protein	20-40	8 (53.33)
	40-60	5 (33.33)
	60-80	2 (13.33)
CSF glucose	More than 2/3 serum glucose	13 (86.67)
	Less than 2/3 serum glucose	2 (13.33)
CSF cell count	Less than 5	11 (73.33)
	From 5-100	4 (26.67)
Type of CSF cellularity	Lymphocytes	11 (73.33)
	Polymorphs	4 (26.67)

Demyelination patches in MRI were multifocal in nine cases (50%), subcortical in five cases (27.78%), at central white matter in three cases (16.67%) (Table 4). At hospital discharge, eight cases (44.44%) were completely cured; eight cases (44.44%) cured with remaining neurological deficit. There were two fatalities due to respiratory failure and status epilepticus. Neurological evaluation after 3 months; 11 cases (68.75%) were cured, four cases (25 %) had hemiparesis, furthermore after 6 months; 12 cases (75%) became cured, three cases (18.75%) had hemiparesis. Assessment of IQ at 3 months; eight cases (50 %) were below average, three cases (18.75%) had moderate mental retardation (MR), while after 6 months, eight cases (50 %) had below average IQ, four cases (25%) had mild MR, and three cases (18.75%) had super average IQ (Table 5). Predictors of outcome were; age groups, GCS, steroids at first day of symptoms and IVIg at first week, thrombocytosis (> 450 000/ mL) (Table 6).

Table 4. MRI brain characteristics of the studied group

Characteristics		n (%)
MRI lesions	Multifocal	9 (50.00)
	Subcortical	5 (27.78)
	Central white matter	3 (16.67)
	Cortical gray white junction	1 (5.56)
Size of demyelination patches	Less than 5 mm to 5 mm	1 (5.56)
	From 5 mm to 5 cm	15 (83.33)
	More than 5 cm	2 (11.11)
Distribution of demyelination	Bilateral	Bilateral

Table 5. Evaluation of studied group after 3 and 6 months

Characteristics		After 3 months	After 6 months	p-value
GCS score	11-14	3 (18.79)	2 (12.50)	1.00
	15	13 (81.25)	14 (87.50)	
IQ finding	Profound MR (<19)	1 (6.25)	1 (6.25)	0.34
	Sever MR (20-35)	1 (6.25)	0	
	Moderate MR (36-49)	3 (18.75)	0	
	Mild MR (50-69)	2 (12.50)	4 (25.00)	
	Below average (70-89)	8 (50.00)	8 (50.00)	
	Super average (110-119)	1 (6.25)	3 (18.75)	
Limb affection	Free	11 (68.75)	12 (75.00)	0.91
	Hemiparesis	4 (25.00)	3 (18.75)	
	Quadriparesis	1 (6.25)	1 (6.25)	
Muscle tone	Normal	11 (58.75)	12 (75.00)	1.00
	Spastic	5 (31.25)	4 (25.00)	
Reflexes	Normal	11 (48.75)	12 (75.00)	1.00
	Hyperreflexia	5 (31.25)	4 (25.00)	
Sphencteric affection	No	12 (55.00)	15 (93.75)	0.33
	Yes	4 (25.00)	1 (6.25)	
Convulsions	No	10 (62.50)	12 (75.00)	0.45
	Yes	6 (37.50)	4 (25.00%)	

4. Discussion

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disorder more common in the pediatric population (15). The present study performed a clinical analysis and prospectively collected the data of eighteen children diagnosed as ADEM. The average age of our series was 5.5 ± 0.9 years and this was consistent with other studies (2, 16) but slightly higher than other reports (17) and lower than other researchers (18-21), this could be related to different scope and age ranges between researchers. The male to female ratio was (1.25:1), this male predominance was comparable to other studies (8, 17, 18, 22). Prodromal events found in 72.22% of cases, this was close to other reports in the literature (1, 8, 23, 24), however higher percentages were reported by others (16, 17, 21), furthermore lower results were obtained by other report (25). The most common complaint was encephalopathy (83.33%, n=15), followed by convulsions (11.11%). (Most patients had multiple complaints). Similar results were obtained by other researchers (1, 8, 16, 18, 19, 25). Neurological evaluation showed 72.22% of cases had pyramidal

tract affection (quadripareisis, hemiparesis and sphenteric affection) which was close to other reports (8, 24, 25). Convulsions in our study were found in 15 cases (83.33 %), 73.33 % of them were generalized. This was close to other studies (8).

Table 6. Some predictors of outcome in the studied group

Characteristics		Outcome			p-value
		Death; n (%)	Neurological deficit; n (%)	Cured; n (%)	
Age (year)	<1	1 (50)	0	0	0.01
	1-4	0	3 (37.50)	4 (50.00)	
	5-8	0	5 (62.50)	3 (37.50)	
	9-12	0	0	1 (12.50)	
	>12	1 (50)	0	0	
GCS score	<6	2 (100)	0	0	<0.0001
	6-10	0	3 (37.50)	6 (75.00)	
	11-14	0	5 (62.50)	2 (25.00)	
Steroid treatment started at:	The first day of symptoms	0	0	4 (50.00)	0.12
	First week	2 (100)	6 (75.00)	3 (37.50)	
	After one week of symptoms	0	2 (25.00)	1 (12.50)	
Immunoglobulin started at:	The first week of symptoms	0	0	5 (62.50)	0.03
	After one week of symptoms	0	2 (25.00)	2 (25.00)	
	Not received	2 (100)	6 (75.00)	1 (12.50)	
Platelet count	150,000-450,000/mcL	0	2 (25.00)	6 (75.00)	0.054
	> 450,000 / mcL	2 (100)	6 (75.00)	2 (25.00)	

The response of seizures to anticonvulsants was partial in 60 %. In contrast, other reports showed that seizures occurred in 50% only and one child developed epilepsy in follow-up (16). Thrombocytosis was found in 10 cases, this was correspondent with similar studies (25). Fifteen cases were subjected to cerebrospinal fluid analysis (CSF), and 86.7 % had elevated CSF proteins, while 26.7 % had mild pleocytosis. These changes in CSF were reported by other studies (19, 25, 26). The results of MRI of the brain showed multiple foci of increased signal intensity in T2 and FLAIR images within the cerebral white matter in all patients. The demyelination patches were multifocal in 50 %. This finding was consistent with other reports (16, 25). Time of corticosteroids initiation ranged from first day to more than one week. Comparable results were obtained in other studies (25), as the time interval between the first symptom and initiation of treatment, ranged from 1 day to 3 months. Nine cases (50%) needed IVIg, and only five cases (55.55 %) received it at first week of symptoms. Data from other reports (9) showed IVIg was needed in 37.5% Furthermore, in another study (21) performed in Tunisia, additional treatment with IVIg was necessary in (13.33%) of patients. This difference between studies could be explained by the nature and severity of cases. In addition our hospital is a tertiary center serving a large area in Upper Egypt, so most of them was severely affected. After 6 months, 75 % of patients were cured and the remaining 25% had neurological deficit (hemiparesis and quadripareisis). Data from other reports were consistent with our findings (8, 16, 21, 22), however higher results (81 % and 94%) were obtained by other researchers (17, 23, 27), furthermore lower results (57%) were obtained by other studies (1). The mortality in our cases (11.12 %) was higher than other reports (16, 28). This can be explained by occurrence of severe complications as status epilepticus and respiratory failure. None of our cases developed relapse (12) or fulfilled the criteria of multiple sclerosis as obtained by other studies (27, 28) as our follow up period was short (only 6 months) and long term follow up is needed to clarify this point. Assessment of IQ demonstrated some impairment in cognitive function, and this finding was consistent with other reports (24, 29, 30). Other data (11) showed that some of them performed at least one standard deviation below age norms in at least one cognitive domain, furthermore criteria for cognitive impairment was met in other reports (4). Finally this study reported some risk factors for outcome of ADEM in children; extreme age groups (< 1 year and > 12 years) and low GCS children (< 6) were vulnerable to mortality while highest neurological disability occurred in the age group (5-8 years)

(62.5%), and children with GCS score between 6-14. Furthermore children cured were more related to the age group (1-4 years), and who had received steroids at first day of symptoms and IVIg at first week.

5. Conclusions

Based on the above information, the clinical pattern of acute disseminated encephalomyelitis is variable. Disturbed level of consciousness was the commonest presentation and seizures were reported in significant percentages while prior prodroma was found in two thirds of the patients. The outcome is generally good, as motor deficit was reported in only one third of cases, meanwhile some cognitive impairment occurred. The predictors of better outcome were children at age group 1-4 years, and those received steroids at the first day of symptoms and intravenous immunoglobulin at the first week, so the combined use of steroids and IVIg has substantial effect on the outcome in children with ADEM. Large series may be needed in the future to explore this issue.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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