FUCTIONAL OUTCOME OF ACUTE DISSEMINATED ENCEPHALOMYELITIS IN CHILDREN

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ABSTRACT

Objective: To determine functional outcome of acute disseminated encephalomyelitis in children and factors affecting outcome at The Children's Hospital, Lahore.

Study Design: Cross-sectional observational study.

Place and Duration of Study: Department of Pediatric Neurology, The Children's Hospital and Institute of Child Health, Lahore from Nov 2014 to Oct 2015.

Material and Methods: Fifteen patients with acute disseminated encephalomyelitis fulfilling the inclusion criteria were enrolled. Detailed history, examination, prior febrile illness and modified Rankin scale score for functional disability at presentation and discharge were recorded through study proforma. All patients underwent lumbar puncture and neuroimaging. Data were analysed in SPSS (v.20) and Chi-square test was applied to find *p*-value.

Results: Out of 15 patients, there was male predominance (10 male 66.7%) with mean age 7.4 ± 2.5 years. Encephalopathy 100% (n=15) followed by fever, fits 73.3% (n=11) and motor deficit 60% (n=9) were common presentation. About 46.7% (n=7) cases had prior febrile illness. MRI brain had >5 lesions in 86.7% (n=13) with sub-cortical area 93.3% (n=14) periventricular area 86.7% (n=13). Functional outcome was good in 80% (modified Rankin scale of 2 or less at time of discharge). Consciousness level and disability score at presentation were statistically significant factors affecting the outcome (*p*-value 0.004 & 0.002 respectively).

Conclusion: Acute disseminated encephalomyelitis in children had variable clinical presentation. It has good outcome with level of consciousness and disability score being significant factors affecting outcome.

Keywords: Acute disseminated encephalomyelitis, Consciousness, Encephalopathy, Prognosis.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an acquired demyelinating disorder of central nervous system caused by immune mediated phenomenon triggered by antecedent viral or bacterial infection. It is polysymptomatic, monophasic disease with particular neuro-radiological findings. Encephalopathy is the hall mark, present in >95% cases[1]. Other clinical features include seizure, visual loss, motor deficit, paraplegia, ataxia, raised intracranial pressure, cranial nerve palsies, spinal cord and brainstem dysfunctions[2-4].

ADEM is a rare disorder and its incidence varies in different countries. In California, it is 0.4/100,000/year[5], and in Canada 0.2/100,000/year[6]. Approximately 3 to 6 cases are seen each year at regional centres in the USA, UK, and Australia[2,7,8].

Although it occurs in all ages, most reported cases are in children and adolescents, with the average age around 5 to 8 years[2,9,10].

Different aetiologies have also been studied and a clear co-relation has been found to the preceding history of febrile illness, viral or bacterial with an afebrile period from 1 to 20 days before the presentation of ADEM in 72% to 77% cases[2,3,7]. Various immunizations like Rabies, Measles, Mumps, Rubella, Pneumococcal, Diphtheria/Pertussis/Tetanus, Hepatitis B, have been found as a triggering factor for ADEM but very rare[11].

Various diagnostic criteria have been applied to make a diagnosis but no single definite diagnostic parameter is there to make the exact diagnosis.

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Received: 15 Jun 2017; revised received: 18 Oct 2017; accepted: 02 Nov 2017

International Pediatric MS Study group has made consensus definition and criteria for the diagnosis of ADEM and other related demyelinating disorders[1].

The outcome of ADEM is highly variable and various factors have been found affecting the outcome. Recovery is usually good and seen in 50% to 75% with increased survival rate upto 70% to 90%. Poor outcome is related with maximum disability at time of presentation and absence of fever[3,12,13].

The early presentation with high index of suspicion for prompt diagnosis and early intervention has lead to good outcome. In our set up outcome has not been studied much. We had conducted the study to determine the functional outcome of patients with ADEM at the time of discharge and looked for the factors which affect the outcome so that we would be able to adopt various regimens to improve the functional outcome of ADEM in our set up.

PATIENTS AND METHODS

After approval from Institutional Review Board (IRB), this cross sectional study was conducted at department of Pediatric Neurology, The Children's Hospital and Institute of Child Health, Lahore, a tertiary care referral centre from Nov 2014 to Oct 2015. Considering incidence of 0.2/100,000/year, sample size was calculated to be minimum of 13 cases with confidence level of 80% within confidence limits of 5% by openEpi version 3 open source calculator sample size equation;

n=[DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)]

After informed consent, total 15 patients fulfilling the inclusion criteria laid down by the International Pediatric MS Study Group i.e. (first monophasic episode having polysymptometic encephalopathy, with acute or subacute onset, showing focal or multifocal hyperintense lesions on MRI predominantly affecting the CNS white matter[1]) from 6 month to 18 years of either sex were enrolled through non-probability consecutive sampling. While patients having meningitis or encephalitis with encephalopathy, acquired demyelinating disorder other than ADEM like multiple sclerosis, transverse myelitis, optic neuritis and neuromyelitis optica or any inherited demyelinating disorders like Leukodystrophies were excluded. After demographic data, all cases were examined neurologically in detail. Clinical data regarding symptoms and sign, any preceding history of upper respiratory tract infection, diarrhoea, vaccination, or measles infection were collected. All cases underwent CSF analysis and MRI of brain and spine with gadolinium enhancement. Treatment given was intravenous methylprednisolone pulses (30mg/ kg/day not more than 1gm) for five days followed by oral steroid for 4-6 weeks. The modified Rankin scale (mRS) for functional disability was applied first at presentation and second at the time of discharge. The factors like duration of sign and symptoms, age, gender, functional disability and consciousness level at the time of presentation were studied. All data collected were analysed by SPSS (v.20). The continuous variables like age were presented as mean and standard deviation while the categorical variables like sex were presented in percentages. Comparison was made between different factors affecting the outcome in terms of functional outcome measured by mRS. These factors included gender, age, duration of illness, conscious level measured by Glasgow coma scale and functional disability score measured by mRS both at time of admission and at time of discharge. Outcome was considered good with mRS score of 2 or less at time of discharge and bad with mRS of 3 or more. Results were presented after determining their significance by using chi-square test in which p-value less than <0.05 was taken as significant.

Modified Rankin Scale runs from 0-6, running from perfect health without symptoms to death[14].

- No symptoms.
- No significant disability: Able to carry out all usual activities, despite some symptoms.

- Slight disability: Able to look after own affairs without assistance, but unable to carry out all previous activities.
- Moderate disability: Requires some help, but able to walk unassisted.
- Moderately severe disability: Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
- Severe disability: Requires constant nursing care and attention, bedridden, incontinent.
- Dead

RESULTS

Out of 15 patients, 66.7% (n=10) were male and age range was 4 to 12 years, mean 7.4 ± 2.5 years. Majority, 40% (n=6) presented between 4-6 years of life and >70% (n=11) were below 10 years as shown in table-I. Prior predisposing factors were present in 46.7% (n=7) of cases, respiratory tract infection being the most common 33.3% (n=5) followed by acute gastroenteritis. About 73.3% (n=11) cases were presented within 5 days of onset of sign and symptoms.

Clinical features were highly variable but disturbed conscious level of some degree was present in 100% (n=15) cases followed by fever, fits {73.3% (n=11)}, motor deficit {60% (n=9)}, and speech and visual disturbance {33.3% (n=5)}. Other clinical features are given in table-II. CSF analysis was insignificant with normal sugar and

Table-I: Age and gender distribution.

Age group	Gender		Total
	Male (n)	Female (n)	n (%)
4-6 years	3	3	6 (40)
7-9 years	4	1	5 (33.3)
10-12 years	3	1	4 (26.7)
Total	10 (66.7%)	5 (33.3%)	15

Table-II: Clinical features of ADEM.

Clinical feature	n (%)
Fever	11 (73.3)
Prior viral or bacterial infection	07 (46.7)
Disturbed conscious level	15 (100)
Seizures	11 (73.3)
Speech loss	5 (33.3)
Decreased visual acuity	5 (33.3)
Motor weakness	9 (60)
Pyramidal signs	14 (93.3)
Extra pyramidal sign	2 (13.3)
Cerebellar sign	1 (6.7)
Brainstem dysfunction	2 (13.3)
Spinal cord dysfunction	3 (20)

Table-III: MRI Anatomical lesions in ADEM in children.

Location	n (%)
Cortex	12 (80)
Periventricular	13 (86.7)
Sub cortical	14 (93.3)
Basal ganglia	5 (33.3)
Optic nerve	2 (13.3)
Brainstem	2 (13.3)
Spinal cord	4 (26.6)

proteins without pleocytosis except in one patient having lymphocytosis with raised CSF proteins. The number of lesions on MRI brain were found to be >5 in 86.7% (n=13) of cases involving predominantly sub-cortical area {93.3% (n=14)}, periventricular area {86.7% (n=13)} and cortical {80% (n=12)} as mentioned in table-III. The functional disability score calculated by mRS at time of admission showed that 73.3% (n=11) of the cases were having mRS score between 4 and 5 (6 having mRS scale of 4 while 5 having scale 5) and 26.7% (n=4) having mRS score of 3. The mRS at the time of discharge was better than that of presentation. Eighty percent (n=12) had good outcome i.e. mRS being 2 or <2 meaning that either had no or slight disability. None of discharged patients was having severe disability compared to 33.3% (n=5) cases having severe disability at the time of admission. Only 20% (n=3) of cases were having moderate to moderately severe disability at the time of discharge (score 3 or 4). None of the patient in our study group died as shown in table-IV.

Table-IV: Comparison of gender, age, duration, GCS & mRS at admission with mRS at discharge.

Variables	Functional disability score (mRS) at time of discharge							n (%)	*p*- value
	No symptoms (0)	No significant disability and able to carry out all usual activities (1)	Slight disability but able to look after own affairs without assistance (2)	Moderate disability requires some help but can walk unassisted (3)	Moderately severe disability, needs help for own bodily needs, unable to walk without assistance(4)	Severe disability Requires constant nursing care and attention, bedridden, incontinent. (5)	Death (6)		
Gender									
Male	2	2	2	2	2	0	0	10 (66.7)	0.463
Female	1	3	0	0	1	0	0	5 (33.3)	
Age									
4-6 y	2	2	1	0	1	0	0	6 (40)	0.452
7-9 y	1	2	1	0	1	0	0	5 (33.3)	
10-12 y	0	1	0	2	1	0	0	4 (26.7)	
Duration									
<5days	2	5	1	1	2	0	0	11 (73.3)	0.546
>5days	1	0	1	1	1	0	0	4 (26.7)	
GCS									
<8/15	0	0	0	0	3	0	0	3 (20)	0.004
8-12/15	0	1	2	1	0	0	0	4 (26.7)	
12-14/15	3	4	0	1	0	0	0	8 (53.4)	
mRS at admission									
3	3	1	0	0	0	0	0	4 (26.7)	0.002
4	0	4	2	0	0	0	0	6 (40)	
5	3	5	2	2	3	0	0	5 (33.3)	
Count (%) of total 15	3 (20%)	5 (33.3%)	2 (13.3%)	2 (13.3%)	3 (20%)	0	0	15 (100)	

Comparison of factors affecting the outcome is shown with their *p*-values in table-IV. Statistically significant factors affecting the outcome in our studies were the level of consciousness and functional disability score at

time of admission (*p*-value 0.004 and 0.002 respectively). Rest of the factors studied were not statistically significant.

DISCUSSION

Acute disseminated encephalomyelitis is usually monophasic, polysymptomatic immune mediated disorder. Encephalopathy is the hallmark of the ADEM present in >95% of cases, along with other symptoms like seizure, focal neurological deficit, visual and speech disturbances, ataxia, paraplegia and spinal cord dysfunction[2-4].

We conducted the study to look for the functional outcome of the patients with ADEM at time of discharge. In our study, ADEM had male predominance (66.7%) with male to female ratio 2:1. This male predominance has been observed in other studies and this ratio correlates like there were 23 males out of 28 in a study done by Hung *et al*[15]. Some other studies also had same male predominance with different ratios[16]. Majority of studies showed mean age of presentation below ten years as found it to be 6.9 years, 7.5 years and 7.2 years in different studies[15,17,18]. We observed the same trend in our study. Results of prior predisposing factors (46.7%) in current study, amongst them respiratory tract infection was the most common, are comparable with the work done by Tomás Vila *et al* and Giri *et al* where they found it to be 40% and 50% respectively[19,20]. On the other hand some authors had found febrile illness as high as 88%[16,21]. Likewise some studies have documented prior febrile illness without any specific organism in >70% of cases.

Presentation of ADEM is highly variable with multifocal neurological sign and symptoms. Encephalopathy is the most prominent feature which ranges from confusion and irritability to deep coma. This altered state of consciousness was the universal findings (100%) in our study followed by fever and fits (73.3%), motor deficit (60%) and speech along with visual disturbances (33.3%). Such variable presentation demonstrates the multifocal involvement of central nervous system. Majority of the studies do mention the encephalopathy as most common presentation as high as >90% of cases[1,15,18,20]. On contrary, there are some studies which had motor deficit as the most common presentation rather than encephalopathy which was second most common feature[16,17].

Cerebrospinal fluid analysis may demonstrate pleocytosis predominantly lymphocytes with moderate increase in CSF proteins but normal sugar. Usually it is done to exclude possible CNS infections. We went for CSF analysis in all patients but only one patient had pleocytosis with raised proteins. Our findings is different from other studies as CSF pleocytosis with raised proteins was present in 28-65% of cases of ADEM[8,22].

Diagnostic modality for ADEM is MRI of brain and at times of spinal cord with gadolinium enhancement. All patients were having abnormal MRI findings with >5 lesions in 86.7% of patients. Sub-cortical and periventricular areas were most commonly involved. Such disseminated lesions have been observed with predominant subcortical white matter (90.5%), periventricular white matter (61.9%) followed by deep grey matter area like basal ganglia. comparable with current study[17,23].

We adopted modified Rankin scale to measure disability at the time of admission as well as at the time of discharge. Eighty percent of cohort had good outcome (disability score of 2 or less at the time of discharge). None was having severe disability and there was no mortality. These results are well comparable with other studies in which there is 100% recovery and >70% having slight or no disability[17,18]. In one prospective long term study along with meta-analysis, good outcome (94%) was even higher than any previous cohorts. Generally the disease has good outcome with slight to moderately severe disability and there is very less chance of mortality. These all results are well comparable to the current study[16].

We studied five factors which could be potential predictors of outcome i.e. age, gender, duration of onset of ADEM, level of consciousness and disability score at time of admission. There was a linear relationship in disability scores measured at the time of admission and discharge. The patients with severe disability at time of admission had less recovery compared with those having less disability at time of admission. Same is the case with level of consciousness. Both disability score and conscious level at presentation were statistically significant in terms of functional outcome at discharge (*p*-value <0.5). Such observations had been evident in a large series of patients of ADEM in Taiwan[13]. Although this study was conducted on all age groups including adults as well but they had found that initial disability score and no fever were the predictor of poor outcome (modified Rankin scale <2). In another study published in 2016 in Egypt, concluded that extreme age groups (age <1 year and >12 years) along with poor GCS were associated with poor outcome[24].

In children, ADEM still is underdiagnosed and high index of suspicion is required so that prompt diagnosis and timely intervention should be done which will help to get good outcome. In order to assess long term outcome, we need to conduct large scale study with long term follow.

CONCLUSION

Study demonstrated that ADEM had multifocal clinical presentation with prior febrile illness. Outcome is generally good with boys affected more than girls. Level of consciousness and disability score at the time of admission are significant factors affecting outcome.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

REFERENCES

1. Krupp LB, Banwell B, Tenembaum S. International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007; 68: 7-12.
2. Paliwal VK. Acute disseminated encephalomyelitis in children. Neurol India 2016; 64: 1193-4.
3. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: A long-term follow-up study of 84 pediatric patients. Neurology 2002; 59: 1224-31.
4. Tenembaum S, Chitnis T, Ness J, Hahn JS. International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007; 68: 23-36.
5. Leake JA, Albani S, Kao AS. Acute disseminated encephalomyelitis in childhood: Epidemiologic, clinical and laboratory features. Pediatr Infect Dis J 2004; 23: 756.
6. Banwell B, Kennedy J, Sadovnick D. Incidence of acquired demyelination of the CNS in Canadian children. Neurology 2009; 72: 232.
7. Dale RC, de Sousa C, Chong WK. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000; 12: 2407.
8. Murthy SN, Faden HS, Cohen ME, Bakshi R. Acute disseminated encephalomyelitis in children. Pediatrics 2002; 110: 21.
9. Koelman DL, Chahin S, Mar SS, Venkatesan A, Hoganson GM, Yeshokumar AK et al. Acute disseminated encephalomyelitis in 228 patients: A retrospective multicenter US study. Neurology 2016; 86: 2085-93.
10. Yang HQ, Zhao WC, Yang WM, Li YL, Sun ZK, Chen S et al. clinical profile and Short-Term Outcome of acute disseminated encephalomyelitis in adult chinese patients. J Clin Neurol 2016; 12: 282-8.
11. Baxter R, Lewis E, Goddard K, Fireman B, Bakshi N, DeStefano F et al. Acute Demyelinating Events Following Vaccines: A Case-Centered Analysis. Clin Ifect Dis 2016; 63: 1456-62.
12. Ben AN, Ben WO, Kraoua I, Benrhouma H, Klaa H, Rouissi A et al. Acute disseminated encephalomyelitis in Tunisia: Report of a pediatric cohort. Rev Neurol 2015; 171: 882-90
13. Lin CH, Jeng JS, Hsieh ST, Yip PK, Wu RM. Acute disseminated encephalomyelitis: A follow-up study in Taiwan. J Neurol Neurosurg Psychiatry 2007; 78: 162–7.
14. Quinn TJ, Lees KR, Hardemark HG, Dawson J, Walters MR. Initial experience of a digital training for modified Rankin scale assessment in clinical trials. Stroke 2007; 38: 2257-61.
15. Hung PC, Wang HS, Chou ML, Lin KL, Hsieh MY, Wong AM. Acute disseminated encephalomyelitis in children: A single institution experience of 28 patients. Neuropediatrics 2012; 43: 64-71.
16. Pavone P, Pettoello-Mantovano M, Le Pira A, Giardino I, Pulvirenti A, Giugno R, et al. Acute disseminated encephalomyelitis: A long-term prospective study and meta-analysis. Neuropediatrics 2010; 41: 246-55.
17. Elhassanien AF, Aziz HA. Acute demyelinating encephalomyelitis: Clinical characteristics and outcome. J Pediatr Neurosci 2013; 8: 26–30.
18. Likasitwattanakul S, Chiewvit P. Acute disseminated encephalomyelitis in Siriraj Hospital: clinical manifestations and short-term outcome. J Med Assoc Thai 2012; 95: 391-6.
19. Tomás-Vila M, Menor F, Otero-Reigada MC, Pérez-Tamarit A, Téllez de Meneses M, Pitarch. Clinico-radiological profile of acute disseminated encephalomyelitis in the childhood population. A retrospective analysis of a series of 20 patients in a tertiary hospital. Rev Neurol 2014; 58: 11-9.
20. Giri PP, Bhattyacharya S, Das D, Mukhopadhaya S. Acute disseminated encephalomyelitis: A clinical and neuroradiological profile of pediatric patients. Neurol India 2016; 64: 1187-92.

21. Erol I, Ozkale Y, Alkan O, Alehan F. Acute disseminated encephalomyelitis in children and adolescents: a single center experience. Pediatr Neurol 2013; 49: 266-73.
22. Das K, Basu S, Mondal GP, Das SK, Roy T, Mukherjee B. Clinical spectrum of acute disseminated encephalomyelitis in relation to aetiology and neuroimaging study. Ann Indian Acad Neurol 2004; 7: 501-6.
23. Absoud M, Lim MJ, Chong WK, Christian G. Paediatric acquired demyelinating syndromes: Incidence, clinical and magnetic resonance imaging features. Multiple Sclerosis J 2012; 19: 76-86.
24. Sadek AA, Mohamed MA, Abou-Taleb A, Mohammed MI. Pattern and outcome of acute disseminated encephalomyelitis (ADEM) in children: Experience in a tertiary center, upper egypt. electron physician 2016; 8: 2679-85.