http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v7i7.37

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Clinical Profile of Acute Disseminated Encephalomyelitis in Children- An Experience from a Tertiary Care Centre in Eastern India

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Abstract
Acute Disseminated Encephalomyelitis (ADEM) as one of the etiology of Acute Encephalitis Syndrome (AES) is an acute widespread immune mediated inflammatory demyelinating event of the central nervous system with multifocal neurological deficit; typically accompanied by encephalopathy of varying degree.
This observational prospective hospital based study was conducted in the Pediatric Medicine department of a tertiary care centre in Eastern India over a period of 18 months. All 6 months to 12 years patients fulfilling the inclusion criteria were included in the study and outcome assessed. Out of a total of 30 children; 17 (57%) were boys and 13 (43%) girls. The youngest of them was 10 months old and the eldest being 12 years old. The most common presenting feature was alteration of consciousness seen in 24 (80%) followed by motor weakness seen in 21(70%) children.Glasgow coma score (GCS) less than 8 was seen in 4 patients at presentation. All children were followed up to one and half years. Out of 24 children who had monophasic course of illness 22 children (73.3% of total patients) made uneventful recovery. It requires early diagnosis and institution of specific therapy to decrease neurologic and psychiatric morbidity.
Keywords: *ADEM, Methylprednisolone, IVIG.*

Introduction

Acute Disseminated Encephalomyelitis (ADEM) as one of the etiology of Acute Encephalitis Syndrome (AES) is an acute widespread immune mediated inflammatory demyelinating event of the central nervous system with multifocal neurological deficit; typically accompanied by encephalopathy of varying degree. It can follow infection or immunization. The disease is usually characterized by multifocal white matter lesions on neuroimaging.

ADEM forms only one of several categories of primary inflammatory demyelinating disorders of the central nervous system. Others include multiple sclerosis (MS), acute transverse myelitis, and Neuromyelitis Optica (Devic's disease).

ADEM can occur at any age but most series report a mean age between 5 and 8 years with slight male preponderance. The true incidence of the disease in India is undetermined and is likely to be more frequent than reported; it may range from

0.07 – 0.4 per 100,000 population in the pediatric population.

Materials and Methods

This observational prospective hospital based study was conducted in the Pediatric Medicine department of a tertiary care centre in Eastern India over a period of 18 months. Acute Disseminated Encephalomyelitis (ADEM) was defined as an initial inflamatory demyelinating event with multifocal neurological deficit; typically accompanied by encephalopathy.

For monophasic ADEM new symptoms/signs within 3 months are considered part of the same ADEM event. However when new event of ADEM (must comprise of encephalopathy) with recurrence of initial ADEM signs and symptoms 3 or more months after initial events and not related to withdrawal of steroids is called as RECURRENT ADEM.

Moreover ADEM followed by new clinical event also meeting criterion of ADEM, but involving new CNS lesions (clinically and radiologically) is termed as MULTIPHASIC ADEM.

All 6 months to 12 years patients fulfilling the inclusion criteria were included in the study and outcome assessed.Children less than 6 months and more than 12 years were excluded from the study. 30 patients including those presenting with first episode during the study period or those who have presented with recurrent disease within the study period were included in the study.Complete hemogram, liver and kidney function tests were done in all cases.Cerebrospinal fluid analysis, neuroimaging and electroencephalogram (EEG) were done in all patients. The patients were meticulously observed during the entire hospital stay to determine the course of disease and to observe effects of drug therapy. All patients were treated with IV methylprednisolone for at least 5 consequtive days followed by gradually lowering doses of oral prednisolone for 4-6 weeks. Cases not responding to IV methylprednisolone may be considered for IV immunoglobulin. Patients were subsequently observed on follow for at least six months after discharge and up to one and half years. Repeat MRI done after 3-6 months to check for resolution of old lesions or appearance of new lesions. Outcome was evaluated in terms of mortality and also neurological outcome up to period of one and half years.

Statistical analysis was performed using GraphPad QuickCalcs. Chi square test was used for comparing categorical variables and student's unpaired t test test was used for comparing the continuous variables. A p-value of less than 0.05 was considered statistically significant.

Results

Out of a total of 30 children; 17 (57%) were boys and 13 (43%) girls. The youngest of them was 10 months old and the eldest being 12 years old. Among all patients, maximum were in the age group 6-12 years constituting 60%. The median age was 8 years. In this study 86.6% (26 out of 30) had history of acute febrile illness prior to the onset of neurologic symptoms. No preceding illness could be identified in 4 (13.3%) children. The interval between the preceding illness and symptoms of ADEM varied from 0 days to 15 days (mean 6.08 days). Two children had history of recent immunization. A 10 year old girl vaccinated with JE vaccine (SA 14-14-2) 4 weeks prior to the onset of illness; and another 10 months old infant vaccinated for measles three weeks prior to the onset of symptoms. The most common presenting feature was alteration of consciousness seen in 24 (80%) followed by motor weakness seen in 21(70%) children. Glasgow coma score (GCS) less than 8 was seen in 4 patients at presentation.Generalized seizures were present in 5 (16.6%) and behavioral abnormalities like agitation, depression seen in 5 (16.6%) children. Cranial nerve involvement was present in 7(23.3%), most common involved was the second cranial nerve 4 (13%), followed by facial nerve 2(6.5%) and one case of palatal palsy.Sudden loss of vision was present in 4 patients, 3 of them having bilateral optic neuritis. Among those children who presented with motor

weakness; 3(10%) had monoparesis, 7 (23.3%) had hemiparesis, and 14 (46.6%) had quadriparesis. Dystonia, ataxia and bowel bladder involvement was present in 1,2 and 2 cases respectively. One-third cases had CSF pleocytosis. CSF oligoclonal band was negative and IgG index was normal in all the 6 patients who had similar history in the past. Most common involvement in Magnetic resonance imaging (MRI) was the parietal lobe & subcortical white matter in 20(66%) cases followed by frontal lobe, temporal lobe and periventricular white matter in 15(50%) and occipital lobe 10(33%)cases. Brainstem 9(30%), corpus callosum 6(20%), cerebellum and cerebellar peduncles 5(17%) and spinal cord 5(17%) was also involved. EEG and VEP abnormalities were found in 4 cases each. 28 children (93.3%) survived and 2 (6.6%) cases died. Out of the 2 children who expired 1 was admitted with first episode of illness, whereas the other child was admitted with relapsing disease. Remission of symptoms within one week of starting steroids was seen in 22(73.3%) cases.One child who had presented with sudden bilateral loss of vision had no improvement after 1 week of treatment but eventually regained full vision after 6 weeks of steroid therapy. 5 cases had residual symptoms even at 6 weeks of steroid therapy and in 3 of them, steroid could not be stopped and are still on daily low dose steroid therapy.

Follow- up MRI was performed in 29 children. Repeat MRI was performed between 3-6 months after discharge. Among 24 children with monophasic course of illness, complete resolution was seen in 16(55%) and resolving lesions in 7 cases.6 children with relapsing disease showed old and new lesions on MRI.

All children were followed up to one and half years. Out of 24 children who had monophasic course of illness 22 children (73.3% of total patients) made uneventful recovery. One 7 year old girl child continued to have convulsion requiring further escalation of anti-epileptic drugs on follow ups alongwith cognitive decline affecting scholastic performance. Similarly another child with monophasic course of illness was seen to have persistent behavioral abnormality and overt cognitive decline at follow up.

Children of age 3 years or more were evaluated using Binet Kamat Test for estimation of IQ and neuropsychological outcome after 6 months of discharge from hospital (n=26). 2 children out of all with monophasic course of illness had borderline impaired IQ, rest had normal IQ. But around 20% patients with monophasic disease had pathological scores in various neuropsychological functions, among which attention was the most clearly affected. Modified Rankin scale was used to assess the degree of disability for all children of age 6 years or more at 6 months follow up in OPD (n=18).

Discussion

In our study, ADEM was most prevalent in age group of 6 to 12 years i.e, 60% (18 out of 30). The youngest was a ten-month-old infant and the oldest child was 12-years-old. The median age was 8 years. Studies in the past have reported comparable findings[3,6,11,13,21]. Likasitwattanakul et al in their study mentioned a median age of 7.2 years[11].

Boys constituted 57% (17 out of 30) which is consistent with studies from India and abroad which report ADEM is more common in boys[2,6,]

In contrast, an Indian study done by Jayakrishnan MP et.al on the clinical profile of ADEM in children constituted 79% girls[1].

Seven (23.3%) patients hailed from 24 Parganas, highest from a single district in West Bengal and 70% of the population were hindus.

The majority of children (87 %) had a nonspecific febrile illness preceding the onset. No child had preceding viral exanthema, a finding consistent with many of the studies in the developed world[2,6,]. The average duration between the preceding illness and ADEM was 6.5 days. Murthy in his article published in year 2002 mentions that ADEM typically begins within 6 days to 6 weeks following an antigenic

challenge[2]. A 10 month-old infant had received measles vaccine 3 weeks prior to the onset of symptoms, and a 10 year old girl was vaccinated with JE vaccine (SA 14-14-2) 4 weeks prior to the onset of illness. Murthy JM mentions in his article that the only epidemiologically and pathologically proven association of the vaccination is with the antirabies vaccination although measles vaccine could also one of the causative agent of ADEM[2].

Table-1: Clinical features and neuroimaging of the multiphasic ADEM cases.

Patient	Sex	Age (years) (1st attack)	Clinical features (1st attack)	MRI findings (1st attack)	Clinical features (2nd attack)	MRI findings (2nd attack)	Clinical features (3rd attack)	MRI findings (3rd attack)
CASE-1	Male	9.5	Convulsion, Altered sensorium, Left sided hemiparesis	Hyperintensities in left parietal and temporal region, subcortical & periventricular region	Age-11yr Altered Sensorium, Left sided hemiparesis, Facial weakness	Hyperintensities in subcortical parietal and adjacent temporal	Age-12 yr Right sided hemiparesis, facial weakness , behavioral abnormalities	Hyperintensities in b/l parietal region, lesions in corpus callosum and pericallosal areas, pons and lower brain stem
CASE-2	Female	8.5	Behavioral abnormality and abnormal movements initially, then altered sensorium and b/l loss of vision	Hyperintensities involving left thalamus, right pons, cerebral cortex of bilateral frontal, parietal & temporal regions.	Age-10 yr Quadreparesis, altered sensorium, b/l loss of vision, behavioral abnormality.	Demyelinating lesion in bilateral frontal, parietal, temporal, and left occipital cortical & subcortical region.	Age-11yr3month Convulsion, unconsciousness & left sided hemiparesis	Lesions involving peri and para ventricular white matter, centrum semi ovale, fronto-parietal and sub cortical white matter of both sides.
CASE-3	Male	10	Convulsion with altered sensorium	T2 hyperintensities involving bilateral frontal, parietal and temporal regions.	Age-10yr 4 month Quadriparesis, convulsion with unconsciousness	Lesions involving b/l frontal, parietal, temporal and occipital cortex , also involvement of b/l thalamus, basal ganglia, periventricular & sub cortical white matter, also involvement of pons + midbrain.		
CASE-4	Male	6	Altered sensorium , generalized seizure	Hyperintensities in b/l frontal, parietal; subcortical & periventricular white matter	Age- 6yr4month Altered sensorium, generalized seizure	Hyperintensities in b/l frontal, parietal; subcortical & periventricular white matter	Age-6yr9month Generalized seizure, Sudden b/l loss of vision, quadriparesis	Confluent b/l multiple Long TR hyperintensities in deep cortical and paraventricular white matter.
CASE-5	Male	1yr3month	Quadriparesis with speech abnormality.	Lesions in bilateral periventricular region and corpus callosum	Age-1yr9month Quadriparesis with speech abnormalities, ataxia	Long TR hyperintensities seen in bilateral centrum semiovale, periventricular white matter, basal ganglia, corpus calosum and middle cerebellar peduncles		

The clinical features of ADEM in the present sample were comparable to those of previous reports[2,3,8]. The most common neurologic presentation was altered sensorium seen in 80% (24 out of 30) children followed by motor deficit seen in 70% (21 out of 30). This is consistent with many studies conducted nationally and abroad [3,6,11,13,17,21].

Cranial nerve involvement was seen in 7 (23%). The second cranial nerve was most commonly involved. This is in contrast to the study conducted by Jayakrishnan MP. where facial nerve palsy was most common[1]. Also 3 out of the 4 children who presented with sudden loss of vision had features of optic neuritis on direct ophthalmoscopy. Optic neuritis is reported to occur in 3-35% of cases in various reports.[7,8]

Speech difficulties were seen in 4 (13%) children. All of these 4 children had involvement of the cerebellum and/or cerebellar peduncles. There is a study done by Parrish JB et,al where they diagnosed 19 patients with acute disseminated encephalomyelitis, six (32%) manifested primary cerebellar involvement. Of these six, four (67%) exhibited acute language disturbance, with three (50%) exhibiting mutism[19].

Psychological manifestations included aggressive behavior, emotional liability, elated or depressed mood, and irritability. A seven year old girl who presented with behavioral abnormality, altered sensorium and extra-pyramidal involvement

developed generalized seizures while on steroids and subsequently developed behavior disorder characterized by aggression. This child was treated with risperidone for her behavioral problems. When there was no improvement, lithium was also added.

The white blood cell count (WBC) ranged from 4500 to 17200 cells / mm with a mean of 9510 cells/ mm. CSF pleocytosis which is described in 28-65% of cases of ADEM[2,8] was present in the 30 % of the children.

MRI revealed involvement of parietal lobe & subcortical white matter most frequently in 66% children; followed by frontal lobe, temporal lobe and periventricular white matter in 50% cases. Weng WC et al in their study demonstrated involvement of sub cortical white matter in 80% cases; although they mention brain stem involvement in 65% cases[17]. Singhi PD. in her study also mentions major involvement of subcortical white matter[3].

Twenty two (73.3%) children had total remission of symptoms within one week of starting steroids. Five(18%) children had residual symptoms at the end of steroid therapy. Singhi PD. in his study mentions dramatic recovery to IV Methylprednisolone administration in 26.9% cases and marked improvement in 51.9% at discharge.[3]

One child who had presented with sudden bilateral loss of vision had no improvement after 5 days of IV Methylprednisolone treatment. He was put on oral steroids but simultaneously IVIg was administered and he eventually regained full vision after 6 weeks. Shahar E et,al mention combined use of high-dose methylprednisolone and intravenous immunoglobulin in severe acute disseminated encephalomyelitis, visual loss, or severe flaccid weakness accompanied by bladder and bowel incontinence in their study.

A 5 years old male who had recurrence of similar neurological symptoms after a period of 2 years with similar MRI lesions was diagnosed as recurrent acute disseminated encephalomyelitis as per the definition[22]. He responded well to IV Methylprednisolone for 5 days followed by oral steroid for 5 weeks.

Another 5 children who had recurrence of neurological symptoms after variable periods (>3 months) with fresh lesions on MRI were considered as multiphasic acute disseminated encephalomyelitis (MDEM) as per the definition[22]. Singhi PD has also shown in her study that out of 52 children included, 4 had relapse of ADEM with new lesion on MRI.None of the clinical or neuroradiologic factors at presentation had any significant correlation with relapse.

The problem faced in treating these children with MDEM were reappearance of symptoms with tapering steroids. As there is no consensus for treating Multiphasic ADEM; these children were treated with either Pulse IV Immunoglobulin therapy for 6 months or monthly Pulse IV Methyl Prednisolone therapy for 6 months to achieve remission[23]. Resistant cases were treated with monthly Pulse IV Cyclophosphamide therapy for 6 months[23]. One children with MDEM expired. Azathioprine is being used in 2 out of 4 children with multiphasic ADEM who survived; for maintenance therapy and as steroid sparing agent. The convulsions and motor disability were controlled but neuropsychiatric manifestations persist in 3 out of these 4 children. Two children had presented with loss of vision but one made no visual recovery.

Mortality of ADEM in our study was 6.66% (2 out of 30). Jayakrishnan MP reported no mortality in his study on clinical profile of ADEM in children[1]. A mortality rate of up to 20% has been reported in earlier studies, with a high incidence of neurologic sequelae in those who survived.[24] Recent studies suggest a more favourable prognosis.[25],[26],[27]

Funding- Nil

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