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Clinical evaluation of the children's suffering from acute disseminated encephalomyelitis (ADEM) in children

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Abstract
Acute disseminated encephalomyelitis (ADEM), or acute demyelinating encephalomyelitis, is a rare autoimmune disease marked by a sudden, widespread attack of inflammation in the brain and spinal cord as well as causing the brain and spinal cord to become inflamed. ADEM also attacks the nerves of the central nervous system and damages their myelin insulation, which, as a result, destroys the white matter. It is often triggered by a viral infection or, perhaps exceedingly rarely specific non-routine vaccinations.
The present study was conducted in Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India. Total 50 cases of the acute disseminated encephalomyelitis (ADEM) were enrolled in the present study.
The data generated from the present study concludes that ADEM most commonly present as a polysymptomatic encephalopathy and initially diagnosis may not be clear. Clinical evaluation, MRI & CSF studies are most useful to establish the diagnosis and rule out important differential diagnosis. There is presence of antecedent illness in case of severe presentation. The age, gender, predisposing factor do not influence the outcome, but the severity of presentation influence the outcome at discharge.

Keywords: Acute disseminated encephalomyelitis, ADEM, children's, etc.

Introduction
Acute disseminated encephalomyelitis (ADEM), or acute demyelinating encephalomyelitis, is a rare autoimmune disease marked by a sudden, widespread attack of inflammation in the brain and spinal cord. As well as causing the brain and spinal cord to become inflamed, ADEM also attacks the nerves of the central nervous system and damages their myelin insulation, which, as a result, destroys the white matter. It is often triggered by a viral infection or, perhaps exceedingly rarely specific non-routine vaccinations [1].
ADEM's symptoms resemble the symptoms of multiple sclerosis (MS), so the disease itself is sorted into the classification of the multiple sclerosis borderline diseases. However, ADEM has several features that distinguish it from MS. Unlike MS, ADEM occurs usually in children and is marked with rapid fever, although adolescents and adults can get the disease too. ADEM consists of a single flare-up whereas MS is marked with several flare-ups (or relapses), over a long period of time. Relapses following ADEM are reported in up to a quarter of patients, but the majority of these 'multiphasic' presentations following ADEM likely represent MS [2]. ADEM is also distinguished by a loss of consciousness, coma and death, which is very rare in MS, except in severe cases.
It affects about 8 per 1,000,000 people per year. Although it occurs in all ages, most reported cases are in children and adolescents, with the average age around 5 to 8 years old. The disease affects males and females almost equally. ADEM shows seasonal variation with higher incidence in winter and spring months which may coincide with higher viral infections in during these months. 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 [3]. The average time to recover from ADEM flare-ups is one to six months.
ADEM produces multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter. Usually these 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 a person has more than one demyelinating episode of ADEM, the disease is then called recurrent disseminated encephalomyelitis or multiphasic disseminated encephalomyelitis (MDEM). Also, a fulminant course in adults has been described [4].
Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating condition that predominately affects the white matter of the brain and spinal cord. The disorder manifests as an acute-onset encephalopathy associated with polyfocal neurologic deficits and is typically self-limiting. ADEM bears a striking clinical and pathological resemblance to other acute demyelinating syndromes (ADS) of childhood, including multiple sclerosis (MS). ADEM in children is readily distinguishable from alternative diagnoses on the basis of clinical features and findings on neuroimaging and laboratory investigations. However, given that ADEM lacks a specific identified biological marker rendering a reliable laboratory diagnosis, long-term follow-up is important as there are instances where an illness initially diagnosed as ADEM is ultimately replaced with a diagnosis of MS [6].
The onset of ADEM usually occurs in the wake of a clearly identifiable febrile prodromal illness or immunization and in association with prominent constitutional signs and

encephalopathy of varied degrees. ADEM is typically a monophasic disease of pre-pubertal children; whereas, MS is typically a chronic relapsing and remitting disease of young adults. Abnormalities of findings on cerebrospinal fluid (CSF) immunoglobulin studies are less common in ADEM. However, the division between these processes is indistinct, suggesting a clinical continuum. Moreover, other conditions along the suggested continuum include optic neuritis, transverse myelitis, and neuromyelitisoptica - clinical entities that may occur as manifestations of either MS or ADEM [7]. Other boundaries of ADEM merge indistinctly with a wide variety of inflammatory encephalitic and vasculitic illnesses as well as monosymptomatic, post infectious illnesses that should remain distinct from ADEM, such as acute cerebellar ataxia (ACA). A further in distinct boundary is shared by ADEM and Guillain-Barré syndrome as manifested in cases of Miller-Fisher syndrome and encephalomyeloradiculoneuropathy (EMRN).

Susceptibility to either ADEM or MS is likely the product of multiple factors, including a complex interrelationship of genetics and exposure to infectious agents and other environmental factors. Of particular interest are the indications that susceptibility to either condition is in part age-related. Most cases of ADEM possibly occur as the result of an inflammatory response provoked by pre-pubertal infection with a virus, vaccine, or other infectious agent. Typically, the manifestations of ADEM occur quickly after this pre-pubertal febrile systemic illness and are monophasic. In a minority of cases, patients with ADEM experience one or two pre-pubertal recurrences followed by remission. MS, on the other hand, typically manifests as a relapsing-remitting illness in ensuing adolescence or young adulthood, a significant and unexplained latency of effect with apparent permanency of immune dysregulation. Bouts of MS occur without a febrile prodrome. Uncommonly, MS develops in pre-pubertal individuals and ADEM develops in post-pubertal individuals. In very rare instances, individuals manifest pre-pubertal ADEM and, after long latency, MS in adolescence.

Multiple sclerosis (MS) and acute disseminated encephalomyelitis (ADEM) bear a close pathological resemblance, each resembling the pathology of experimental allergic encephalomyelitis (EAE). The prominence of perivenular round cell inflammation in either illness is a feature that is shared with many forms of encephalitis, but patchy demyelination with preservation of axon cylinders and the prominence of microglial cells in the inflammatory exudate are not.

The pathology of various developmental stages of the MS plaque is more fully characterized than the pathology of the lesions of ADEM. This is because most patients with ADEM recover completely and without apparent pathological residua. Few biopsies have been obtained or submitted to postmortem analysis. MS plaques are known to exhibit organization features, especially in the margins of active plaques that are not found in cases of ADEM. On the other hand, the general pathological similarities suggest but do not confirm the possibility that ADEM is a formefruste of MS that is somehow effectively and permanently controlled after one, or possibly a few, demyelinating bouts.

Patients with large tumor-like demyelinating lesions may exhibit a combination of pathological features consistent with both MS and ADEM. The possible relationship between these illnesses is further supported by the similarity of clinical manifestations in either illness and the development of MS during adolescence in a small minority of patients who have had typical ADEM bouts in the first decade of life.

The pathophysiological similarities of these illnesses suggest that the immunologic constitution of susceptible individuals is in some fashion permissive of ADEM, MS, or both and that the degree of susceptibility may describe a gradient with regard to severity and risk for recurrence. The threshold for an initial bout of demyelinating illness may be determined by the combination of this immunologic constitution and the nature of a given antigenic stimulus; the likelihood of recurrence may be determined by the fertility of that constitution for persistence of immuno-dysregulation. Immuno-dysregulation in MS or ADEM may consist of responses that are inadequate, too exuberant, or the combination of both.

If a pathophysiological continuum between MS and ADEM exists, achieving better understanding of the manner in which susceptible individuals with ADEM are able to bring a monophasic or temporarily recurrent immuno-dysregulative response under permanent control is of obvious importance. Cases with characteristics that fall in the indeterminate area of this continuum, such as those that might be labeled multiphasic ADEM, represent an important challenge for accurate classification. In some of these cases, appropriately crediting the immune system with tardy but permanent compensation may be important, thus avoiding inappropriate diagnosis of MS, fraught as that is with psychosocial consequences.

The mechanisms of these demyelinating illnesses remain incompletely understood despite the extraordinary richness and complexity of immunologic abnormalities that have been identified after more than a century of clinical, pathological, and laboratory studies. Experimental observations have depended greatly on EAE, a research model that may be more pertinent to ADEM than MS.

However, the possibility of provoking spontaneously recurrent demyelination with this model further supports the concept that ADEM and MS represent a continuum. Basic studies have shown that, in the earliest stages of inflammation, both MS and ADEM are likely to be mediated by stimulated clones of T-helper cells sensitized to auto-antigens such as myelin proteins. Some studies have even identified serum autoantibodies to various myelin proteins that help to differentiate ADEM from MS. In particular, ADEM appears to be characterized by class-switched IgG autoantibodies, supporting the hypothesis of an antigen-driven immune response in ADEM cases; whereas, MS cases are characterized by serum IgM autoantibodies [8]. The complex ensuing inflammatory cascade entails the local action of cytokines and chemokines as well as lymphokine-induced chemo taxis of other cellular mediators of inflammation (eg, other T cell lines, B cells, microglia, phagocytes).

Pathogenic differences of MS and ADEM are likely to arise in part because of differences in details concerning pro-inflammatory and anti-inflammatory cytokines and chemokines. Interleukin (IL)–1beta, Il-2, IL-4, IL-5, IL-6, IL-8, IL-10, interferon (IFN)–gamma, tumor necrosis factor-alpha, and macrophage inflammatory protein-1-beta are significantly elevated in CSF compared with the CSF of controls. Granulocyte colony-stimulating factor shows a particularly striking elevation at as much as 38-fold greater

concentration than is found in the CSF from control subjects. Elevations of IFN-gamma, IL-6, and IL-8 have been significantly correlated with CSF cell counts and protein concentration in individuals with ADEM. The pattern of cytokine elevation suggests that ADEM involves activation of macrophages, microglial cells, and various Th (T helper)–1 and Th2 cells. [93]

Additionally, in 2006, Franciotta *et al*. demonstrated that adults with ADEM have higher CSF concentrations of chemokines that recruit or activate neutrophils (CXL1 and CXL7), monocytes (CCL3 and CCL5), Th1 cells (CXCL10), and Th2 cells (CCL1, CCL17, and CCL22) than healthy normal controls. [4] Moreover, ADEM-associated concentrations of certain of these neutrophils (CXL7 neutrophil activator and the CL1, CCL17, and CCL22 Th2 activators) are higher in the CSF from individuals with ADEM than those with MS. On the other hand, CSF concentrations of the chemokine CCL11 is lower in adults with MS than in the CSF from adults with ADEM or in normal controls.

CSF Th1/Th2 cytokine concentrations were not significantly different in adults with MS, those with ADEM, or in normal healthy controls. No significant differences in serum concentrations of cytokines or chemokines were noted in the 3 adult groups. These findings raise the possibility that elevated chemokine concentrations might serve as biomarkers for ADEM and that they may provide keys to understanding the nature of and differences in the pathogenesis of ADEM and MS.

Disturbance of the blood-brain barrier is likely to be an important event. The elaboration of antibodies occurs but remains of uncertain significance. In particular, multiple researchers have demonstrated the presence of serum IgG antibodies to myelin oligodendrocyte glycoprotein (MOG) in up to 40% of children with ADEM, though these antibodies do not appear to be specific to ADEM. Still the presence of anti-MOG antibodies in ADEM may affect the nature and course of the disease. A recent study has demonstrated that MOG-positive ADEM patients are more likely to have large, bilateral and widespread lesions and longitudinally extensive transverse myelitis on MRI and are more likely to have a favourable clinical outcome when compared to MOG-negative ADEM patients [8].

The present study was planned to analyse the epidemic variable, risk factors, clinical course, laboratory, radiological finding & treatment, in order to improve the diagnostic & treatment & to distinguish ADEM from other aetiologies of encephalopathy.

Methodology

The present study was conducted in Upgraded Department of Paediatrics, Patna Medical College and Hospital, Patna, Bihar, India. Total 50 cases of the Acute disseminated encephalomyelitis (ADEM) were enrolled in the present study.

All the patients included were with informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Investigations carried out for systemic diseases were unremarkable including blood cultures, LFT, RFT and blood sugar. CSF examination showed proteins 100 mg/dl, lymphocytes 20 cells/ml with normal sugar. CT-scan of brain was normal but MRI showed multiple areas of abnormal contrast enhancement

Results & Discussion

Acute disseminated encephalomyelitis (ADEM) is an acute immune mediated demyelinating disease with a variable clinical presentation. It is a self-remitting disease that follows viral infection or rarely vaccination. No clinical or laboratory feature is pathognomonic and computed tomography (CT) scan of head is not sensitive for diagnosis. MRI brain should be considered early in patients with acute onset of unexplained encephalopathy or focal neurological deficit. It has improved prognosis with immunomodulatory agents like steroids. Patients in our series, diagnosed as ADEM, had variable unusual polysymptomatic presentation and their clinico-radiological profile is presented here.

ADEM is an immune-mediated disease of the brain. It usually occurs following a viral infection, but may appear following vaccination, bacterial, or parasitic infection [10]. The annual incidence of ADEM is reported to be 0.4–0.8/100,000 and the disease more commonly affects children and young adults, probably related to the high frequency of exanthematous and other infections and vaccination in this age group [11]. In dengue infection, the pathophysiology of neurologic manifestations may be related to direct viral invasion; systemic complications related to dengue infection; or immune-mediated, autoimmune reaction secondary to dengue infection

Demyelinating lesions of ADEM are better visualised by MRI. These demyelinating lesions of ADEM usually exhibit no mass effect and can be seen scattered throughout the white matter. Though white matter involvement predominates grey matter can alsobe affected, particularly basal ganglion, thalami, and brainstem Thalamic involvement may be seen in 40% patients of ADEM, making this finding a potentially useful discriminator.

There are a number of pathogens which have been linked to the development of ADEM. The most commonly cited viral causes include coxsackie, cytomegalovirus, esptein-barr, herpes simplex, hepatitis, measles, coronavirus, rubella and varicella zoster. In recent literature numerous non-viral organisms have been linked to ADEM including Leptospira, Mycoplasma pneumoniae, beta haemolytic streptococcus, rickettsia and Borreliaburgdorferi [12].

Given the link to antecedent infections the most widely accepted hypothesis for the pathogenesis of ADEM is the ‘molecular mimicry’ hypothesis. This describes an acquired autoimmune phenomenon in genetically susceptible populations which form post-infectious autoantibodies to myelin proteins (e.g. proteolipid protein, myelin basic protein and myelin oligodendrocyte protein) [13-15].

An alternate theory is that ADEM occurs secondary to an inflammatory response causing vascular congestion and increased permeability of central nervous system vasculature following e exposure to a foreign antige. This is then thought to cause an inflammatory cascade involving perivenous haemorrhage, oedema and infiltration of inflammatory cells resulting in demyelination gliosis and necrosis [16].

Based on these theorized mechanisms, numerous case reports and a number of uncontrolled studies have determined that immunosuppression is the mainstay of ADEM treatment. Several studies have demonstrated benefit with high dose IV methylprednisolone treatment for three to five days, followed by an oral taper over six weeks [17].

Along with the intial steroid treatment, empiric antimicrobial cover is recommended unit infectious causes have been ruled out. In patients showing a poor response or failure of high dose glucocorticoids, IVIG therapy for five

to seven days has been recommended. Current estimates show that approximately half of patients with ADEM that fail a trail of high dose glucocorticoids will respond to IVIG. The final line in management of ADEM is plasma exchange; however the optimum regiment and benefit are still poorly defined in the literature [17].

Table 1: Age & Sex of Patient

Age in Years	No. of Cases
0 – 3 years	13
4 – 8 years	21
9 – 12 years	12
13 – 15 years	4
Sex	
Males	37
Females	13
Total	50

Table 2: Presenting Symptoms

Symptoms	Number of Cases
Convulsion	31
Fever	30
Altered sensorium	28
Paralysis	22
Vomiting	12
Headache	8
Speech abnormality	8
Bowel & bladderchanges	6
Abnormal movement	4
Blurring of vision	3
Rash	3
Double vision	2
Dysphagia	1
Neck retraction	1

Table 3: Pattern of neurological involvement

Sign	Number of Cases
Motor deficit	34
Encephalopathy	43
Autonomic involvement	21
Cranial nerve involvement	13
Cerebellar sign	11
Aphasia	8
Meningeal sign	6
Involuntary movement	4

Table 4: Pattern of MRI abnormality

MRI abnormality	Number of Cases
T1 hypointensity	16
T2 hypointensity	37
FLAIR hyperintensity	35
DWI restriction	24
Temporal shrinkage	7
Contrast enhancement	3
Gyral thickening	3
Sinusitis	3
Perifocaledema/mass effect	2
T2hyperintensity of spinal cord	5
Normal	2

Table 5: Area of brain involved

Area of brain	Number of Cases
Fontal lobe	27
Temporal lobe	26
Parietal lobe	25
Occipital lobe	19
Thalamus	8
Basal ganglia	7
Centrum Semiovale	7
Cerebellum	6
Subcortex	4
Corona radiata	4
Midbrain	4
Pons	2
Occipitoperitrigonal region	2
U fibre	1
Medulla	1
Perisylvian region	1
Infrasylvian region	1
Cervical cord	1
Medullary cord	1
Entire cord	1
Meninges	1

Table 6: Response to treatment

Outcome at discharge	No. of Cases
Complete recovery	16
Partial or no recovery	27
Death	7
Total	50

In general demyclinating lesions of ADEM usually exhibit no mass effect and can be seen scattered throughout the white matter of posterior fossa and cerebral hemispheres [18]. CT-Scan brain was normal in our patient and MRI helped in clinching the diagnosis. A similar experience of superiority of MRI in diagnosing ADEM has been reported by different authors. Typical ADEM lesions are patchy areas of increased signal intensity on T2 weighted images and on fluid attenuated inversion recovery (flair) sequence [19].

Lesions can enhance after gadolinium administration. As seen in our case, gray matter lesions usually predominate. It is not clear whether ADEM exists as a separate entity from relapsing, remitting MS. ADEM at times is difficult to distinguish from MS though prior history of immunization and infection is present in majority of ADEM cases [20].

Acute encephalopathy and acute meningitis - pyogenic, tubercular, fungal or viral - are other examples of acute central nervous system (CNS) diseases due to infectious or non-infectious aetiologies that can and must be differentiated from acute encephalitis. In acute encephalopathy, brain pathology is non-inflammatory, often biochemical; hence, CSF shows no pleocytosis. Onset is often without prodromal phase and tends to be in the morning hours, the child having been well the previous evening. Changes in sensorium, seizures and upper motor neuron-type muscle tone abnormalities and abnormal movements point to cerebral dysfunction. Encephalopathy occurring in clusters is often conflated with acute encephalitis outbreak [21-23]. Acute meningitis is diagnosed when the clinical presentation points to meningeal inflammation - with fever, headache, neck rigidity, positive Kernig and Brudzinski signs and high pleocytosis in CSF. In pyogenic meningitis, CSF cells are predominantly

polymorphonuclear leucocytes, while in most others, these are predominantly lymphocytes. While viral meningitis is often self-limited, bacterial and fungal meningitis will progress to severe brain dysfunction and death, if left untreated. When features of encephalitis and meningitis co-exist, the disease is called meningoencephalitis.

Some systemic infectious diseases with their own distinct clinical features may occasionally present with brain function derangement. Some are due to invasion of the pathogens into CNS, as with dengue fever [24], chikungunya [25], scrub typhus [26] and leptospirosis, but even in such instances, these should be labelled as a complication of the primary disease, instead of acute encephalitis.

Conclusion

The data generated from the present study concludes that ADEM most commonly present as a polysymptomatic encephalopathy and initially diagnosis may not be clear. Clinical evaluation, MRI & CSF studies are most useful to establish the diagnosis and rule out important differential diagnosis. There is presence of antecedent illness in case of severe presentation. The age, gender, predisposing factor do not influence the outcome, but the severity of presentation influence the outcome at discharge.

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