ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) PRESENTING AS A MULTIPHASIC ENCEPHALOPATHY: A CASE REPORT

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ABSTRACT

Acute disseminated encephalomyelitis (ADEM) is one of the demyelinating disorders of central nervous system (CNS) causing acute or relapsing-remitting encephalopathy. We report a male child, who presented with fever, fits and altered sensorium, with two identical events, 3½ months apart. Neuroimaging showed high signal lesions on the T2 weighted images reflecting areas of demyelination and edema, consistent with ADEM. He responded with complete recovery after pulse steroids and intravenous immunoglobulin (IVIG) therapy.

Key Words: *ADEM, encephalopathy, multiphasic ADEM*

INTRODUCTION

ADEM is one of the demyelinating diseases of childhood occurring as an acute inflammatory, demyelinating event with multifocal neurological deficits, encephalopathy being the hallmark of the disease.[1] Diagnosis is suspected in any child with focal or multifocal features of CNS inflammatory demyelinating disorder preceded by infection or vaccination; neuorimaging suggesting diffuse bilateral symmetrical lesions.[2-6] It responds favorably to high dose intravenous methyl prednisolone, IVIG and plasmapheresis and has good prognosis with mostly full recovery.[7] Here we present a child with the unusual presentation of recurrence.

CASE SUMMARY

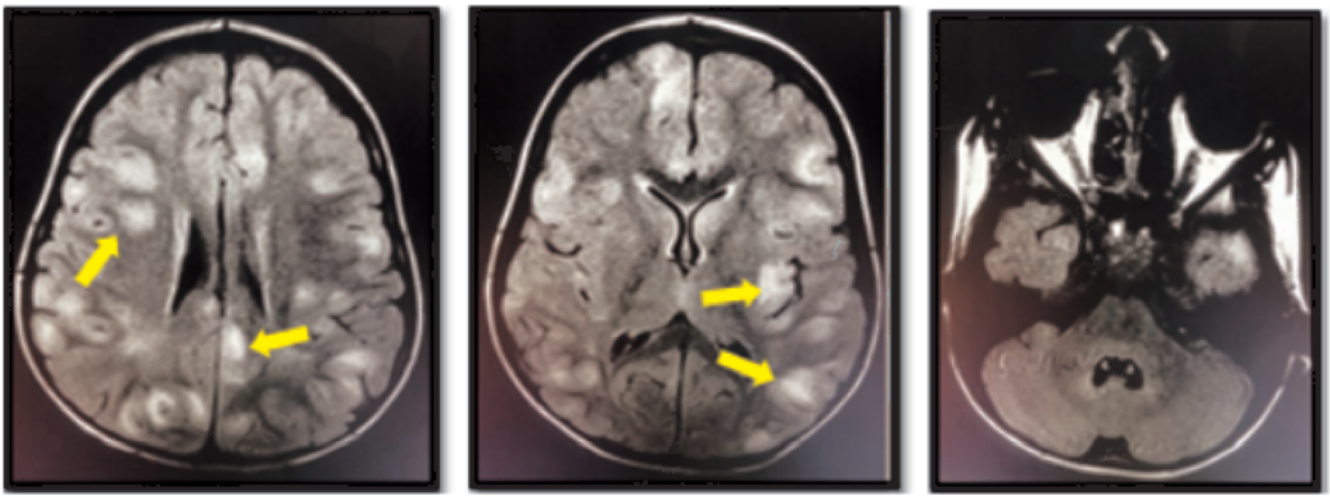
A four years old boy presented with high grade fever for 1 week and fits for 1 day, followed by drowsiness and altered sensorium 3½ months ago. There was also history of sore throat with difficulty in swallowing and history of few episodes of loose stools for last few days. There was no history of respiratory distress or drug ingestion. There was previous history of a viral rash with fever 1 month back, which was treated symptomatically. He was previously healthy and had achieved normal developmental milestones and had received age appropriate vaccination. His family history was non-contributory.

On examination he was drowsy with a Glasgow Coma scale (GCS) of 7/15, vitals included oxygen (O_2) saturation 98%, heart rate of 100/min, and respiratory rate of 35/min. There was neck stiffness. The cranial nerves examination, power and reflexes in all limbs were normal with bilateral extensor plantars. Rest of the physical examination was unremarkable. The provisional diagnosis of meningoencephalitis was made. As his O2 saturation was dropping, he was electively intubated. Initial management included vancomycin, ceftriaxone and acyclovir, phenytoin and intravenous fluids. Dexamethasone was added after MRI.

His initial laboratory evaluation revealed white cell count of 12300/ul with neutrophils 80%, lymphocytes 16%, hemoglobin 10.76 g/dl and platelet count 132000/uL. Serum electrolytes, glucose and renal function tests were normal. CSF analysis showed WBC count 40 cells/uL (polymorphs 20%, lymphocytes 80%), RBCs 140 cells/uL, protein 25.3 mg/dL and glucose of 63 mg/dL. All viral and bacterial cultures were negative. A magnetic resonant imaging (MRI) of the brain showed multifocal patchy areas on T2 and FLAIR bright signal areas in cortical and subcortical white matter of both cerebral hemispheres (Figure 1).

There was no definite restricted diffusion on DWI sequences. Slightly accentuated leptomeningeal enhancement was also noted. Bright T2 signal was also noted in the optic nerve sheath bilaterally with slight flattening of posterior globes at the site of optic disc.

Figure 1 (A-C) Axial FLAIR MRI Images showing multifocal patchy areas on T2 (arrows).



Rest of brain structures were normal. He was discharged home after 10 days on oral Dexamethasone (0.5 mg/kg/day) for 9 days tapered over 6 days, phenytoin and clarithromycin. He made a full recovery in 6-7 days.

This time he presented again after 3½ months with high-grade fever for 2 days, 2 episodes of fits for 1 day and drowsiness, rigidity and stiffness of the whole body with urinary and fecal incontinence for few hours. On examination his 02 saturation was 57% in air, a GCS of 7/15, heart rate of 134/min and respiratory rate of 34/min. Pupils were bilaterally reactive. There were upper motor neuron signs in lower limbs. Rest of neurological examination was normal. Throat was congested with enlarged tonsils and some follicular exudates. Rest of the examination was unremarkable. His lab evaluation revealed white blood cell 14700/uL (polymorphs 29%, lymphocytes 69%), hemoglobin 11.64 g/dl, and platelet count 132000/uL. C-reactive protein was 6.18 mg/L. Serum electrolytes, renal function tests and glucose were within normal limits. CSF analysis showed WBC 40 cells/uL (polymorphs 65%, lymphocytes 35%), RBCs 80 cells/uL, protein 39.5 mg/dL and glucose of 74 mg/dL, gram staining and cultures were negative; herpes simplex virus by PCR was not detected; oligoclonal bands were negative. EEG was abnormal suggestive of moderate diffuse encephalopathy / moderate diffuse brain dysfunction with clear epileptiform activity seen. MRI brain showed interval decrease in the abnormal signal foci involving bilateral subcortical white matter with interval development of additional abnormal signal foci in bilateral thalami, left half of pons, left middle cerebellar peduncle and right cerebellar hemisphere (Figure 2).

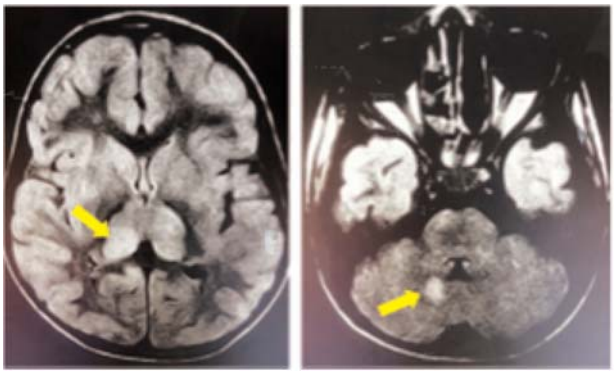


Figure 2 (A,B). Axial FLAIR MRI Images with additional abnormal signal foci in bilateral thalami, left half of pons, left middle cerebellar peduncle and right cerebellar hemisphere (arrows).

Based on the clinical presentation and neuroimaging findings final diagnosis of multiphasic ADEM was made. In addition to ventilator support, mannitol, vamcomycin, ceftriaxone, acyclovir and phenytoin, he was given injection Methylprednisolone 30 mg/kg/day for 3 days followed by IVIG (400 mg/kg/day) for 5 days. He was extubated on day 2. Residual deficit at discharge was mild gait ataxia that improved with physiotherapy over the next 2 weeks. At follow up after 2 weeks he showed full neurological recovery (Figure 3). A repeat MRI will be done after 3 months.

Figure 3. At follow-up the child had excellent recovery

DISCUSSION:

ADEM is a disease mainly affecting children with peak age between 5 to 8 years. Initial symptoms of ADEM include lethargy, fever, meningeal signs including status epilepticus, typically accompanied byencephalopathy.[1] Common neurological signs include visual problems, bladder/bowel dysfunction, ataxia and motor or sensory signs. Preceding infections associated with ADEM include *influenza, Epstein-Barr virus, .*cytomegalovirus, varicella, enterovirus, measles, mumps, rubella, herpes simplex and mycoplasma pneumonia.[1]

MRI brain is the study of choice, and shows multifocal T2 lesions usually in the white and often in the gray matter of the brain. Cerebral hemispheres, cerebellum, brainstem, thalami and basal ganglia are usually involved.[1] CSF studies often show pleocytosis with lymphocytic or monocytic predominance.[1-4] CSF protein can be elevated specially in repeat studies. Upto 10% of ADEM have oligoclonal bands in the CSF and/or elevated CSF immune globulin production.[1-5] EEG often shows encephalopathy.[6]

ADEM is treated with high dose intravenous steroids. An oral prednisone taper over 1 month may prevent relapse. Other treatment options include intravenous immune globulins or plasmapheresis. Most of the children recover completely after ADEM but some are left with residual deficits.[7,8]

ADEM is usually a monophasic illness but cases of multiphasic and recurrent ADEM have been reported, mainly in isolated case reports.[9-11] In recurrent ADEM new event occurs with recurrence of initial symptoms and signs 3 or more months after the first ADEM event. MRI shows no new lesions; original lesions may have enlarged.[12] In multiphasic ADEM first event is followed by new clinical event also meeting criteria for ADEM and on neuroimaging new anatomic areas are involved. The subsequent event occurs at least 3 months after the initial event. The subsequent event must include a polysymptomatic presentation, including encephalopathy, with neurological symptoms and signs that differ from the initial event (mental status changes may not differ from the initial event).[12]

This child most likely fits into multiphasic ADEM as he had recurrence of events 3½ months apart, both events meeting the criteria of ADEM and neuroimaging showed new lesions, while old lesions were regressing in size. Differential diagnosis of childhood Multiple Sclerosis was also kept in mind but the points favouring multiphasic ADEM against MS were age at the onset of disease, antecedent event in this child (viral infection), altered sensorium, non-progressive course of the disease, diffuse bilateral lesions on MRI and rapid and complete recovery.[13] See Table 1.

Table 1

Features	ADEM (Acute Disseminated Encephalomyelitis)	MS (Multiple Sclerosis)
Age	Less than 8 years	More than 8-10 years
Antecedent Events	Infections/Vaccinations	No recognizable event
Clinical Features	Altered sensorium, encephalopathy	Focal signs
Clinical Course	Non progressive	Relapsing/Remitting and/or progressive
MRI Findings	Diffuse bilateral, symmetrical lesions	Periventricular lesions/holes
Oligoclonal bands	Usually absent	Usually present
Prognosis	Rapid and complete recovery	Variable recovery

The monophasic clinical hallmark of ADEM is challenged by such rare cases of recurrent multiphasic ADEM. Although in this child the clinical, pathological and imaging criteria of multiphasic ADEM were met, the diagnosis of such a rare entity is usually based on clinical evidence and the lack of pathological evidence is a common limitation of many clinicopathologic series of ADEM.[13-16]

The long term risk of developing MS in such patients is reported to be about 10% but could be higher depending upon the variability of clinical features at the onset of the disease. Risk for MS is higher in children whose ADEM onset was afebrile, without any antecedent event, without mental status changes or without generalized EEG slowing. Therefore long term follow up is recommended in patients with ADEM.[17] Given the wide spectrum of clinical manifestations of MS, disease modifying therapy (DMT) has a significant role in MS; but till date DMT has not been reported to play a role in ADEM.[18]

In Pakistan ADEM has been rarely reported. Over a period of three years (2006-2008) a case series of 25 children with ADEM were reported who all had only polysymptomatic monophasic disease. [19] To our knowledge multiphasic ADEM has not been reported from Pakistan.

REFERENCES

1. Robert M. Kliegman, MD, Bonita M.D. Stanton, MD, Joseph St. Geme, Nina Schor, MD, PhD and Richard E. Behrman, MD. The nervous system. Nelson Textbook of Pediatrics, 19th edition, 2011.
2. Tenembaum S, Chitnis T, Ness J, Hahn JS. International Pediatric MS Study Group. Acute Disseminated Encephalomyelitis. Neurology. 2007;68:S23-36.
3. Anlar B, Basaran C, Kose G, Guven A, Haspolat S, Yakut A, et al. Acute disseminated Encephalomyelitis in Children: Outcome and Prognosis. Neuropediatrics. 2003;34:194-9.
4. Wingerchuk DM, Weinshenker BG. Multiple Sclerosis: Epidemiology, genetics, classification, natural history and clinical outcome measures. Neuroimaging Clin North Am. 2000;10:611-24.
5. Singh S, Alexander M, Sase N, Korah IP. Solitary Hemispheric Demyelination in Acute Disseminated Encephalomyelitis. Australas Radiol. 2003;47:29-36.
6. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000;123:2407-22.
7. Pohl D, Tenembaum S. Treatment of acute disseminated encephalomyelitis. Department of Neurology, Children's Hospital of Eastern Ontario, University of Ottawa. 2012 Jun;14(3):264-75
8. M. Alexander and J. M. K. Murthy. Acute disseminated encephalomyelitis: Treatment guidelines. Ann Indian Acad Neurol. 2011 July; 14(Suppl1): S60-S64.
9. Menge T, Hemmer B, Nessler S, Wiendl H, Neuhaus O, Hartung HP, et al. Acute disseminated encephalomyelitis: An update. Arch Neurol. 2005;62:1673-80.
10. Krupp LB, Banwell B, Tenembaum S. The International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple Sclerosis and related childhood disorders. Neurology. 2007;68:S7-12.
11. Cohen O, Steiner-Birmanns B, Biran I, Abramsky O, Honigman S, Steiner I. Recurrence of acute disseminated encephalomyelitis at the previously affected brain site. Arch Neurol. 2001 May;58(5):797-801.
12. Tenembaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: A long-term follow-up study of 84 pediatric patients. Neurology. 2002;59:1224-31.
13. Marchioni E, Tavazzi E, Franciotta D, Ravaglia S. Recurrent ADEM versus MS: differential diagnostic criteria. Neurol Res. 2008 Feb;30(1):74.
14. Singh S, Alexander M, Korah IP. Acute Disseminated Encephalomyelitis: Pictorial Essay. Am J Roentgenol. 1999;173:1101-7.
15. Idrissova ZR, Boldyreva MN, Dekonenko EP, Malishev NA, Leontyeva IY, Martinenko IN, et al. Acute disseminated encephalomyelitis in children: Clinical features and HLA-DR linkage. Eur J Neurol. 2003;10:537-46.
16. Murthy JM. Acute disseminated encephalomyelitis. Neurol India. 2002;50:238-43.
17. Tur C, Tellez N, Rovira A, Tintore M, Rio J, et al. Acute disseminated encephalomyelitis: study of factors involved in a possible development towards multiple sclerosis. Neurologia. 2008 Nov; 23(9): 546-54.
18. Spalice A, Parisi P, Papetti L, Nicita F, Ursitti F, et al. Clinical and pharmacological aspects of inflammatory demyelinating diseases in childhood: an update. Child neurology, pediatric department, faculty of medicine, "Sapienza University", Rome, Italy. Curr Neuropharmacol. 2010, June; 8(2): 135-48.
19. Muhammad Akbar Malik, Muhammad Arif Tarar, Muhammad Nadeem Malik, Haroon Hamid, et al. Clinical and laboratory features of childhood acute disseminated encephalomyelitis: experience at the Children's hospital Lahore. Pak Paed J. Apr - Jun 2011;35(2):94-102.