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Acute Disseminated Encephalomyelitis: A case series and review of literatures

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ABSTRACT

Acute disseminated encephalomyelitis is a rare immune mediated and demyelinating disease of the central nervous system that usually affects children.
It is a monophasic disorder related with multifocal neurologic symptoms. In this paper, we report seven cases of Acute disseminated encephalomyelitis in pediatrics in addition; a review of literatures is presented.

Introduction

Acute disseminated encephalomyelitis (ADEM) is an acute widespread demyelinating condition, which principally affects brain and spinal cord. The disease is characterized by multifocal white matter lesions on neuroimaging.[1, 2] ADEM generally follows an infection or vaccination. Clinical presentations of ADEM are usually multifocal and poly-symptomatic. Long term

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prognosis of ADEM is favourable and spontaneous improvement has been reported frequently.[1, 3, 4] With regard to feeble evidence related to this disorder in Iran, we decided to provide a complete data of patients admitted with diagnosis of ADEM during the recent ten years in this paper in the referral center of pediatrics, Northern Iran. Table 2 indicates the several similar studies conducted in this field in the past decade.

Methods

In this paper our cases were; hospitalized and treated patients as ADEM, and also an overview on clinic-laboratory features of ADEM is provided. Reported cases were admitted to Bou-ali-Sina Hospital, Sari, Iran between January 2003 and March 2013. The most common main chief complaints were fever, seizure, headache, and neurological deficits. Complete histories were taken and physical examinations performed. Brain MRI was done for suspicious diagnosis of ADEM. Evidences revealed hyperdense signals on T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) sequences sub-cortical and deep white matter regions in the several parts in brain in all patients which had been confirmatory for ADEM diagnosis.

Results

In the present case series study, we reported seven cases of ADEM diagnosed by clinical and radiological results. General characteristics of the patients and also their clinical presentations are summarized in table 1. The patients had variable signs and symptoms at first. Para-clinical evaluations such as CT-scan and brain MRI were performed that showed several disturbances. MRI showed multiple foci of increased signal intensity on T2 and FLAIR images within the cerebral white matter, in the centrum semiovale, periventricular region, corpus callosum and brainstem (figure 1). Steroids and IVIG were administered in our cases and based on the conducted follow up, their prognosis is good.

Epidemiology

ADEM almost involves children with the incidence rate of 0.4/100000 yearly in patients less than 20 years-old. The peak incidence of ADEM is among 5 to 8 of age.[5, 6] Male to female ratio is the same. Seasonal distribution shows an increased prevalence in winter/spring.[7] ADEM nowadays occurs following unspecific upper respiratory tract infection in the developed countries, due to the progresses in controlling infections. In the developing countries, its prevalence is more than the reported rate because of disordered vaccinations.[8] ADEM happens in result in 1 per 1000 cases of measles before and 1 per 500 cases after rubella infection.[1, 4, 9] The mortality rate after varicella and rubella is less than measles infection. The most related bacterial infection is mycoplasma. Other common form of ADEM is followed by vaccination.[10] The incidence of neuroparalitic complications after rabies vaccination is 1/600 to 1/1575 cases. Now, most cases take place after measles, mumps and rubella vaccination.[11, 12]

Pathology and Pathogenesis

The histopathologic hallmarks of this disease are: Encephalitis after infection of demyelinated zones and infiltration of lymphocytes and macrophages. The other changes include: hyperemia, endothelial swelling, invagination of inflammatory cells to vessels wall and prevascular edema and haemorrhage which happens in small vessels of brain white and gray matter.[13, 14] Macrophages increases and lymphocytes decreases during these times. Finally fibrotic lesions could be seen. ADEM after infection usually affects white matter, although the gray matter can also be involved.

Basal ganglia, thalamus and also cortical gray matter may involve. The results of the investigations show that ADEM is as the result of transient autoimmune response against myelin or other auto-antigens through similarity and molecular mimicity or unspecific activation of auto-reactive T cell clone.[12, 15] Genetic factor is an important agent. Within all types of Major histocompatibility complex (MHC) and non-MHC genes which are attributed to disease susceptibility; the human leukocyte antigen class II genes have the most significant affect. Acute haemorrhagic encephalomyelitis (AHEM) is a mortal and hyper acute form of ADEM that results in necrotizing vacuities of venuls. The main molecular mechanism of oligodendrocytes death in ADEM and other types are unknown, but it is suggested that a collections of cytokines, chemokine and adhesion molecules are responsible for molecular happenings and also the inflammatory encephalitis. Based on a hypothesis, free radicals have effective role in the death of premature oligodentrocytes. [9, 10, 16]

Clinical features

The clinical signs and symptoms are related to the place and severity of brain lesions.[1] They occur after days or few weeks after viral infections. Most of them had a past history of infection during the last weeks that vaccination is the less frequent one. Fever, headache, nausea and vomiting and meningismus are often seen at the time of the first implications that may exist during hospitalization time.[3, 17] Encephalopathy is the main characteristic of disease that can rapidly progress due to the multifocal neural deficiencies.[18, 19] Despite of this, other neural symptoms and signs may exist, such as: Unilateral or bilateral pyramidal symptoms (60-95%), acute hemiplegia (76%), ataxia (18-65%), cranial nerve palsy (22-45%), loss of visual power due to optic neuritis (7-23%), seizure (13-35%), spinal cord involvement (24%), speech impairment (5-21%), hemiparesthesis (2-3%) and finally changes in levels of consciousness from lethargy to coma. Bladder and bowel dysfunction secondary to spinal cord involvement may result in constipation and urinary retention.[20, 21] Acute phase of ADEM lasts 2-4 weeks. Most of the children experience some new neurological signs after discharge. Although some of them may have few sequelae, a great amount of them will be improved.[22]

Paraclinic evaluations:

Electroencephalography (EEG)

Changes in EEG are common but not specific. Some changes like spindle coma and alternative patterns are reported. Because of low specificity and sensitivity of EEG, it is not used for diagnosis.[23, 24] The other patterns which can be seen in EEG of these patients are: increase of sleep, mild generalized slowing to severe generalized slowing and epileptiform discharges.[25, 26]

Cerebrospinal Fluid (CSF) changes

CSF may be normal, but some changes can be seen, such as: increase of pressure, lymphocytic pleocytosis and elevation of protein levels (Often <1 mg/l). And also increase in levels of Gammaglobulin and IgG and rarely oligoclonal IgG in CSF might be seen.[21, 27-29]

Neuroimaging

Imaging is a valuable diagnostic tool. Computed Tomography (CT) is often normal at first, but changes during 5-14 days later. CT changes include: multifocal lesions in subcortical zone of white matter with low attenuation.[1, 10, 14, 20, 30] Demyelinating lesions are better seen in MRI. Often they do not have mass effect and can distribute throughout the white matter of posterior fossa and cerebral

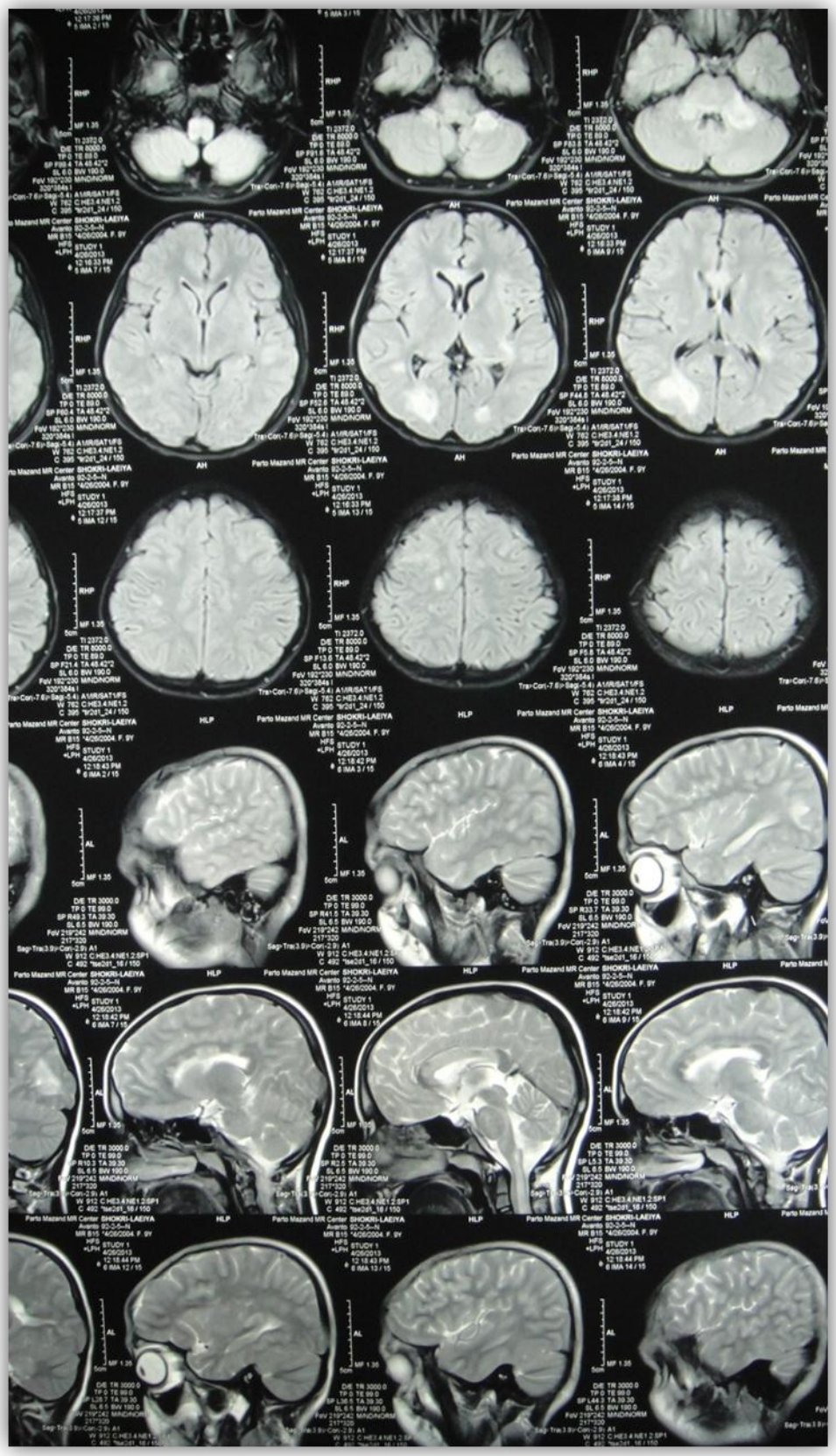

Figure 1: Brain MRI of our patient with ADEM.

Table 1: Clinical, neurophysiologic, spinal-fluid, and neuro-radiologic features of 7 patients at clinical onset and during follow-up

Cases	Season	Trigger Factor	Age	Sex	Clinical Feature	CSF Findings	MRI Results	Treatment	Outcome
Case1	Winter	MMR[a]+ G.E[b]	1yr	Male	Seizure and Lower extremity paresis	Normal	Multiple hyper intensities lesions	IVIG[c] + Prednisolone	Complete recovery
Case2	Autumn	URTI[d]	12yr	Male	Seizure and Fever	Normal	Multiple foci of increased signal intensity	Prednisolone	Complete recovery
Case3	Spring	None	9yr	Female	Cranial nerve involvement , Seizure and Fever	WBC=15 P/L[e]=45/55 Prot[f]=NL Gluc[g]=NL	Multiple hyper intensities lesions	Prednisolone	Speech disorder
Case4	Winter	None	2yr	Female	Fever and Vertigo	Normal	Multiple hyperintensities	IVIG + Prednisolone	Expired
Case5	Autumn	Mumps + OPV	6yr	Female	Seizure and Generalized weakness	Normal	Multiple hyperintensities in basal ganglia, right thalamus, centrum semiovalis	IVIG	Complete recovery
Case6	Winter	URTI	7yr	Female	Fever and seizure	Increased Protein	Multiple foci of increased signal intensity	IVIG	Complete recovery
Case7	Spring	URTI	9yr	Female	Fever and generalized weakness	WBC=73 Prot=22 Gluc=69	Multiple foci of increased signal intensity within the cerebral white matter	Methyl-prednisolone	Relative recovery

Abbreviations: a) MMR= Measles, Mumps, and Rubella vaccine; b) G.E=Gastroenteritis ; c) IVIG= Intravenous immunoglobulin; d) URTI= Upper respiratory tract infections; e) P/L=polymorphonuclear/ lymphocyte ; f) Prot= Protein; g:Gluc= Glucose

Table. 2: Acute disseminated encephalitis in literatures

Authors	Date	Para-clinic findings	Treatment
N. Khosroshahi[15]	2007	subcortical and periventricular lesions	corticosteroids and intravenous immunoglobulin
Yukifumi Monden[31]	2012	centrally-located long spinal cord lesion	steroid pulse therapy
R.N. Sener[32]	2003	in the cerebral white matterlesion	intravenous Methylprednisolone
Hung P.C.[30]	2012	Lesions found in the subcortical white matter of frontal and parietal lobes	high dose Methylprednisolone and dexamethasone
Sundar U.[4]	2012	subcortical and periventricular white matter involvement	high-dose steroids
Madan S.[14]	2005	non-specific hypodensity	high-dose steroids
R. ReigSáenza[20]	2012	showed white matter and basal ganglia lesions	high-dose immunoglobulin
Margherita Di Costanzo[10]	2011	areas of hyperintensity showed in T2-weighted and Fluid Attenuated Inversion Recovery (FLAIR) images	High-dose steroids
Momoko Oka[33]	2012	Increased levels of tau protein in cerebrospinal fluid are found,	IV immunoglobulin and steroids
Majid Aziz[34]	2012	bilateral asymmetric high T2/FLAIR signal abnormalities	Methylprednisolone
Daniela Pohl[22]	2012	non-specific hypodensity	intravenous Methylprednisolone
Amit Agrawal[35]	2012	asymmetrical hyperintense signals on T2	intravenous Methylprednisolone
Suqin Chen[36]	2013	large lesions with poorly defined margins located in her bilateral basal ganglia in imaging	high dose Methylprednisolone
Michael Absoud[37]	2013	Deep grey nuclei وlarge white matter وand cortical grey matterhigh T2 signal lesions.	intravenous corticosteroids
R. K. Garg[38]	2002	Typical cerebrospinal fluid changes include increased pressure, lymphocytic pleocytosis (as much as 1000/ mm^3, sometimes polymorphonuclear leucocytosis initially), and raised protein	Methylprednisolone andintravenous immunoglobulin, Plasmapheresis
Yun Jin Lee[39]	2011	Deep and subcortical white-matter lesions and gray-matter lesions such as thalami and basal ganglia on MRI	Corticosteroids

Table 3: Differential diagnosis as imaging findings

MRI patterns	Diseases
Multifocal discrete lesions[40]	Multiple sclerosis Primary CNS vasculitis Secondary CNS vasculitis (CNS lupus, Behcet's disease) Neurosarcoidosis Hashimoto encephalopathy (SREAT) Mitochondrial; POLG-related disorders Mitochondrial; MELAS Posterior reversible encephalopathy syndrome (PRES)
Bithalamic/bistriatal lesions[42]	Acute necrotizing encephalopathy Autosomal dominant acute necrotizing encephalopathy Bithalamic glioma Deep cerebral vein thrombosis Japanese encephalitis West Nile virus encephalitis Epstein Barr virus encephalitis Mitochondrial; Leigh disease Extrapontine myelinolysis
Bilateral and diffuse large lesions of white matter[43]	Leukodystrophies Toxic leukoencephalopathies Hemophagocytic lymphohistiocytosis Gliomatosiscerebri
Tumefactive lesions[40]	Astrocytomas

Abbreviations: MELAS: mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, POLG: DNA-polymerase subunit gamma, SREAT: steroid-responsive encephalopathy associated with autoimmune thyroiditis.

hemispheres. Cerebella and brain stem involvement are common. MRI characteristics include patchy lesions with severe increase of signals in conventional T2-Weighted and FLAIR imaging.[28, 29] Although, white matter is the most common place of involvement, gray-matter especially basal ganglia, thalamus and brain stem can be involved. Corpus callosum is usually intact.[3, 4, 10, 14, 15, 20, 22, 30-34, 40] Its involvement is suggestive and has the characteristic of Multiple Sclerosis (MS). Thalamus involvement in MS is very rare, but can be seen in 40% cases of ADEM.[35] Honkaniani et al. reported that MRI changes can provide the important data following up the disease.[12]

Differential diagnosis

CSF and MRI are not able to differentiate ADEM from MS. 50% of cases with ADEM have MRI suggesting of MS.[22, 35- 39] Some researchers suggest that the main differentiating factors of ADEM from MS are: viral prodrome, high load of lesions in MRI, early onset ataxia, deep cortical gray matter involvement and loss of oligoclonal bands.[30, 41] Other differential diagnoses are summarized based on the imaging characteristics in table 3.

Treatment

The main aim of treatment in ADEM is to amplify the immune system that impaired by infectious agent and reduced CNS inflammatory responses the soonest.[1, 3, 22, 40] High dose intravenous corticosteroids are approved as the first line of treatment, although two third of patients profit from this. Near 30% of the patients are "non-responders" and half of these non-responders potentially benefited from receiving intravenous immunoglobulin (IVIG).

Plasmapheresis is also a useful remedy.[31, 44] If these will not be effective, therefore the effect of some other immune-suppressors such as methotrexate and cyclophosphamide should be considered. Based upon the previous hypothesis suggest that persistent infection may be related to the CNS inflammation and demyelination; It has been discussed that antimicrobial therapy, can possibly limit the infection resulting to neurotoxic immune response, if administers soon enough.[3, 35, 45] Unfortunately, because of the lack of any effective treatments for many of viruses in ADEM, so this is theoretically possible now.

Discussion

Acute disseminated encephalomyelitis (ADEM) is a rare acute autoimmune mediated disease that involves the central nervous system.[2, 18, 40] It is an inflammatory process manifested by rapid onset of multifocal neurological impairment. ADEM is a monophasic disease and this disease rarely can relapse frequently.[41] If these relapses are thought to represent part of the same acute monophasic illness, it is named multiphasic ADEM.[23, 46-48]

Acute disseminated encephalomyelitis (ADEM) is a disorder which usually affects children.[45,49, 50] Here in this study, we evaluated the patients from 1 to 12 years. ADEM typically begins within 6 days to 6 weeks following an antigenic challenge. Microorganisms directly through the infection or attenuated pathogens as vaccines can be the main causes of it.[51] Our patients had ranges of triggering factors such as vaccinations and URTI. Clinical manifestations are divided into non-specific and neurologic signs and symptoms.[52] Non-specific symptoms such as fever, headache, nausea, and vomiting and lethargy often precede neurological presentations. These symptoms also existed in our patients.[24, 42, 53] Rezai et al.[1] reported such cases with first symptoms like fever; vomiting and intermittent irritability. Computed tomography and MRI are worthwhile tools in establishing the diagnosis of ADEM. Of course MRI is the most extremely diagnostic tool based on most studies.[54, 55] The other variables are cerebrospinal fluid changes; often include increased CSF pressure, raised protein and lymphocytic pleocytosis. Glucose is usually in a normal range.[21, 27-29, 55-58] Oligoclonal band of IgG may be occasionally found in CSF.[25, 45, 59] These variables were evaluated in this study, too. The results were compatible to the things reported in literatures. Treatment of ADEM is still a discussion-oriented matter and no definite therapy has been confirmed by controlled trials.[19, 26] Nevertheless, the administration of the high-dose steroids as first choice of treatment, plasma exchange and IV immunoglobulin are also suggested.[39, 44, 60] Corticosteroids and IVIG were administered to our patients, and most of them are in a complete recovery phase now. Corticosteroid was not administered to some cases, due to suspicious diagnosis of herpetic encephalitis and loss of adequate diagnostic equipment.

Conclusions

ADEM is an acute inflammatory and demyelinating disease distinguished pathologically by numerous foci of demyelination scattered throughout the brain and spinal cord. The clinical picture reflects the diffuse CNS involvement and is characterized by the acute onset of headache, fever, stiff neck, confusion, and focal neurologic signs often corresponding to the location of the lesions. Convulsions are common and severe cases may present with stupor and coma. Uncommon presentations include isolated behavioural disturbances and psychosis. The illness may occur concurrently with, or more commonly shortly after, the onset of a viral exanthema, other infection, or vaccination. Occasionally, it

occurs without any clearly defined preceding trigger. The outcome varies from death or permanent substantial neurologic deficit to complete recovery, with the acute stage signs out of proportion to the permanent structural damage. The presumed pathogenesis involves a T-cell–mediated immune attack against myelin antigens. MRI is helpful in making the diagnosis because it often reveals diffuse, symmetric white matter demyelinating lesions that homogeneously enhance with contrast administration. The lesions also involve the deep gray matter, especially the thalamus. Treatment is mostly supportive with conflicting evidence on the effectiveness of steroids. Nevertheless, early steroid administration before permanent damage ensues may be helpful. Other potential unproven modalities include immunoglobulin administration, Plasmapheresis, and Glatiramer acetate.

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Conflict of Interest

None declared.

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