

## UNUSUAL CLINICAL CASES THAT MIMIC ACUTE DISSEMINATED ENCEPHALOMYELITIS

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**SUMMARY** – Acute disseminated encephalomyelitis (ADEM) is an immune-mediated monophasic inflammatory demyelinating disorder of the central nervous system which poses a diagnostic challenge. We report on six cases of different etiologies that mimicked the clinical and radiologic findings of ADEM. The cases were collected from four different reference hospitals in Turkey. The same radiologist from the Akdeniz University Faculty of Medicine examined the magnetic resonance images of all patients. Three (50%) patients had antecedent infections. Initial symptoms of the patients were as follows: fever in 50%, altered consciousness in 33.3% and convulsions in 16.7% of patients. Neurologic examination showed long tract signs in 83.3%, ataxia in 50% and altered consciousness in 50% of patients. Cerebrospinal fluid examination revealed lymphocytic pleocytosis only in case 6. Four patients received steroid pulse therapy and one of these initially underwent intravenous immunoglobulin therapy. The patients' definitive diagnoses were as follows: paraspinal neuroblastoma-associated paraneoplastic syndrome; histiocytic sarcoma; mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy in one patient each, while two patients had hemophagocytic syndrome. The present case series demonstrated difficulties in diagnosing ADEM while revealing extremely rare disorders that mimic ADEM radiologically and clinically.

**Key words:** *Encephalomyelitis, acute disseminated; Child; Diagnosis, differential; Case reports*

### Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated monophasic inflammatory demyelinating disorder of the central nervous system (CNS). Although most often observed as a single episode, relapsing or recurrent forms are also present<sup>1</sup>. It can occur at any age, but it is predominantly a childhood disease.

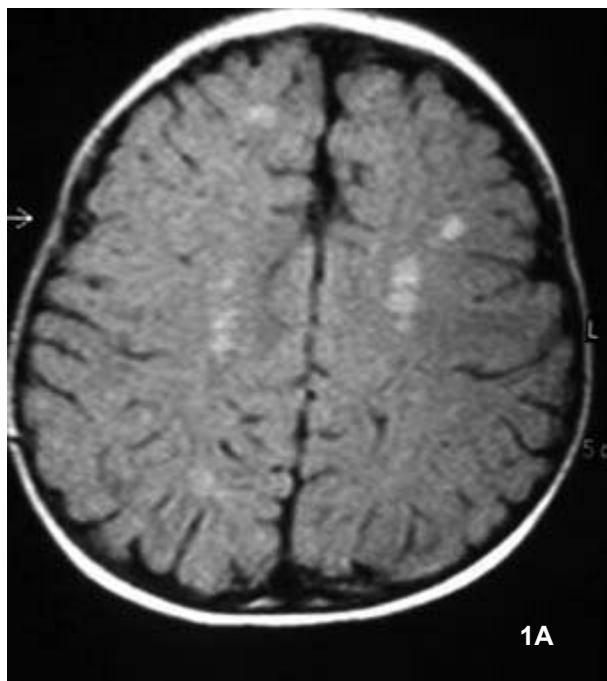
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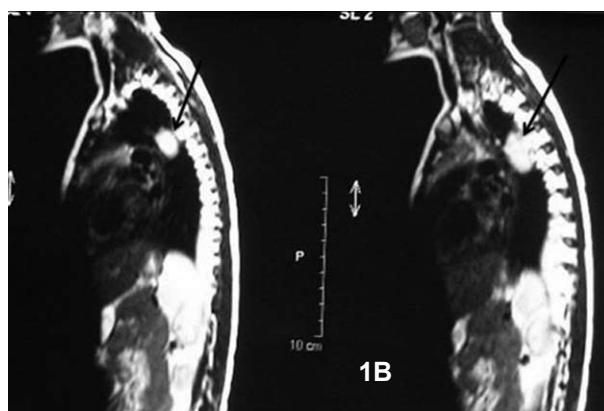
The diagnosis of ADEM is based on a history of acute onset multifocal neurological deficits, usually following a febrile illness. Cerebrospinal fluid (CSF) analysis usually shows pleocytosis with lymphocytic predominance, not caused by any viral or bacterial infection. However, there are no specific clinical presentations or specific para-clinical tests that can accurately diagnose ADEM<sup>2</sup>. Differential diagnosis of ADEM is broad and depends on the exclusion of other diseases that present as ADEM. The main conditions to be considered in the differential diagnosis are other inflammatory disorders including vasculitis, ischemic vascular disease, tumors such as lymphoma and glioma, paraneoplastic disorders, infectious diseases, and

exposure to toxic agents<sup>3-5</sup>. Magnetic resonance imaging (MRI) is a very powerful tool in the diagnosis of ADEM. Usually, there are multifocal white matter and basal ganglia lesions, which may show contrast enhancement. Posterior fossa and spine may also be involved. Although the lesions are highly suggestive, it should be kept in mind that similar patterns may be seen in some other relatively rare disorders. Herein, we report on six rare cases where clinical and radiological findings mimicked ADEM.



altered consciousness level (33.3%) in cases 1 and 4; and convulsions (16.7%) in case 2. Upon neurologic examination, 83.3% of the patients were found to have long tract signs, 50% ataxia, 50% altered consciousness level, and 33.3% hemiparesis. Cranial and spinal MRI results are shown in Table 1 and patient MRIs in Figures 1-6. CSF examination showed that only case 6 had lymphocytic pleocytosis. Four of the patients were put on steroid pulse therapy, and one of these also underwent intravenous immunoglobulin (IVIG)

*Fig. 1. (A) Fluid-attenuated inversion recovery (FLAIR)-weighted transverse image shows multiple hyperintense lesions in frontoparietal white matter on both sides; (B) T2-weighted sagittal images show hyperintense paravertebral mass lesion (arrows); definitive diagnosis was neuroblastoma.*

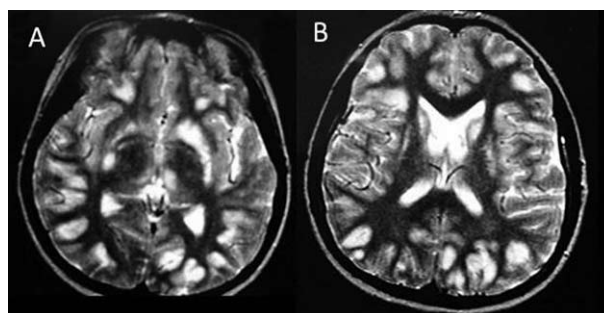


## Materials and Methods

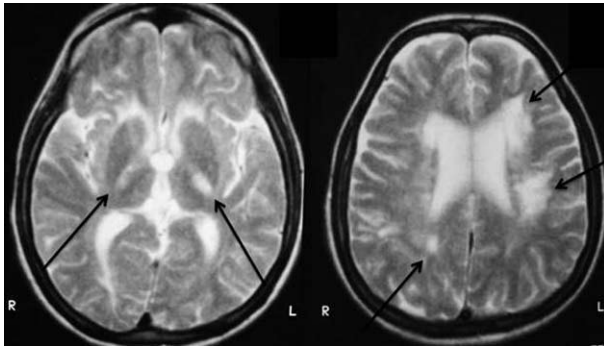
Six cases, considered as ADEM on differential diagnosis between January 2003 and January 2008 were included in the present study. The cases were collected from four different reference hospitals in Turkey. The same radiologist from the Akdeniz University evaluated MRI findings of all these patients.

## Results

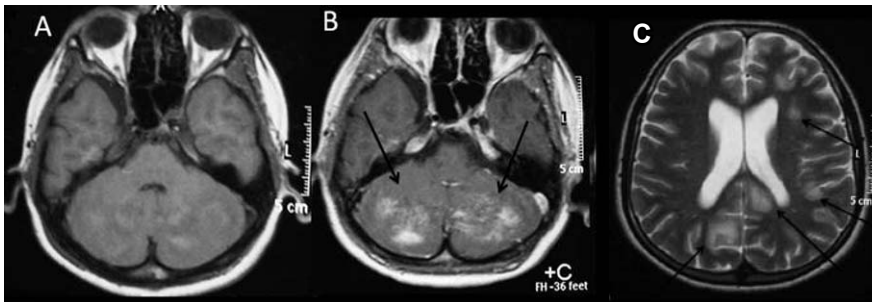
Demographic characteristics, and clinical and laboratory results of the patients are shown in Table 1. Three (50%) patients had antecedent infections (two had upper respiratory tract infections and one had acute gastroenteritis). Initial symptoms of the patients were as follows: fever (50%) in cases 1, 4 and 5;



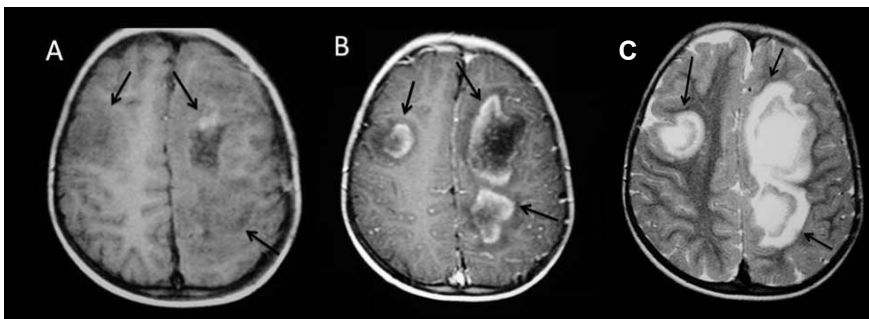
*Fig. 2A and B. Two consecutive T2-weighted transverse images show multiple hyperintense lesions on basal ganglia and subcortical white matter in both cerebral hemispheres; definitive diagnosis was mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS).*



*Fig. 3. T2-weighted transverse image shows hyperintense lesions on both internal capsules and supratentorial white matter (arrows); definitive diagnosis was cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).*



*Fig. 4. Precontrast (A) and postcontrast (B) transverse T1-weighted images show marked enhancement of the cerebellar lesions (arrows); (C) T2-weighted transverse image shows cortical and subcortical white matter hyperintensities on both parietal and left frontal lobes (arrows); definitive diagnosis was hemophagocytic syndrome.*



*Fig. 5. Precontrast (A) and postcontrast (B) transverse T1-weighted images show incomplete ring-type enhancement of the lesions (arrows); on precontrast image (B), there are also hyperintensities, suggesting hemorrhage; (C) T2-weighted transverse image shows round hyperintense lesions in frontal white matter of both lobes (arrows); definitive diagnosis was histiocytic sarcoma.*

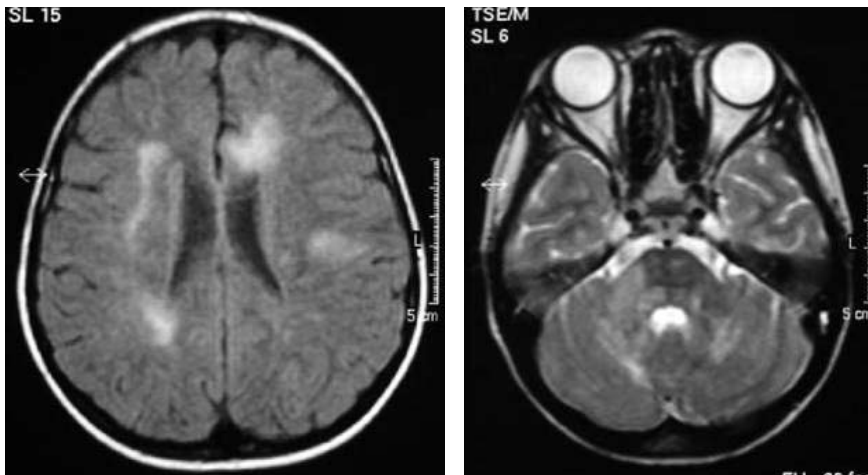
therapy. The final diagnosis was established by spinal MRI in case 1, by muscle biopsy and mitochondrial analysis in case 2, with clinical and laboratory findings in case 3, by bone marrow and spleen aspiration material examination in cases 4 and 6, and by brain biopsy from the lesion area in case 5.

### Discussion

Herein, we report on six rare cases with different etiologies in which ADEM, a relatively rare disorder, was considered as the initial diagnosis. Of these, two were finally diagnosed as hemophagocytic syndrome, and one each as malignancy, paraneoplastic syndrome, cerebral autosomal dominant arteriopathy with sub-

cortical infarcts and leukoencephalopathy (CADASIL), and mitochondrial cytopathy. Some of these diseases have been rarely reported in the literature as being considered on differential diagnosis of ADEM.

The diagnosis of ADEM depends on clinical, radiological, and CSF examination findings, all considered together<sup>2</sup>. Neurologic signs and symptoms of patients afflicted with ADEM have been reported to develop for days and to lead to hospitalization within a week<sup>6,7</sup>. If clinical presentation such as this is accompanied by infection with a latency period of 2-30 days, the diagnosis of ADEM should be considered. The International Pediatric Multiple Sclerosis Study Group emphasizes the importance of encephalopathy in making the diagnosis of ADEM; it is acknowledged, however, that irritability and behavior



*Fig. 6. Brain MRI showing patchy white matter hyperintensities on the right middle cerebellar peduncle, on cerebellar white matter in both hemispheres and in both semioval centers; definitive diagnosis was hemophagocytic syndrome.*

changes are more difficult to define, especially when children are febrile, fearful, or in pain<sup>8,9</sup>. Of our patients, 50% had antecedent infections. In different case series studies, the clinical onset of disease has been reported to be preceded by infections in about 50% to 75% of all cases, mostly nonspecific upper respiratory tract infections<sup>6,10,11</sup>. This was one of the misleading criteria that led us to consider ADEM as a differential diagnosis in cases 1, 4 and 5.

The initial symptoms of ADEM are nonspecific, including headaches, fever and lethargy, with distinct functional, neurologic or cognitive defects developing gradually. However, no pathognomonic clinical features have been discerned for ADEM<sup>12</sup>. Most of our patients presented with nonspecific initial findings, such as fever, altered consciousness level, and stammering. In other reported series, long tract signs, hemiparesis and ataxia have been reported as the most commonly detected signs on neurologic examination of patients with ADEM<sup>1,4,6</sup>. Our neurologic examination results were in concordance with these studies; 83.3% of our patients had long tract signs, 50% had ataxia, 50% had altered consciousness level, and 33.3% had hemiparesis. The most important laboratory finding in patients with ADEM is lymphocytic pleocytosis in CSF examination. Tenembaum *et al.* report that 28% of their patients had CSF abnormalities<sup>6</sup>. Only one of our patients, however, had lymphocytic pleocytosis.

Cranial MRI is important for the diagnosis of ADEM. Some experts consider the diagnosis of ADEM only if the MRI is consistent with dissemi-

nated CNS demyelination<sup>6,10,11</sup>. However, there are no identified MRI criteria specific for ADEM<sup>13,14</sup>. Characteristic MRI findings of ADEM include widespread, multifocal, or extensive (lesion load >50% of total white matter volume) white matter lesions and lesions in the deep gray matter (thalamus, basal ganglia)<sup>11,14,15</sup>. The lesions are bilateral but usually asymmetric. The initial MRI, performed 2-3 days after the onset of symptoms, may not show evidence of the disease<sup>16</sup>. Therefore, follow-up MRI is highly warranted in the context of clinical suspicion<sup>12</sup>.

Our first case exhibited CNS demyelination secondary to autoantibodies to spinal neuroblastoma. Reports of CNS demyelination associated with paraneoplastic syndrome in children are very rare. In our patients, CNS demyelination lesions mimicked ADEM and their size decreased with adrenocorticotropic hormone and IVIG treatment. Two of our patients were primarily diagnosed as ADEM and later they were found to have CNS hemophagocytosis. CNS inflammation with variable neurologic manifestations is frequently observed in CNS hemophagocytic lymphohistiocytosis (HLH) and may appear prior to the onset of other symptoms and signs<sup>17</sup>. Some authors have suggested that HLH should routinely be included in the differential diagnosis of CNS inflammatory disease in children<sup>18-21</sup>. Malignancies may clinically or radiologically mimic ADEM, or *vice versa*<sup>12,22,23</sup>. Usually, CNS metastasis of a systemic malignancy, or primary CNS neoplasms typically present with a more insidious onset than ADEM. Some clinical characteristics, however, are similar to those of

Table 1. Demographic characteristics, and clinical, laboratory and radiological findings of study patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (yrs)	2	17	18	15	5	9
Sex	Male	Female	Female	Male	Female	Female
Antecedent infection	Upper respiratory tract infection	No	No	Acute gastroenteritis	Upper respiratory tract infection	No
Clinical presentation	Confusion, ataxia, fever	Convulsions, weakness, dysarthria, vertigo, confusion	Facial paralysis, ataxia, weakness, vertigo	Altered consciousness level, fever	Weakness, fever	Fatigue, ataxia
Neurologic examination	Cerebellar dysfunction, long tract signs	Hemiparesis, long tract signs	Right central facial paralysis, cerebellar dysfunction signs	Coma, long tract signs	Hemiparesis, long tract signs	Ataxic gait, long tract signs
CSF exam	N	N	N	N	N	6 WBC/mm <sup>3</sup>
Spinal MRI findings	T3-T5 paraspinal tumor	Not performed	N	N	Not performed	Not performed
Brain MRI findings	Multiple hyperintense lesions in frontoparietal white matter on both sides	Multiple hyperintense lesions on basal ganglia and subcortical white matter in both cerebral hemispheres	Hyperintense lesions on both internal capsules and supratentorial white matter	Cortical and subcortical white matter hyperintensities on both parietal and left frontal lobes	Round hyperintense lesions in frontal white matter of both lobes and incomplete ring-type enhancement of the lesions	Patchy white matter hyperintensities on the right middle cerebellar peduncle, and on cerebellar white matter in both hemispheres and in both semioval centers
Angiography	Not performed	N	N	Not performed	Not performed	Not performed
Differential diagnosis	ADEM	ADEM, MS, vasculitis	ADEM, MS, vasculitis	ADEM, malignancy	ADEM, encephalitis, malignancy	ADEM, Lyme disease (brucellosis)
Treatment	Pulse steroid	IVIg	-	Acyclovir, pulse steroid	-	Pulse steroid, IVIg
Definitive diagnosis	Neuroblastoma/Paraneoplastic syndrome	MELAS	CADASIL	Hemophagocytic syndrome	Histiocytic sarcoma	Hemophagocytic syndrome
Follow up duration	2.5 years	18 months	3 years	2 years	7 months	6 months
Findings on last examination	Subsiding of complaints and lesion after tumor extraction	No additional problems	No additional problems	Bone marrow transplantation, exitus secondary to sepsis	Chemotherapy complications, exitus	Chemotherapy complications, exitus secondary to sepsis

ADEM = acute disseminated encephalomyelitis; CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; IVIg = intravenous immunoglobulin; MELAS = mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes; MS = multiple sclerosis; N = normal

ADEM, including altered cognition, headaches, and focal neurologic signs and symptoms. In the present study, one of our patients had a CNS malignancy. Her clinical and radiological presentation was compatible with hemorrhagic ADEM. She was finally diagnosed with histiocytic sarcoma, a rare, lymphohematopoietic malignant neoplasm composed of tumor cells showing morphological and immunophenotypic features of mature tissue histiocytes. Histiocytic sarcoma presenting with CNS symptoms is extremely rare in children. To date, histiocytic sarcoma in the CNS has been reported in only a few children<sup>24,25</sup>. Our patient presented with acute onset hemiparesis. In her MRI, there were multiple white matter lesions with gadolinium enhancement, mimicking encephalitis, intracranial malignancy, or acute hemorrhagic leukoencephalitis. Hemorrhagic ADEM has been reported to mimic encephalitis or malignancies in some patients. Another two of our patients were finally diagnosed with CADASIL and mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), which are also rare conditions. Mitochondrial encephalopathies such as MELAS may cause recurrent episodes of migraine-like headaches, focal neurologic deficits, and signs of encephalopathy during infancy. Affected children typically display failure to thrive and deafness. MRI of the CNS frequently shows white matter lesions that are compatible with ADEM. Elevated lactate levels, histopathologic findings of ragged red fibers in biopsied muscle tissue, and a commercially available test that detects mutations in the mitochondrial tRNA (Leu-UUR) gene confirm the diagnosis.

There is no simple test to secure the diagnosis of ADEM, and its clinical presentation is polymorphic. Diagnosis depends on a synthesis of history, laboratory tests, neurologic findings, treatment outcomes, and exclusion of other diseases. Although MRI is a powerful tool in making the diagnosis, it should be kept in mind that in some rare cases, asymmetric white matter lesions with enhancement or even with hemorrhagic intensities might be seen. Our case series has demonstrated the difficulties in diagnosing ADEM and provided samples of extremely rare disorders that radiologically and clinically mimic ADEM.

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#### Sažetak

### NEUOBIČAJENI KLINIČKI SLUČAJEVI KOJI OPONAŠAJU AKUTNI DISEMINIRANI ENCEFALOMIJELITIS

Ö. Duman, V. A. Yürekli, P. Gencpinar, K. Karaali, H. Gümüş, Ç. Okuyaz, V. Hazar i Ş. Haspolat

Akutni diseminirani encefalomijelitis (ADEM) je immuno posredovana monofazna upalna demijelinizacijska bolest središnjega živčanog sustava koja je dijagnostički vrlo zahtjevna. Prikazuje se šest slučajeva različite etiologije gdje su klinički i radiološki nalazi oponašali ADEM. Slučajevi su prikupljeni iz četiri različite referentne bolnice u Turskoj. Slikovne prikaze dobivene magnetskom rezonancom u svih bolesnika pregledao je isti radiolog s Medicinskog fakulteta Sveučilišta u Akdenizu. Troje (50%) bolesnika imalo je prethodnu infekciju. Početni simptomi bili su groznica u 50%, poremećaj svijesti u 33,3% te konvulzije u 16,7% bolesnika. Neurološki pregled pokazao je znakove oštećenja srednjeg ili gornjeg dijela leđne moždine (*long tract signs*) u 83,3%, ataksiju u 50% te poremećaj svijesti u 50% bolesnika. Pregled likvora otkrio je limfocitnu pleocitozu samo u slučaju br. 6. Četiri bolesnika primilo je pulsnu steroidnu terapiju, a jedan od njih je prvotno bio na terapiji intravenskim globulinom. U bolesnika su postavljene sljedeće konačne dijagnoze: paraneoplastični sindrom udružen s paraspinalnim neuroblastomom; histiocitni sarkom; mitohondrijska miopatija, encefalopatija, laktična acidoza i epizode slične moždanom udaru (MELAS); i cerebralna autosomna dominantna arteriopatija sa subkortikalnim infarktima i leukoencefalopatijom (CADASIL) u po jednog bolesnika, te hemofagocitni sindrom u dvoje bolesnika. Ovaj niz slučajeva ukazuje na teškoće u dijagnosticiranju ADEM-a i istodobno pokazuje iznimno rijetke bolesti koje radiološki i klinički oponašaju ADEM.

Ključne riječi: *Encefalomijelitis, akutni diseminirani; Dijete; Dijagnostika, diferencijalna; Prikazi slučaja*