

Clinical Presentation and outcome of acute disseminated encephalomyelitis in Saudi Arabia

Tertiary Center Experience

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ABSTRACT

الأهداف: تقييم الاعراض، والعلاج والنتائج المستقبلية لالتهاب الدماغ والنخاع الحاد المنتشر لدى الأطفال في مدينة الملك عبد العزيز الطبية في الرياض، المملكة العربية السعودية.

الطريقة: تم جمع جميع السجلات الطبية لجميع المرضى الذين تقل أعمارهم عن 18 سنة والذين تم علاجهم وتشخيصهم بالتهاب الدماغ والنخاع الحاد المنتشر في مدينة الملك عبد العزيز الطبية من فترته يناير 1996 إلى ديسمبر 2016 وهم بمجموع 20 مريض.

النتائج: من العشرين مريض الذين تم تجميعهم، 13 مريضا (65%) كانوا من الإناث. فصلي الخريف والشتاء هي أكثر المواسم شيوعاً التي ظهر فيها المرضى بنسبه (60%). 19 مريضا (95%) كان لديهم تاريخ مرضي لالتهاب فيروسي قبل اصابتهم بالمرض. أكثر الاختلالات العصبية التي ظهرت عند بداية المرض هي الضعف (85%)، الترنح (45%)، وترجع الحدقة الاضطرابي (45%). الآفات القشرية وتحت القشرية كانت أكثر التغيرات شيوعاً لدى المرضى في الرنين المغناطيسي للدماغ بنسبه (60%). تلقى 17 مريضا (85%) فقط الكورتيزون واستمر 16 مريضا فقط المتابعة الطبية بمتوسط مدة 7 أشهر. جميع المرضى الذين أكملوا المتابعة الطبية تحسناً، 11 مريضا عادوا الى طبيعتهم و5 مرضى مازال لديهم اختلالات عصبية، لكن لم ينتكس أي مريض.

الخاتمة: معظم المرضى في هذا البحث لديهم نتائج ومتابعات ممتازة ولم يكن هنالك أي انتكاسات للمرض. ننصح بالمزيد من الدراسات لهذا المرض.

Objectives: To evaluate the clinical presentation of acute disseminated Encephalomyelitis (ADEM) in pediatric age group, treatments, and to assess the outcome at King Abdulaziz Medical City, Riyadh, Kingdom of Saudi Arabia.

Methods: The medical records of all patients younger than 18 years of age with a diagnosis of ADEM and treated at King Abdulaziz Medical City from January

1996 to December 2016 were collected. A total of 20 patients were included.

Results: Of 20 patients enrolled in our study, 13 (65%) were female. Autumn and summer were the most common seasons in which ADEM presented (60%); 19 (95%) patients had a history of preceding viral illnesses. The most common neurological deficits on presentation were weakness (85%), ataxia (45%), and nystagmus (45%). Cortical and subcortical lesions (60%) were the most common finding on cranial magnetic resonance imaging. Seventeen patients (85%) received steroid only. Only 16 patients continued with follow-up, with a mean duration of 7 months. All 16 patients improved: 11 patients were recovered and 5 patients still had a neurological deficit at the clinic visits. No patient had relapsed.

Conclusion: Most of the patients in this case series have an excellent outcome and attended follow-up visits and no disease relapses were identified. Further exploration of the disease is recommended.

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Acute disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the white matter in the central nervous system (CNS) that is caused by an immune-mediated monophasic inflammatory attack. The incidence is higher in the pediatric age group, varying worldwide from 0.3-0.6 per 100,000 children per year.^{1,2} The pathogenesis in ADEM is not fully understood; the existing evidence suggests that the disease results from a reaction to myelin-derived antigens triggered by immunization or infection.³ Preceding vaccination or infection has been reported in 67% of cases in multiple cohort studies.⁴ The ADEM has been reported to occur more commonly in winter and spring because of the increased likelihood of infection at these times.⁵

The ADEM has a wide range of clinical presentations. Encephalopathy is usually the first clinical sign and develops suddenly, with alterations in consciousness, behavioral changes, or postictal symptoms that are unexplained by fever.⁶ From 2 to 8 days, the clinical presentation progressively worsens and deficits are maximized. Radiological findings are distinctive. The most common presenting feature on MRI is the presence of multiple bilateral T2-enhancing supratentorial white matter lesions. Accompanying lesions are often present in the thalamus and/or basal ganglia (40% of cases) and the brainstem and/or cerebellum (45% of cases).⁷⁻¹³

Most patients will make a good recovery after ADEM, though it usually takes 4-6 weeks. At follow-up, approximately 60-90% of individuals have minimal or no neurological deficits.^{4,6,14} The relapse rate for ADEM is between 2-29%.¹⁵ As it is a very uncommon disease worldwide and in Saudi Arabia, data on clinical presentation and outcome of ADEM are lacking. To address this information gap, we have explored the clinical features and patterns of ADEM in children and young people in Saudi Arabia.

Methods. This study is a retrospective chart review on pediatric patients with ADEM presenting to one tertiary center in Saudi Arabia from January 1st 1996 to 31st December 2016. King Abdulaziz Medical City (KAMC) is a tertiary Center located in Central Region in Saudi Arabia in Riyadh City with average of 5,500 pediatric admissions per year in different wards.

The cases were identified via specific codes through medical records. Charts were reviewed for information

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on the clinical features, investigations, and management of all patients between the age of 1 month to 18 years who presented with ADEM at KAMC, Riyadh, Kingdom of Saudi Arabia during the study period.

Inclusion criteria: 1. Age between 1 month and 18 years. 2. ADEM diagnosis was based on clinical basis of first polyfocal clinical demyelinating event with abnormalities on MRI suggestive of the diagnosis and does not match the criteria for dissemination in space and time for a diagnosis of Multiple Sclerosis. The exclusion criteria is evidence of central nervous system infection.

Twenty patients were included in the case series in total, with all patients admitted to the wards at KAMC and followed up in Neurology Clinics. Based on the limited sample size of 20, the margin of error of the outcome variable (complication of ADEM) was estimated to be $\pm 18\%$, based on a 95% confidence level and an expected outcome of 50% for complications. All available cases were selected.

Charts were reviewed on an individual basis by the investigators for the following data: demographic characteristic; clinical presentation; preceding symptoms; laboratory tests; neurophysiological findings; imaging studies; and treatment. The data collected were entered in Microsoft Excel. Baseline demographics were presented as frequencies and percentages. The frequencies and percentages for categorical variables and mean \pm standard deviation for the numerical variables were calculated. The main outcome variable was encephalopathy.

Ethical approval. The study was approved by the Institutional Review Board, King Abdullah International Medical Research Centre, Ministry of National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia.

Results. Out of the 20 patients enrolled in our study, 13 (65%) were female. The mean age at clinical presentation was 9.5 ± 6 years (range= 6 months–17 years). Autumn and summer were the most common

Table 1 - The demographic data for the patients.

| Variables | n (%) |
|---------------|---------|
| Age (y) | 9.5+/-6 |
| Gender | |
| Female | 13 (65) |
| Male | 7 (35) |
| Season | |
| Autumn | 6 (30) |
| Summer | 6 (30) |
| Spring | 5 (25) |
| Winter | 3 (15) |

Table 2 - Preceding symptoms, and clinical and CSF findings. N=20

| Variables | n | (%) |
|-----------------------------------|----|------|
| <i>Preceding symptoms</i> | | |
| URTI | 12 | (60) |
| Fever | 12 | (60) |
| Headache | 5 | (25) |
| Vomiting | 4 | (20) |
| <i>Neurological deficit</i> | | |
| Weakness | 17 | (85) |
| Cerebellar signs | 9 | (45) |
| Decreased level of consciousness | 4 | (20) |
| Cranial nerve deficit | 2 | (10) |
| Seizure | 7 | (35) |
| <i>CSF analysis abnormalities</i> | | |
| Pleocytosis | 12 | (60) |
| High protein | 6 | (30) |

Table 3 - The distribution of T2 and FLAIR lesions on MRI. N=20

| Site of the lesion | n | (%) |
|------------------------------|----|------|
| Cortical and subcortical | 17 | (85) |
| Deep white matter | 17 | (85) |
| Periventricular white matter | 2 | (10) |
| Thalamus | 9 | (45) |
| Basal ganglia | 5 | (25) |
| Cerebellum | 7 | (35) |
| Brainstem | 8 | (40) |
| Spinal cord | 5 | (25) |
| Cervical | 3 | (60) |
| Thoracic | 3 | (60) |
| Lumbar | 1 | (20) |

seasons in which ADEM cases presented, with 6 cases (30%) presenting in each, 5 cases (25%) presenting in spring and the remaining 3 cases (15%) in winter (Table 1).

A history of preceding viral illness was present in 19 patients (95%): upper respiratory tract infection symptoms in 12 patients (60%); fever in 12 patients (60%); headache in 5 patients (25%); and vomiting in 4 patients (20%). No patient had recently been vaccinated.

The most common neurological deficit on presentation was pyramidal-tract-related weakness in 17 patients (85%), of whom nine (45%) had quadriplegia, 7 (35%) had hemiparesis, and one (5%) had paraparesis. The second most common deficit, affecting 9 patients (45%), was cerebellar dysfunction, with patients presenting with ataxia, dysarthria, and nystagmus. Seven patients (35%) had seizures. Four patients (20%) had a decreased level of consciousness. Only 2 patients (10%) presented with cranial nerve

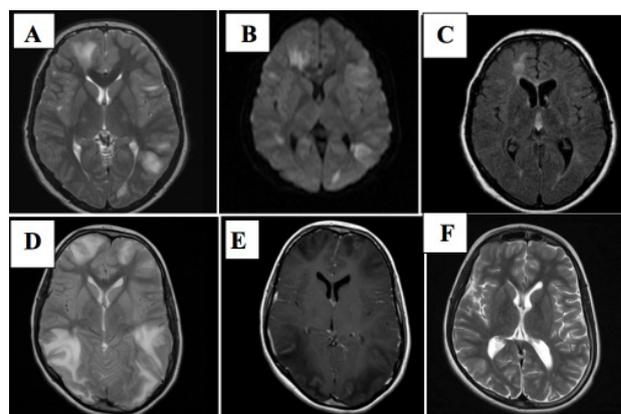


Figure 1 - Patient (1): diffuse patchy asymmetrical bilateral subcortical and deep white matter hyperintense signals in T2 (A) with diffusion restriction (B); follow up MRI after 7 months (C), deep white matter abnormal T2 signal residual lesions; Patient (2), diffuse extensive white matter high T2 signal (D), with no enhancement on T1 (E), and remarkable improvement after 6 month (F).

deficit (one had bilateral facial nerve deficit, the other had sixth nerve deficit) (Table 2).

With regard to the laboratory results, cerebrospinal fluid (CSF) analysis was performed for 18 patients (90%) (the families of 2 patients refused the lumbar puncture procedure). The analysis showed pleocytosis in 12 patients (60%), with lymphocytic predominance in ten patients (50%). Six patients (30%) had high levels of protein in the CSF. All the patients had negative CSF bacterial cultures. Herpes simplex virus polymerase chain reaction (PCR) was performed for 10 patients (50%): only one patient had positive results where the patient has initial diagnosis of HSV encephalitis with good recovery on acyclovir treatment but 2 weeks after treatment she developed encephalopathy again with features of ADEM on brain MRI.

Cranial magnetic resonance imaging (MRI) was performed for all patients and was abnormal. Spinal MRI was performed for some patients. All patients had bilateral involvement with asymmetrical multiple hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. Cortical and subcortical lesions were the commonest, being present in 17 patients. Thalamic lesions were present in 9 patients. Lesions in the brainstem were present in 8 patients. Cerebellum lesions were present in 7 patients, and 5 patients had lesions in the spinal cord and basal ganglia (Table 3).

The mean duration of hospitalization was 22.6 ± 23.3 days. In total, 17 patients (85%) received steroid only: methylprednisolone was given at 20 or 30 mg/kg/day

Table 4 - Summary of all cases with a diagnosis of acute disseminated Encephalomyelitis at King Abdulaziz Medical City from January 1996 to 31st Decemeber 2016.

| SNo | A/G | Pre-inf | Clinical presentation | MRI brain | treatment | Outcome |
|-----|---------|---------------------------|--|--|------------|---|
| 1 | 17y/M | URTI | SE, rt HP, ALC | Extensive sWM, dWM, CC body | MPD, PE | Mild Cognitive dysfunction and epilepsy |
| 2 | 5 y/M | URTI, Fever | GTCS | Bilateral diffuse frontal and parietal sWM & dWM | MPD | Mild Cognitive dysfunction |
| 3 | 7y/F | URTI, Fever, vomiting | Ataxia, ALC, rt CNVI&CNVII palsy, dysarthria | C spine, Thalamus Medulla, Pons, Brachium Pontis, cerebellum | | normal |
| 4 | 6.5 y/F | URTI, Fever, headache | Mild quadreparesis | Lt more than rt frontal and parietal sWM & dWM. | MPD | normal |
| 5 | 11y/F | Fever, headache | Paraparesis & sensory level at T3 | Bilateral scattered multiple supratentorial sWM & dWM & T-L spine. | MPD, IVIG, | normal |
| 6 | 2y/F | URTI | Mild quadriparesis | Bilateral scattered multiple supratentorial sWM T spine. | MPD | normal |
| 7 | 17y/F | URTI, headache | Ataxia, nystagmus, dysarthria and mild quadriparesis | Bilateral scattered multiple supratentorial sWM & dWM, Thalamus, midbrain, pons | MPD | normal |
| 8 | 6y/M | URTI | Paraparesis, sphincter dysfunction | Bilateral scattered multiple supratentorial sWM & dWM & Thalamus, C-T spine | MPD | normal |
| 9 | 17y/F | URTI, Fever, headache | Mild quadreparesis ataxia, dysarthria bilateral CNVII palsy, nystagmus | Bilateral scattered multiple supratentorial sWM & dWM & C spine, pons, medulla, cerebellum | MPD | dysarthria, ataxia |
| 10 | 4.5y/F | Fever, Lethargy | Paraparesis, Seizure | Bilateral scattered multiple supratentorial sWM & dWM, pons, medulla | MPD | normal |
| 11 | 11y/M | Diarrhea | Lt HP | Bilateral scattered multiple supratentorial sWM ,midbrain, cerebellum, thalamus | MPD | normal |
| 12 | 15y/F | | Ataxia, dysarthria, nystagmus | Lt more than rt supratentorial dWM, lt thalamus, cerebellum | MPD | normal |
| 13 | 17y/F | Fever, headache, vomiting | Ataxia, dysarthria, nystagmus | Bilateral scattered multiple supratentorial dWM ,midbrain, pons, cerebellum | | Lost Follow up |
| 14 | 17y/M | URTI, Fever, vomiting | Ataxia, dysarthria, nystagmus, mild paraparesis | Bilateral diffuse multiple supratentorial sWM & dWM, Thalamus | MPD | normal |
| 15 | 3y/F | Pneumonia | ALC, paraparesis, Myoclonic seizures | Bilateral diffuse multiple supratentorial sWM & dWM , thalamus, midbrain and pons. | MPD | Unable to stand |
| 16 | 4.5y/F | Fever and vomiting | Lt HP, ataxia | Bilateral diffuse multiple supratentorial sWM & dWM, thalamus, pons, cerebellum | MPD | normal |
| 17 | 2y/F | Fever, Irritability | Spastic quadreparesis, ALC, seziures. | Bilateral occipital and parietal sWM & dWM, Thalamus | MPD | Lost Follow up |
| 18 | 15y/M | URTI | Ataxia, dysarthria | Bilateral scattered multiple supratentorial dWM, cerebellum | MPD | normal |
| 19 | 12y/F | URTI, Fever | Ataxia, GTCS | Bilateral diffuse frontal and parietal sWM & dWM | | normal |
| 20 | 6m/M | URTI, Fever | GTCS | Bilateral diffuse frontal and parietal sWM & dWM | MPD | Lost Follow up |

SE - Status epilepsy, RT - Right, LT - Left, HP - Hemiparesis, ALC - Altered level of consciousness, sWM - Subcortical white matter, dWM - Deep white matter, CC - Corpus collosum, MPD - Prednisolone, PE - Plasma Exchange, GTCS - Generalized Tonic-clonic seizure, C - Cervical, T- L - Thoracic-Lumbar, y -year, F- female, M - Male, URTI- Upper respiratory tract infections

over 3-5 days and oral prednisolone was then tapered over the following 2–6 weeks. One patient received methylprednisolone 20 mg/kg/day plus intravenous immunoglobulin (IVIg) 2g/kg over 5 days. Three patients (15%) received oral prednisolone at 1mg/kg/day for 1week. Three patients did not receive any immunosuppressant therapy, with 2 receiving acyclovir. Ceftriaxone and acyclovir were also given to 5 patients (25%) who were treated with pulse steroid.

Only 16 patients continued with follow-up, with a mean duration of 7 months. All 16 patients improved: 11 patients were back to normal and 5 patients still had mild neurological deficit at the clinic visits mainly cognitive dysfunction. No patient relapsed and no death was encountered.

Discussion. This study found that 60% of ADEM cases presented during summer and autumn seasons, in contrast to previously reported studies worldwide in which ADEM was reported to occur most commonly during the winter and spring seasons.⁷ The predominance of females (65%) is, again, in contrast to the findings of other studies in pediatric cohorts, which reported ADEM to be more predominant in males (59%).¹¹⁻¹⁵ There is no clear explanation of these epidemiological findings in our study but this could be related to the small number but also it could be related to different predisposing preceding infections in our area but this needs prospective studies to clarify this finding.

In our series of 20 cases, preceding infection was seen in 95% of the cases, with pyramidal-tract related weakness in 85% followed by cerebellar signs in 45%. These findings were similar to a previous study from Argentina on a large group of patients of 84 cases.¹⁶ In another study from Australia on 31 cases, ataxia was the most common neurological sign.¹⁷ However, Seizures and change level of consciousness were seen less frequently in our study at 35% and 20% of cases respectively. Of particular interest is the relatively decreased proportion of patients who has change of level of consciousness during presentation in our study compared to other studies was presenting 46–83% of the largest reported pediatric cohorts.^{11-15,18} While similar to an other study reported by Gupte et al in 33%.¹⁹ As such, only these 20% would meet the proposed pediatric international MS Study Group definition for ADEM, which mandates the presence of encephalopathy; the rest would be considered to have isolated clinical syndrome.¹⁰ However, as the definition remains controversial, we did not apply it. Furthermore, seizures affected 35% of our cases which was considered a differentiating feature from multiple sclerosis in one

study where 6/24 ADEM and 0/26 MS cases had seizures at presentation.²⁰

With regards to neurological outcome, our cases showed a very good outcome with normal neurological outcome in the majority and minimal neurological dysfunction in the rest of cases came to follow up. Of interest no deaths, relapses nor severe deficit were seen at follow up. Good outcome has been reported in most of the studies ranging 57-92%.^{16,17,21-23} Other studies reported adverse outcome of significant neurological disability of 11-30% of cases.^{16,17,20,22,23} Mortality is rarely encountered in literature, in one study from USA by Leake et al, 2/42 (4.7%) of cases died due to severe brain edema and high intracranial hypertension.²⁴ The overall very good outcome in most of our cases may be due to aggressive treatment with immunomodulation therapy that are started as soon as the diagnosis is suspected but it is possible that our cases is milder in severity compared to cases reported in the literature. Furthermore, the severe hemorrhagic form of ADEM called acute hemorrhagic leukoencephalitis which was reported to affect about 2% of cases was not encountered in our series.¹⁶

The main limitation of this is the retrospective nature with inadequate documentation of information and the relatively short duration at follow up. However, multicenter prospective studies are needed to clarify these findings and study better the long term outcome particularly evolution to multiple sclerosis and long term subtle neurological deficit.

In conclusion, motor deficit rather than encephalopathy is the most presenting feature in this population of ADEM patients with excellent neurological outcome, however, further exploration of this disease is recommended.

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