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BRIEF REPORT

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Acute disseminated encephalomyelitis in the intensive care unit: clinical features and outcome of 20 adults

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Abstract *Objective:* Because acute disseminated encephalomyelitis (ADEM) is a rare disease in adults admitted to the intensive care unit (ICU), we describe its characteristics and patient outcomes. *Design and setting:* A retrospective (2000–2006), observational, multicenter study was conducted in seven medical ICUs. Clinical, biological and neuroimaging features of patients diagnosed with ADEM were evaluated. Functional prognosis was graded using the modified Rankin (mR) scale. *Interventions:* None. *Measurements and results:* At ICU admission, the 20 patients' median (25th–75th percentile) Glasgow coma score (GCS) was 7 (4–13), temperature 39 (38–39) °C. Six (30%) patients had seizures, 17 (85%) had a motor deficit and 14 (70%) required mechanical ventilation. Fifteen (75%) patients had cerebrospinal fluid pleocytocis. All patients had white-matter lesions on their magnetic resonance images. All patients received high-dose steroids. Five (25%) patients died. Fourteen (70%) patients were able to walk without assistance (mR $\leq$ 3) at follow-up [7 (3–9) months]. Compared to the latter, patients who died or were severely disabled at the follow-up evaluation [6 (30%) patients, mR > 3] had significantly lower GCS (4 (3–4) vs. 12 (7–13), $p = 0.002$) and more frequent seizures [4 (67%) vs. 2 (14%), $p = 0.02$] at admission. *Conclusions:* Unlike previous reports, our results showed that ADEM requiring ICU admission is a severe disease causing high mortality, and 35% of the patients had persistent functional sequelae. Intensivists should be aware of ADEM's clinical features to initiate appropriate immunomodulating therapy.

Keywords Encephalomyelitis · Demyelination · Post-infectious · Adults · Vaccination

Introduction

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the central nervous system (CNS) [1]. It is predominantly a pediatric disease with an incidence of 0.4/100,000 [2]. Also known as post-infectious encephalomyelitis, it typically follows a minor infection with a latency period of 2–30 days and is thought to be immune-mediated [3, 4].

ADEM is clinically characterized by the acute onset of focal neurological signs and encephalopathy. Cerebrospinal fluid (CSF) analysis usually shows predominant lymphocytic pleocytosis but, unlike viral or bacterial encephalitis, no evidence of direct CNS infection is found. Cerebral magnetic resonance imaging (MRI) is essential to ADEM diagnosis, detecting multifocal or diffuse lesions throughout the white matter.

Although ADEM in adults was studied previously, to the best of our knowledge, severe forms necessitating ICU admission have not been thoroughly described [5]. The aim of this study was to analyze the clinical, biological and neuroimaging features and outcomes of adult ADEM patients admitted to the ICU.

Materials and methods

Patients

We retrospectively studied ADEM patients admitted to medical ICUs between January 2000 and November 2006, identified by responses to letters mailed to 14 adult medical ICUs in the Paris area. ADEM was initially diagnosed by the treating physician; however, all patients fulfilled the following ADEM criteria adapted from published definitions [5, 6]: (1) acute onset of encephalopathy (impaired consciousness, e.g., lethargy, coma > 24 h) and neurological symptoms (e.g., seizures, motor deficit, ataxia, cranial nerve abnormality, language disturbances); (2) no history of unexplained neurological disease or a clinical episode with features of a prior demyelinating event; (3) MRI displaying one or multiple lesions, predominantly affecting white matter on T2-weighted sequences, without evidence of anterior demyelination ("black holes" on T1-weighted sequences); (4) no other etiologies that could explain the event. Twenty adults (> 18 years) with ADEM were identified in 7 of the 14 ICUs (including one neurological ICU).

Simplified acute physiology score (SAPS) II [7], Glasgow coma score (GCS) without sedation [8] and neurological examination findings were determined at ICU admission. All other parameters determined within 24–72 h thereafter are reported in Table 1. White blood cell counts and CSF characteristics were noted. Neuroimaging (computed tomography, brain and spinal cord MRI) performed at admission was reviewed by a neuroradiologist (I.K.). Therapeutic regimens and time between ICU admission and starting appropriate therapy were determined for each patient.

A follow-up study was performed by contacting each patient's treating physician at hospital discharge. Data

Table 1 Clinical and laboratory characteristics of 20 adult ADEM patients at ICU admission

Parameter	All patients ($n = 20$)	Good outcome ($n = 14$)	Adverse outcome ($n = 6$)
Age, years	37 (27–51)[a]	34 (28–49)	44 (30–58)
Fernale sex, *n* (%)	11 (55)	8 (57)	3 (50)
Preceding infectious disease, *n* (%)	14 (70)	9 (64)	5 (83)
Latency period, days	8 (6–14)	9 (5–14)	7 (6–8)
SAPS II	33 (15–45)	31 (13–45)	35 (23–41)
MV, *n* (%)	14 (70)	9 (64)	5 (83)
Temperature, °C	39 (38–39)	38.7 (37.9–39)	39 (37–39.4)
Neck stiffness, *n* (%)	10 (50)	6 (43)	4 (67)
GCS	7 (4–13)	12 (7–131)*	4 (3–4)*
Seizures, *n* (%)	6 (30)	2 (14)**	4 (67)**
Motor deficit, *n* (%)	17 (85)	12 (86)	5 (83)
Spinal card symptoms, *n* (%)	11 (55)	7 (50)	4 (67)
PNS involvement, *n* (%)	5 (25)	2 (14)	3 (50)
CSF cells, *n*/mm^3	90 (60–378)	76 (10–271)	59 (18–246)
CSF predominance of neutrophils, *n* (%)	5 (25)	4 (29)	1 (17)
CSF protein, g/l	1.3 (0.5–1.9)	1.3 (0.5–1.6)	1.3 (0.5–2.6)
Time between ICU admission and steroid administration, days	3 (1–9)	3 (1–9)	3 (1–4)
Steroid dose, g	10 (6–10)	10 (6–10)	10 (9–10)
IVIg, *n* (%)	6 (30)	3 (21)	3 (50)
Duration of MV, days	26 (10–36)	12 (10–27)	29 (25–52)
Length of ICU stay, days	19 (13–36)	15 (13–34)	30 (15–48)

SAPS, simplified acute physiology score; *MV*, mechanical ventilation; *GCS*, Glasgow coma score; *PNS*, peripheral nervous system; *CSF*, cerebrospinal fluid; *IVIg*, intravenous immunoglobulins; *ICU*, intensive care unit

[a] Values are medians (25th–75th percentiles) unless stated otherwise.

* $p = 0.002$; ** $p = 0.02$

concerning survival and disability were extracted from the patient's file.

Functional outcome was graded using the modified Rankin (mR) scale, validated for neurological diseases, with scores ranging from 0 (no symptoms) to 6 (death) [9]. Patients' outcomes were classified as good ($mR \leq 3$, able to walk without assistance) or adverse ($mR > 3$, severe disability or death) according to the neurological evaluation at follow-up.

Statistical methods

Results are expressed as numbers (%) for categorical variables and as medians (25th–75th percentiles) for continuous variables. Fisher's exact test and/or the chi-square test were used to compare categorical data and the Mann–Whitney test for continuous data. A p value < 0.05 was considered significant. Statistical analyses were conducted with Statview software (version 5.0).

Table 2 Distribution of MRI-detected lesions in the 20 adult ADEM patients

MRI lesions	*n* (%)
Supratentorial white matter	18 (90)
Extensive	6 (30)
Multifocal[a]	12 (60)
Infratentorial white matter	8 (40)
Cerebellum	3 (15)
Brainstem[b]	6 (30)
Cortical gray matter	7 (35)
Deep gray matter[c]	3 (15)
Gadolinium enhancement	5 (25)
Cerebral edema	6 (30)
Mass effect	4 (20)
Spinal cord involvement	11/13 (85)

MRI, magnetic resonance imaging
[a] Subcortical ($n = 10$), semi-oval center ($n = 10$), periventricular ($n = 6$), corpus callosum ($n = 2$);
[b] Pons ($n = 3$), bulb ($n = 1$), mesencephalus ($n = 2$);
[c] Thalamus ($n = 3$), basal ganglia ($n = 1$)

Results

Among the 20 patients, 14 (70%) had an infectious illness during the 2 weeks preceding ICU admission, mainly lower respiratory tract infections or flu-like symptoms, but a potential triggering pathogen was documented in only 2 (Epstein–Barr virus and enterovirus, 1 each). One patient had recently been immunized against yellow fever. The time between the preceding illness and onset of neurological signs was 8 (6–14) days, and that between the latter and ICU admission was 2 (1–7) days.

Patients usually presented with impaired consciousness and fever, 10 (50%) of them with neck stiffness. Fourteen patients (70%) required mechanical ventilation (MV). Neurological findings consisted of focal deficits (motor weakness, e.g. paraplegia or hemiplegia) in 17 patients (85%), sensory disturbances in 15 (75%), cranial nerve abnormalities (facial or oculomotor nerve palsy) in 8 (40%), acute urinary retention in 7 (35%), cerebellar dysfunction in 3 (15%), and language disturbances in 3 (15%). Twelve (60%) patients had multifocal neurological findings (clinical abnormalities involving different CNS areas) at initial examination.

CSF leukocyte counts were elevated in 15 patients (75%), with lymphocytic pleocytosis [65 (20–100)% lymphocytes] in 10, while neutrophils predominated for 5. CSF analyses were normal for 3 patients (15%). All CSF cultures and polymerase chain-reaction testing for herpes simplex virus-1 and -2 and varicella-zoster virus were negative. White blood cell counts were high in 9 patients (45%) [14,400 (13,800–17,300)/mm^3] and 6 others (30%) were lymphopenic [695 (683–775)/mm^3].

Cerebral computed tomography scans showed abnormalities in 6 patients (30%), consisting of hypodensities in the cerebral white matter and focal or diffuse cerebral edema. Within 24–72 h after ICU admission, all patients underwent brain MRI. All patients had MRI abnormalities, which are reported in Table 2. We identified two MRI lesion patterns: multifocal (60%) or diffuse (30%) supratentorial white-matter involvement (Fig. 1).

All patients received high-dose steroids (methylprednisolone pulses). Time between ICU admission and steroid administration was 3 (1–9) days (Table 1). Other treatments included intravenous immunoglobulins [IVIg, 6 patients (30%)] and plasma exchanges [2 (10%)].

Five (25%) patients died. The deaths were retrospectively attributed to: sepsis (1), brain death (2), and severe neurological disabilities (2). Seven patients (35%) had functional sequelae (mainly sensory or motor disability, cranial nerve abnormality, cognitive impairment) at hospital discharge. At the follow-up evaluation [7 (3–9) months], 14 patients (70%) were able to walk without assistance ($mR \leq 3$). The 6 patients (30%) who died or were severely disabled ($mR > 3$) had had, at ICU admission, lower GCS ($p = 0.002$) and a higher rate of seizures ($p = 0.02$).

Discussion

The results of our study showed that ADEM patients can be referred to the ICU because of severely impaired consciousness, seizures, or symptoms of CNS infections, mainly fever and neck stiffness. Although ADEM is a rare disease in adults, it should be considered in all cases of unexplained encephalitis, especially in a setting of recent infectious disease or vaccination. Diffuse and focal CNS signs and peripheral nervous system (PNS) involvement

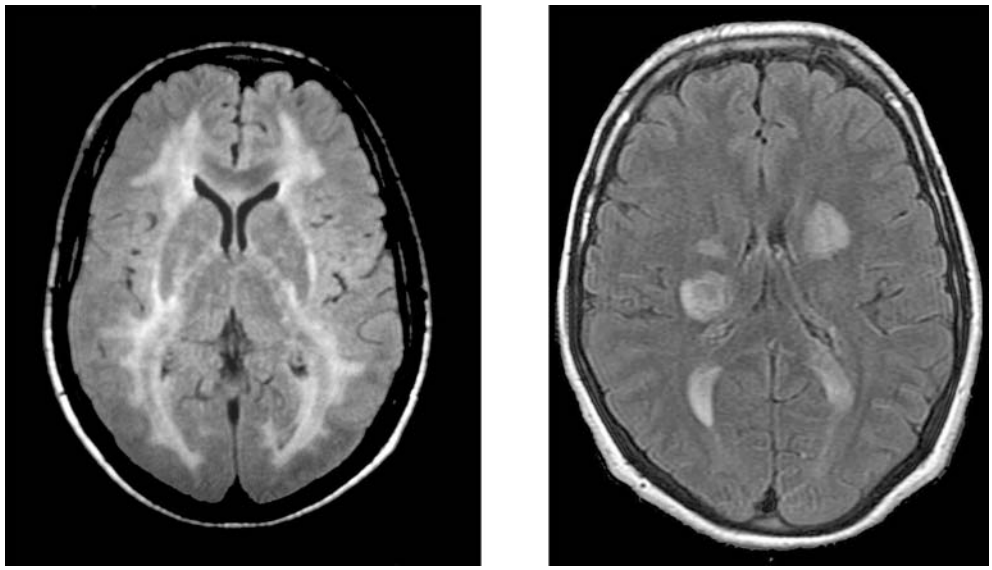

Fig. 1 Fluid-attenuated inversion recovery (FLAIR)-weighted brain MRI of a 20-year-old man, admitted to the ICU for acute change of mental status and fever, showing diffuse extensive white-matter lesions suggestive of ADEM (*left*) and of a 34-year-old woman, admitted to the ICU for confusion, fever and focal deficit, showing multifocal white-matter lesions (*right*)

may be present simultaneously at physical examination, as previously reported [10].

Because ADEM symptoms can mimic CNS infections and most patients are febrile at disease onset, lumbar puncture is systematically indicated to rule out infectious (viral or bacterial) meningoencephalitis. CSF findings of ADEM patients are usually non-specific and include lymphocytic pleocytosis with elevated protein levels and sterile cultures. However, our observations demonstrated that neutrophils predominated in approximately one-fourth of the patients but did not seem to be associated with an adverse outcome.

Brain MRI is mandatory for ADEM diagnosis, to look for evidence of white-matter inflammation and disseminated demyelination on T2- and FLAIR-weighted sequences. Spinal cord MRI might also show confluent intramedullary lesions [6, 11, 12]. In accordance with those studies, the majority of our patients had the typical MRI presentation, consisting of multifocal, patchy lesions. It should be noted that another pattern, consisting of diffuse supratentorial involvement, was frequent (30%) in our patients and might reflect the severity of their disease. Associated deep or cortical gray-matter involvement was observed in 15% and 35% of our patients, respectively, in agreement with numerous studies, and should not lead the clinician to exclude a diagnosis of ADEM [5, 13, 14]. Notably, cortical gray-matter lesions were more frequent in these severe ADEM patients than reported previously [5, 15]. This finding could explain the higher seizure rate we observed, compared to published data on adults [5].

High-dose intravenous steroids are widely accepted as first-line ADEM therapy, and the authors of several studies also reported beneficial effects of plasma exchanges, IVIg, and/or immunosuppressants [3, 5, 16]. Because all of our patients received high-dose steroids, with or without adjunctive immunomodulating therapy, it is difficult to discuss further therapeutic options.

We found that ADEM in adults requiring ICU admission is a severe disease, with 25% mortality, and that 35% of the patients had persistent sensory or motor sequelae. Because our patients represent the most severe ADEM cases, mortality was higher than had been reported in one of the largest follow-up studies on 26 adult ADEM patients, most of whom survived with moderate or no neurological impairment [5]. Acute hemorrhagic leukoencephalitis has been described as a hyperacute form of ADEM but was not diagnosed in our cohort and thus could not explain the high mortality we observed [17]. Fever, seizures and encephalopathy were also more frequent in our patients than in the published data on adults [5]. Moreover, seizures or severely impaired consciousness at ICU admission seem to be associated with poor functional outcome.

Although, to our best knowledge, this is the first reported study on ADEM in adults requiring ICU admission, it has several limitations. Because of the retrospective design of our study, ADEM diagnosis was initially determined by the treating physician. However, all patients' files were reviewed by the authors and published ADEM criteria were applied [5, 6]. All potential ADEM-triggering pathogens were not systematically sought, which might have diminished the ability to identify all preceding infections. Sometimes ADEM cannot be distinguished from multiple sclerosis with certainty at initial presentation. None of our patients had developed any recurrences suggestive of multiple sclerosis during 7 months of follow-up. Establishing a diagnosis of multiple sclerosis could require more prolonged follow-up. Other than GCS and seizures at ICU admission, identification of additional

factors predictive of outcome was not possible based on our small cohort.

In conclusion, ADEM in a subset of adults requiring ICU admission is associated with a poor prognosis. Intensivists should be aware of the salient clinical and neuroimaging features in order to initiate appropriate immunomodulating therapy.

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