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Acute Disseminated Encephalomyelitis in PICU.

[1]Dalila Boumendil, [2]Abdelnour Sellam, [3]Zahia Mentouri

[1]*Pediatric Intensive Care Unit, University of Oran1, Ahmed BEN BELLA, Algeria, ACCIPED.*

[2]Neurophysiology, *University of Oran1, Ahmed BEN BELLA, Algeria, ACCIPED.*

[3] *Pediatric Intensive Care Unit, University of Oran1, Ahmed BEN BELLA, Algeria.*

Abstract:

Introduction: Acute disseminated encephalomyelitis (ADEM) is a demyelinating central nervous system disorder. The experience in children in our area is limited.

Purpose: We describe a cohort of consecutive children with ADEM.

Methods: Clinical and MRI of brain characteristics, treatment and outcome of a series of ADEM hospitalized in PICU, Oran University Hospital center (Algeria) from January 2011 to may 2016 were reviewed.

Results: There were 07 males and 03 females. The mean age (median) at onset was 48 months [range, 6 –132 months]. All children had a prodromal event (infectious 08 cases or vaccination 02 cases).

The mean interval between the febrile prodrome and the beginning of neurologic disturbance was 14 days (range, 3 to 30 days).

Limb weakness (02 cases), ataxia (02 cases), ophtalmoplegia (02 cases) and acute hemiparesis (02 cases) were the most prominent initial findings. Aphasia was noticed in one patient.

Seizure was observed in 07 patients. Consciousness disturbance (n=5) evolved into coma with cardiomyopathy of stress in one patient**.**

CSF lymphocyte pleocytosis was found in 3 patients (9 – 208 cells/mm3). Initial MRI showed a deep gray matter involvement in 6 cases.

Electroencephalogram (EEG) showed slowing of background activity in 04 patients.

05 patients were treating with IV immunoglobulin alone and 03 with high-dose IV methylprednisolone pulse.

Among 10 patients, five had long-term neurological squeals.

Conclusion: We conclude that early diagnosis and prompt treatment of ADEM will probably reduce morbidity and the seizures are not uncommon in ADEM.

Keywords: Encephalopathy, ADEM, Brain Magnetic Resonance Imaging, Children, Outcome.

Abbreviations: ADEM = acute disseminated encephalomyelitis, FLAIR = fluidattenuated inversion-recovery, MS = multiple sclerosis, CNS: central nervous system. PICU: Pediatric Intensive Care Unit.

Introduction

Acute disseminated encephalomyelitis (ADEM) is a condition characterized by inflammatory demyelinating lesions **[1],** mediated by an autoimmune mechanism **[2]** predominant in the white matter of the central nervous system (CNS) **[1] [3].** It is rare but It is rare but usually occurs in children (typically <15 years old), often within 2 weeks after an antigenic challenge—either an infection (50%–75%, frequently upper respiratory) or a vaccination. **[4][5]** The annual incidence of ADEM is estimated in children at 0.4 / 100,000 per year. **[5]**

ADEM is clinically characterized by acute encephalopathy with multifocal neurological signs requiring intensive care in the event of disturbances of consciousness, seizures, or quadriplegia. **[3]**

ADEM mortality is currently less than 5% in children. **[6]** The prognosis seems more severe for forms hospitalized in intensive care, with mortality of up to 25%. **[3][6]**

The aims of this work are to determine the clinical and radiological characteristics as well as the therapeutic modalities and the outcome of a series of ADEM hospitalized in pediatric intensive care.

Materials and Methods

Clinical and MRI of brain characteristics, treatment and outcome of a series of ADEM hospitalized in PICU, Oran University Hospital (Algeria) from January 2008 to may 2016 were reviewed.

The diagnosis was according to the criteria of the International Pediatric MS Study Group (2007).

International MS Study Group monophasic ADEM criteria [7]

- No history of prior demyelinating event
- First clinical event with presumed inflammatory or demyelinating cause
- Acute or subacute onset
- Affects multifocal areas of central nervous system
- Must be polysymptomatic
- Must include encephalopathy (ie, behavioral change or altered level of consciousness)
- Neuroimaging shows focal/multifocal lesion(s) predominantly affecting white matter
- No neuroimaging evidence of previous destructive white matter changes
- Event should be followed by clinical/radiologic improvements (although may be residual deficits)
- No other etiology can explain the event
- New or fluctuating symptoms, signs, or magnetic resonance imaging findings occurring within 3 months are considered part of the acute event

Results

1. Patients and Gender

In the present case series study, we reported ten cases of ADEM diagnosed by clinical and radiological results.

These are 07 boys and 03 girls; the mean age at onset of the disorder was 48.2 months [range: 6 months – 11 years]. Most of the children were neurologically normal at the start. All children had an infectious type prodromal event in 08 patients and a DTCOQPOLIO vaccination type event in 02 patients.

The average delay between the febrile event and the onset of neurological disorders was 14 days (range: 3 to 30 days). Ataxia (02 cases), ophthalmoplegia (02 cases), acute hemiparesis (02 cases), and paraplegia (02 cases) were the main signs of onset. Aphasia has been observed in one patient.

Convulsions were observed in 07 patients. Consciousness disorders were noted in 05 patients, one of whom developed into a coma associated with stress cardiomyopathy. **(Figure 5)**

The general characteristics of the patients, their clinical and radiological presentations are summarized in (**Table 2, 3, 4).**

2. Paraclinic evaluations.

2.1. Spinal fluid (CSF) abnormalities

CSF abnormalities were found in 4 children with lymphocyte pleocytosis (9 – 208 cells/mm3) or high elevated protein (> 3 g/dL) in one patient.

2.2. Brain Neuroimaging

Cerebral computed tomography was performed in 07 patients and revealed abnormal results in 05 patients, after an average interval of 4.25 ± 3.2 days from the first symptoms (median 3 days). The CT scan showed hypodense areas of the cerebral white matter and deep gray. **(Figure 1)** TDMC was normal in 02 patients.

Brain Magnetic Resonance Imaging (MRI) was performed in all our patients and showed multifocal 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 2, 3, 4)**

Initial MRI showed a deep gray matter involvement in 6 cases. **(Figure 2, 3, 4)** These lesions were bilateral and asymmetrical.

The IV injection of gadolinium diethylene triamine penta-acetic acid revealed an enhancement in the peri-lesional crown in two children and in punctate in one child. Meningeal contrast enhancement was noted in one child. The T2 FLAIR hypersignal lesions were strewn with some hemorrhagic changes (02 patients). **(Figure 2)**

2.3. Electroencephalography (EEG)

Interictal EEG records were assessed during the acute stage of the disease in 04 patients. Diffuse slow background activity was observed in 04 and focal (frontal) spikes in one.

2.4. electroneuromyogram (ENMG)

The ENMG was performed in 03 patients and showed an aspect of peripheral neurological damage.

3. Treatment

All patients received symptomatic treatment during the acute phase of the disease, two patients required artificial ventilation due to respiratory failure with profound impairment of consciousness. Antiepileptics were administered to 07 patients. Acyclovir has been prescribed to all patients for possible HSV infection.

high-dose IV methylprednisolone pulse (30 mg/kg/day) for 3 days followed by oral prednisolone (1 mg/day) for 20 days was administered to 02 patients prescribed by pediatricians before admission to PICU.

The other children received Intravenous immunoglobulin associated with dexamethasone at a rate of 0.4 mg/Kg/ day for 05 days

4. Outcome:

At discharge, all the children were alive; the average length of hospital stay was 60.8 days. Of the 10 patients, five had clinical and electrical seizures after long-term monitoring, two of whom also had dystonia, and one died after 07 months of development.

One patient had had a recurrence episode after 19 months and whose TDMC objectified new lesions but the evolution was favorable under high-dose corticosteroid. A total of 05 patients had a complete recovery.

5. Tableaux et illustrations

Table 1: The clinical characteristics of the 10 ADEM patients hospitalized in PICU.

Patients	Sex	Age (months)	Season	Trigger Factor	Delai (d)	Clinical Feature	CSF Findings
P1	Male	78	Winter	Varicella	30	Seizure, Somnolence, Nystagmus and Meningeal stiffness.	**WBC** =09 /mm3 lymphocytes
P2	Male	48	Spring	Nonspecific febrile illness	20	Generalized seizures, Left convergent squint, Meningeal stiffness, Babinski Sign, Consciousness impairment 13/15 on the Glasgow coma scale.	Pr = 0,9g/l WBC =09 /mm3 lymphocytes
P3	Male	24	Summer	Nonspecific febrile illness	7	Seizures	WBC =208/mm3
P4	Male	27	Spring	Tonsillitis	20	Paraplegia of the lower limbs, axial hypotonia, bilateral ptosis, areflexia and swallowing disorder. the plantar reflex is indifferent	Pr = 3,1 g/l. WBC=0
P5	Male	6	Winter	Tdap-IPV Vaccine	07	Disorder of the state of consciousness 11/15 on the Glasgow coma scale. Généralised tonic-clonic Seizures; the plantar reflex is indifferent	Pr = 0,16 WBC =02 /mm3
P6	Male	9	Spring	Nonspecific febrile illness	15	Generalized convulsive status epilepticus, Disorder of the state of consciousness 11/15 on the Glasgow coma scale.	Normal
P7	Male	48	Winter	Nonspecific upper respiratory tract infection	6	Generalized convulsive seizures, Disorder of the state of consciousness 11/15 on the Glasgow coma scale.	Normal
P8	Female	132	Summer	Flu syndrome	8	Headache, Asthenia, Cerebellar ataxia, Flaccid paraplegia, Babinski Sign.	Pr = 0,22 g/l WBC =28/mm3 lymphocytes
P9	Female	87	Winter	Angina	10	Left acute spastic hemiparesis, Partial convulsions, aphasia, left facial palsy, Babinski Sign	Normal
P10	Female	27	Winter	Nonspecific upper respiratory tract infection	16	Coma, quadriplegia, hypertonia, neurovegetative dysautonomia.	Normal

Tdap-IPV Vaccine : **T**etanus, Diphteria, Pertussis, Polio (Tdap-IPV) Vaccine ; **Pr** : Protein , **WBC** : white blood cells

Table 2: Neuroradiological characteristics of the 10 ADEM patients hospitalized in PICU.

Patients	Brain CT scanning	*MRI Findings*			
		Type of lesion	**Location of lesions of demyelination**	**Signs of hemorrhage**	**Gadolinium-enhancing lesions**
P1	Multiple parenchymal nodules	Multiple nodular lesions	In Cortical Gray Matter and deep gray matter structures (thalami)	+	ring enhancement
P2	hypodense areas parietal, thalamic and brainstem	Diffuse lesions	In Cortical white and gray mater periventricular white matter, centrum ovale, internal capsules and deep gray nuclei the brainstem, cerebellar peduncle	—	
P3	Not performed	Confluent lesions	In subcortical white mater, periventricular white matter, centrum ovale and deep gray nuclei	—	ring enhancement and meningeal
P4	Normal	Confluent lesions	In subcortical white mater	—	
P5	hypodense areas thalamic and of the post arm of the adjacent internal capsule	Butterfly wing appearance	white mater, deep gray nuclei and the brainstem	—	
P6	Not performed	diffuse lesions	white mater	—	
P7	hypodense lesions in cortical and subcortical of left frontal and parietal lobes	diffuse lesions	periventricular white matter lesions, bilateral vermio-cerebellar and Brainstem	+	Low
P8	Normal	Confluent lesions	Subcortical white mater	—	
P9	Periventricular hypodense areas	Confluent lesions	Asymmetrical bilateral involvement of the white matter, involving the centrum ovale, the internal and external capsules, the corpus callosum associated with lesions in the midbrain.	—	
P10	Not performed	Confluent lesions	multiple hyperintense lesions in bilateral cortical and subcortical area, in deep gray nuclei and periventricular white matter	—	linear and focal

Table 3: Electrical characteristics of ADEMs hospitalized in PICU.

Patients	EEG	ENMG
P1	Not performed	Not performed
P2	Diffuse slow background activity	Not performed
P3	Not performed	Not performed
P4	Not performed	sensitivomotor polyneuropathy with signs of denervation
P5	Not performed	Not performed
P6	Not performed	Not performed
P7	Diffuse slow background activity + frontal spikes	Peripheral neuropathy with signs of denervation
P8	Not performed	Normal
P9	Diffuse slow background activity	Not performed
P10	Diffuse slow background activity	polyneuroradiculopathy.

NF : Non fait

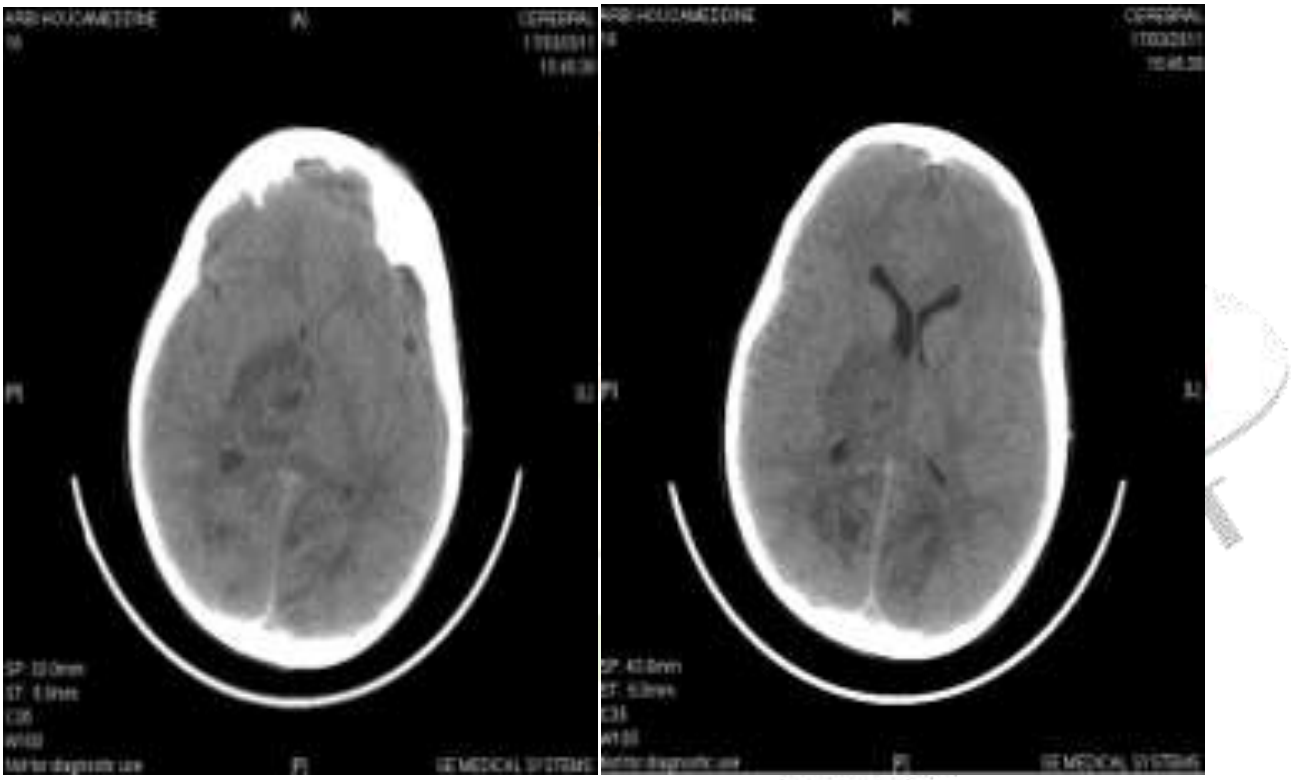

Fig 1: Multiple parenchymal nodules which suggest a secondary location.

Table 4: Treatment and Outcome of the 10 ADEM patients hospitalized in pediatric intensive care.

Patients	Artificial ventilation	Steroids	IVIG (Intravenous immunoglobulin)	Outcome	Hospital stay
P1	NO	Dexaméthasone 0.4 mg/Kg/d	IVIG	Complete recovery	6 days
P2	NO	Cortancyl 2 mg/Kg/d	—	Complete recovery Recurrence after 12 months	4 days
P3	NO	Cortancyl 2 mg/Kg/d	—	Complete recovery after 03 months	10 days
P4	NO	Déxamethasone 0.4 mg/Kg/d	IVIG	Complete recovery	21 days
P5	NO	Déxamethasone 0.4 mg/Kg/d	IVIG	Complete recovery	90 days
P6	YES	Méthylprednisolone à 30mg/Kg/d.	IVIG	Complete recovery after 03 months	07 days
P7	YES	Déxamethasone 0.4 mg/Kg/d	IVIG	Severe neurological sequelae Slow recovery after 06 months	120 days
P8	NO	Déxamethasone 0.4 mg/Kg/d	IVIG	Complete recovery	04 days
P9	NO	Méthylprednisolone à 30mg/Kg/d.	IVIG	Recovery after 05 weeks	05 days
P10	NO	Méthylprednisolone à 30mg/Kg/d	IVIG	Severe neurological complications died after 07 months	47 days

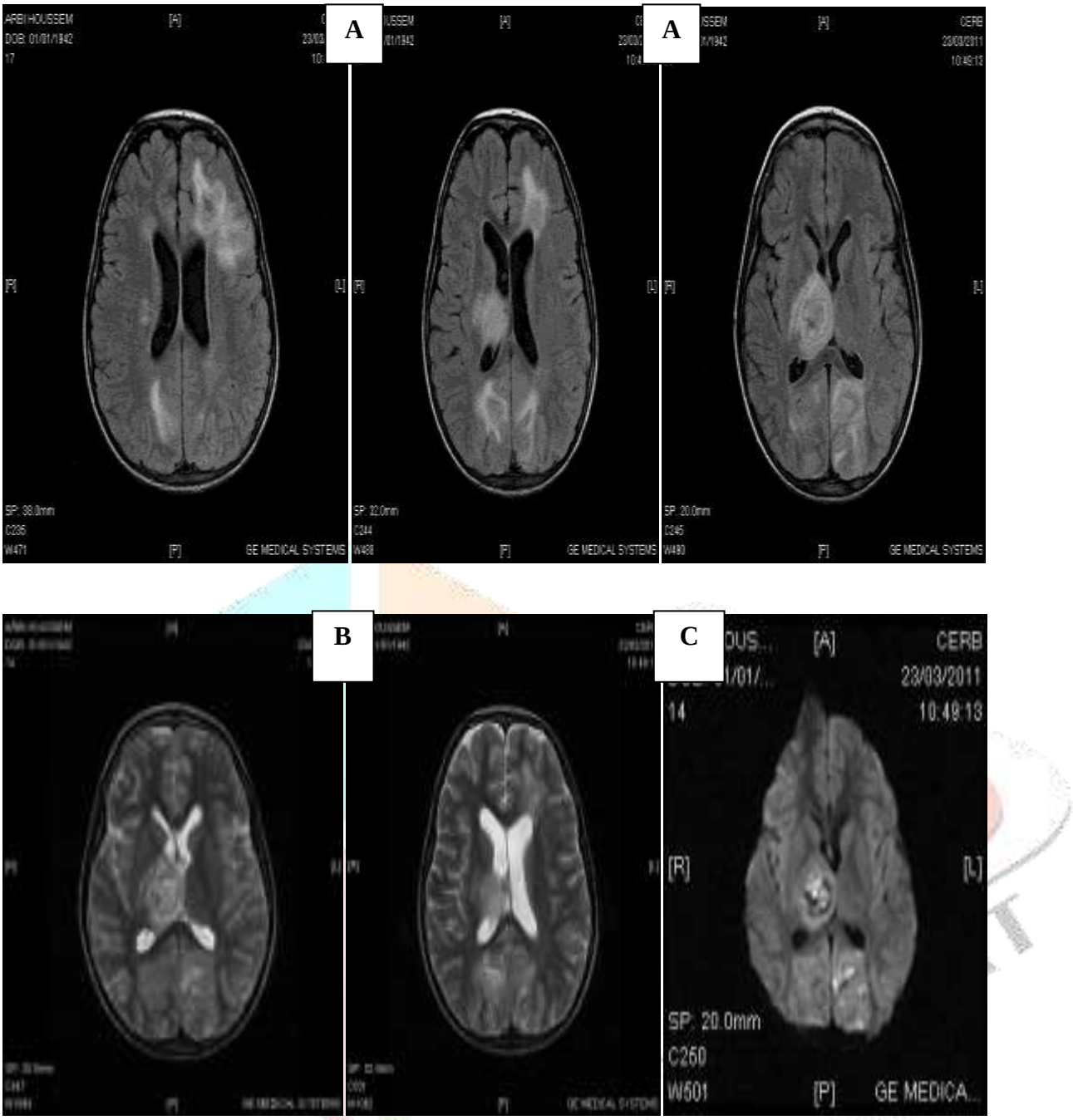

Fig: 2

A) : Brain MRI T2 and FLAIR: Images at the level of the right thalamus

B) : T2 showing multiple hyper intensities lesions in the right thalamus and cerebral white matter (occipital, frontal).

C) : Diffusion sequence.

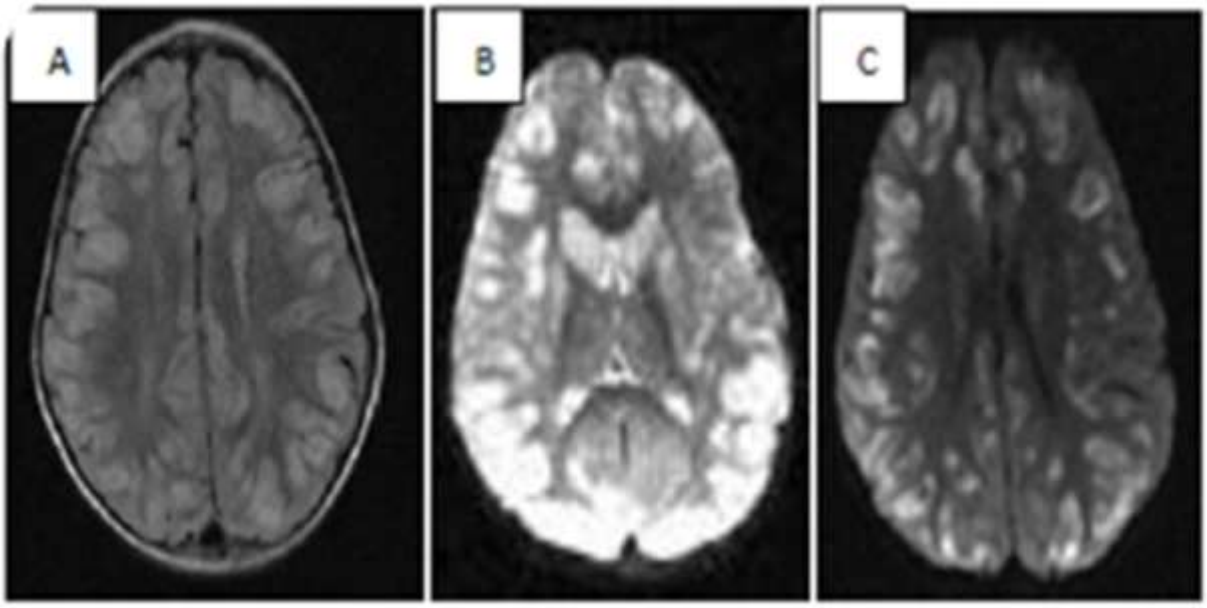

Fig 3 :
(A) : Brain MRI T2 and FLAIR;
(B) : T2 showing Multiple hyperintensities lesions in the cerebral white matter and deep Gray Nuclei.
(C) : Hypersignal B1000 with restriction of the diffusion on the ADC cartography.

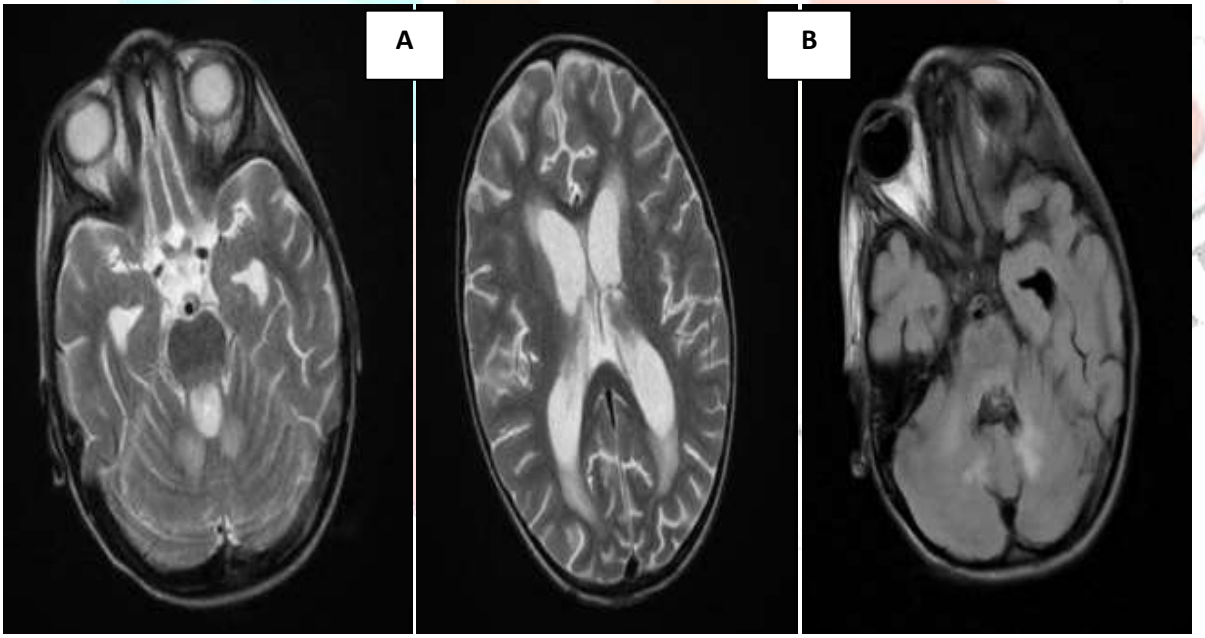

Fig 4:
(A) : AX T2 ;
(B) : T2 FLAIR ;
Multiple signal abnormalities of the bilateral periventricular and vermis-cerebellar substance, as well as of the posterior part of the bulb and bridge, of the brainstem, and cerebellar peduncles.

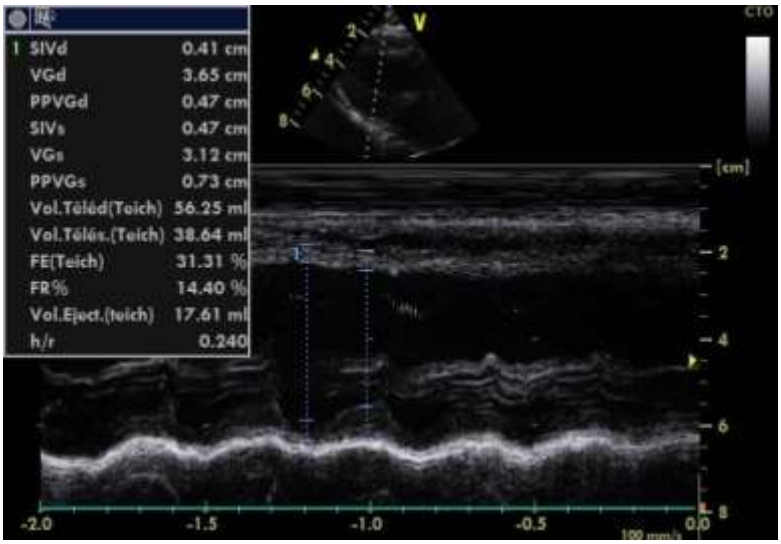

Fig 5: cardiomyopathy of stress in a patient with ADEM

Discussion

Ten cases of ADEM were identified over a period of 5 years and 06 months in the PICU of Oran University hospital. Boys were more frequently affecting which is also reported in several pediatric cohorts.A male predominance has been noted which is also reported in several pediatric cohorts. **[1][8]** There seems to be a seasonal predominance, with a peak in winter and spring, **[2][6]** which corroborates with our results.

Neurological disorders often appear after a free interval in relation to a trigger, the duration of which varies from 2 to 30 days. **[9]** The infection of the upper respiratory tract is often the trigger for ADEM. Many viral and bacterial strains have been associated with ADEM but none of them has been recognized as the cause. Immunization against rabies, diphtheria-pertussis-tetanus, or other pathogens may also be associated with ADEM. **[10]** In our series, the trigger was present in all our patients. The onset is sudden or rapidly progressive; symptoms develop in a few days, on average 05 days.

The clinical presentation of ADEM is widely variable; studies have previously reported an encephalopathy in 21% to 74% of patients. **[1][6][9][22]** 19 to 69% had altered mental status, **[1][5]** and had seizures in 13 to 35% of cases in children. **[9][11][12]** 07/10 in our series had presented with disturbances of consciousness ± seizures. Focal deficit signs are frequent. Hemiplegia is noted in about 75% of cases (02/10 in our series).

In our series we had two patients; one of them had acute paraplegia and the other had quadriplegia which were related to spinal cord injury, many studies report a frequency of 20 to 25%. **[1][2][9][13]** Although aphasia was considered rare in ADEM, it was noted in one patient.

Analysis of the CSF is fundamental and first of all makes it possible to exclude an infectious meningoencephalitis. The CSF may show non-specific abnormalities such as lymphocytic pleocytosis associated with high elevated protein. In our series, the CSF analysis was abnormal in 05 patients.

Pavone and colleagues **[14]** reported abnormal CT scans findings in 86% of patients after a mean interval of 2.5 days from initial neurologic presentation, which corroborates with our results.

The Brain MRI is the key element of the diagnosis, **[12][16][17]** The presence of abnormalities in T2 hypersignal and /or FLAIR and /or diffusion is mandatory to carry the diagnosis of ADEM. **[18]** In some situations, abnormalities in the Brain MRI are only observed after a few weeks of the disease, thus leading to a diagnostic and therapeutic delay. **[9][10]**

All of our patients had an abnormal brain MRI in favor of ADEM with the detection of lesions in hypo- or isosignal in T1 and in hypersignal on the T2-weighted sequences and fluid-attenuated inversion recovery (FLAIR).

The expansion of the radiological lesions was associated with a severe outcome in one patient from our series. **(Fig 2)** Enhancement of the lesions is noted in around 30% of cases **[2],** in the form of crowns or clods. **[2]** (4/10 in our series). Meningeal contrast enhancement is rare, noted in one patient in our series.

The predominant lesions are those of the subcortical white matter, the centrum semiovalis, and the SB-SG junction. Periventricular white matter can also be affected (30–60%) **[2].** The involvement of the basal ganglia is frequent, **[19]** especially that of the thalami which is usually symmetrical **[20].** The corpus callosum is rarely affected. **[2]** All of this data corroborates with our results.

The initial value of the ADC (apparent diffusion coefficient) represents a prognostic element. **[21]** The low ADC values (abnormal diffusion restriction) are in favor of a more serious impairment with greater neurological sequelae compared to patients who have a high ADC. In our series, 2 children presented hypersignal diffusion with low ADC. These are two patients with different outcome: one was severe **(Fig. 2)** and the other was good.

The prognosis for ADEM in children is generally favorable, attributed to corticosteroid treatment. **[9][11][13][22]** In our series, the clinical course was favorable with total recovery in 05 patients. The others developed secondary epilepsy, two of which had an aggressive course, resulting in the death of a child after 07 months of progression in a picture of malnutrition and generalized hypertonia.

Although ADEM is generally described as a monophasic disease that lasts 2 to 4 weeks, relapses have been reported **[1][9][23][24],** which raises the question of whether these cases represent multiple sclerosis (MS). The therapeutic approach is based on immunomodulatory treatments. The most widely used treatments are intravenous corticosteroids, polyvalent immunoglobulins (IVIG), and plasma exchanges.

The majority of people who receive corticosteroid treatment see their condition improve within a few days and recover fully or almost completely within six months of the onset of ADEM.

The use of Intravenous immunoglobulin is less widespread but it has been described in some case reports and small series **[23][25][26][27] [28]** in children, generally for patients who have not responded to corticosteroids.

In our study, the brain MRI check was not carried out after 06 months for financial problems, whereas it is advisable to practice at least 2 MRI exams after the first normal MRI check and this over a monitoring period of 5 years from the initial episode **[20].**

Conclusion

Acute disseminated encephalomyelitis is an inflammatory demyelinating disease of the central nervous system. Seizures are not uncommon. Brain MRI is essential for diagnosis.

The multiphasic form constitutes a diagnosis and therapeutic challenge given the possibility of confusion with multiple sclerosis. The treatment of ADEM is based on high-dose corticosteroids, possibly associated with Intravenous immunoglobulin.

Early diagnosis and prompt treatment of ADEM are likely to reduce morbidity and mortality.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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