How MRI can contribute to the diagnosis of acute demyelinating encephalomyelitis in children

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ABSTRACT

الأهداف : تسليط الضوء على 10 حالات مُصابة بالتهاب النخاع والدماغ المنتثر الحاد وذلك من ناحية الصفات السريرية، بالإضافة إلى أهمية التشخيص بالتصوير الإشعاعي (وخصوصاً التصوير بالرنين المغناطيسي) في الكشف عن المرض، وعلاجه، والتحكم به .

الطريقة : أُجريت هذه الدراسة الاسترجاعية في قسم الأطفال بمستشفى الهادي شاكر، صفاقس، تونس وذلك خلال الفترة من يناير 2002م إلى ديسمبر 2008م، حيث قمنا بمراجعة سجلات 10 أطفال مصابين بمرض التهاب النخاع والدماغ المنتثر الحاد . ولقد أخذنا بعين الاعتبار صفات ونتائج التصوير بالرنين المغناطيسي .

النتائج : لقد تمت معاينة الأطفال المصابين بالتهاب النخاع والدماغ المنتثر الحاد بعد ظهور بعض العلامات العصبية المتعددة والمختلفة والتي غالباً ما تحدث بعد الإصابة بالالتهاب وخصوصاً التهاب الجهاز التنفسي العلوي . وأشارت نتائج الدراسة بأن التصوير بالرنين المغناطيسي قد قام بتأكيد التشخيص وذلك بالكشف عن آفات زوال النخاعين إما في جذع النخاع، والمخيخ، والمادة الدماغية البيضاء والسنجابية، أو في الحبل الشوكي .

خاتمة : يتميز التهاب النخاع والدماغ المنتثر الحاد بظهور آفات زوال النخاعين المتعددة البؤر والتي بدورها تؤدي إلى مجموعة من العلامات العصبية المختلفة . وأثبتت الدراسة مدى فعالية التصوير بالرنين المغناطيسي في الكشف عن هذه الآفات .

Objective: To illustrate through 10 pediatric cases, the clinical features, course, and importance of neuroimaging (especially MRI) in guiding the diagnosis of acute disseminated encephalomyelitis (ADEM) and controlling patients after treatment.

Methods: A retrospective review of 10 pediatric cases of ADEM, with special regard to the MRI features, presenting to the Pediatric Departments, Hedi Chaker Hospital, Sfax, Tunisia between January 2002 and December 2008.

Results: Children with ADEM presented with variable and multiple neurological signs most often occurring after an infectious episode, especially after upper respiratory tract infection. The MRI permitted confirmation of the diagnosis by showing demyelinating lesions either in the brainstem, the cerebellum, the cerebral white and grey matter, or in the spine of all patients.

Conclusion: Acute disseminated encephalomyelitis is characterized by multifocal demyelinating lesions resulting in varied neurological signs. The MRI is the technique of choice to show these lesions.

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disorder of the CNS involving the brain and the spine with diffuse neurological signs. Children are predominantly affected. Acute disseminated encephalomyelitis is thought to be immune mediated, often following an infection or an immunization.[1] Because of the lack of an identified biomarker, the diagnosis of ADEM is still based on clinical and neuroimaging features. The brain CT scan is often falsely reassuring. The brain MRI is the best modality of diagnosis.[2] Although disseminated encephalomyelitis usually has a monophasic course, recurrent and multiphasic forms have been reported, leading to difficulties in distinguishing these cases from multiple sclerosis (MS). The differentiation of

ADEM from a first attack of MS has prognostic and therapeutic implications.[1] The purpose of this review is to summarize, through 10 observations and the available literature on ADEM, its pathogenesis, the main clinical, and especially the neuroimaging features at presentation, and how to differentiate it from other conditions with acute impact in the CNS. Particular attention is paid to recurrent and multiphasic variants of ADEM and their differences from MS.

Methods. We retrospectively reviewed the clinical records, laboratory results, and imaging features of 10 patients with the diagnosis of ADEM between January 2002 and December 2008. This study was conducted in the Pediatric Departments, Hedi Chaker Hospital, Sfax, Tunisia. The ethical committee of the hospital certified that no ethical approval was needed for our work. We included patients whose diagnosis of ADEM was based on a typical history as well as on clinical and further investigation findings (CSF, EEG, CT, MRI), and in whom a follow-up of several months was obtained. A CSF analysis was considered essential to exclude a direct infectious CNS disease. It included cell count and differentiation, protein, and glucose levels in all patients. The CSF specific oligoclonal IgG bands were performed only in one patient. The EEG was carried out in 2 patients. The visual evoked potentials (VEP) were performed in 3 cases. Brain CT was carried out in half the cases. During the hospital stay, all patients

underwent MRI using 1.5 Tesla machine (General Electric, Milwaukee, Wisconsin, USA) for one patient and one Tesla machine (Siemens, Forchheim, Germany) for the others. It was repeated once in 4 patients. The protocol included T1 and T2 weighted sequences in all patients, and FLAIR sequence in one patient. Diffusion weighted imaging (DWI) and spectroscopy were not performed. Application of a paramagnetic contrast agent was performed in all examined patients. The spine was examined in all cases. No statistical tests were used, only frequencies were calculated.

Results. The patients' details, presenting features, investigations, treatments, and outcomes are summarized in **Tables 1-3**. The series included 8 boys and 2 girls. The mean age at presentation was approximately 7 years, ranging from 5 months to 13 years. Preceding infection involved the upper respiratory tract (5 cases) and gastrointestinal tract (one case). Tonsillitis preceded the onset of neurological symptoms in 3 cases. No infectious localization was found in one case, and in the first attack of the first case. The neurological signs occurred 1-15 days after the onset of the first infectious symptoms. They were variable from one patient to another. Kinetic cerebellar syndrome was noted in 3 cases, pyramidal syndrome in 9 cases (5 with tetraparesis, one with hemiparesis, 2 with paraparesis, and one with monoparesis of the right upper limb), diplopia in 2 cases, and generalized seizure in 2 cases. Urinary retention

Table 1 - Clinical and non imaging features of patients with acute demyelinating encephalomyelitis.

Case number	Gender	Age (years)	Preceding infection	Onset of symptoms	Presenting features	CSF	EEG
1	M	3					
1st attack			Isolated fever	Acute	Ataxia, nystagmus, strabismus, cerebellar syndrome	0*	0
2nd attack			URTI (4 months after the first attack)	Acute	Fever, tetraparesis, pyramidal syndrome	Normal	0
2	F	7	Gastroenteritis	Acute	Fever, agitation, meningism syndrome, pyramidal syndrome, cerebellar syndrome	Normal	0
3	M	7	URTI	Acute	Consciousness trouble, pyramidal syndrome, cerebellar syndrome	Normal	Diffuse slowing activity
4	F	11	URTI	Acute	Fever, lower limbs weakness, sensitive level, meningism	Lymphocytic pleocytosis, polyclonal Ig	0
5	M	13	Tonsillitis	Acute	Fever, meningism, diplopia, tetraparesis	Lymphocytic pleocytosis	0
6	M	11	Tonsillitis	Acute	Headache, diplopia, left hemiparesis	0	0
7	M	11	Tonsillitis	Acute	Fever, consciousness trouble, tetraparesis	Lymphocytic pleocytosis	0
8	M	1.5	Not found	Acute	Paraparesis, pyramidal syndrome	0	0
9	M	5 months	URTI	Acute	Coma, seizure, pyramidal syndrome	Normal	Fast with no rhythmic activity
10	M	4	URTI	Acute	Fever, seizure, pyramidal syndrome	0	0

*not carried out, URTI - upper respiratory tract infection

occurred in 2 cases. Two patients presented additional disorders of consciousness. The CSF examination was performed in 7 patients. Four of them had a normal examination. Lymphocytic pleocytosis was noted in 3 cases. Oligoclonal bands were detected in one patient. The EEG was performed in 2 cases showing a diffuse slowing activity in one case, and fast with no rhythmic activity in the other case. The VEP were normal in 2 cases and showed bilateral retrobulbar optic neuritis in the tenth case. Brain CT scan, performed in 5 cases, was normal in 3 cases, and showed low density of the white matter in 2 cases (case 7 and 9). All the patients had MRI exams, and the most common abnormality was rounded ill-limited high signal foci on T2-weighted images having been bilateral but asymmetrical in most cases. Their signal on T1WI was variable: either low or intermediate signal. Their size did not exceed 3 cm. All patients had lesions of the same age. Their number varied from 2 to more than 10 lesions. No mass effect was detected. Lesion enhancement was found in only one

case. No pial enhancement was found. They occurred mostly in the white matter (7 cases) either peripheral (2 cases) or periventricular (6 cases) (**Figure 1**). The corpus callosum was involved only in one case (**Figure 2**). The grey matter was also involved: the basal ganglia with constant lesions of the thalami in 5 cases (**Figures 1 & 3**) and the cortical ribbon in one case (case 10) (**Figure 4**). Lesions of the brainstem were detected in 6 cases (**Figures 1 & 3**), and in the cerebellum in 2 cases (**Figure 3**). The spine was affected in 3 cases (2 patients showed only cervical spine lesions and one patient had cervical and thoracic spine lesions [**Figure 1**]). Follow-up MRI scans were obtained in 3 children with monophasic ADEM (cases 2, 4, and 6) within 10 days to 3 months after the treatment onset. They showed improvement of the initial lesions after 10 days in one case and total resolution of them in 2 cases. Six patients had total recovery. Spontaneous recovery was noted in 2 cases and in the first attack of the first case. Corticoids were administered in 7 cases and in the second attack of the

**Table 2 -** Imaging investigations of patients with acute demyelinating encephalomyelitis.

| Case number	CT scan	Location of high signal foci on T2WI on the first MRI exam/enhancement	MRI control
1			
1st attack	0*	Medulla, cerebellum, and the basal ganglia without enhancement	0
2nd attack	0	Medulla and basal ganglia enhancing after gadolinium injection	Normal
2	0	Midbrain, cerebellar peduncle, centrum semiovale, deep white matter (periventricular)	Improvement
3	Normal	Basal ganglia, brainstem	0
4	0	Periventricular white matter, the brainstem, cervical, and thoracic spine	Normal
5	Normal	Periventricular white matter, basal ganglia, brainstem, and cervical spine. Enhancing after gadolinium injection	0
6	Normal	Fronto-parietal white matter and the right thalamus unchanged after gadolinium injection	Normal
7	Cerebral edema	Periventricular white matter, corpus callosum, and basal ganglia unchanged after gadolinium injection. Swallowing medulla and cervical spine	0
8	0	Periventricular white matter and the basal ganglia unchanged after gadolinium injection	0
9	Low density of the peripheral white matter	Peripheral hemispheric white matter with gyral enhancement. Anomalies of the basal ganglia	0
10	0	Cortex and peripheral hemispheric white matter with gyral enhancement	0

*not carried out, T2WI - T2 weighted images

Table 3 - Treatment and outcome of patients with acute demyelinating encephalomyelitis.

| Case number	Treatment	Outcome
1		
1st attack	0*	Total recovery within 24 hours
2nd attack	Corticoids, kinesitherapy	Paraparesis
2	Acyclovir, corticoids, phenobarbital	Total recovery within 9 days
3	0	Total recovery within 7 days
4	Corticoids, acyclovir, kinesitherapy	Urinary incontinence
5	Antibiotics, corticoids, kinesitherapy	Total recovery within 48 hours
6	Corticoids	Neurologic improvement within 5 days. Total recovery within 2 months
7	Corticoids, kinesitherapy	Neurologic improvement within 4 days. Total recovery within 2 months
8	0	Total recovery within 2 days
9	Phenobarbital, acyclovir, corticoids, assisted ventilation	Death
10	Acyclovir, antibiotics, phenobarbital, corticoids, kinesitherapy	Language disturbance, generalized seizure

*not carried out
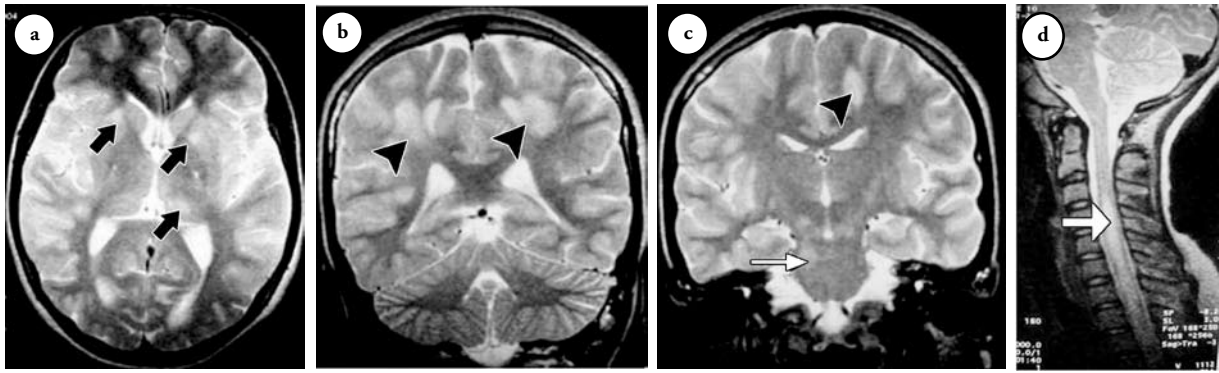
Figure 1 - Case no. 4 - showing **a)** Axial, **b, c)** coronal T2 weighted images of the brain, and **d)** sagittal T2WI of the cervical spine. High signal foci in the peripheral and periventricular white matter (black arrowheads), the basal ganglia (black arrows), the brainstem (thin white arrow) and the spine (thick white arrow).
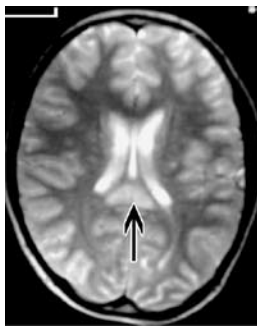
Figure 2 - Case no. 7 - axial T2 weighted image showing high signal foci in the splenium of the corpus callosum (arrow).
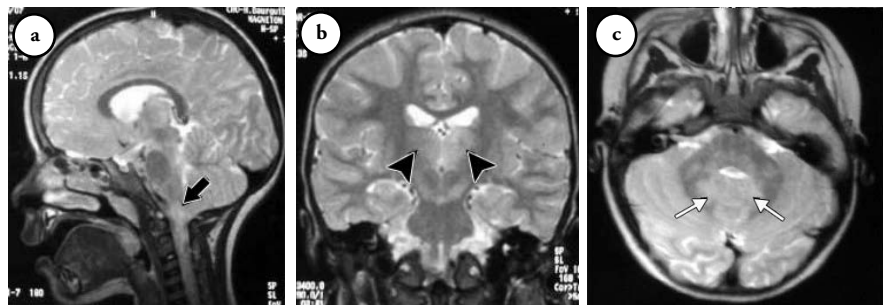
Figure 3 - Case no. 1 - first attack showing **a)** sagittal, **b)** coronal, and **c)** axial T2 weighted images. High signal foci in the medulla (black arrow), the thalami (black arrowhead) and the cerebellum (white arrows).
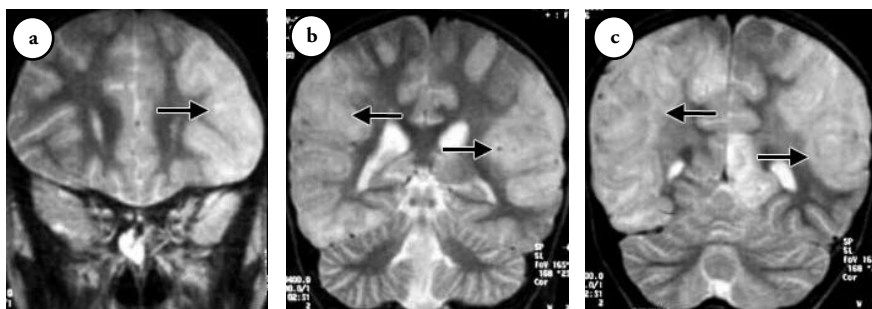
Figure 4 - Case no. 10 - coronal T2WI showing high signal in the cortical ribbon (arrows).

first case. One child died because of a status epilepticus and 3 had ongoing neurological disabilities. In case one, there were 2 attacks, and this was considered recurrent ADEM.

Discussion. The incidence of ADEM has been estimated to be 0.4 per 100,000 population per year,[3,4] and it may represent 30% of all childhood encephalitic illnesses.[4] Young and adolescent children are most commonly affected,[5] probably due to the higher frequency of immunizations and primary exposure to antigens.[3,5-7] The mean age of onset in children ranges from 5 to 8 years,[3,5,8,9] which is concordant with our study as the mean age was around 7 years. Numerous cases among adults and even elderly patients have also been reported;[10] however, the incidence may be considerably lower. We reported the cases of 2 girls and 8 boys, which is concordant with the literature as

a male predominance has been described in 2 pediatric cohorts, with reported female: male ratios of 0.6,[7-11] and 0.8,[9,11,12] as opposed to a 2:1 female preponderance frequently described for MS.

Acute disseminated encephalomyelitis typically follows an antigenic challenge,[3] such as infection, or vaccination, proven in 8 of our cases, which activates the immune system. Rare cases are described following organ transplantation.[13] However, absence of a clear precedent event is reported in 26% of patients.[9] In around 50-75% of all cases,[4,7-9] the clinical onset of the disease is preceded by viral or bacterial infections, mostly nonspecific upper respiratory tract infections having occurred in 5 of the cases we reported. Vaccination-associated ADEM is most frequently observed after measles, mumps, or rubella vaccinations. No case in our series was found. However, it is also reported after polio and European tick-borne encephalitis vaccination.[14] Post-infectious encephalomyelitis is characterized by perivenous demyelination and infiltration of lymphocytes and macrophages.[15,16] Although postinfectious encephalomyelitis typically involves the white matter, lesions in the grey matter are also seen. Basal ganglia, thalamus, and even cortical grey matter may be involved.[15]

Acute disseminated encephalomyelitis is classically described as a monophasic disorder appearing days to weeks after infection or vaccination, with an average latency of 4-13 days.[9,10] This latency varied from 1-15 days in our series. In general, neurological symptoms develop subacutely over a period of days and lead to hospitalization within a week.[8-10] A prodromal phase with systemic symptoms like fever, malaise, myalgia, headache, nausea, and vomiting often precede the neurological symptoms.[6,15] The clinical presentation is "heterogeneous," reflecting widespread CNS involvement.[3-5] The most prevalent neurological symptoms and signs described in recently reported pediatric series are unilateral or bilateral pyramidal signs (60-95%), acute hemiplegia (76%), ataxia (18-65%), visual loss due to optic neuritis (7-23%), seizures (13-35%), spinal cord involvement (24%), impairment of speech (slow, slurred or aphasia) (5-21%), and hemiparesthesia (2-3%) in different combinations, with the invariable involvement of consciousness status, ranging from lethargy to coma.[7] Seizures are mainly seen in children younger than 5 years of age.[6] All these signs were found with variable combinations in our series. Acute disseminated encephalomyelitis can also show a rapid progression of symptoms to coma and decerebrate rigidity.[17] Respiratory failure secondary to brainstem involvement or severe impaired consciousness occurs in 11-16% of cases.[9,17] We noted 2 cases of consciousness disturbance leading to death in the ninth case.

Acute disseminated encephalomyelitis in adults and ADEM in children have similar clinical features. However, some differences can be noticed. In fact, headache, fever, meningismus, and sensory deficits are more frequent in children and optic neuritis is more frequent in adults.[10,15] The CSF should be analyzed to exclude differential diagnoses of ADEM, especially the CNS infections. The CSF is abnormal in nearly 75% of ADEM patients and is characterized by lymphocytic pleocytosis, which was noted in 3 of our cases. Elevated proteins and normal sugar values help differentiating ADEM from infectious diseases. Electrophysiological studies are not routinely used to diagnose ADEM. They may show signs of increased sleepiness, mild or severe generalized slowing with infrequent focal slowing and epileptiform discharges.[18] The CT has a low sensitivity in white matter diseases and may not reveal abnormal findings of ADEM. Among the 5 cases in which CT scan was performed, only 2 of them showed abnormal low density of the white matter, matching the literature. It has been reported that the initial CT imaging may be normal in 40% of cases, as lesions may appear only 5-14 days after the onset of clinical signs.[19] When it is abnormal, it usually shows non-specific, low attenuation subcortical white matter lesions as we noted in 2 of our cases. Contrast enhancement can appear in the subacute phase of disease. At present, MRI is considered the imaging modality of choice. It is more sensitive than CT in detecting demyelinating lesions and may help exclude other similarly appearing entities. The lesions vary from small and round to large, amorphous, and irregular.[1] Occasionally, a "fried-egg" appearance with central rounded hyperintensity on T2 weighted images corresponding to the "egg yolk" is seen. We did not find this feature in our study, probably because of the small size of lesions, not exceeding 3 cm. The most common MRI findings, as we found in all the cases we reported, were foci of homogeneous or slightly heterogeneous high signal on conventional T2-weighted images and fluid attenuated inversion recovery sequence (Flair), and intermediate to low signal intensity lesions in white matter and gray matter on T1 weighted images. These lesions have ill-defined borders, may involve the central grey matter and are not perpendicular to the corpus callosum.[18] On T1 weighted images, the overlying cortical ribbon may be spared. Hemorrhage is rare. No hemorrhagic lesion was found in our series.

The laterality, number, and size of lesions are variable. A lesion may be solitary and of a variable size, ranging from one cm to several centimeters. Multiple large bilaterally asymmetric lesions are the most common presentation. Most of the brain lesions that we found were bilateral, asymmetric, but not large in size. Tumefactive demyelination appears as a large

white matter lesion with mass effect.[3] Brainstem lesions usually do not show mass effect. Tumor-like lesions have also been reported in a few patients.[15] No mass effect has been detected in our series. Involvement of the gray matter is less commonly described then the white matter. The involvement of the basal ganglia, especially the thalami occurs in a typically symmetrical pattern.[9] However, we reported in our series, the involvement of the basal ganglia in half the cases. It is noted that the involvement of grey nuclei can also be seen in MS in young children.[18] White matter lesions are most frequently situated in subcortical areas, cerebellum, brain stem, and spinal cord.[3,20] In our series, peripheral white matter was involved in only 2 cases, whereas deep white matter was involved in 6 cases. Although it has been reported that the corpus callosum may be affected when involvement is extensive,[3,20] case 7 showed a corpus callosum lesion whereas the involvement of the remaining white matter was limited. This patient had a myriad of clinical signs probably because of the involvement of the brainstem (**Table 1**). However, he had total recovery within 2 months.

Spinal cord involvement in ADEM has been described in 11-28%.[5,9,21] We report nearly a similar rate (30%). An isolated spinal cord lesion is very rare and is usually associated with encephalitis. The MR imaging findings are unspecific. Rarely severe hemorrhage may occur and usually reveals a long segmental involvement with large lesions and mild swelling of the spinal cord, most commonly in the thoracic region.[3] The reported frequency of gadolinium enhancing lesions on T1-weighted sequences is variable in ADEM (8-100%), depending on the stage of inflammation,[8,9,22] and the size of the lesions. The pattern of enhancement is nonspecific because a similar one may be seen in other demyelinating diseases. Acute lesions may show spotty, nodular, diffuse, amorphous, or gyral patterns of enhancement, or may form an incomplete or a complete ring of enhancement.[20] The enhancement was found in only one of our cases probably because of delay between the clinical onset of the symptoms and the MRI being carried out after the inflammatory stage. Lesions may show a uniform pattern of enhancement because they have the same age. Old or inactive lesions may not show enhancement. Pial enhancement, absent in our study, is rarely seen. Enhancement of spinal cord lesions is variable or absent. Meningeal enhancement of the brain or spinal cord is unusual.[6] Occasionally, initial MR images may be normal and lesions may appear on later repeated images in the course of the disease or even during clinical improvement.[23] None of our patients showed initial normal MRI. Follow up imaging after a short period of treatment usually shows a decrease in the size and number of lesions and a change in their signal intensity, paralleling clinical improvement.[24] Complete resolution of white matter abnormalities on follow-up MRI scanning has been described in 37-75% of ADEM patients (as we reported in 30% in our series) and partial resolution in 25-53% of patients.[9,25]

Advanced MR techniques such as proton MR spectroscopy and diffusion-weighted imaging are sensitive to ADEM. Diffusion MRI studies demonstrate 2 distinct patterns occurring simultaneously in the cerebral white matter. This is a restricted diffusion reflecting presence of ischemia (cell-swelling) or accumulation of inflammatory cells associated with ADEM. Therefore, there are high-signal regions on $b=1000mm^2/s$ images with low apparent diffusion coefficient (ADC) values. Demyelinating pattern shows an increased diffusion representing with high ADC values.[26] In the early acute stage of ADEM, there is evidence of restricted diffusion, in contrast to the later stage. Quantitative proton MR spectroscopy imaging demonstrates acute demyelination in cases of high disease activity and may then aid in the differential diagnosis.[27] The N-acetyl-aspartate ratios show a decrease in the later stage along with an increase in the choline/creatine ratio, whereas there is not much of a change in the acute stage.[28] The identification of this restricted diffusion coupled with unchanged metabolite ratios in the earlier stage may not only help in staging the disease, but may provide an understanding of its temporal evolution and obviate the need for biopsy.[26,27] Resolution of MRI abnormalities within 6 months of the demyelinating episode favors the diagnosis of ADEM.[3,29] It did not go beyond 3 months in the 4 cases controlled with MRI in our series.

Recurrence may make differentiating acute disseminated encephalomyelitis from MS difficult without the appropriate clinical, laboratory, electrophysiological and multimode evoked-potential studies. Recurrence occurred in the first case we reported. The occurrence of a precedent URTI and a normal CSF examination helped differentiating ADEM from MS. Acute demyelinating encephalomyelitis usually has a monophasic course, but relapses can occur in 5-25% of cases.[9] The relapsing forms can be subdivided into 2 categories. In the recurrent form (80%), the disease recurs at least 2 months after its onset with no space dissemination of lesions. In the multiphasic form (20%), the lesions present dissemination in space and time.[30] In the first case we reported, we concluded a recurrent form as the second attack took place 4 months after the first one. In both categories, relapses generally occur 6-18 months after the onset, and can be much more severe than the first episode.[30]

The most important and most common differential diagnosis with regards to therapeutic options and prognosis is MS. It is acknowledged that a proportion

of children with ADEM may develop MS.[4,21] However, it remains unclear what proportion of children who present an ADEM event will be later diagnosed with MS, since numbers from published studies vary from 9.5-29%.[4,21] It is also unclear if ADEM and MS are 2 distinct clinical disorders or part of the same disease spectrum.[31] It is difficult to distinguish ADEM from MS at the first attack. That is why there should be an operational definition of ADEM as it has been for MS (for example, Poser et al 1983[32] and McDonald et al 2001[33]). The currently proposed definition for ADEM requires poly focal deficits accompanied by encephalopathy, whereas the diagnosis of MS should be made only after 2 subsequent non-ADEM events.[18] There are several clinical, imaging, and laboratory parameters that may be useful to distinguish between them. The ADEM usually presents with multifocal neurological signs and widespread CNS involvement, whereas MS usually presents as a monosymptomatic syndrome with optic neuritis, subacute myelopathy, or ataxia. In our series, the presentation of all children was polysymptomatic. Motor troubles were the most common clinical features. They were associated either with cerebellar syndrome, oculomotor disorders, or seizure. The ADEM can also present with optic neuritis, which is usually bilateral (as reported in case 10), as opposed to the unilateral involvement seen in MS.[33] Myelopathy in MS is usually partial, while in ADEM it may be complete and associated with areflexia. Oligoclonal bands of IgG, although more commonly seen in MS, can also be seen in ADEM. Persistence of oligoclonal bands in serial CSF examinations suggests MS, so may help to differentiate between the 2 conditions.[32] Often, distinction between ADEM and MS cannot be made with certainty unless a serial MRI follow-up is performed.[20] In relapsing or multiphasic ADEM, white matter lesions are typically large, often asymmetrical, and may involve the adjacent grey matter.[18] However, in our series, the lesions were small even in the first case, which was considered as relapsing ADEM. Periventricular perpendicular ovoid lesions (PVPOL) strongly suggest the diagnosis of MS. Children with PVPOL at first demyelinating event should be described as "clinically isolated syndrome suggestive of MS" and followed as high-risk patients for the subsequent diagnosis of MS.[1]

In MS, the plaques are typically small, circumscribed, and symmetrical in the deep white matter. In ADEM the lesions are typically of the same age as shown in the series we reported, while in MS they are usually of different ages.[18] Follow-up MRI scans showing the presence of new lesions would favor a diagnosis of MS. In the first case we reported, no new areas of involvement were detected in the second attack, which led to the diagnosis of ADEM. However, every MRI feature should be correlated to the clinical symptoms. An MRI of children with ADEM should not show the accrual of clinically silent lesions, in contrast to MS.[18] In summary, the relationship between ADEM or relapsing ADEM and MS is unclear. The ADEM is diagnosed on the basis of demyelination with multifocal CNS involvement seen clinically and on MRI. If a further separate mono- or polysymptomatic demyelination occurs at a new site, MS can be diagnosed. If clinically or on MRI this relapse is indistinguishable from ADEM, it may be classified as relapsing ADEM, considered to be probably a special more favorable type of MS. If the second demyelination occurs early, in close temporal relationship to steroid withdrawal, multiphasic ADEM can be diagnosed.[11] In the first case we reported, the patient had in the second attack the same symptoms as the first attack, and a pyramidal syndrome had been newly detected. On MRI, no new lesions were detected so that the diagnosis of a relapsing ADEM was established. Enhancement of the lesions, especially the enhancement in the medulla made the difference with the first attack and could explain the pyramidal syndrome.

Of all other differential diagnoses of ADEM, the exclusion of acute CNS infections should be the first and most important diagnostic clue to be considered by lumbar puncture and further laboratory tests,[6] showing especially low sugar levels in the CSF. A gadolinium-enhanced MRI of the brain and spinal cord should be performed to define the regional distribution and MRI lesion appearance. Brain malignancies, Schilder's disease, Marburg's variant of MS, and brain abscess should be considered when large focal tumor-like lesions are detected on MRI.[34] Diffusion and spectroscopy imaging can help the diagnosis. Brain abscess, tuberculomas, neurocysticercosis, toxoplasmosis, and histoplasmosis should be excluded when there are complete-ring enhanced lesions, as they are unusual in ADEM.[22,35] Lesions in the basal ganglia, commonly seen in poststreptococcal ADEM with auto-reactive antibasal ganglia antibodies, can also be seen in aciduria, infantile bilateral striatal necrosis, *M. pneumoniae* infection, voltage-gated potassium channel antibody associated encephalitis.[36,37]

There is no proven standard treatment for post-vaccination and other causes of ADEM. Once ADEM is diagnosed and an acute infectious etiology excluded, treatment should be instituted as soon as possible.[15] Even though, 3 of the cases we reported received no treatment and had a complete recovery. The spontaneous recovery is also reported in the literature. Present treatments are centered on immunosuppression and immunomodulation. The options include corticosteroids, plasma exchange, and

intravenous immunoglobulin. Corticosteroid therapy is widely accepted as first line therapy for ADEM and was administered to the majority of our cases. Plasma exchange is recommended in patients who respond poorly to intravenous corticosteroids. Intravenous immunoglobulin is reserved for ADEM that fails to respond to corticosteroid treatment and where plasma exchange is contraindicated or difficult to access. In our series, no patient received plasma exchange.

We tried through our study to discuss the clinical course and the imaging features of ADEM. Some limitations exist however. In fact, the sample of patients is small as we chose to include only the patients with typical clinical course and imaging features. The MRI procedure did not include diffusion and spectroscopy as they were not currently used in our center during the period of the study.

In conclusion, ADEM is an important and treatable cause of acute CNS deterioration, predominantly in children. The pathogenesis of this illness is thought to involve autoimmune mechanisms. As reported in our series, MRI is the most important investigation for ADEM diagnosis that typically demonstrates multifocal demyelinating lesions, which often cannot be detected by CT. The widespread availability of MRI means that more cases are now being recognized and actively managed more promptly, which probably reduces morbidity. However, clinical evaluation and CSF study, even non-specific, are useful to rule out important differential diagnoses. The first diagnosis that must be excluded is the CSF infection. The relationship between ADEM or relapsing ADEM and MS is unclear. Distinguishing between ADEM and the first relapse of MS can be difficult (because of the largely similar clinical presentation, cerebrospinal fluid analysis, and neuroimaging appearance). The MRI, however, can be helpful differentiating them when showing lesions of a large size and of the same age leading to the diagnosis of ADEM. When there is a relapsing ADEM, MRI shows no new lesions. Early diagnosis can lead to early treatment and may improve the outcome. Diffusion and spectroscopy sequences can help differentiating ADEM from abscesses and glial tumors.

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