ADEM vs MS: A diagnostic dilemma - a follow-up study.

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Authors: G. LIATOPoulos, A. Anastasiou, G. BARmpalios, D. KYRIAKOU, E. Varfiami, D. I. Zafeiriou; THESSALONIKI/GR
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Learning objectives

The aim of this follow-up research is to distinguish the diagnostic criteria between acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) after close observation of 28 children that visited Hippokratio General Hospital after an acute neurological dysfunction, and were about to receive a diagnosis of an inflammatory demyelinating disorder. ADEM is a self-limited disease that does not require long-term immunomodulatory therapies, in contrast with MS, which is a lifelong chronic disorder, with a progressive course, in which long-term immunomodulatory or immunosuppressive treatment is necessary. An early discrimination of these two similar pathological entities can assist the immediate treatment and prevent the progress of the disease, especially if it is characterized from a fulminant onset.

Magnetic resonance imaging (MRI) can represent a major component in the differential diagnosis between ADEM and MS in pediatric patients and contribute mainly for prognostic and therapeutic purposes. Furthermore, another diagnostic method that has been used and has contributed in this research is the examination of the cerebrospinal fluid (CSF) that determinates the presence of oligoclonal bands and assists the evaluation of the IgG index.

Last but not least, the presence of two additional disorders in our research that of Guillain Barre' syndrome and neuromyelitis optica, served the purpose of further extending our knowledge on inflammatory-demyelinating disorders and discriminating them from the two principal diseases which mainly concern our research.
Background

In the present research 28 children, between the age of 4 and 15 were included. Follow-up duration was at least 2 years. The study population had documented abnormal brain MRI findings. Fifteen patients had a definitive diagnosis of ADEM, nine had a definitive diagnosis of MS, three had a Guillain Barre' syndrome and one patient was diagnosed with neuromyelitis optica (NMO). All the patients were examined with MRI scans (T2WI/FLAIR and T1WI before and after gadolinium administration) and their lesions were categorised based on their size and location.

ADEM is an inflammatory demyelinating disease that usually occurs after a viral infection or vaccination, characterized by an acute clinical-neurological event with a polysymptomatic presentation and a mono- or multiphasic course.

Monophasic ADEM is represented by the first clinical-demyelinating event with an acute or subacute onset and a multifocal distribution of the central nervous system (CNS). This inciting ADEM event must always includes features of encephalopathy, such as lethargy, confusion, irritability or other alterations of the behavioural and emotional status. The acute neurological attack of the monophasic ADEM must be followed by improvement of the symptoms or the MRI findings and in case that we have new neurological symptoms or MRI findings three months beyond the first acute event these must be evaluated as a part of the same inciting ADEM event.

Multiphasic disseminated encephalomyelitis (MDEM) is represented by a new clinical event that occurs at least three months after the initial ADEM attack. There is involvement of new areas of the CNS demonstrated from the MRI findings and the clinical examination and a complete or partial resolution of the MRI lesions seen on the first ADEM event. There is always a polysymptomatic manifestation but with different neurological symptoms from the first ADEM event and encephalopathy is always present.

MS is an immune-mediated, chronic inflammatory demyelinating disease characterized by relapses and remissions that usually demonstrates isolated symptoms (monosymptomatic) and commonly leads to a significant impairment of the affected person. Relapses are typical for MS patients. In the case that the relapse occurs after 6-7 months from the inciting clinical event we are directed towards MS as an initial diagnosis. However, if a relapse appears earlier a diagnostic problem could emerge since MS could be confused with MDEM.

Guillain Barre' syndrome is an acute inflammatory demyelinating polyneuropathy (AIDP) that affects the peripheral nervous system. It is frequently severe and usually manifests as a non-trauma-induced ascending paralysis with weakness in the legs that spreads to the upper limbs and the face along with complete loss of deep tendon reflexes.
NMO or Devic's syndrome is a rare inflammatory demyelinating disease that typically affects optic nerves and spinal cord.

In order to discriminate these two analogous diseases, ADEM and MS, and arrive to a conclusive diagnosis the target population of the 28 pediatric patients was divided into four groups based on their demographics, clinical, radiological and CSF findings as shown in Figure 1 below.

**Figure 1.** ADEM=acute disseminated encephalomyelitis, MS=multiple sclerosis, GB=Guillain Barre’ syndrome, NMO=neuromyelitis optica.

**Methods - Criteria**

The study population included in this research was examined just after their first clinical-neurological event from 2000 to the present. The average follow-up duration for the ADEM/MDEM patients was approximately 3.5yrs and 5.5 for the MS patients. All the clinical information about the patients was analysed with the contribution of the pediatricians in the 1st Pediatric Clinic of Aristotle University of Thessaloniki.

The diagnosis of MS was based on McDonald’s criteria with evaluation of the lesions disseminated in space and in time. Although there are not defined criteria for ADEM, necessary requisites to establish the diagnosis seem to be a polysymptomatic manifestation with encephalopathy associated with multiple CNS lesions and no relapse beyond three months from the first attack. Recurrent clinical events without different symptoms from the inciting episode or demonstration of new lesions on neuroimaging were not viewed as a true relapse. All the MRIs were performed in a 1.5T magnet. In almost all the patients MRI studies of the spinal cord were performed to demonstrate possible lesions and evaluate the progression of the disease, mostly for prognostic purposes.

**Results**

Thirteen children were diagnosed with ADEM, two with MDEM, three with Guillain Barre’ syndrome, one child with neuromyelitis optica and nine fulfilled the criteria for MS. Three patients on the MS group presented lesions also in the cervical region of the spinal cord.

**Demographics**

None of the children presented a family history of the diseases. The research findings revealed a male predominance, nine boys and six girls, in the group of ADEM/MDEM, and also in the group of MS, six boys and three girls. The age of the ADEM/MDEM group ranged between 4 and 6 years with average age four and a half years. By contrast, the group of children with MS ranged between 8 and 15 years old with a peak incidence the
age of 10. Furthermore, three boys were admitted with Guillain Barre’ syndrome and one girl with neuromyelitis optica.

**Neurological symptoms at the first attack**

**ADEM/MDEM**

One of the characteristics of the ADEM/MDEM group was that no one of the children presented a predemyelinating illness or a history of recent vaccination. Eleven of the ADEM/MDEM patients (73%) were admitted to our hospital with the typical presentation of encephalopathy, a required feature for the diagnosis of ADEM. Nine children (60%) demonstrated a polysymptomatic manifestation with fever, meningism, headache and weakness. Seizures occurred in 5 patients (33%). Other symptoms that originated from the pyramidal (in 4 children) and the sensory system (in 3 children) and from the brainstem (in 4 children) and the cerebellum (in 5 children) were almost similar in the MS group as well.

**MS**

As in the ADEM/MDEM group there was no history of a prior infection found in the MS group. No one of the MS children that were admitted after the first acute neurological event presented symptoms characteristic of encephalopathy, such as irritability, somnolence, lethargy or coma. Diplopia was one of the symptoms that presented in high frequency in the children with MS. Two patients presented unilateral optic neuritis and one myoclonus. Symptoms like hemiparesis, ataxia and impairment of the visual acuity (optic neuritis) were more frequent in the MS group.

**GB**

All three boys of this group presented symptoms of hypo- or areflexia with weakness of the legs. No involvement of the cranial nerves was noticed. The symptoms were improved in a period of 2-3 months.

**NMO**

One girl was admitted with bilateral vision loss and paresis.

**Blood and CSF findings**

Elevated white cell count was observed in eight out of fifteen in the ADEM/MDEM group and in three out of nine in the MS group.

The main characteristic of the CSF studies was the presence of oligoconal bands in the MS patients. Intrathecal synthesis of oligoclonal bands was observed in six out of ten members of the MS group. By contrast, no patient of the ADEM/MDEM group was positive
for oligoclonal bands on the CSF evaluation. The IgG index was elevated (>0.70) only in the MS patients (77%). The girl with neuromyelitis optica was positive for the NMO-IgG antibody in the NMO-IgG test, a highly specific marker of this disease.
Imaging findings OR Procedure details

The periventricular lesions and the development of new lesions at follow-up were more frequent in patients with MS. On the other hand, bilateral, asymmetric and hyper intense (FLAIR/T2WI) lesions, larger than 1 - 2cm in the supratentorial or infratentorial white matter and in grey matter (basal ganglia and thalamus), were typical for ADEM.

Neuroimaging

ADEM/MDEM

MRI scans were performed in all the children on the ADEM/MDEM group at the first demyelinating-neurological event. Repeated MRI scans were also performed in the next follow-up controls in all the pediatric patients of the group during the period of convalescence to evaluate complete or partial resolution of the lesions. No one of the ADEM children presented new lesions in the following MRI controls and usually there was a partial resolution of the lesions (60%). Three patients on the MDEM group presented new lesions on the MRI on the successive follow-up and other different neurological symptoms from the inciting ADEM event. The follow-up was usually performed after a period of 4-5 months or after indication of the clinicians and its average duration was approximately 3.5 years.

All of the typical MRI sequences (T2/FLAIR/T1 before and after gadolinium enhancement) were performed on the ADEM/MDEM group as well as in the MS group. Very useful for the evaluation of the lesions appeared to be the T2 and FLAIR sequences. The lesions of the ADEM/MDEM group often presented poorly defined margins with a typical distribution in the white matter. These, mostly asymmetrical, supratentorial lesions presented predominantly subcortical and deep white matter dissemination with relative sparing of the periventricular white matter (Table 1.). Rare, but not infrequent location for the lesions of the ADEM/MDEM group were the thalamic regions and the basal ganglia, in contrast to the MS group where this was a very uncommon location. Similar lesions were also present in a high frequency in the cerebellar white matter. Most of the lesions of this group presented dimensions less than 1-2cm.

"figure table 1"

MS

As in the ADEM/MDEM group, all the pediatric patients of the MS population were examined with the typical sequences of the MRI both at the first neurological event and at the following relapses. The lesions of the MS presented more defined margins in contrast to the ADEM/MDEM group. Typical location of the plaques in the MS group was the periventricular white matter, with a slight predominance respect of the lesions in the subcortical white matter (Table 2.). Periventricular perpendicular ovoid lesions were
demonstrated in five children (55%), best seen in sagittal FLAIR sequences. Involvement of the thalamic region and the basal ganglia was observed in a minor percentage of the MS group compared to the ADEM/MDEM group. No one of the children presented tumor-like massive demyelinating lesions. The plaques measured in the MS patients were approximately 1 cm. Six patients (66%) demonstrated enhancement of some lesions after gadolinium administration on T1 sequences at the first attack. All the patients demonstrated relapses with presence of new lesions, some of them enhancing, on an average follow-up duration that lasted approximately 5.5 years. The follow-up was effectuated in periods of exacerbations and during remissions of the disease. Three of the patients that developed MS lesions in the cervical region of the spinal cord had associated lesions in the brain. The MS lesions of the cervical region were located in the posterolateral part of the spinal cord and were extending over more than two vertebral segments.

"figure table 2"

GB

There was characteristic enhancement and thickening of the cauda equina in postgadolinium T1-weighted images in all the patients of the group.

NMO

The affected optic nerves demonstrated swelling and enhancement in post-gadolinium MR sequences. The associated myelitis was manifested by expansion of the affected region of the spinal cord.

(a)

(b)

Figure 2. : (a) ADEM lesions with high signal intensity in axial T2W images of the thalamic regions, brainstem and cerebellar hemispheres (green arrows). (b) Improvement of the MR imaging on the follow-up after 27 days from the first attack with almost complete resolution of the lesions of the thalamic regions and partial resolution of the lesions in the brainstem and the cerebellar hemispheres (green arrows).

(a)

(b)

(c1)
Figure 3. ADEM lesions with high signal intensity in FLAIR sequences affecting the brainstem, the left temporal lobe, the occipital lobes and the splenium of the corpus callosum (green arrows). Minor lesions are present in the right thalamic area and in the left putamen. (b) Improvement of the MR imaging on the follow-up after 25 days from the first attack with complete resolution of the lesions of the brainstem, the left temporal lobe, the putamen, the thalamus and the corpus callosum and partial resolution of the lesions in the occipital lobes. (c) Coronal T1W images after gadolinium administration demonstrating the same enhancing lesions (2 upper images) and complete resolution on the follow-up after 25 days (2 below images).

Figure 4. (a) MS lesions in axial T2W images with cortical and subcortical distribution of the left and right frontal and temporal lobes (green arrows). (b) Expansion of the lesions of the frontal and temporal lobes and extension to the left parietal lobe (green arrows) with presence of a new lesion on the left occipital lobe (red arrow) 13 days after the first MR imaging.

Figure 5. Gadolinium-enhanced sagittal T1-weighted images demonstrating thickening and enhancement of the nerve roots of the cauda equina in a child with Guillain Barre syndrome (green arrows).

Figure 6. (a) Patient with neuromyelitis optica demonstrating 3 lesions in FLAIR sequences in subcortical white matter (green arrows). (b) STIR sagittal images demonstrating a lesion in the cervical spinal cord that extends over more than 2 vertebral segments (green arrow). (c) MEDIC images demonstrating the same lesion in left lateral, eccentric location (2 upper images), with partial enhancement after gadolinium administration (2 below images) in axial T1W images (green arrows). (d) Bilateral thickening and enhancement of the optic nerves in axial post-gadolinium T1W FS images.
Table 1. MRI distribution of the lesions at first attack

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<thead>
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<th>Location</th>
<th>ADEM/MDEM patients n=15</th>
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<tr>
<td>Periventricular white matter</td>
<td>4 (26)</td>
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<tr>
<td>Subcortical/deep white matter</td>
<td>9 (60)</td>
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<tr>
<td>Cortical gray matter</td>
<td>3 (20)</td>
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<tr>
<td>Brainstem</td>
<td>6 (40)</td>
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<tr>
<td>Cerebellum</td>
<td>7 (46)</td>
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<tr>
<td>Thalamus</td>
<td>5 (33)</td>
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<tr>
<td>Basal ganglia</td>
<td>4 (26)</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>-</td>
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</table>

**Fig. 0:** Table 1

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Table 2. MRI distribution of the lesions at first attack

<table>
<thead>
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<td>Periventricular white matter</td>
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<td>Subcortical/deep white matter</td>
<td>5 (55)</td>
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<tr>
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<td>Brainstem</td>
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<td>Cerebellum</td>
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<td>2 (22)</td>
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<td>Spinal cord</td>
<td>3 (33)</td>
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</tbody>
</table>

**Fig. 0:** Table 2

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**Fig. 0:** Figure 2a

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**Fig. 0:** Figure 2b

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Fig. 0: Figure 3a

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Fig. 0: Figure 3b

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**Fig. 0:** Figure 3c1

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Fig. 0: Figure 4a

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Fig. 0: Figure 4b

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Fig. 0: Figure 5

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Fig. 0: Figure 6a

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Fig. 0: Figure 6b

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Fig. 0: Figure 6c1

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Fig. 0: Figure 6c2

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**Fig. 0:** Figure 6d

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Conclusion

Repeated MRI scans, in combination with the symptoms of the patients and the CSF findings is an important diagnostic tool for distinguishing ADEM from MS. The major diagnostic problem still remains the discrimination of these two pathologic entities in case of the first neurological-demyelinating attack and its possible future relapse, a fact that can affect the prognostic and the therapeutic strategies of the pediatric patient.

In our cohort, the age distribution of children with ADEM demonstrated early childhood predominance (4-6yrs), in contrast with MS, where the target population showed slightly older age predominance (8 -15yrs).

Patients admitted in our hospital with encephalopathy (confusion, irritability, somnolence), did not demonstrate any relapse and there was improvement of their MRI findings on the follow-up study. In addition, a polysymptomatic presentation that includes symptoms like meningism, fever, headache, vomiting and seizures was typical for ADEM.

Oligoclonal bands in cerebrospinal fluid tests were usually positive in MS patients and IgG index was also more frequently elevated in MS rather than in ADEM patients.

In neuroimaging, subcortical white matter lesions with relative sparing of the periventricular white matter were more suggestive for ADEM. By contrast, MS lesions demonstrated both a periventricular and subcortical white matter distribution. Gray matter lesions were characteristic for ADEM.

In our research we tried to improve the diagnostic criteria between these 2 disorders through presentation of the radiological, clinical and CSF data.

In many cases, especially if there is a fulminant onset of the disease, there is a great difficulty to distinguish these two similar demyelinating disorders and only the long-term clinical and radiological follow-up represents the best modality to arrive in a definitive diagnosis.
G. Liatopoulos, A. Anastasiou, G. Barmpalios, D. Kyriakou, E. Vargiami, D. I. Zafeiriou; Department of Radiology, Hippokratio General Hospital, Konstantinoupoleos 49, 54642, Thessaloniki, Greece. mail to: liatosgeor@yahoo.gr D. I. Zafeiriou, E. Vargiami; 1st Pediatric Clinic, Aristotle University of Thessaloniki, Hippokratio General Hospital.
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