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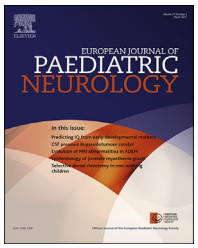

Original article

Evolution of MRI abnormalities in paediatric acute disseminated encephalomyelitis

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ABSTRACT

Objective: Acute disseminating encephalomyelitis (ADEM) is an inflammatory demyelinating disease affecting the central nervous system and mainly occurs in young children. Children who initially presented with ADEM can be diagnosed with multiple sclerosis (MS) in case new non-encephalopathic clinical symptoms occur with new lesions on MRI at least three months after onset of ADEM. We aim to study the timing of MRI abnormalities related to the evolution of clinical symptoms in our Dutch paediatric ADEM cohort.

Methods: The Dutch database for acquired demyelinating syndromes (ADS) was screened for children under age eighteen fulfilling the international consensus diagnostic criteria for ADEM. Children were eligible when the first MRI was performed within the first three months after onset of clinical symptoms and at least one brain follow-up MRI was available for evaluation. Forty-two children with ADEM were included (median age four years two months). All available MRIs and medical records were assessed and categorised as 'improved', 'deteriorated' and 'unchanged'.

Results: We found that during clinical recovery, new lesions and enlargement of existing MRI lesions occurred in the first three months in about 50% of the performed MRIs. In contrast, this was rarely seen more than three months after first onset of ADEM.

Conclusion: We recommend to perform a brain MRI as a reference scan three months after onset. Follow-up imaging should be compared with this scan in order to prevent an incorrect diagnosis of MS after ADEM.

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1. Introduction

Acute disseminating encephalomyelitis (ADEM) is a rare immune-mediated demyelinating disease affecting the central nervous system. ADEM is mainly observed in young children and usually has a monophasic disease course. A previous diagnosis of ADEM with encephalopathy is shown to be a negative predictor of a future diagnosis of multiple sclerosis (MS).[1–4] Several small studies have reported that MRI abnormalities may appear later than the clinical symptoms and progression of MRI lesions has been reported during clinical improvement.[5–7] This is a potential problem as the 2012 International Paediatric Multiple Sclerosis Study Group (IPMSSG) diagnostic criteria state that MS diagnosis can be made after ADEM, when new clinical symptoms occur with new MRI lesions at least three months after the onset of ADEM. Here we aim to study the timing of MRI abnormalities related to the evolution of clinical symptoms in our Dutch paediatric ADEM cohort.

2. Methods

2.1. Patients

We included children less than 18 years old diagnosed with ADEM according to the IPMSSG criteria.[8] Patients were identified by screening the Dutch database for children with acquired demyelinating syndromes (ADS) from January 1995 to October 2015.[2,9] Children were eligible for this study when the first MRI was performed within the first three months after onset of clinical symptoms and at least one brain follow-up (FU) MRI was available for evaluation. Patients were excluded if the clinical data were incomplete. This study was approved by the Medical Ethical Committee of Erasmus MC in Rotterdam. Written informed consent was obtained from all patients and/or their families.

2.2. Demographic and clinical data

Demographical and clinical data, including the clinical status at every MRI scan, were collected. The clinical status was scored as 'improved', 'deteriorated' or 'unchanged' when compared with previous documentation of the neurological examination. FU duration was determined by the last visit or telephone contact with a neurologist or paediatrician.

2.3. MRI data

Brain MRIs were performed at 1.0 or 1.5 Tesla scanners and consisted of T1, T2, and proton density 3–5 mm images. In most cases FLAIR images were available. The MRIs were evaluated for change in size of the lesions and presence of new T2 or FLAIR lesions by two assessors (YYW and EDvP). A third assessor (RFN) was consulted in case there was no consensus. Each FU MRI was compared with the previous MRI. The change was categorised as: 1) improved: decreased amount and/or size of the lesions 2) deteriorated: increase of size and/or amount of lesions; 3) unchanged. In case of multiphasic disease course only MRI scans preceding the second episode were evaluated.

2.4. Statistical analysis

We used SPSS, version 21.0, for statistical analysis. Categorical data were analysed by Chi square test and the Fisher's exact test. Continuous data were analysed with the Student's T-test. A p-value <0.05 was considered significant.

3. Results

3.1. Patients

Sixty-three children with ADEM were identified of whom 42 met our inclusion criteria. In 30 children at least two MRIs were performed in the acute phase. In 25 children FU imaging after three months was available. Demographic and clinical data are shown in Table 1. No significant differences were found in age, gender and FU duration.

Acute treatment consisted of intravenous methylprednisolone (IvMP) for 3–5 days. In ten patients this was subsequently followed by intravenous immunoglobulins (IvIG) in case of insufficient clinical improvement. Three patients did not receive acute treatment because of mild disease severity. Eight patients were given oral prednisone taper (OPT) after acute treatment with a median duration of 2.4 months (range 0.8–5.1 months).

3.2. MRI abnormalities and clinical features in the acute phase

Three of the 42 patients had a normal first MRI scan at presentation (performed 3 days, 7 days and 30 days after onset). In these children MRI abnormalities were observed at the second MRI at 26, 36 and 40 days after onset respectively.

In the 30 children with multiple MRIs during the first three months, a total of 44 FU MRIs were performed. Twenty-one of the 44 FU MRIs showed deterioration (48%), of which 11 scans showed enlargement of the existing lesions and in 14 new lesions appeared. One MRI scan normalized in the acute phase. In total 16/30 patients showed radiological deterioration in the acute phase (53%). The delay of MRI abnormalities compared to clinical status is demonstrated in Table 2.

In this group of 30 patients only five patients were given OPT directly after acute treatment. Three out of five showed improvement on FU MRIs while being treated with OPT after previous radiological deterioration. These three patients also had FU imaging after the acute phase and after discontinuation of OPT for at least four weeks, that showed further improvement of FU MRIs.

Two patients who also received OPT after acute treatment, showed deterioration of MRI. The first patient discontinued OPT three weeks before FU MRI in the acute phase. The second patient started OPT after the FU scan in the first three months was performed and no FU MRI after the acute phase was available.

Table 1 – Demographic and clinical data.

	Patients with ≥1 MRI scans in first 3 months after onset n = 30	Patients with FU MRI scans after first three months n = 25	Patients with multiple MRI scans within and after the acute phase n = 13	All patients n = 42
Male, n (%)	13 (43)	13 (52)	7 (54)	20 (48)
Age, y, median, IQR	5.0 (3.—6.6)	3.5 (2.2–5.7)	5.5 (3.0–7.0)	4.2 (1.0–14.6)
Neurological symptoms at presentation				
• Optic neuritis	4 (13)	11 (44)	2 (15)	13 (31)
• Transverse myelitis	2 (7)	4 (16)	1 (8)	5 (12)
• Pyramidal signs	20 (67)	20 (80)	8 (62)	32 (76)
• Cerebellar signs	13 (43)	9 (36)	5 (39)	17 (41)
• Brainstem	3 (10)	5 (20)	1 (8)	7 (17)
• Seizures	10 (33)	8 (32)	4 (31)	14 (33)
Admission to ICU, n (%)	9 (30)	6 (24)	5 (39)	10 (24)
Follow-up duration (years), mean (SD)	3.5 (2.9)	4.1 (2.9)	4.0 (3.1)	3.7 (2.8)
Multiphasic disease, n (%)	6 (20)	3 (12)	3 (23)	6 (14)
Time from onset to first MRI (days), median, IQR	9 (3–18)	10 (5–19)	10 (5–26)	N/A
Time from onset to last MRI (days) in the acute phase, median, IQR	37 (19–92)	N/A	44 (21–94)	N/A
Time from onset to FU MRI after acute phase (months), median, IQR	N/A	6.8 (4.9–9.4)	6.4 (4.7–9.0)	N/A

N/A = not applicable.

Table 2 – Comparison of clinical status and MRI evolution in the acute phase of ADEM.

44 FU MRIs in the acute phase	MRI improved, n (%)	MRI unchanged, n (%)	MRI deteriorated, n (%)
Clinically improved, n = 29	20 (69)	1 (3)	8 (28)*
Clinically unchanged, n = 7	0	2 (29)	5 (71)**
Clinically deteriorated, n = 8	0	0	8 (100)***

Forty-four FU scans were obtained in the acute phase in 30 patients. When patients were clinically worse compared to their clinical status at the previous scan, MRI was also worse in 100% of the scans. On the other hand when patients were clinically improving at time of FU scans, MRI status was congruent in only 69% of the imaging. Twenty-eight percent showed deterioration (either enlargement of existing lesions or new lesions or both) despite of clinical improvement. The proportion of deteriorating scans with new lesions is as following: * 4/8 new lesions, ** 3/5 new lesions, *** 7/8 new lesions.

3.3. *MRI abnormalities and clinical features after the acute phase*

In 25 patients FU imaging was performed after the acute phase of three months. Twenty-three patients showed improvement of their MRI abnormalities. However, only one normalized. Two patients showed deterioration of MRI lesions during FU after the acute phase. The first patient was given OPT after acute treatment at onset and ceased OPT six months before FU MRI was obtained. No MRI was made between the first brain MRI and FU imaging. The second patient showed new lesions without new clinical symptoms 7 months after onset. These two children had evident encephalopathy and were 2 and 7 years old at presentation. Extensive testing was performed and these patients did not fulfill diagnostic criteria for other differential diagnosis than ADEM. During follow up of respectively 8 years and 2 years they did not fulfill the diagnostic criteria for MS.

In this group of 25 patients six were prescribed OPT. Except for the one patient mentioned above, five out of six showed improvement of MRI during FU after the acute phase. FU MRIs were all obtained after cessation of OPT for at least 4 weeks.

3.4. *Patients with both MRIs in the acute phase and after the acute phase*

Due to the observations made in the results shown in paragraph 3.2 and 3.3, a subanalysis was performed in patients who had MRIs in both the acute and post-acute phase for better comparison of the MRI-scan evolutions within each patient. For this subanalysis patients were eligible when at least two MRIs in the acute phase and at least one FU MRI after the acute phase were available. Thirteen of the initial 42 patients were included.

A total of 24 FU MRIs were performed during the acute phase. Fourteen of these showed deterioration (58%), of which 12 showed enlargement of previously observed lesions, and 8 with observed new lesions. In total 10/13 patients showed radiological deterioration in the acute phase (77%).

When observing the MRIs after the acute phase, all patients showed radiological improvement compared to the last scan in the acute phase except for one patient. This concerned the patient with new observed lesions at 7 months after onset as previously described in paragraph 3.3.

Three patients received OPT after acute treatment. These patients showed radiological improvement on FU MRIs while being treated with OPT after previous deterioration in the acute phase. The FU MRIs after the acute phase and after discontinuation of OPT were improved in all three patients.

4. Discussion

This study confirms that evolution of MRI abnormalities in children with ADEM can be delayed compared to the evolution of clinical symptoms, as suggested by some case reports.[5–7] Also, a normal MRI in the first days after symptom onset does not rule out a diagnosis of ADEM.

The lack of a strict FU MRI protocol limited the evaluation of the exact timing of MRI abnormalities and clinical features. Due to the young age of our patients the decision to perform or not perform a FU MRI was based on individual circumstances, i.e., the need for sedation and clinical features.

It is likely that timing of discontinuation of corticosteroid treatment can potentially influence the FU MRI results. In our study this did no play a large role as only a small group received an OPT. Furthermore in most of these children FU imaging was performed at least 4 weeks after OPT was stopped.

We observed that MRI deterioration occurs often in the acute phase and rarely occurs more than three months after ADEM onset. This observation was further confirmed in the performed subanalysis of patients who had images available in both the acute and post-acute phase. The proportion of patients showing radiological deterioration is higher in the subanalysis compared to all patients who had multiple MRIs in the acute phase (77% and 53% respectively). This might be explained due to the selection bias of performing FU MRIs more often in children who showed deterioration on last MRI in the first three months.

The message that MRI deterioration rarely occurs three months after onset is important, because the latest revised diagnostic criteria for ADS including MS in children allow MS diagnosis when a first episode of ADEM is followed by a new non-encephalopathic episode with new MRI abnormalities.[8] Therefore it is important to critically assess the patient whether new clinical symptoms are truly present in case of new MRI abnormalities.

5. Conclusion

Our study shows that new MRI abnormalities may occur in the first three months even when clinical symptoms are improving, and this rarely occurs after 3 months. Therefore we recommend to perform a brain MRI three months after onset as reference scan. Further FU imaging should be compared with this reference scan in order to avoid false positive results and as a consequence an incorrect diagnosis of MS after a first episode of ADEM.

Conflicts of interest

None.

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