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Acute disseminated encephalomyelitis in children - clinical and MRI decision making in the emergency department

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ABSTRACT

Background: Acute disseminated encephalomyelitis (ADEM) is an uncommon, treatable, primarily pediatric, immune-mediated disease. Diagnosis of ADEM requires two essential elements: typical clinical presentation and magnetic resonance imaging (MRI) findings. The aim of this study was to evaluate how clinical findings in the initial emergency department (ED) presentation influenced the timing of MRI.
Methods: A retrospective chart review was conducted of children diagnosed with ADEM, over a 12-year period, in a tertiary care pediatric center. Clinical presentation at ED admission was recorded and patients who underwent an MRI as part of their ED evaluation (early MRI) with those who had MRI performed during ward hospitalization (late MRI) were compared.
Results: 30 patients were diagnosed with ADEM during the study period. Encephalopathy and polyfocal neurological signs were described in 80% and 50% of patients ED charts, respectively. Seven patients underwent early MRI and polyfocal neurological signs were more common in this group (p = 0.006). Fever was more common in the late MRI group (p = 0.02). Following diagnosis, all patients were treated with immune-modulation therapy, improved clinically, and were discharged.
Conclusion: 20% of ADEM patients were not encephalopathic at ED presentation. Polyfocal neurological signs and absence of fever at ED presentation were related to earlier MRI utilization and thus earlier diagnosis and treatment. Familiarity with the ADEM constellation of signs, and a high index of suspicion, may help the ED clinician in early diagnosis and treatment of this rare disease.

1. Background

Acute disseminated encephalomyelitis (ADEM) is an uncommon, treatable, primarily pediatric, immune-mediated disease [1]. It is an inflammatory demyelinating disorder typically affecting subcortical white matter and is characterized by encephalopathy and polyfocal neurologic symptoms that typically occur following a viral infection or a vaccination [2]. First described by Lucas in the 18th century [3], it commonly followed childhood infections such as measles, smallpox, and chickenpox, and was associated with significant morbidity and mortality. Nowadays it has a much more favorable outcome, especially in children and young adults who are diagnosed and treated promptly [4].

Diagnosis of ADEM requires two essential elements: a typical clinical presentation and brain magnetic resonance imaging (MRI) findings [5]. It usually presents with a rapidly developing encephalopathy and polyfocal neurologic abnormalities, dependent on the location of the central nervous system (CNS) lesions [6]. The ED clinician should consider this diagnosis in their differential, and utilize an MRI to establish it, even while addressing other possible etiologies such as CNS infection [7,8]. Diagnosis of encephalopathy can be challenging in the young pediatric patient [9,10]. When the typical combination of encephalopathy with polyfocal neurological signs are unrecognized at presentation, the possibility of ADEM as an etiology may not be considered and MRI may not be done, delaying diagnosis and treatment [11]. Immuno-modulatory treatment, particularly high-dose corticosteroids as first line, is usually effective, and results in clinical and radiological improvement [12]. Consideration of the diagnosis of ADEM and early utilization of brain imaging are of paramount

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importance for early diagnosis and prompt treatment of this condition [13].

The purpose of this study was to describe the clinical presentation of a large cohort of pediatric ADEM patients and to compare the clinical presentations in patients deemed to need immediate MRI during ED evaluation, versus those who had MRI performed later, during hospitalization in the inpatient ward. We hoped that the data we generated would help guide the busy ED clinician in how best to approach patients with the constellation of symptoms and signs commonly associated with ADEM.

2. Methods

A retrospective study was conducted of all patients who underwent MRI and were diagnosed with ADEM at a tertiary care pediatric center between January 2005 and December 2016. All patients were followed up after discharge by pediatric neurologists.

Criteria for ADEM diagnosis were as follows [14]:

1. A first, polyfocal clinical CNS event with a presumed inflammatory demyelinating cause.
2. Encephalopathy (alteration in consciousness or behavior unexplained by fever, systemic illness, or postictal syndrome).
3. Brain MRI abnormalities consistent with demyelination during the acute (initial three month) phase.
4. No new clinical or MRI findings three months or more after clinical onset.

ED and hospital charts, including the notes of senior ED physicians, pediatric residents and pediatric neurologists, were accessed and the following were recorded: demographic and clinical characteristics, MRI timing and findings, disease course and treatments provided.

Early MRI was defined as MRI ordered by the ED physician and performed on the day of admission to our center. Late MRI was defined as an MRI performed subsequently, during hospitalization. MRI has been available at our institution since 1999, since when it has been performed for every patient suspected of having ADEM.

The protocol was approved by the Ethics Committee of the University of Tel Aviv Sourasky Medical Center.

Statistical Analysis: Data were abstracted by a single investigator from the Dana-Dwek Children's Hospital and transferred to an electronic spreadsheet (Excel 2007). The data were analyzed using SPSS 24.0 statistical software (IBM, Amonk, NY, United States). Demographic and clinical characteristics of the study group (n = 30) were analyzed using descriptive statistics. Comparisons between early (n = 7) and late MRI patients (n = 23) were analyzed using the nonparametric two sided Mann-Whitney test for continuous variables (due to non-Gaussian distribution) and Fisher's exact test for categorical variables.

3. Results

During the 12-year study period 30 children were diagnosed with ADEM in our center. All patients had MRI results showing bilateral deep and subcortical white matter lesions consistent with ADEM and all received 10–30 mg/kg/day (up to a maximum of 1 g/day) of methyl prednisolone for 3–5 days. 17 patients (57%) required second line treatment with intravenous immunoglobulin (IVIG), plasma exchange, or both. After treatment, 28 of our patients (93%) showed marked improvement and were discharged home. Two patients were discharged to a pediatric rehabilitation center with residual motor deficits. None of our patients was lost to follow-up or died.

Ages of patients ranged from 0.3 to 14.5 years, with a median of 3.4 years, and 15 (50%) were male (Table 1). Encephalopathy was the most common sign documented on ED charts; described in 80% of children on admission. Fever and drowsiness were also common symptoms, described in 66% and 63% of cases respectively. Polyfocal neurological signs were observed in 50% of children during their ED examination.

Seven patients (23.3%), diagnosed through MRI during their ED evaluation, constituted the early MRI group; the remaining 23 (76.7%) constituted the late MRI group. Prevalence of encephalopathy, apathy, confusion, seizures and ataxia was similar in the two groups. All children in the early MRI group presented with polyfocal neurological signs, compared with only 35% of children in the late MRI group ($p < 0.05$). A later decision to order an MRI was correlated with less polyfocal neurological signs (Fig. 1). Fever was more common in the late MRI group and this difference was statistically significant (78% versus 28%, $p < 0.05$).

We would like to describe two of our cases. The first patient represents a classic case of ADEM in whom a MRI was performed early, during ED evaluation: a 2.9 year old healthy child presented to our center's ED with a chief complaint of weakness and refusal to eat and walk for the past day. Physical examination revealed encephalopathy, nuchal rigidity, decreased muscle strength in the legs, brisk deep tendon reflexes and optic neuritis. Brain MRI revealed white matter disease typical of ADEM. Neurological consultation was obtained and treatment with high dose corticosteroids was started. The second patient was a 3.5 year old girl referred to our center by her primary physician due to general deterioration in her condition on the seventh day of a febrile illness. On ED examination she was encephalopathic and sleepy with nuchal rigidity. No focal impairment was noted on neurological examination. Cultures from blood and cerebrospinal fluid were taken and antibiotic treatment was started. She failed to improve under antibiotic treatment and on the third day of hospitalization she experienced a focal seizure with subsequent facial nerve palsy. MRI confirmed a diagnosis of ADEM. There was marked clinical improvement following immune modulation therapy.

4. Discussion

ADEM lacks a specific biological marker, and diagnosis depends upon retaining a high index of clinical suspicion and always considering the condition in differential diagnoses [15]. Our finding that polyfocal neurological signs were significantly commoner, and fever significantly less common, in patients deemed to need MRI early, during their initial ED evaluation, could aid in this difficult task. All early MRI patients had polyfocal neurological signs, a distinctive hallmark of ADEM, evident during their ED examination. Prior studies have shown that new clinical symptoms may continue to develop, only appearing during subsequent hospitalization [7,16].

Encephalopathy, an essential diagnostic criterion for ADEM, was not described on ED presentation in six of the 30 children in our cohort, although it was noted during subsequent examinations. Encephalopathy in a pediatric patient may present with nonspecific, subtle and transient symptoms, such as sleepiness or irritability, which can be easily overlooked [9], especially in the ED setting [10]. We believe that these six patients may have had minor behavioral changes that were difficult to recognize as encephalopathy at presentation, and that they developed clearer signs later during their hospitalization. It is interesting to note is that each of these patients did have polyfocal neurological signs on ED presentation. This could serve as a prompt to the busy ED physician to consider further evaluation with MRI to establish

Table 1
Demographic and presenting features of the study cohort (n = 30).

Clinical characteristics	Total n = 30	Early MRI* n = 7	Late MRI** n = 23	P value
Sex: number (%)	Male: 15 (50%) Female: 15 (50%)	5 (71.4%) 2 (28.6%)	10 (43.5%) 13 (56.5%)	0.39
Age in years: mean ± SD (range)	4.9 ± 3.8 (0.3–14.5)	5.4 ± 3.7 (2.9–13.5)	4.7 ± 4.2(0.3–14.5)	0.39
Duration of illness prior to presentation in days: mean ± SD (range)	5 ± 4.1 (0–14)	4.7 ± 4.5 (1–11)	5.0 ± 4.1(0–14)	0.651
Presenting symptoms: number (%)				
Overt encephalopathy	24 (80%)	6 (86%)	18 (78%)	1
Polyfocal neurological signs	15 (50%)	7 (100%)	8 (35%)	0.006
Fever	20 (66.7%)	2 (28.6%)	18 (78.3%)	0.026
Seizures	9 (30%)	2 (28.6%)	7 (30.4%)	1
Confusion	9 (30%)	2 (28.6%)	7 (30.4%)	1
Headache (n = 26)***	10 (38%)	4 (57.1%)	6 (26.1%)	0.38
Weakness	16 (53.3%)	2 (28.6%)	14 (60.9%)	0.204
Tremor	5 (16.7%)	0	5 (21.7%)	0.304
Drowsiness	19 (63.3%)	2 (28.6%)	17(73.9%)	0.068
Visual impairment (n = 26)***	5 (19.2%)	2 (28.6%)	3 (13%)	0.588
Vomiting	14 (46.7%)	3 (42.9%)	11 (47.8%)	1
Nuchal rigidity	6 (20%)	3 (42.9%)	3 (13%)	0.120
Apathy	15 (50%)	3 (42.9%)	12 (52.2%)	1
Ataxia	7 (23.3%)	2 (28.6%)	5 (21.7%)	1

SD = standard deviation.
* Early MRI = performed on day one, while in ED.
** Late MRI = after day one, while on inpatient ward.
*** No record of headache or visual impairment in 4 patients who were preverbal and too young to voice these abnormalities.

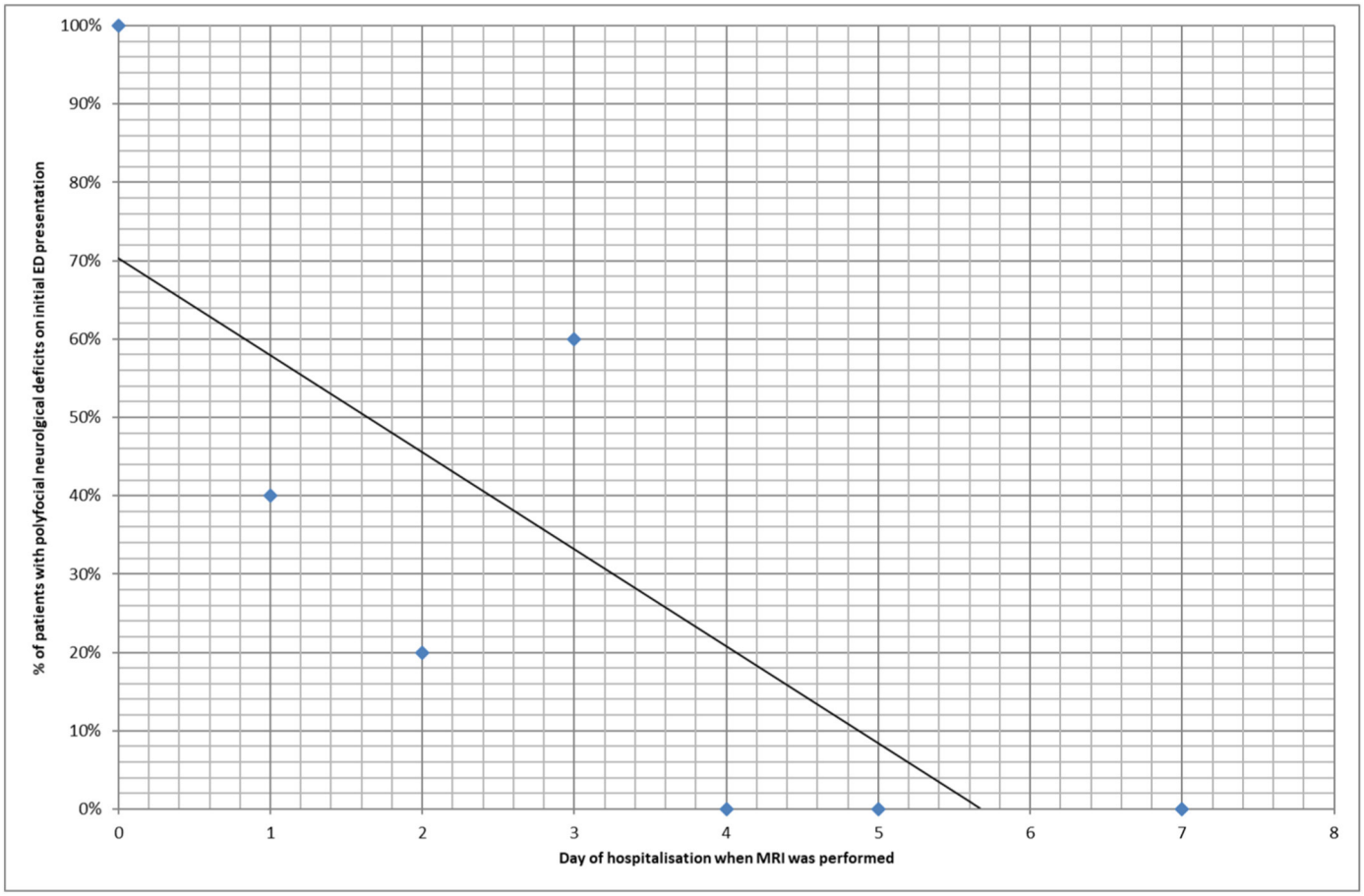

Fig. 1. Association between day MRI was performed and polyfocal neurologic signs.

the diagnosis of ADEM when confronted with a patient presenting with polyfocal neurological abnormalities.

Fever was seen more commonly in the late MRI group, and may have made clinicians more confident that an infectious process was the probable etiology, delaying the decision to order neuroimaging. It is important to emphasize that fever *is* one of the prominent signs of ADEM [17,18], and, in contrast to other immune-mediated diseases which typically present sometime after their

'immunological trigger', ADEM can present *during* the initial febrile illness [19].

Since approximately 25% of children are admitted to the intensive care unit after a first presentation of ADEM [20], mortality rates of 1–3% have been reported [21], and long-term cognitive deficits can been observed [22], early diagnosis and treatment is of utmost importance. Although therapy for ADEM has not been established through randomized controlled trials, there is increasing evidence of decreased mortality and improved outcomes in patients treated with high dose intravenous corticosteroids, IVIG and plasma exchange [23]. Our data emphasizes that patients febrile on initial presentation experienced delayed neuroimaging, with an accompanying delay in receiving the prompt treatment that improves neurological outcome.

We feel that educating clinicians engaged in the hospital care of children with ADEM, stressing the modes of presentation and the potentially misleading presence of fever, may assist in the effort to secure early treatment and improve outcomes of this rare disease.

Conflict of interest statement

The authors report no declaration of interest.

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