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ORIGINAL COMMUNICATION

Acute disseminated encephalomyelitis: prognostic value of early follow-up brain MRI

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Abstract Patients with acute disseminated encephalomyelitis (ADEM) are presumed to have radiological monophasic disease, but this is uncertain since follow-up brain MRI is not routinely performed. We aimed to ascertain combined radiological and clinical monophasic disease in ADEM patients and to assess whether performing early (<6 months) follow-up brain MRI has prognostic value for subsequent multiphasic disease. We retrospectively studied the medical records of patients initially diagnosed with ADEM (years 2000–2014) at the Massachusetts General Hospital, USA. A neuroimaging specialist, masked to clinical events, reviewed all available brain MRIs. We included 62 patients (25 male; 30 pediatric; median clinical follow-up 3 years) and classified them into two subgroups: (1) clinically monophasic (no new, recurrent or worsening neurological symptoms >3 months after onset) ($n = 45$), and (2) clinically multiphasic (clinical relapse >3 months after onset) ($n = 17$). All clinically monophasic patients with brain MRI follow-up ($n = 30$) also had radiological monophasic disease a median of 2 years after ADEM onset. New lesions (58 vs. 14%) and persistent lesions (100 vs. 18%) on early brain MRI [available in 40 patients (65%)], as well as clinical flares (53 vs. 20%), were more common in clinically multiphasic versus monophasic patients. These early follow-up data allowed us to predict multiphasic disease with reasonable accuracy in a multivariable model (AUC = 0.73). We conclude that performing early follow-up brain MRI routinely in ADEM patients would aid clinicians in predicting multiphasic disease and may stratify patients who would benefit from initiation of disease-modifying therapy for multiple sclerosis.

Keywords Acute disseminated encephalomyelitis · Prognostic factors · Multiple sclerosis · No evidence of disease activity (NEDA) · MRI

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Introduction

A quarter of patients initially diagnosed with acute disseminated encephalomyelitis (ADEM) experience clinical relapses of central nervous system (CNS) demyelinating disease [1]. Although a small subgroup of these patients has a multiphasic form of ADEM, most patients with relapsing disease are misdiagnosed at initial presentation and are best classified as having multiple sclerosis or, rarely, neuromyelitis optica spectrum disorder.

Radiological disease activity in demyelinating disorders is, however, not always associated with a clinical correlate, as is especially well known in multiple sclerosis. The term 'no evidence of disease activity (NEDA)' used in patients with multiple sclerosis therefore includes both clinical and radiological disease-free survival [2]. It is assumed that clinically monophasic ADEM patients are also radiologically monophasic. Brain MRI is, however, not routinely performed in the follow-up of ADEM patients since no guidelines exist to recommend performing it. Therefore, the proportion of patients with combined clinical and radiological monophasic disease following an initial ADEM diagnosis is uncertain. Follow-up brain MRI in the early phase may be helpful in predicting subsequent multiphasic disease [3]. A detailed clinical and radiological depiction of disease activity following a first diagnosis of ADEM in a large group of patients may guide future patients on treatment strategies, clarify prognostically relevant factors, and provide earlier points of intervention in patients who will go on to have a diagnosis of multiple sclerosis.

In this study, we retrospectively assess the proportion of patients with confirmed clinical and radiological monophasic disease following an ADEM diagnosis by evaluating long-term follow-up brain MRIs in clinically monophasic patients for radiological disease activity. We then assess the value of follow-up brain MRI when performed in the early phase (<6 months) to predict subsequent multiphasic disease. In addition, we summarize the therapeutic management during different phases of ADEM to place our cohort among the comparable reports of ADEM outcomes.

Patients and methods

Patient selection

We identified patients in the Partners Health Care' Research Patient Data Registry with the International Classification of Diseases 9th edition codes for ADEM (323.61 and 323.81). All patients, initially diagnosed with ADEM by a treating neurologist, who presented between January 1, 2000 and December 31, 2014 at the Massachusetts General Hospital, Boston, MA, USA, were included through a retrospective medical records review. The initial presentation of our US cohort, their inclusion and exclusion criteria, and the prevalence of relapsing diseases has been reported [1]. Patients with acute hemorrhagic leukoencephalopathy were excluded given their distinct pathology and generally worse outcomes [4]. Patients who were subsequently diagnosed with non-demyelinating disease (e.g., CNS lymphoma, rabies, CNS lupus) were also excluded [1].

Data collection

Details of the events of clinical disease activity were systematically collected, including the date of symptomatic presentation, clinical symptoms, laboratory results, and treatment choice and timing. Events were included from the time of symptomatic ADEM onset until the date of last follow-up, death, or the date of censoring (June 1, 2016). We presumed clinical symptoms to be absent if not reported in the medical record. No patient in our cohort was tested for myelin oligodendrocyte glycoprotein (MOG)-antibodies since this test was not clinically available during the study timeframe in the USA. A modified Rankin Scale (mRS) [5] score $\leq$2 was considered favorable in the determination of patient outcomes.

Clinical disease activity was the presence of neurological symptoms related to CNS demyelinating disease, including new, recurrent, or worsening symptoms. Radiological disease activity was the presence of new T2 hyperintense lesions (enhancing or non-enhancing), expansion of existing T2 hyperintense lesions, or new gadolinium enhancement of old lesions. A relapse or multiphasic presentation was defined as the occurrence of clinical or radiological disease activity more than 3 months after the initial ADEM presentation. We defined patients without a clinical relapse as clinically monophasic, and patients with a clinical relapse as clinically multiphasic. A flare, defined as the occurrence of clinical disease activity within 3 months of the initial ADEM presentation, could be consistent with clinically monophasic disease if there was no new disease activity after 3 months from the first ADEM symptoms [6].

Neuroimaging evaluation

A neuroimaging specialist (J.P.K.), masked to clinical events and for study purposes alone, retrospectively reviewed all available brain MR imaging for radiological disease activity. We considered brain MRIs performed within 6 months of the initial presentation as early follow-up brain MRI, if the scans preceded a clinically multiphasic presentation. Early brain MRIs performed routinely (not because of a clinical flare) were additionally reviewed for the degree of lesion resolution, which was categorized as no to slight resolution, marked resolution, and complete resolution. Multiple MRI machines were used for clinical purposes (1.5 and 3.0 Tesla). MRI machines may have also differed in the evaluation of a single patient over time due to convenience for the patient's transit time, scanner availability, and/or insurance access. T1-weighted sequences with and without gadolinium contrast and T2-weighted sequences (including T2-FLAIR) were reviewed. We defined combined clinical and radiological monophasic disease in patients who had neither clinical nor radiological

disease activity more than 3 months after the initial presentation during the observed follow-up period.

Institutional review board

This study was approved by the Partners Health Care institutional review board.

Statistical analysis

Patient characteristics were summarized using counts and proportions for categorical variables and median and interquartile range (IQR) for continuous variables. Multivariable logistic regression models were developed to predict multiphasic disease status 2 years after the 3-month follow-up period (27 months after the initial ADEM presentation). This analysis excluded patients with follow-up of <3 months. Patients with follow-up <27 months were assumed to remain monophasic as short follow-up in clinical practice is associated with disease-free survival. The predictive performance of each model was assessed using the cross-validated area under the receiver operating characteristic (ROC) curve (AUC) [7]. The AUC can be interpreted as the probability that the predicted probability of multiphasic disease for a randomly selected multiphasic patient is higher than that of a randomly selected monophasic patient. Thus, values of AUC at 0.5 indicate poor predictive performance, while values near to 1 indicate strong predictive performance. Confidence intervals for the estimated cross-validated AUC were computed using influence function-based variance estimates [8]. Statistical analyses were implemented with the R programming language (Vienna, Austria).

Results

There were 62 patients (25 male; 30 pediatric (age <18 years); 0 observed deaths) included in the analysis (Table 1; Fig. 1). The median observed clinical follow-up was 3.0 years (IQR 5.1); 53 patients (85%) were followed for ≥1 year, 42 patients (68%) for ≥2 years. There were 45 patients who remained clinically monophasic (22 pediatric), and 17 patients who experienced clinically multiphasic disease (8 pediatric). The median observed clinical follow-up was longer for multiphasic patients than monophasic patients [7.4 years (IQR 6.9) vs. 2.4 years (IQR 2.8)]. The median time to the first clinical relapse was 1.3 years (IQR 1.9), with 13 patients (76%) experiencing clinically multiphasic disease within 27 months of the initial ADEM presentation. Clinical outcome was favorable (mRS score ≤2) in 30 pediatric and 23 adult patients (100 vs. 72%), and in 39 monophasic and 14 multiphasic patients (87 vs. 82%).

Table 1 Demographic, clinical, CSF, and MRI features at initial presentation

Features	62 patients
Demographic	
Age	19 (30)
Pediatric	30/62 (48)
Male	25/62 (40)
Clinical presentation	
Preceding event	39/62 (63)
Polyfocal onset	60/62 (97)
Encephalopathy	33/62 (53)
Headache	28/62 (45)
Nausea/vomiting	21/62 (34)
Fever	23/62 (37)
Seizures	9/62 (15)
Weakness	33/62 (53)
Ataxia	22/62 (35)
Gait abnormality	37/62 (60)
Optic neuritis	10/62 (16)
Other visual disturbances	19/62 (31)
Other cranial nerve palsies	27/62 (44)
Sensory abnormalities	19/62 (31)
CSF findings	
Pleocytosis (>5 cells/μL)	38/56 (68)
Elevated protein (>45 mg/dL)	24/54 (44)
Oligoclonal bands present	8/46 (17)
MRI findings	
Abnormal brain MRI	62/62 (100)
Periventricular involvement	19/61 (31)
Corpus callosum involvement	14/61 (23)
Infratentorial lesions	41/61 (67)
Abnormal spinal cord MRI	22/61 (36)
Gadolinium enhanced[a]	46/46 (100)
No/variable/simultaneous enhancement[b]	15/13/18

Data are presented as *n*/*N* (%) or median (interquartile range)

[a]Brain MRI imaging at initial presentation was available for expert review in 46 patients

[b]No/variable/simultaneous enhancement in monophasic patients: 11/9/15. There were various patterns of enhancement at initial presentation: monophasic patients: nodular (10), patchy ($n = 8$), rim ($n = 4$), or leptomeningeal ($n = 2$) enhancement; multiphasic patients: nodular ($n = 6$) or rim ($n = 1$) enhancement

Long-term follow-up brain MRI

Clinically monophasic patients

Brain MRIs following the initial presentation were available for 30 of the 45 clinically monophasic patients (67%). The median MRI follow-up in these patients was 1.9 years (IQR 3.0); 19 patients (63%) had MRI follow-up for ≥1 year, 15 patients (50%) for ≥2 years. MRI review did

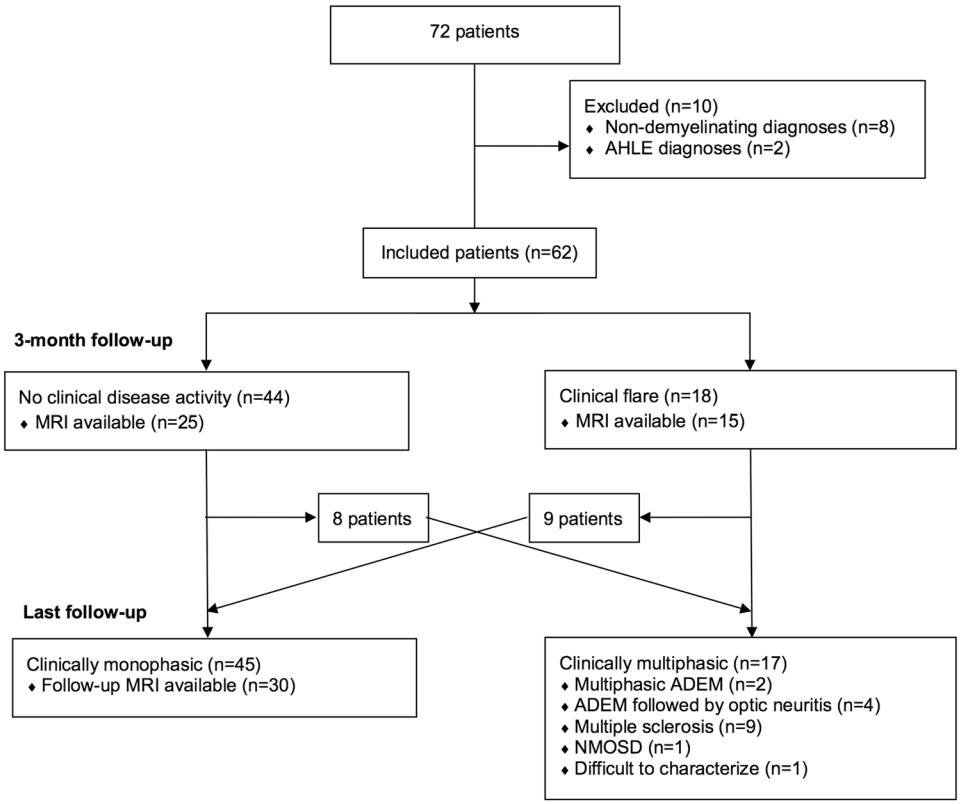

Fig. 1 Patient flow chart. *AHLE* acute hemorrhagic leukoencephalitis, *ADEM* acute disseminated encephalomyelitis, *NMOSD* neuromyelitis optica spectrum disorder

not identify ongoing radiological disease activity in these monophasic patients. Therefore, we characterized all clinically monophasic patients as having combined radiological and clinical monophasic disease.

Clinically multiphasic patients

There were 16 clinically multiphasic patients with brain MRIs available during the first relapse, all of whom had radiological evidence of disease activity except for two patients with optic neuritis who did not. Radiological disease activity preceded clinically multiphasic disease in four patients with a final diagnosis of relapsing remitting multiple sclerosis. New lesions on brain MRIs were noted in these four patients when performed between 2 and 9 months before the clinical relapse occurred.

Early clinical and radiological follow-up

Early follow-up brain MRI was available for 40 patients (65%). Three patients were followed for <3 months clinically (42, 54 and 56 days); these patients did not experience a clinical flare nor was early follow-up brain MRI performed of them. They were not included in the multivariable statistical model.

Clinical flare

Eighteen patients (29%) had a clinical flare at a mean of 24 days (range 5–50 days) after the initial presentation. Brain MRI was performed in the acute phase of 15 patients with a clinical flare, with variable findings from no radiological disease activity, to expansion or increased enhancement of prior lesions, and new lesions (Table 2).

Patients without clinical flares

Twenty five of the 44 patients without a clinical flare had a follow-up MRI within 6 months of the initial presentation: 20 of the 36 clinically monophasic patients and 5 of the 8 clinically multiphasic patients (all prior to their multiphasic presentation). Brain MRI identified new lesions in five patients, a median of 48 days after the initial presentation (range 30–109 days), of whom three patients remained clinically monophasic.

Monophasic versus multiphasic patients

In retrospect, several features of the early follow-up phase differed between monophasic and multiphasic patients (Table 2). A greater proportion of multiphasic patients experienced a clinical flare compared to the monophasic patients (53 vs. 20%). Multiphasic patients were more

Table 2 Comparison of clinically monophasic and multiphasic patients during early follow-up

Features	All ($n = 62$)	Monophasic ($n = 45$)	Multiphasic ($n = 17$)
Clinical flare			
No. of flares	18/62 (29)	9/45 (20)	9/17 (53)
Timing >4 weeks after initial presentation	8/18 (56)	1/9 (11)	7/9 (78)
Subtype			
Recurrence or worsening	8/18 (44)	4/9 (44)	4/9 (44)
New symptoms	5/18 (28)	1/9 (11)	4/9 (44)
New and recurrence/worsening	5/18 (28)	4/9 (44)	1/9 (11)
Clinical presentation			
Encephalopathic	2/18 (11)	2/9 (22)	0/9 (0)
Weakness	8/18 (44)	5/9 (56)	3/9 (33)
Ataxia	3/18 (17)	1/9 (11)	2/9 (22)
Optic neuritis	8/18 (44)	3/9 (33)	5/9 (56)
Brain MRI finding			
New lesions	6/15 (40)	1/8 (13)	5/7 (71)
Increase of lesions/enhancement	4/15 (27)	3/8 (38)	1/7 (14)
Stable and/or decrease of lesions	5/15 (33)	4/8 (50)	1/7 (14)
Routine early brain MRI findings			
New lesions	5/25 (20)	3/20 (15)	2/5 (40)
Complete lesion resolution	5/20 (25)	5/17 (29)	0/3 (0)
Marked lesion resolution	9/20 (45)	9/17 (53)	0/3 (0)
Persistent or slight lesion resolution	6/20 (30)	3/17 (18)	3/3 (100)

Data are presented as *n*/*N* (%) or median (interquartile range)

likely to experience their flare >4 weeks after the initial presentation compared to monophasic patients (78 vs. 11%). On early follow-up brain MRI, new lesions were more common in multiphasic than monophasic patients (58 vs. 14%) (Fig. 2). Marked or complete resolution of lesions was only identified in monophasic patients (82 vs. 0%) (Fig. 3).

Therapeutic management through ADEM follow-up

Treatment of ADEM patients at the initial presentation mainly consisted of 3–5 days of intravenous methylprednisolone 1 g daily, followed by second line treatment options depending on disease severity (Table 3). Therapeutic management of flares was variable, but most often consisted of the increase of oral prednisone or a new course of intravenous methylprednisolone. Two thirds of the clinical flares occurred during or within 1 week of discontinuation of steroid treatment. Patients with new lesions on early brain MRI without a clinical correlate were not usually treated, but one patient was started on interferon beta-1a as disease-modifying therapy for relapsing remitting multiple sclerosis. Multiple sclerosis disease-modifying therapy was initiated in a high proportion of patients with multiphasic disease.

Multivariable prediction of relapses

A multivariable logistic regression model based on clinical features at initial presentation and the occurrence of a clinical flare lead to a fair prediction of combined clinical and radiological monophasic disease (Table 4, model 1). A model solely based on the early phase following the initial ADEM diagnosis including new lesions detected in early follow-up brain MRI and the occurrence of a clinical flare, resulted in similar predictive performance as model 1 (Table 4, model 2). Further, including resolution of lesions on early follow-up brain MRI to model 2 increased the predictive value (Table 4, model 3). The plotted ROC curves of the multivariable prediction models show a potential benefit of model 3, although the models did not differ significantly in their AUC (Fig. 4).

Discussion

We characterize the clinical and radiological spectrum of CNS demyelinating disease following an initial diagnosis of ADEM. Given the long clinical observation period and the high proportion of patients who had MRIs, we provide composite data on clinical outcomes and the prognostic value of early brain MRI for patients. We identified that (1)

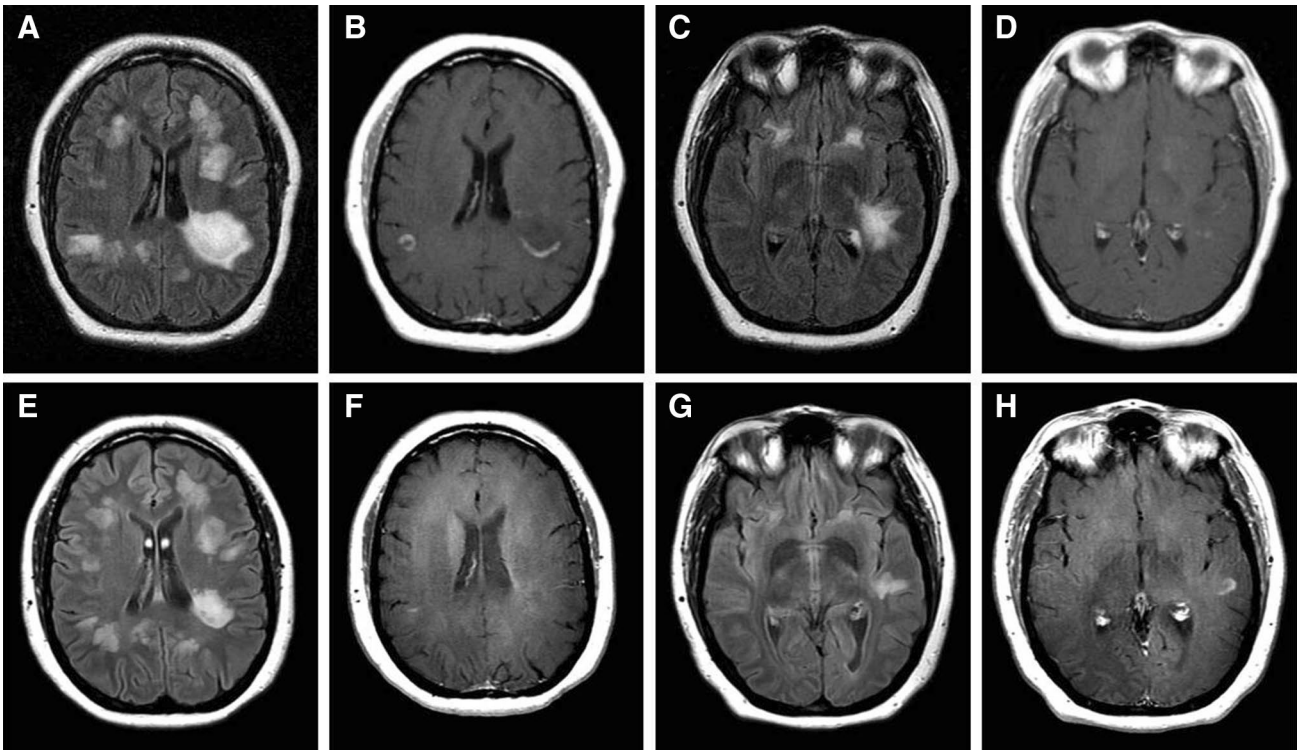

Fig. 2 New lesions on early brain MRI. New lesions on early brain MRI in a 31-year-old patient with multiphasic disease. Axial T2-FLAIR (**a**, **c**) and T1-post contrast (**b**, **d**) images of the brain show multifocal large and small lesions in the bi-hemispheric subcortical white matter. Some of these lesions have an open-rim of enhancement including a large edematous lesion in the left parietal lobe (**b**). Other lesions are non-enhancing. Axial T2-FLAIR (**e**, **g**) and T1-post contrast (**f**, **h**) images of the brain obtained 2 months after the images shown in **a**–**d** show partial resolution of some lesions and interval development of several new lesions in the bi-hemispheric subcortical white matter. Some of these new lesions enhance, including a lesion with an open rim of enhancement in the left temporal lobe (**h**)

monophasic ADEM patients did not have persistent radiological disease activity on brain MRI, and that (2) brain MRI performed in the early phase may have prognostic value for long-term monophasic disease.

Long-term follow-up brain MRI did not identify radiological evidence of disease activity in any of the clinically monophasic ADEM patients during a median follow-up of 2 years. This largely confirms that disease activity in ADEM is associated with a clinical correlate, and that radiological monophasic disease can be presumed in clinically monophasic ADEM patients.

Half of patients with a clinical flare experienced subsequent relapsing CNS demyelinating disease. However, clinical flares that occurred soon after the initial presentation, and clinical flares without radiological confirmation may not be as predictive for subsequent relapsing disease. The identification of new lesions on early follow-up brain MRI, and the degree of lesion resolution in the early phase of patients were helpful in predicting subsequent multiphasic disease. Our multivariable prediction model including features from the early phase following the initial ADEM diagnosis led to a reasonably accurate prediction for multiphasic disease at 2 years.

It has been hypothesized that gadolinium-enhanced MRI, which was routinely performed in our cohort, may prove useful in distinguishing monophasic from subsequent multiphasic disease [9]. However, as confirmed in our cohort, gadolinium enhancement is variable in ADEM patients and does not necessarily occur in all lesions simultaneously [10, 11]. Specific enhancement patterns, however, such as patchy enhancement, might be helpful in distinguishing ADEM from other relapsing demyelinating diseases.

In a Dutch cohort of pediatric patients with ADEM according to the International Pediatric Multiple Sclerosis Study Group criteria, deterioration on MRI was seen in 16 of the 30 patients with MRI follow-up in the first 3 months, but only in 2 of the 25 patients with MRI follow-up after 3 months [12], thereby largely confirming the 3-month cut-off value used to distinguish between a flare and a relapse. One patient in our cohort had new lesions identified on early brain MRI 109 days after the initial presentation, thus >3 months, but remained clinically monophasic at more than 3 years of follow-up.

Limitations of this study include the retrospective nature and inconsistent clinical and radiological follow-up without

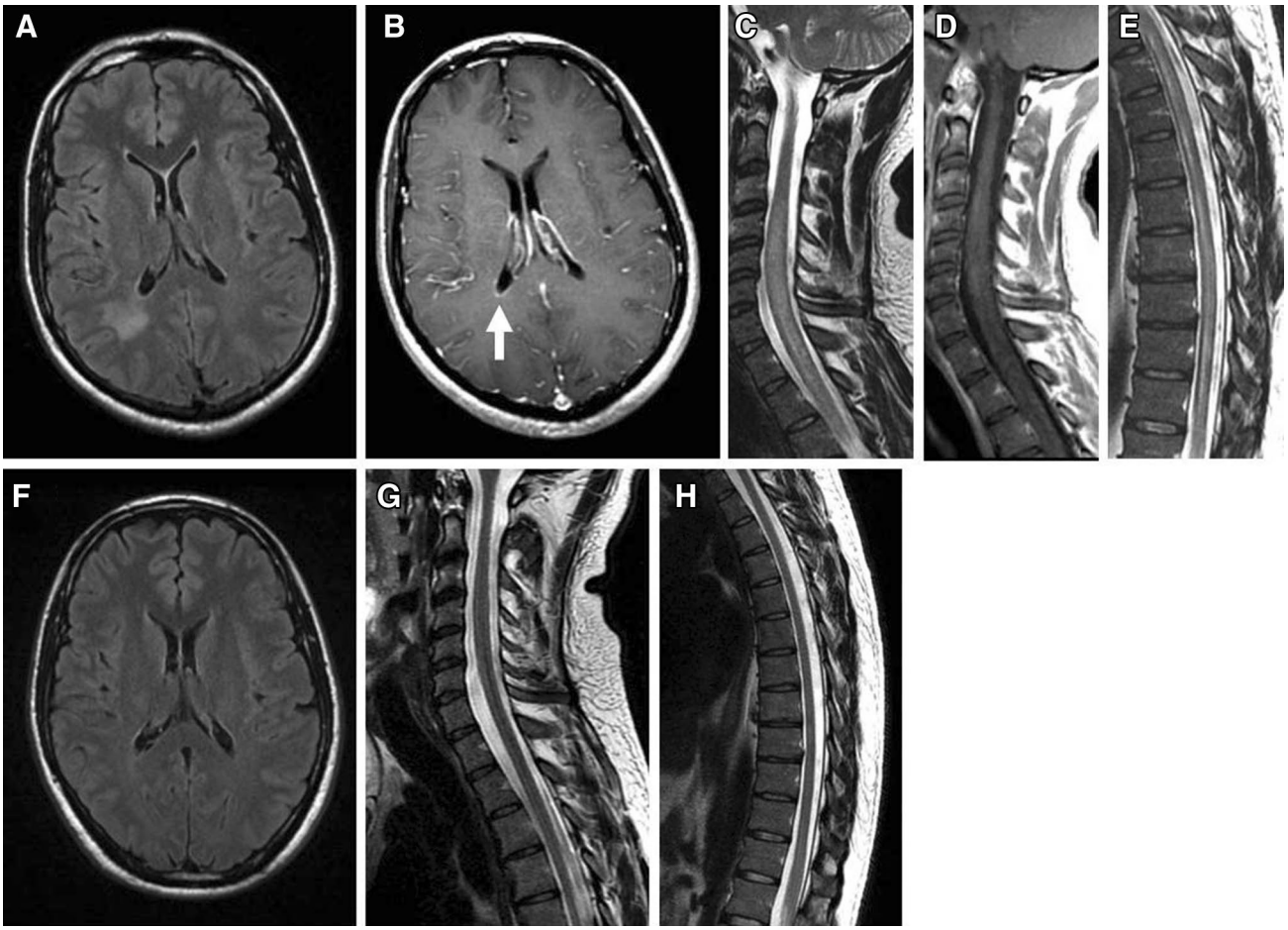

Fig. 3 Complete lesion resolution on early brain MRI. Complete lesion resolution on early brain MRI in a 30-year-old patient who remained monophasic during >2 years of observed follow-up. **a** Axial T2-FLAIR image shows a large T2 hyperintense lesion in the periventricular white matter of the right parietal lobe. **b** Axial T1-post contrast image shows mild enhancement along the ventricular surface (*arrow*) abutting the lesion seen in **a**. Sagittal T2 (**c**) and T1-post contrast (**d**) images of the cervical spine show a longitudinally extensive T2 hyperintense and partially enhancing lesion. **e** Sagittal T2 image of the thoracic spine shows longitudinal extension of the lesion throughout the entire thoracic spinal cord. **f–g** Axial T2-FLAIR image of the brain and sagittal T2-weighted images of the cervical and thoracic spine obtained 3 months after the images shown in **a–e** show complete resolution of all lesions

Table 3 Therapeutic management through ADEM follow-up

	Clinical onset ($n = 62$)	Flares ($n = 23$)	Relapses ($n = 17$)
Therapeutic management	MPS ($n = 42$) MPS + IVIG ($n = 7$) MPS + PLEX ($n = 2$) MPS + IVIG + PLEX ($n = 3$) MPS + IVIG + RTX IVIG ($n = 1$) IVIG + PLEX ($n = 1$) No treatment ($n = 4$) Unknown ($n = 1$)	MPS ($n = 11$) MPS + IVIG ($n = 1$) OPT increased ($n = 3$) IVIG + PLEX + RTX ($n = 2$) No treatment ($n = 6$) DMT initiated ($n = 1$)[a]	MPS ($n = 8$) MPS + IVIG ($n = 1$) OPT reinitiated ($n = 2$) No treatment ($n = 4$) Unknown ($n = 2$) DMT initiated ($n = 9$)

MPS methylprednisolone, *IVIG* intravenous immunoglobulin G, *PLEX* plasma-exchange, *RTX* rituximab and/or cyclophosphamide, *DMT* multiple sclerosis disease-modifying therapy

[a]This patient had stopped using interferon beta-1a (Rebif) after having taken it for 1.5 years after experiencing a radiological flare, and experienced a multiple sclerosis defining event 4 months later

Table 4 Multivariable logistic regression prediction models for combined clinical and radiological monophasic disease

	Variables and equations	AUC value (95% CI)	Specificity (95% CI) at 70% sensitivity
Model 1	Pediatric, sex, clinical flare expit(−1.8 + 0.47 × pediatric − 0.74 × male + 1.33 × clinical flare)	0.68 (0.53–0.84)	0.57 (0.46, 0.68)
Model 2	Clinical flare, new lesions on early follow-up MRI expit(−2.1 + 1.11 × clinical flare − 0.22 × MRI available + 1.86 × new lesions on MRI)	0.68 (0.54–0.83)	0.49 (0.37, 0.61)
Model 3	Clinical flare, new lesions on early follow-up MRI, lesion resolution on early follow-up MRI expit(−2.1 + 1.25 × clinical flare − 0.41 × MRI available + 2.02 × new lesions on MRI + 1.81 × resolution of lesions available − 17.89 × resolved lesions)	0.73 (0.62–0.84)	0.73 (0.62, 0.84)

AUC area under the receiver operating characteristic curve, *CI* confidence interval

In the model equations, expit(x) = exp(x)/(1 + exp(x)) and all variables are either '0' (indicating 'no') or '1' (indicating 'yes'). In model 3, if a patient experienced a clinical flare or if new lesions were identified on early follow-up MRI, 'resolution of lesions available' and 'resolved lesions' were both considered '0'

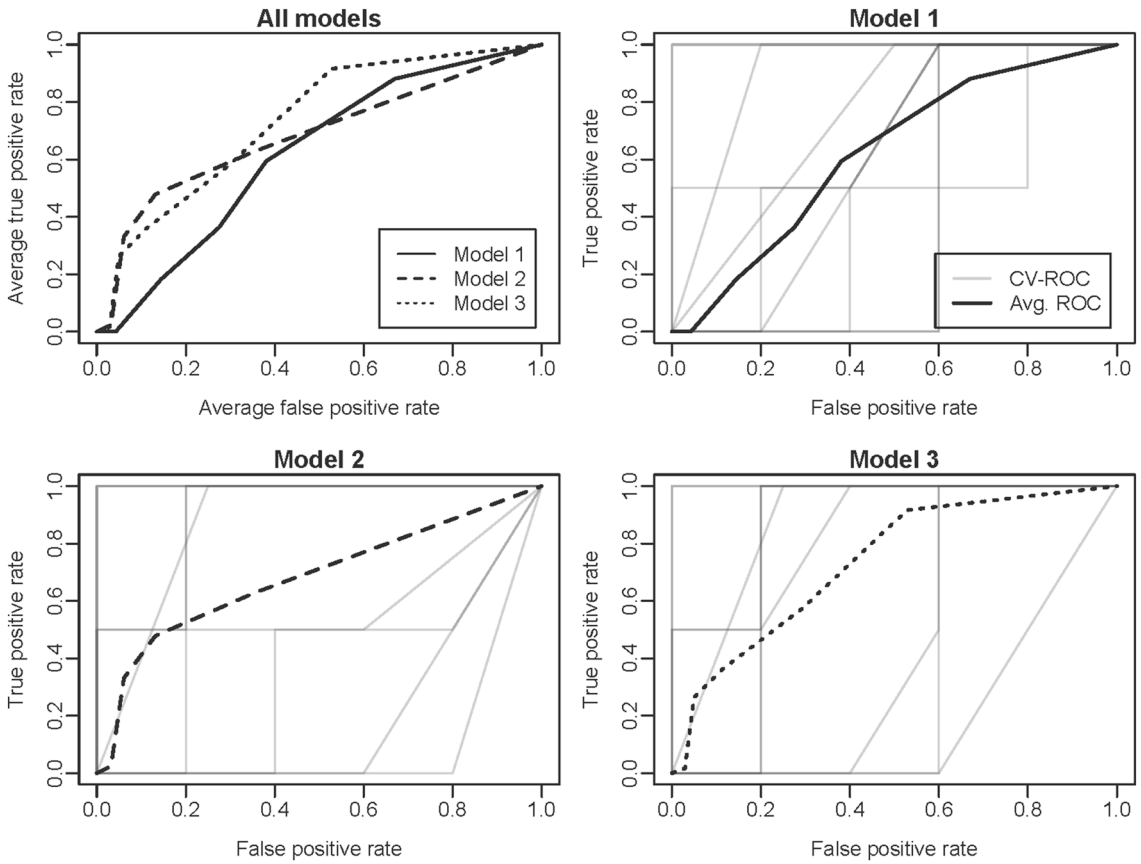

Fig. 4 ROC curves of the multivariable prediction models. Tenfold cross-validated receiver operating characteristic (ROC) curves. *Black lines* denote the average ROC curve computed by averaging the true positive and false positive rates over tenfolds for each threshold value. *Gray lines* denote the tenfold-specific ROC curves computed in validation samples based on models fit in training samples

a standard MRI protocol. MRIs in the early phase were not performed routinely, were performed at different time intervals from the initial presentation, and were performed at the discretion of the treating neurologist. The MRI machines used for imaging differed between patients, and at times, among the same patient who had subsequent scans with different MRI machines. The degree of lesion resolution is subjective, and interpretation may differ among radiologists. It is possible that some clinically monophasic patients do experience radiological disease activity escaping

identification, either because of non-routine MRI performance, or because ADEM lesions may resolve rapidly and are only identifiable for a short period. MRIs are 'snapshots' in time only. We aggregated children and adults due to the low sample size. Though, adults with ADEM do not seem to have a necessarily higher occurrence of multiphasic disease [1, 13]. The inclusion of patients presenting at a large, tertiary referral hospital attracts the more diagnostically complex patients with potentially higher frequencies of flaring and relapsing CNS demyelinating disease.

Nevertheless, the diagnosis by a subspecialized neurologist, the detailed clinical characterization of patients, the assessment of MR images masked to clinical events, and the long-term follow-up brain MRIs, enable us to report results with implications for clinical practice.

Our study emphasizes the added value of routine early clinical and radiological follow-up after an initial ADEM diagnosis in predicting the subsequent disease course. We show that the absence of a clinical flare, the absence of new MRI brain lesions, and marked resolution of lesions on MRI in the early phase, are each predictive for retaining monophasic status and combined, allowed us to predict with reasonable accuracy whether a relapse of CNS demyelinating disease will occur in the longer term. Therapies used in ADEM are heterogeneous as evidence and guidelines are lacking. We currently do not know whether the initial therapeutic decision making ultimately influences the subsequent disease course. Prospective studies are therefore needed. However, early initiation of disease-modifying therapy in patients with subsequent multiple sclerosis is beneficial. It is therefore advisable to perform routine early clinical and brain MRI follow-up after the initial ADEM diagnosis, as it may help clinicians predict multiphasic disease and provide early stratification of patients who would benefit from initiation of disease-modifying therapy instead.

Author contributions DLHK has contributed in drafting and revising the manuscript for content, study design, analysis and interpretation of the data, acquisition of data, and study coordination. DCB has contributed in drafting and revising the manuscript for content, analysis and interpretation of the data, and statistical analysis. JPK has contributed in drafting and revising the manuscript for content, acquisition of the data, and analysis and interpretation of the data. FJM has contributed in drafting and revising the manuscript for content, study design, analysis and interpretation of the data, and study supervision.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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