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# MRI prognostic factors for relapse after acute CNS inflammatory demyelination in childhood

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## Summary

**The prognostic factors for relapse of the initial MRI findings after a first episode of acute CNS inflammatory demyelination are unclear in children. In this study we aimed to identify initial MRI factors that are predictive of a second attack and disability after a first episode of acute CNS inflammatory demyelination in childhood. A cohort of 116 children who had a first episode of acute CNS inflammatory demyelination between 1990 and 2002 was studied using survival analysis methods. The initial MRI data were reviewed in a systematic, standardized, double-blind manner. The average follow-up was 4.9 ± 3 years. Multivariate analysis showed that the rate of second attack was higher in patients with corpus callosum long axis perpendicular lesions (34 out of 116 patients, 30%) on the initial MRI [hazard ratio (HR) 2.89; 95% confidence interval (CI) 1.65–5.06] and/or with the sole presence of well-defined lesions (46 out of 116 patients, 40%) (HR 1.71; 95% CI 1.29–2.27). Both criteria were more specific predictors (100%) of relapse, demonstrating conversion to multiple sclerosis, than the three Barkhof criteria (63%), but were less sensitive (21% compared with 52%). None of the MRI criteria was predictive of severe disability. Using initial MRI and survival analysis methods, we identified two specific predictors of relapse and conversion to multiple sclerosis after a first episode of acute CNS inflammatory demyelination in childhood. Their low sensitivity, however, shows that this prediction remains difficult.**

**Keywords**: children; cohort; disability; MRI; multiple sclerosis

**Abbreviations**: ADEM = acute disseminated encephalomyelitis; DSS = Disability Status Scale

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## Introduction

When a first episode of acute CNS inflammatory demyelination occurs in childhood, it would be useful to be able to predict the risk of relapse and disability, both for the families and for future therapeutic decisions. In young to middle-aged adults, the finding of three or more white matter lesions on a T2-weighted MRI is a very sensitive predictor (>80%) of the subsequent development of clinically definite multiple sclerosis within the next 7–10 years, especially if one of these lesions is located in the periventricular region (Frohman *et al*., 2003). New diagnostic criteria for multiple sclerosis, including MRI criteria, were recently proposed (McDonald *et al*., 2001), but they are most relevant to individuals aged between 10 and 59 years, as were the previous Poser criteria for multiple sclerosis (Poser *et al*., 1983). The predictive value of initial

MRI data for relapse in children remains unknown and it is not currently possible to differentiate accurately between monophasic and recurrent diseases on the basis of initial MRI findings.

Patients who suffer from a clinical relapse are usually considered to meet the criteria for multiple sclerosis; this is also the case in young children as the disease can appear before 10 years of age (Duquette *et al*., 1987; Ghezzi *et al*., 1997, Ghezzi, 2002; Ruggieri *et al*., 1999; Boiko *et al*., 2002; Simone *et al*., 2002). Acute disseminated encephalomyelitis (ADEM) is usually a monophasic disease that is associated with multifocal neurological symptoms and altered mental state. According to the literature, the MRI criteria for ADEM are: fuzzy, poorly defined lesions and a high lesion load, associated with thalamus and/or basal ganglia lesions (Stonehouse *et al*., 2003). However, relapses occur within a 2-year interval in 10–30% of patients initially diagnosed with ADEM (Dale *et al*., 2000; Hynson *et al*., 2001; Tenembaum *et al*., 2002; Mikaeloff *et al*., 2004). Moreover, inflammation occurring at an isolated CNS site (transverse myelitis, optic neuritis, brainstem dysfunction) can also have a monophasic or recurrent pattern.

We used survival analysis methods to analyse the prognostic value of initial MRI findings concerning the occurrence of a second attack and a severe disability in a large cohort of children with childhood-onset acute CNS inflammatory demyelination.

## Subjects and methods

### *Subjects and source of data*

Patients came from the French cohort of childhood-onset acute CNS inflammatory demyelination (the KIDMUS neuropaediatric cohort), described in a previous publication (Mikaeloff *et al*., 2004). For practical reasons, our study was restricted to the paediatric neurology reference centres located in three regions of France: Paris (Bicêtre and Saint-Vincent de Paul University Hospitals), North (Lille University Hospital) and West (Tours, Angers and Nantes University Hospitals). All children meeting the inclusion criteria were included and underwent identical evaluations (including MRI). We included children who had a first neurological episode compatible with a first attack or the progressive onset of an inflammatory demyelinating disease of the CNS before 16 years of age. They were identified between January 1990 (the date after which good quality, comparable MRI data are available for all patients) and April 2002. Exclusion criteria included a previous neurological abnormality, infectious or metabolic aetiology, and systemic immunological disorder. The baseline characteristics of the studied patients are reported in Table 1. They had similar baseline characteristics when compared with the entire cohort. Patients were followed up during routine clinical visits from the onset of their condition until April 2003.

The study received approval from the CCPPRB (coimté consultatif pour la récherche medicale et biologique).

### *Data collection*

Data were collected from the medical records and entered into a computer system. The criteria for MRI analysis were determined by a group of experts including paediatric and adult neurologists and neuroradiologists (members listed in Acknowledgements). They took into account the new MRI diagnostic criteria for multiple sclerosis (Barkhof *et al*., 1997; Tintore *et al*., 2000; McDonald *et al*., 2001) and other MRI features known to be associated with acute CNS inflammatory demyelination. Initial MRI was performed with 0.5 T magnet or more (usually 1.5 T), with sagittal T1, axial T2 and/or fluid attenuated inversion recovery (FLAIR) sequences. When gadolinium was injected, T1 sequences were acquired at least 5 min after injection. No spectroscopy or diffusion sequences were routinely performed during the study period.

The following terms are used in the text and for clarity are defined here: *periventricular lesions*: abutted the lateral ventricle or third ventricle surfaces; *cortical lesions*: located within the grey matter; *juxtacortical lesions*: located within the subcortical white matter immediately adjacent to grey matter ('U fibres'); *well-defined lesions*: lesions with well-defined limits; *corpus callosum long axis perpendicular lesions*: well-defined ovoid lesions perpendicular to the corpus callosum long axis (Fig. 1A); *focal lesions*: round or ovoid lesions

**Table 1** *Baseline characteristics of patients (n = 116)*

| | All patients [*n* (%)] |
|---|---|
| Duration of follow-up (years) | |
| Mean ± SD | 4.9 ± 3 |
| Median (range) | 4.5 (0.6–13.1) |
| Male sex | 46 (40) |
| Infection during the month preceding the onset | 45 (39) |
| Symptoms at the first attack | |
| Long tract dysfunction | 87 (75) |
| Brainstem dysfunction | 50 (43) |
| Optic neuritis | 27 (23) |
| Altered mental state | 57 (49) |
| Polysymptomatic | 93 (80) |
| CSF findings at the first attack | |
| Cells ⩾10/μl | 47 (41) |
| Proteins ⩾0.5 g/l | 40 (35) |
| Oligoclonal bands* | 22 (19) |

One hundred and five patients studied at onset.

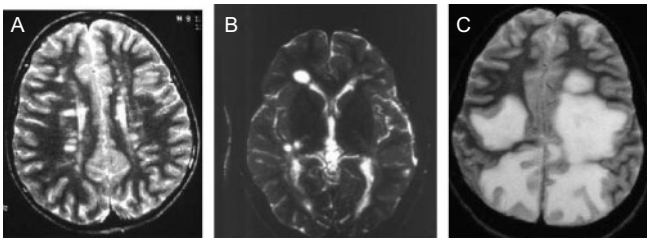


**Fig. 1** Brain MRI, T2-weighted sequence, axial plan. (**A**) Multiple corpus callosum long axis perpendicular lesions; (**B**) sole presence of well-defined lesions; (**C**) large areas.

located in grey (cortex, thalamus and/or basal ganglia) and/or white matter (maximal diameter <2 cm on all the slices where the lesion is seen) (Fig. 1B); *large area*: irregular-shaped lesion located in grey and/or white matter (maximal diameter >2 cm on all the slices where the lesion is seen) (Fig. 1C); *thalamus and basal ganglia lesions*: located predominantly within grey matter rather than along the adjacent white matter surface bordering the thalamus, caudate nucleus, putamen or globus pallidus; *tumour-like lesion*: lesion with mass effect; *lesion load with threshold superior or inferior to 50%*: ratio of abnormal brain (lesions) versus normal brain considering both the number and the area of the lesions.

MRI data were randomly evaluated by one of two teams using a standardized procedure. Each consisted of a paediatric neurologist and an expert paediatric neuroradiologist, blind to clinical symptoms and evolution. Inter-observer concordance was assessed on a sample of 15 randomly selected MRI, blind to clinical symptoms and evolution. Brain MRI was performed in all patients at onset, 26 out of 116 (22%) had additional spinal cord MRI.

Baseline demographic and disease-related data were available for all patients (date of birth, sex, onset date, symptoms, and clinical and MRI characteristics at onset). Each referring practitioner was contacted and asked to liaise with the patients' families. The families were first contacted by letter (for written consent) and subsequently by telephone. A telephone questionnaire was used to confirm residual disability and the incidence of further neurological episodes. Patients were considered lost to follow-up (nine out of 116, 8%) when their last data were >2 years old. The mean duration of follow-up for these nine patients was 2.5 years (range 0.6–7), age at onset of the disease was >10 years in four out of nine, three out of nine had a second attack, and three out of nine reached a Disability Status Scale (DSS) score of $\geqslant$4.

### *Prognostic factors and outcomes*

The outcomes included a second attack and a DDS score of $\geqslant$4 (Kurtzke, 1983). A second attack at least 1 month after the first attack qualified for conversion to multiple sclerosis, as defined in a previously published article on the same cohort (Mikaeloff *et al*., 2004). For the final diagnosis of multiple sclerosis, we used the gold standard for comparison, which is the subsequent development of multiple sclerosis by purely clinical criteria of dissemination in time and space, i.e. clinically definite multiple sclerosis (Poser *et al*., 1983; Frohman *et al*., 2003). A DSS score was considered irreversible when confirmed for a minimum of 12 months.

### *Statistical analyses*

Descriptive data were compared using the $\chi^2$-test or Fisher's exact test for proportions, and the *t*-test or the Wilcoxon test for continuous measures. Time zero for the survival analysis was taken as the date of the very first cohort-defining episode. The end-point was the date when the outcome occurred. For event-free subjects, the follow-up period ended on the date of the last known visit, at which point the time was censored. Survival curves were estimated using the Kaplan–Meier method. Cox's proportional hazards model was used to evaluate the prognostic value of each MRI factor measured at onset. Variables with a significance level of $P < 0.20$ in the univariate analyses were included in the multiple regression analysis with backward elimination of variables to identify the set of variables with independent prognostic significance. A variable with $P < 0.05$ was considered significantly associated with the survival function.

Numbers of true positives [TP; MRI criteria considered positive, second attack (disease)], true negatives (TN; MRI criteria considered negative, no second attack), false positives (FP; MRI criteria considered positive, no second attack) and false negatives (FN; MRI criteria considered negative, second attack) were used to determine the following: (i) sensitivity: the proportion of tests that identified disease among those with the disease (TP/TP + FN); (ii) specificity: the proportion of tests that found no disease among those who do not have the disease (TN/TN + FP); (iii) positive predictive value: the proportion of patients with a positive test result who have the disease (TP/TP + FP); (iv) negative predictive value: the proportion of patients with a negative test result who do not have the disease (TN/TN + FN); and (v) accuracy: the proximity to the true value (TP + TN/TP + TN + FN + FP). Analyses were performed using the SPSS software for Windows (version 11.5).

## Results

Fifty-two patients out of 116 (45%) had a second attack and therefore met the criteria for clinically definite multiple sclerosis; 33 (28%) were >10 years of age; and 10 (9%) were initially diagnosed with ADEM. Fifty patients (43%) were diagnosed with monophasic ADEM and 14 (12%) had another monophasic episode (transverse myelitis, optic neuritis, brainstem dysfunction). The initial MRI characteristics associated with the occurrence or absence of a second attack are reported in Table 2. Corpus callosum long axis perpendicular lesions, focal lesions, the sole presence of well-defined lesions and total number of lesions greater than nine were significantly associated with the occurrence of a second attack. A large area and a lesion load >50% were significantly associated with a monophasic disease. Thalamus and/or basal ganglia lesions were equally frequent in both monophasic and recurrent diseases.

The results of multivariate Cox survival analysis are reported in Table 3. For all patients, only corpus callosum long axis perpendicular lesion and/or the sole presence of well-defined lesions were significantly associated with the occurrence of a second attack. We assessed survival functions as regards to the time preceding the second attack (Fig. 2) according to corpus callosum long axis perpendicular lesions and the sole presence of well-defined lesions (i.e. the two 'MRI KIDMUS' criteria). For patients with those lesions, the mean time between the first and second attacks was 1.1 years (range 0.4–1.8), compared with 7.1 (range 5.7–8.5) for those without these two lesions ($P < 0.001$).

**Table 2** *Initial MRI characteristics of patients*

| | All patients ($n$ = 116*) | | $P$ value ($\chi^2$ test) |
|---|---|---|---|
| | Monophasic disease ($n$ = 64) | Second attack ($n$ = 52) | |
| Localization of lesions | | | |
| ⩾3 periventricular lesions | 26 (41) | 26 (50) | 0.3 |
| Corpus callosum lesions | 17 (27) | 20 (39) | 0.2 |
| Corpus callosum long axis perpendicular lesions | 10 (16) | 24 (47) | <0.001 |
| Juxtacortical lesions | 33 (53) | 29 (57) | 0.7 |
| Cortical lesions | 13 (21) | 10 (20) | 0.9 |
| Thalamus and/or basal ganglia lesions | 32 (51) | 24 (46) | 0.6 |
| Optic nerve lesions† | 1 (2) | 2 (4) | 0.5 |
| Brainstem lesions | 24 (38) | 29 (56) | 0.06 |
| Cerebellum lesions | 19 (30) | 17 (33) | 0.8 |
| Spinal cord lesions‡ | 7 (11) | 13 (25) | 0.05 |
| Aspect of lesions | | | |
| Hyposignal intensity on T1 sequences | 41 (65) | 31 (61) | 0.6 |
| Large area | 41 (65) | 21 (40) | <0.01 |
| Focal lesions | 33 (52) | 39 (75) | <0.001 |
| Sole presence of well-defined lesions | 17 (27) | 29 (56) | <0.01 |
| Gadolinium enhancement§ | 8 (13) | 12 (24) | 0.1 |
| Extent of lesions | | | |
| Tumour-like lesion | 8 (13) | 7 (14) | 0.9 |
| Bilateral lesions | 45 (73) | 38 (75) | 0.4 |
| >9 lesions (supra and/or infratentorial) | 22 (34) | 28 (54) | 0.04 |
| Lesion load >50% | 8 (13) | 0 (0) | <0.01 |

*Data are given as $n$ (%). Four patients had an initial normal brain MRI (and no spinal cord MRI); †63 patients studied; ‡26 patients studied; §61 patients studied.

**Table 3** *Multivariate analysis of radiological prognostic factors of a second attack (independent radiological covariates)*

| | Number of patients (%) | Crude hazard ratio | Hazard ratio (95% confidence interval) | $P$ value |
|---|---|---|---|---|
| Corpus callosum long axis perpendicular lesions | 34 (30) | 1.7 | 2.89 (1.65–5.06) | <0.0001 |
| Sole presence of well-defined lesions | 46 (40) | 1.55 | 1.71 (1.29–2.27) | <0.0001 |

Fifty-one (44%) of the 116 patients had three Barkhof criteria (25 with age at onset >10 years; 27 relapsing), 30 (26%) had four Barkhof criteria (12 with age at onset >10 years; 17 relapsing), and 11 (9.5%) had the two MRI KIDMUS criteria (10 with age at onset >10 years; 11 relapsing). The two MRI KIDMUS criteria were more specific predictors of relapse than the Barkhof criteria (Table 4). However, the two MRI KIDMUS criteria were less sensitive than the Barkhof criteria. All criteria were less sensitive in the younger patients.

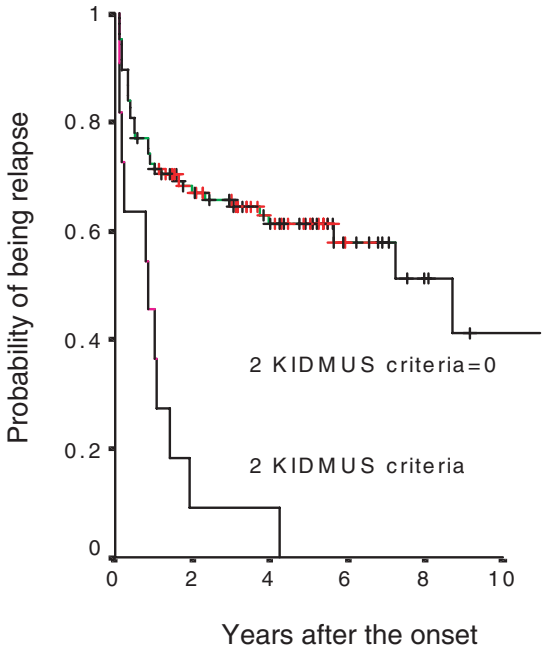


**Fig. 2** Survival functions as regards to the time preceding the second attack according to the presence of the two MRI KIDMUS criteria on the initial MRI (corpus callosum long axis perpendicular lesions and sole presence of well-defined lesions) ($P$ < 0.001, calculated using the log-rank test).

By the end of the follow-up period, 96 (83%) of the 116 patients had either no disability or a disability score of between 1 and 3. Ten (17%) patients had a disability score of 3, and 14 (12%) had a disability score of ⩾4. In multivariate Cox analysis, having an irreversible DSS score of ⩾4 was not associated with MRI covariates. None of the MRI criteria was predictive of the occurrence of severe disability.

## Discussion

This is the first study to use wide inclusion criteria related to all possible onsets of multiple sclerosis in childhood to assess MRI prognostic factors for relapse and disability without bias due to the mode of inclusion. To improve data accuracy (MRI quality at the first attack), we limited the date of eligibility. Hospital-based selection bias is possible but limited because most paediatric patients are referred to a reference centre in their geographical area at least once. We excluded patients with conditions that can mimic multiple sclerosis or the associated MRI findings, including patients with a previous neurological abnormality or with an infectious, metabolic or systemic immunological disorder. As recommended when comparing outcomes, we used the subsequent development of multiple sclerosis by the purely clinical criteria of dissemination in time and space (Frohman *et al*., 2003). ADEM is more frequent in children than in adults and is usually considered to be a

**Table 4** *Comparison of initial MRI criteria predictive of the occurrence of a second attack in the entire cohort (n = 116) and based on age at onset*

| | 3 Barkhof criteria | | | 4 Barkhof criteria | | | 2 MRI KIDMUS criteria | | |
|---|---|---|---|---|---|---|---|---|---|
| | All | Age <10 years | Age ⩾10 years | All | Age <10 years | Age ⩾10 years | All | Age <10 years | Age ⩾10 years |
| Sensitivity (%) | 52 | 37 | 61 | 33 | 32 | 33 | 21 | 5 | 30 |
| Specificity (%) | 63 | 59 | 72 | 80 | 74 | 94 | 100 | 100 | 100 |
| PPV (%) | 53 | 27 | 80 | 57 | 33 | 92 | 100 | 100 | 100 |
| NPV (%) | 38 | 31 | 50 | 59 | 72 | 44 | 61 | 72 | 44 |
| Accuracy (%) | 58 | 52 | 65 | 59 | 62 | 55 | 65 | 72 | 55 |

Barkhof criteria: (1) at least one gadolinium-enhancing T1 lesion or nine T2 lesions; (2) at least one infratentorial T2 lesion; (3) at least one juxtacortical T2 lesion; (4) three or more periventricular T2 lesions. MRI KIDMUS criteria: (1) corpus callosum long axis perpendicular lesion; (2) sole presence of well-defined lesions. PPV = positive predictive value; NPV = negative predictive value.

monophasic disease. However, relapses in patients initially diagnosed with ADEM have been reported in several series and cohorts; these relapses can occur at different sites and times (Dale *et al*., 2000; Hynson *et al*., 2001; Tenembaum *et al*., 2002; Mikaeloff *et al*., 2004). The relationship between ADEM and multiple sclerosis remains controversial, especially in children (Wingerchuk, 2003), and ADEM should be included in the spectrum of possible onsets of multiple sclerosis in childhood.

Our multivariate survival analysis showed that two MRI criteria, corpus callosum long axis perpendicular lesions and sole presence of well-defined lesions, are predictive of a second attack and conversion to multiple sclerosis. They were selected as the most powerful prognostic factors among all other MRI criteria in multivariate survival analysis. They were more specific predictors of relapse, meeting the criteria for conversion to multiple sclerosis, than the Barkhof criteria. However, they were less sensitive, and concerned only 9.5% of all patients. The association between large area and monophasic disease was of interest, but 'large area' was not a sufficiently powerful prognostic factor to be retained in the multivariate survival analysis.

Corpus callosum long axis perpendicular lesions, also known as 'Dawson's fingers', have been attributed to perivenular inflammation and are considered to be a relatively specific indicator of multiple sclerosis (Osborn, 1994; Palmer *et al*., 1999). Their pattern is characteristic, with ovoid plaques in which the long axis is perpendicular to the corpus callosum long axis (which is also the long axis of the whole brain). These lesions are part of subcallosal striations that can be precisely described on sagittal, thin-section, FLAIR MRI sequences (Palmer *et al*., 1999). The sole presence of well-defined lesions is evocative of multiple sclerosis (Barkhof *et al*., 1997). The new McDonald criteria for the diagnosis of multiple sclerosis do not include this information. However, we standardized the evaluation of limits of lesions by examiners and included it in our study, owing to its value for the description of ADEM characteristics in children (Hynson *et al*., 2001).

The length of patient follow-up varied in our cohort. A recent report on the usefulness of MRI for the confirmation of suspected multiple sclerosis in adults showed that measures of sensitivity and specificity, as well as predictive values and accuracy, do not take into account the varying lengths of follow-up periods (Frohman *et al*., 2003). The same report stressed the scarcity of studies using survival analysis methods and showed how essential they are to circumvent the limitation of the varying lengths of follow-up periods. The main objective of this study was to compare multiple independent MRI criteria using survival analysis methods, rather than to estimate sensitivity and specificity measures.

In our previous study, multivariate survival analysis showed that the second attack occurs later if the first attack occurs before the age of 10 years (Mikaeloff *et al*., 2004). In the present study, we confirmed that the Barkhof criteria are not adapted to younger children (<10 years of age), as evoked by the International Panel (McDonald *et al*., 2001). However, even using initial MRI, survival analysis methods and a 5-year mean follow-up, it remained difficult to predict conversion to multiple sclerosis after a first episode of acute CNS inflammatory demyelination in young children.

None of the MRI criteria predicted the occurrence of severe disability. However, a more prolonged follow-up might help to identify such criteria. In adults, a moderate association has been reported between increases in volume of the lesions seen on brain MRI in the first 5 years and the degree of long-term disability (Brex *et al*., 2002). Advances in neuroimaging techniques (diffusion sequence, etc.) will help to define more sensitive and/or specific predictors for disability. We intend to study the evolution of MRI using time as a prognostic factor for second attack and disability.

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