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Risk of multiple sclerosis after a first demyelinating syndrome in an Australian Paediatric cohort: clinical, radiological features and application of the McDonald 2010 MRI criteria

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Abstract

Background: The risk of multiple sclerosis (MS) is dependent on multiple variables, including geographical location. There is increasing interest in the early recognition and treatment of MS in children.

Method: Using univariate and multivariate analysis, we determined the clinical and radiological features that were predictive of MS in 88 children from New South Wales, Australia, with a first acute demyelinating syndrome (ADS) who were followed for a minimum of one year. We tested the McDonald, KIDMUS, Callen and Verhey MRI criteria for paediatric MS.

Results: After a mean follow-up of 5.2 years, 13/88 (15%) of children had MS. Using multivariate analysis, preceding infection was protective of MS, and corpus callosal lesions, the combined presence of both well and poorly demarcated lesions, and contrast-enhancing lesions on MRI were predictive of MS. The sensitivity and specificity of the respective radiological criteria were McDonald 2005 (69%, 68%), McDonald 2010 (58%, 95%), KIDMUS (8%, 100%), Callen (69%, 85%) and Verhey (62%, 84%). When McDonald 2010 criteria were applied to baseline and serial scans, the sensitivity and specificity was 91% and 93%.

Conclusion: Despite the long follow-up, the risk of MS appears lower in New South Wales children compared to previously reported cohorts. Radiological features are more predictive than clinical features in predicting MS. The McDonald 2010 criteria performed well although the dissemination in time criteria on baseline scans is difficult to apply to children with encephalopathy.

Keywords

Multiple sclerosis, acute disseminated encephalomyelitis, clinically isolated syndrome, MRI, McDonald 2010 criteria

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Introduction

Children who experience their first acute demyelinating syndrome (ADS) are categorised as having either a clinically isolated syndrome (CIS) or acute disseminated encephalomyelitis (ADEM) according to their clinical presentation and magnetic resonance imaging (MRI) findings as outlined by the 2007 consensus criteria.[1] Differentiating between a monophasic demyelinating illness (ADEM, CIS) and a recurrent demyelinating disorder such as multiple sclerosis (MS) is important because a number of adult studies have shown that early introduction of disease-modifying therapies can delay disability and halt the appearance of new T2 high-signal lesions on MRI.[2] Although this has yet to be confirmed in children, the deleterious effects of central nervous system (CNS) demyelination on neurodevelopment make the potential use of disease-modifying therapy of paramount importance.[3]

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Clinical characteristics are useful in differentiating ADEM from CIS but are less useful in reliably predicting which children will be diagnosed with MS. It is established in the literature that having a CIS in combination with an abnormal MRI brain has a higher risk of MS compared to ADEM.[4,5] However, between 10% and 29% of children with ADEM will be subsequently diagnosed with MS.[6–8]

A number of paediatric MRI MS criteria have been proposed to help predict which patients are likely to be diagnosed with MS based on neuroimaging alone.[9–11] Recently the adult McDonald 2010 MRI MS criteria have been recommended for use in children presenting with CIS to diagnose MS from a baseline MRI scan.[12]

Geographical latitude has been shown to influence the risk of MS in adults, with disease rates rising with increasing distance from the equator in both the northern and southern hemispheres. In children this relationship is less clear. The rate of MS after a first ADS has mainly been investigated in children from Western Europe and North America.[5,7,13–15] These studies and rates are from countries defined as being at 'high risk' of MS according to adult data.[16] The risk of MS for adults living in New South Wales (NSW), Australia, is lower than more southerly states such as Victoria and Tasmania, supporting the 'latitude hypothesis'.[17]

We performed a retrospective study of all children presenting to the Children's Hospital at Westmead (a tertiary-referral centre) in Sydney, NSW, Australia, with their first ADS between 1997 and 2010 to determine the risk of MS in this population of children. We describe the clinical and MRI characteristics of children with ADS in NSW, Australia, and test the reliability of the previously proposed paediatric MRI MS criteria and the adult McDonald MRI MS criteria.

Method

Case identification and data collection

Patients who presented to the Children's Hospital Westmead, NSW, Australia, with their first ADS between January 1997 and June 2010 were identified using the hospital coding system. The age cut-off was 16 years. Ethics approval was given by the hospital ethics committee (07/CHW/1). The Children's Hospital is a tertiary and quaternary hospital in greater Sydney where paediatric specialist care is highly centralised. A total of 221 patient records were reviewed and patients were excluded if their first demyelinating episode was prior to 1997, if they had an infectious, developmental, toxic or genetic disorder or if their follow-up was less than 12 months. There were 88 patients who met the inclusion criteria. These patients presented with their first ADS associated with consistent MRI findings that fulfilled criteria as outlined by the 2007 consensus.[1] Detailed clinical, biochemical and neuroimaging information at initial presentation were reviewed and recorded, then the patients were classified as either ADEM or CIS.[1]

Follow-up study

Follow-up was via inpatient and outpatient clinic records as well as a telephone questionnaire. The questionnaire entailed a series of questions to determine if there were residual deficits following the first ADS, if further demyelinating events had occurred and/or if the patient had been diagnosed with a chronic demyelinating disorder (MS, neuromyelitis optica (NMO)) according to the consensus criteria.[1] MS diagnoses were confirmed with treating physicians.

The functional status at follow-up was determined using a telephone questionnaire in 74/88 (84%), in conjunction with the most recent clinic review. There were 14/88 (16%) patients whose outcome was determined by outpatient clinic notes alone after a minimum follow-up of 1 year.

According to the follow-up information, patients were classified into two groups: MS (clinically definite) and non-MS. Non-MS included chronic relapsing inflammatory optic neuropathy (CRION),[13] NMO, or a monophasic demyelinating event.

MRI study

MRI were acquired using a 1.5T magnet (Philips Integra) with T1 and T2 sequences and slice thickness of 3–5 mm. Fluid-attenuated inversion recovery sequences (FLAIR) were available in most studies. There were 86/88 brain MRIs available from the first ADS for analysis. Two patients did not have a baseline brain MRI; one of these patients presented with clinical transverse myelitis (TM) and had MRI of the spine only. The other patient had clinical bilateral ON and did not undergo neuro-imaging. Contrast (gadolinium) studies were performed in 78/88. MRI spine was performed in 42/88 patients. A serial MRI scan was performed in 54/88 (61%) patients.

All images were reviewed by two assessors blinded to clinical information and outcome (KP and RCD). Lesion characteristics were recorded, including location, distribution, border outline, symmetry, number, and size (> 2 gyri). The presence or absence of black holes on T1 (a lesion that is hypointense relative to cortical grey matter) and whether there was gadolinium enhancement was also analysed. All components of the McDonald 2005,[18] McDonald 2010,[12] KIDMUS,[9] Callen,[19] and Verhey[20] MRI MS criteria were tested on the baseline MRI scan and serial scan where appropriate (Table 1).

Serial scans were reviewed for partial/complete lesion resolution and for the presence of new lesions (n = 54).

Table 1. Summary of established adult (McDonald) and proposed paediatric MRI MS criteria.

McDonald, 2005[18]	**DIS**[a] An MRI must show three of the following: 1. ≥ nine white matter lesions in the brain or spinal cord OR one gadolinium-enhancing lesions in the brain or spinal cord 2. ≥ one infratentorial (or spinal) lesion 3. ≥ one juxtocortical lesion 4. ≥ three periventricular lesions	**DIT**[b] Can be fulfilled in two ways; 1. Gadolium-enhancing lesion > three months after initial event OR 2. New T2 lesion at least 30 days after baseline scan
McDonald, 2010[12]	**DIS** An MRI must show one T2 lesion in at least two of four areas; 1. Periventricular 2. Juxtacortical 3. Infratentorial 4. Spinal cord (must not be a symptomatic lesion)	**DIT** Can be fulfilled in two ways: 1. Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time (including baseline scan) OR 2. New T2 and/or gadolinium-enhancing lesion on serial MRI
KIDMUS[9]	An MRI must have both: 1. Sole presence of well-defined lesions AND 2. the presence of lesions perpendicular to the long axis of corpus callosum	
Callen[10] (for diagnosing paediatric MS)	To diagnose paediatric MS an MRI must show two or more of the following; 1. ≥ five T2 lesions 2. ≥ two periventricular lesion 3. ≥ one brainstem lesion	
Callen[19] (for differentiating ADEM from MS)	To diagnose MS as opposed to ADEM an MRI must have two or more of the following: 1. ≥ two periventriuclar lesions 2. Black holes on T1 images 3. Lesion distribution that is not diffuse bilateral.	
Verhey[11]	A future diagnosis of MS strongly correlated with an MRI that showed both: 1. ≥ one periventricular lesions and 2. ≥ one T1-hypotense lesions	

MRI: magnetic resonance imaging; MS: multiple sclerosis; [a]DIS: dissemination in space, the presence of lesions in multiple areas of the brain; [b]DIT: dissemination in time, evidence of lesion accumulation with time; ADEM: acute disseminated encephalomyelitis.

Statistical method

Statistical analyses were completed using SPSS software (version 17.0). Comparisons between ADEM and CIS and then MS and non-MS were performed using Pearson's Chi square test for nominal categorical variables (e.g. sex, fever), and the Mann-Whitney U Test was used for continuous variables (e.g. age in months). P values were reported and the null hypothesis rejection criterion α was set at 0.05.

We used a survival modal analysis in SPSS for calculating the hazard ratio with 95% confidence interval (CI). We constructed Cox proportional hazards models for the univariate analysis, where zero time was the first ADS and the event of interest was MS diagnosis. For the non-MS patients, the time calculated was between the first ADS and most recent follow-up.

The proportional hazards condition was applied. Significant covariates from the univariate analysis were applied via a Cox regression in the multivariate analysis.

The hazards ratio (HR) assumes that all patients who have a first episode of CNS demyelination will eventually develop MS, and even though this is not the case in paediatric demyelination, this method is commonly applied to paediatric data to try to predict outcome.[5,20]

Annualised relapse rate (ARR) is calculated as the number of relapses for each subject divided by the number of years followed in the study for that subject. The value reported is the mean across all subjects.

Results

There were 88 patients who met our inclusion criteria (Figure 1). The first ADS episode diagnosis was ADEM in 36/88 (41%) and CIS in 52/88 (59%).

The hospital coding system was used to identify all children presenting with their first acute demyelinating syndrome (ADS). The search terms were broad and included acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS), multiple sclerosis (MS), neuromyelitis optica (NMO), transverse myelitis (TM), optic neuritis (ON), myelitis, demyelination, encephalitis and cerebellitis. There were 88 children identified as having their first ADS and between 1997 and 2010. The 2007 consensus criteria[1] were applied. Children diagnosed with clinically definite MS (CDMS) had either two episodes of demyelination and met the dissemination in space (DIS) and dissemination in time (DIT) criteria for

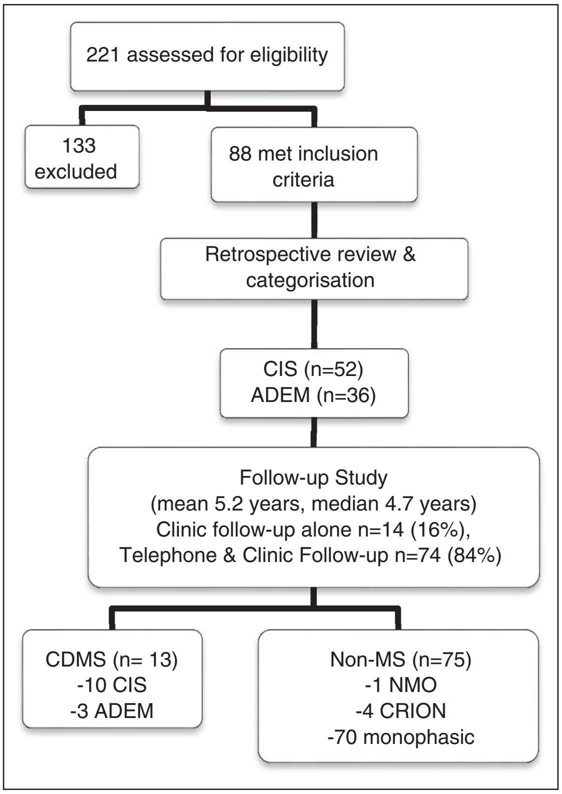

Figure 1. Breakdown of cohort of patients from selection to follow-up diagnosis.

MS or one episode of ADEM followed by at least two non-ADEM events with supportive magnetic resonance imaging (MRI) findings of DIS and DIT.[1] The patient diagnosed with NMO had an episode of TM with an MRI of the spine that showed longitudinally extensive transverse myelitis (LETM) and was found to be anti-NMO antibody positive. The four children diagnosed with chronic inflammatory optic neuropathy (CRION) had normal MRI at baseline and on subsequent ON episodes.

First episode diagnosis and comparison: ADEM vs CIS

We compared the clinical findings of patients presenting with ADEM and CIS. ADEM patients were female in 39% compared to 56% of CIS patients (not significant (ns)). ADEM patients were younger, with a mean age of 6.2 years (range 1.7–14.6 years) compared to 9.8 years (range 1.3–15.4 years) for CIS patients ($p < 0.00$). ADEM patients had statistically significantly more presentations with a preceding infection (92% vs 42%, $p < 0.00$), concomitant fever (58% vs 15%, $p < 0.00$), pyramidal tract signs (69% vs 14%, $p < 0.00$), cerebellar signs (58% vs 19%, $p < 0.00$), brainstem signs (31% vs 12%, $p = 0.03$), seizures (33% vs 6%, $p < 0.00$) and extrapyramidal signs (17% vs 0%, $p < 0.00$). Clinical or radiological evidence of transverse myelopathy was present in 14/36 (39%) ADEM patients and 17/52 (33%) CIS patients (ns). Sensory symptoms were less common in ADEM patients compared to CIS patients (5% vs 33%, $p = 0.01$). Although 44% of ADEM patients presented in winter (June–August), there was no significant difference in season of presentation.

Cerebrospinal fluid (CSF) was analysed on 32/36 patients with ADEM and in 31/52 with CIS. ADEM patients had higher mean polymorphonucleocyte (nine vs one, $p = 0.02$), mononucleocyte (22 vs nine, $p = 0.02$), and protein level (0.38 vs 0.33, $p = 0.14$) compared to CIS patients. Oligoclonal bands (OCB) were analysed in 15 ADEM patients and 25 CIS patients using isoelectric focusing. Intrathecal OCB were found in no ADEM patients and only two CIS patients (ns).

Follow-up diagnosis comparison: MS vs non-MS

The mean follow-up of the total cohort was 5.2 years (median 4.7 years, range 1–13.9 years). Thirteen (13/88, 15%) patients had clinically definite MS (CDMS) after a mean follow-up of 5.2 years (median 4.7 years, range one to 12.4 years). Seventy-five (75/88) patients had non-MS after a mean follow-up of 5.2 years (median 4.7 years, range one to 13.9 years).

We compared our MS risk to those published from cohorts internationally, and this is shown in Table 2 in order of geographical latitude, although it should be noted that many of the studies were multicentre, therefore the latitude is an approximation.

MS cohort

Three of 36 (8%) ADEM and 10/52 (19%) CIS patients had a follow-up diagnosis of MS. All three ADEM patients diagnosed with MS at follow-up had cerebellar signs. The presenting phenotype of the 10/52 (19%) CIS patients with CDMS were as follows: four had ON, three had TM, two had paraesthesia, and one patient had both paraesthesia and internuclear ophthalmoplegia.

The mean time from first ADS to MS diagnosis (second clinical event) was 2.2 years (median 1.0 years, range 0.3 to eight years). The cumulative percentage of patients fulfilling MS diagnosis is shown in Figure 2. More than 70% of patients had their MS defining event within two years (Figure 2). In the 13 MS patients, there were a total of 37 relapses (mean 2.9, median 2.0, range one to 10) and the mean annualised relapse rate was 1.04.

Therapies that were reported at time of follow-up were as follows; β-interferon (n = five), fingolimod (n = one), natulizamab (n = one), mycophenolate (n = one), 'alternative therapy' (n = one) and unknown (n = four).

In the non-MS group ($n = 75$) there was one patient who had neuromyelitis spectrum disorder (NMOSD) and four

Table 2. Risk of MS after a first episode of CNS demyelination according to country of residence. Studies are presented in descending order of latitude.

Country (latitude)	Consensus definitions used	Cohort size (*n*)	Upper age limit (years)	Population base	FU period	% Risk of MS	Source
Netherlands 52'22 N	Yes	86	18.0	Multi-centre	4 years	23%	Ketelslegers et al., *J Neurol* 2012[13]
UK 51'32 N	Yes	40	16.0	Quaternary	2.2 years	35%	Dale and Pillai, *DMCN* 2007[15]
France 48'48 N	No	296	16.0	Multi-centre	2.9 years	57%	Mikaeloff et al., *J Paediatr*, 2004[7]
Canada 43'40 N	Yes	302	18.0	Multi-centre	3.1 years	21%	Banwell et al., *Lancet Neurology* 2011[5]
USA 37'47N	Yes	81	18.5	Multi-centre	3.3 years	35%	Langer-Gould et al., *Neurology* 2011[14]
Australia 34'0S	Yes	88	16.0	Single tertiary	5.2 years	15%	This study

MS: multiple sclerosis; CNS: central nervous system; FU: follow-up; UK: United Kingdom; USA: United States of America.

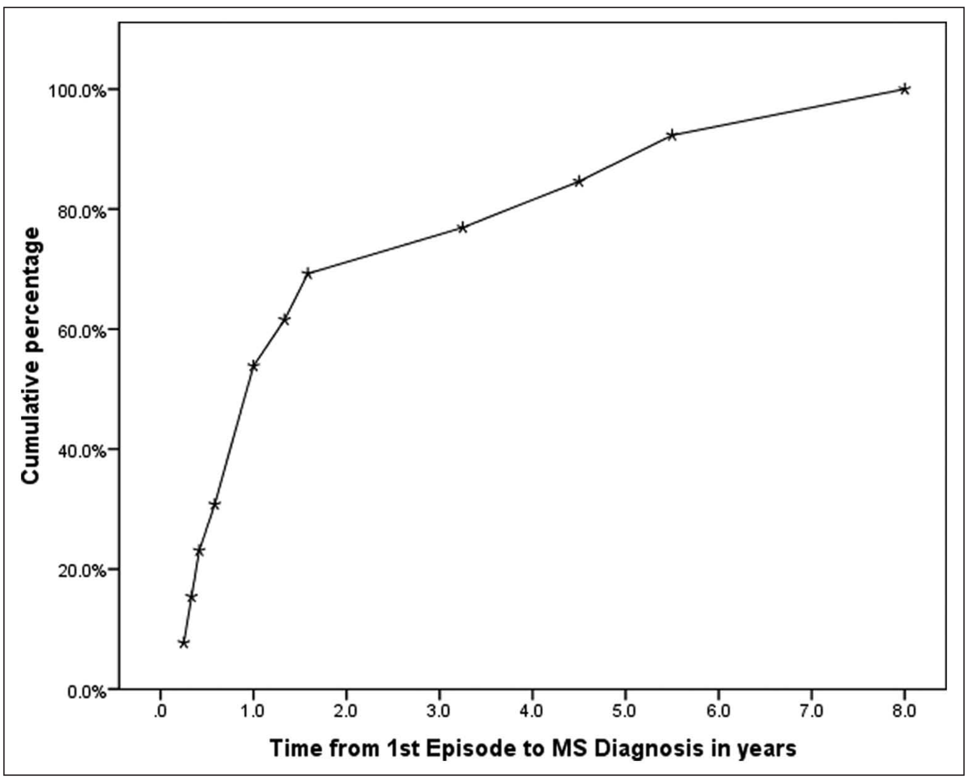

Figure 2. Cumulative percentage of patients diagnosed with clinically definite MS (CDMS) as a function of time in years.

with chronic inflammatory optic neuropathy (CRION), but the remaining 70 patients had a monophasic course.

Comparing the MS and non-MS groups, six (six of 13, 46%) MS patients were female, which was not significantly different from those with non-MS 37/75 (49%). The mean age of first ADS episode in patients with MS (10.4 years, range 2.5 to 14.9 years) was not significantly different from those with non-MS (8.1 years, range 1.3 to 15.4 years).

The first episode clinical findings in patients with a follow-up diagnosis of MS and non-MS were compared using univariate analysis and are presented in Table 3. Cerebellar signs at presentation were associated with an increased risk of MS (HR 4.31 (CI 1.35–13.74, $p = 0.01$)) and a preceding infection was associated with a reduced risk (HR 0.23 (CI 0.07–0.75, $p = 0.01$)).

There was no significant difference between the CSF polymorphs, lymphocytes, or protein between patients with MS and non-MS. OCB analysis was performed in four MS patients and 36 non-MS patients; OCB was found in one patient with MS and one with non-MS (ns).

MRI analysis

The univariate analysis comparing the baseline MRI brain lesions in patients with MS and non-MS is shown in Table 4.

Table 3. Univariate analysis results of clinical characteristics at presentation that were associated with a diagnosis of MS vs non-MS. A value higher than 1 suggests increased risk, and less than 1 suggests reduced risk.

CHARACTERISTIC		Univariate analysis	*p* value
Sex	**Female**	**1.70 (0.55–5.19)**	0.76
Season presenting	**Spring**	**0.62 (0.19–2.02)**	0.43
	Summer	**0.67 (0.54–6.24)**	0.67
	Autumn	**0.75 (0.22–2.94)**	0.75
	Winter	**0.56 (0.44–4.62)**	0.56
Preceding infection		0.23 (0.07–0.75)	0.01[a]
Fever present		**0.56 (0.15–2.02)**	0.37
Encephalopathy		**0.43 (0.12–1.57)**	0.20
Pyramidal signs present		**0.04 (0.00–12.25)**	0.28
Transverse myelitis		**1.15 (0.32–4.20)**	0.83
Sensory disturbance		**1.64 (0.45–5.96)**	0.45
Cerebellar signs		4.31 (1.35–13.74)	0.01[a]
Brainstem signs		**1.32 (0.36–4.81)**	0.67
Bulbar weakness		**0.91 (0.12–7.10)**	0.93
Optic neuritis		**0.87 (0.27–2.86)**	0.82
Urinary and/or faecal incontinence		**0.30 (0.04–2.30)**	0.25
Seizures		**0.91 (0.20–4.13)**	0.91
Extrapyramidal signs		**0.04 (0.00–216.23)**	0.47
Peripheral neuropathy		**0.05 (0.00–1.69)**	0.05
First episode diagnosis CIS		**2.22 (0.61–8.10)**	0.23

MS: multiple sclerosis; CIS: clinically isolated syndrome; [a]statistically significant findings that were applied to multivariate analysis with significant radiological characteristics.

When we co-analysed the significant MRI characteristics (univariate analysis) with the two significant clinical characteristics (univariate analysis) using multivariate analysis, three MRI characteristics were highly predictive of MS as shown in Table 5, and one clinical characteristic was protective of MS, also shown in Table 5. The presence of all three MRI characteristics is highly predictive of a follow-up diagnosis of MS in our cohort (Figure 3).

Table 6 depicts the results from testing the McDonald 2005[18] and 2010[12] MRI MS criteria, as well as the paediatric MRI MS criteria proposed by KIDMUS,[9] Callen[10,19] (two versions) and Verhey.[20] The sensitivity of all MRI criteria excluding the KIDMUS were similar. The specificity was greatest in the McDonald 2010, KIDMUS, Verhey and Callen (ADEM vs MS) criteria.

McDonald 2010 MRI MS criteria

We further analysed our cohort with respect to the different components of the McDonald 2010 criteria in view of the caution of applying this criteria to young children and to those presenting with ADEM.[12] The results of this sub-analysis are shown in Table 7. The McDonald 2010 criteria yielded the best combined sensitivity (91%) and specificity (93%) in our total cohort even with ADEM patients included.

In total 12/13 patients who had CDMS fulfilled the McDonald 2010 criteria. By contrast, only four of 75 non-MS patients fulfilled the McDonald 2010 criteria. One of these non-MS patients who fulfilled the McDonald 2010 criteria on baseline scan was diagnosed with NMO. Of the remaining three patients, the first patient had an initial presentation of ON (CIS) at age 13 years and had one new lesion on MRI eight months after the first event (DIT serial only). He has since been followed for 4.3 years by an adult neurologist experienced in MS (with further negative serial MRI scans) who is of the opinion that this patient does not have MS. The second patient initially presented with a brainstem-CIS at 13.4 years and was subsequently diagnosed with seizures and intracranial hypertension. He fulfilled DIT on a baseline and on a serial scan (16 months after first MRI). After a follow-up of 13.7 years, this patient has had no further clinical or radiological demyelinating events, and is still being treated for raised intracranial hypertension and seizures. Given this atypical course, he has not been given a diagnosis of MS. The last patient initially presented with TM-CIS at 15.0 years of age. She fulfilled DIT on baseline scan only. After 4.8 years she has had no further events. All four of these patients have been categorised as non-MS in our cohort despite fulfilling the McDonald 2010 MRI criteria (baseline and/or serial scan).

MS after initial presentation of CIS-ON

Brain MRI was performed in 23/24 patients with ON. All four ON patients who had MS at follow-up had an abnormal baseline MRI brain scan with lesions outside the optic pathway (four of four). Four of 12 (33%) of ON patients with an

Table 4. Univariate analysis of MRI lesion characteristics for patients with MS (n = 13) compared to those with non-MS (n = 75). Hazard ratio (HR) is shown with reference to MS diagnosis as the outcome of interest; 95% confidence intervals are also shown. The characteristics marked with an a ([a]) were analysed in the multivariate analysis.

Characteristic			
LESIONS SITE	HR	**95.0% CI**	**p value**
Periventricular	144.9	1.09–19218.69	0.05
Deep white matter	15.83	2.05–121.98	<0.00[a]
Juxtacortical	7.92	1.03–60.97	0.05
Corpus callosum	5.78	1.87–17.90	<0.00[a]
Dawsons fingers	19.68	6.16–62.89	<0.00[a]
Internal capsule	2.83	0.96–8.42	0.06
Cortical grey	1.46	0.49–4.36	0.5
Basal ganglia	0.04	0–11.52	0.26
Thalamus	1.07	0.33–3.48	0.91
Brainstem	1.99	0.67–5.97	0.22
Cerebellar	2.79	0.94–8.32	0.07
LESION DISTRIBUTION			
Asymmetrical white lesions	6.9	0.89–53.08	0.06
Symmetrical white lesions	1.34	0.17–10.49	0.78
Asymmetrical grey matter lesions	2.82	0.92–8.65	0.07
Symmetrical grey matter lesion	0.23	0.00–8.70	0.03
Bilateral lesions	42.5	0.38–4714.89	0.12
LESION LOAD (NUMBER)			
T2 lesions < five	1.75	0.63–4.86	0.28
T2 five to nine lesions	0.96	0.45–2.04	0.9
T2 > nine lesions	5.18	1.41–19.03	0.01[a]
Periventricular lesions > two	7.76	2.521–23.87	<0.00[a]
Periventricular lesions > three	7.75	2.55–23.56	<0.00[a]
LESION CHARACTERISTIC			
Solely poorly defined lesions	0.19	0.05–0.71	0.01[a]
Solely well-defined lesions	3.09	0.68–13.98	0.14
Both well- and poorly defined lesions	17.85	5.79–54.95	<0.00[a]
T1 black holes present	3.43	1.12–10.51	0.03[a]
Large lesions > 2 gyri	0.65	0.2–2.13	0.48
Contrast-enhancing lesions (n = 78)	17.31	3.77–79.41	<0.00[a]
Asymp. enhancing and non-enhancing lesions (n = 78)	15.65	4.93–49.72	<0.00[a]

MRI: magnetic resonance imaging; MS: multiple sclerosis; CI: confidence interval.

Table 5. Using multivariate analysis, one clinical feature was protective of MS. Three MRI features were predictors of MS at first episode of CNS demyelination using multivariate analysis.

Characteristic	Hazard ratio (HR)	95.0% Confidence interval (CI)		p value
		Lower	Upper	
Preceding infection	0.16	0.03	0.89	0.04
Corpus callosum lesions	14.33	2.38	86.21	<0.00
Presence of poorly and well-defined lesions	9.97	2.35	42.33`	<0.00
Contrast-enhancing lesions	8.70	1.77	42.79	0.01

MS: multiple sclerosis; MRI: magnetic resonance imaging; CNS: central nervous system.

abnormal brain MRI had CDMS at follow-up (mean follow-up 6.9 years, range 1.3–11.9 years) compared to 0/11 (0%) of ON patients with a normal brain MRI (mean follow-up 6.7 years, range 2.85–11.9 years).

MS after initial presentation of CIS-TM

Brain MRI was performed in 16/17 patients with TM. All three TM patients who had MS at follow-up had an abnormal MRI brain scan at baseline (three of three). Three of

Table 6. Comparative analysis of established adult (McDonald) and proposed paediatric (KIDMUS, Callen, Verhey) neuroimaging criteria for diagnosing MS based on MRI brain scan performed during first episode of CNS demyelination. McDonald 2005 and 2010 criteria were both tested. Callen's two imaging criteria are also represented, the first used in differentiating ADEM from MS[19] and the second for diagnosing paediatric MS.[10] All criteria in this table use baseline scans only.

Accuracy	McDonald 2005 DIS[18a]	McDonald 2010[12b]	KIDMUS[9]	Callen ADEM vs MS[19]	Callen paed MS[10]	Verhey[20]	This study[c]
Sensitivity %	69%	58%	8%	69%	69%	62%	100%
(data)	(9/13)	(7/12)	(1/13)	(9/13)	(9/13)	(8/13)	(13/13)
95% CI	39–89%	29–84%	0–38%	39–90%	39–90%	32–85%	72–100%
Specificity %	68%	95%	100%	85%	66%	84%	77%
(data)	(50/73)	(63/66)	(73/73)	(62/73)	(48/73)	(61/73)	(56/73)
95% CI	56–79%	86–99%	94–100%	74–92%	54–76%	73–91%	65–85%
PPV %	28%	70%	100%	45%	26%	40%	43%
(data)	(9/32)	(7/10)	(1/1)	(9/20)	(9/34)	(8/20)	(13/30)
95% CI	14–47%	35–92%	5–100%	24–68%	14–45%	20–64%	26–62%
NPV %	93%	93%	86%	94%	92%	92%	100%
(data)	(50/54)	(63/68)	(73/85)	(62/66)	(48/52)	(61/66)	(56/56)
95% CI	81–98%	83–97%	76–92%	84–98%	81–98%	82–97%	92–100%

[a]The 2005 McDonald DIT criteria is based on a progress scan done > three months after first demyelinating event and thus was not used in this comparison, which examined the five sets of criteria and their ability to predict MS based on the initial scan from the first demyelinating event.
[b]As per McDonald 2010 criteria, we applied the dissemination in time criterion (DIT) to the baseline scan (presence of asymptomatic gadolinium-enhancing and non-enhancing lesions) to test the ability of this criteria to predict MS based on the initial scan alone.
[c]One of three: lesion in the corpus callosum, contrast-enhancing lesions, or both the presence of both well- and poorly defined lesions.
MS: multiple sclerosis; MRI: magnetic resonance imaging; CNS: central nervous system; CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value; DIS: dissemination in space; DIT: dissemination in time; ADEM: acute disseminated encephalomyelitis.

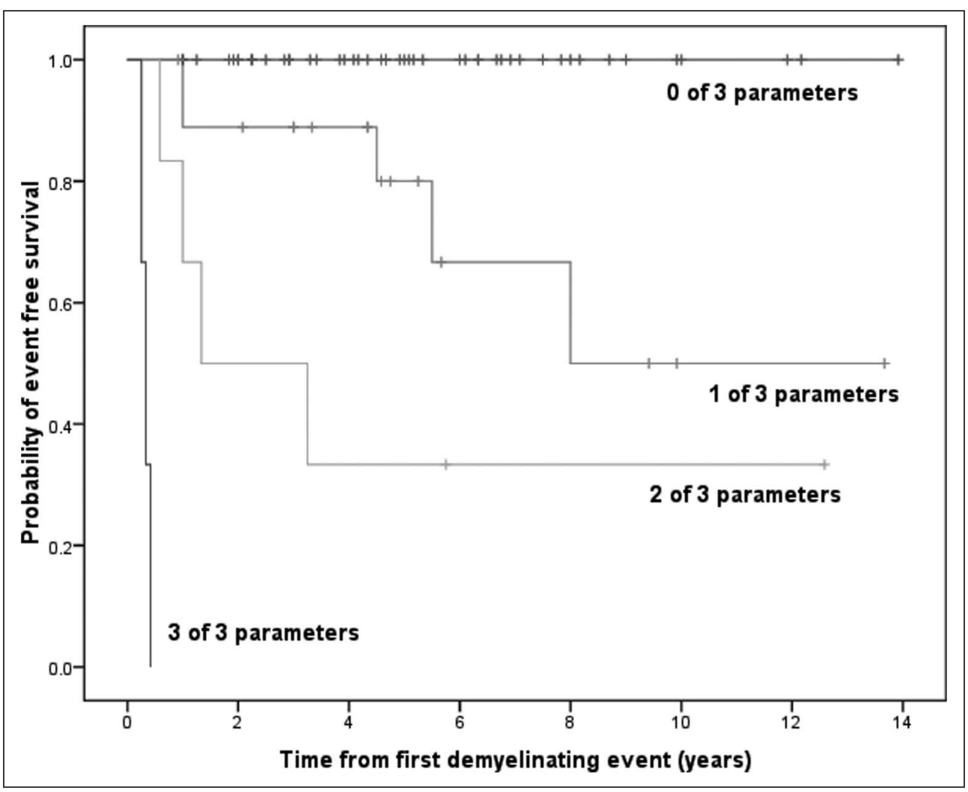

Figure 3. Kaplan-Meier graph depicting the risk of developing multiple sclerosis (MS) if children have 0, one, two, or three of the magnetic resonance imaging (MRI) characteristics that were statistically significant on the multivariate analysis as described in Table 5. Patients with either one of three, two of three, or three of three of these parameters are depicted on the curves as labelled.

Table 7. Analysis and comparison of the McDonald 2010 criteria subdivided into dissemination in space (DIS) and the two components of the dissemination in time criteria (DIT). 'Baseline scan' refers to the first MRI performed at the first demyelinating event. 'DIT baseline' scan refers to the presence of asymptomatic gadolinium-enhancing and non-enhancing lesions on the MRI of patients given contrast. 'DIT any' refers to either of the DIT criterion being present on the baseline MRI and/or a serial MRI brain scan. The criteria were tested only on patients who had the appropriate scans performed for analysis.

Factors considered	Total MRI Cohort				CIS MRI Cohort only			
	DIS (*n* = 86)	DIT baseline (*n* = 78)	DIS plus DIT baseline (*n* = 78)	DIS plus DIT any (*n* = 51)	DIS baseline (*n* = 50)	DIT baseline (*n* = 44)	DIS plus DIT baseline (*n* = 44)	DIS plus DIT any (*n* = 27)
Sensitivity (95% CI)	92% (62–100)	58% (29–84)	58% (29–84)	91% (57–100)	90% (54–99)	70% (35–92)	70% (35–92)	100% (63–100)
Specificity (95% CI)	44% (32–56)	95% (86–99)	95% (86–99)	93% (79–98)	60% (43–75)	91% (75–98)	91% (75–98)	83% (58–96)
Positive predictive value (95% CI)	23% (13–37)	70% (35–92)	70% (35–92)	77% (46–94)	36% (19–57)	70% (35–92)	70% (35–92)	75% (43–93)
Negative predictive value (95% CI)	97% (82–100)	93% (83–97)	93% (83–97)	97% (85–100)	96% (78–100)	91% (75–98)	91% (75–98)	100% (75–100)

MRI: magnetic resonance imaging; CI: confidence interval.

nine (33%) of TM patients with an abnormal baseline MRI brain had CDMS at follow-up (mean 3.7 years, range one to 10.6 years), compared to 0/7 (0%) of TM patients with a normal baseline MRI brain at follow-up (mean 6.1 years, range three to 12.2 years).

Discussion

In our retrospective review of 88 children presenting to a tertiary children's hospital with a first ADS, the majority of children in our cohort presented with CIS (*n* = 52, 59%) as opposed to ADEM (*n* = 36, 41%). The proportion of our cohort whose initial presentation was ADEM is high (41%) compared with Canada (22%),[21] the United Kingdom (UK) (30%),[15] The Netherlands (24%)[13] and France (29%).[7] The reason for this higher number of ADEM presentations is unclear, although because of detailed cross-checking of searches, we are confident we captured all patients with CNS demyelination seen at our hospital.

The presentations of ADEM in our cohort were similar to those previously described. Patients with ADEM were younger, had a history of a preceding infection, pyramidal tract signs, seizures and brainstem signs compared to those with CIS.[6–8,22] Children with CIS were more likely to present with ON and TM as would be expected, and as previously described.[13,21,23,24]

After a mean follow-up of 5.2 years, the risk of CDMS in NSW children is 15%, which is low in comparison with the reported risk in previous cohorts (21%–57%).[5,7,13–15] Direct comparison of risk rate with previously published studies has to be made with caution for the following reasons. Firstly, some studies included patients up to 18.5 years of age, which would influence the MS risk as MS risk increases with increasing age.[13,25] Secondly, our study has reported clinically definite MS only, whereas others have included radiological relapse as per McDonald criteria.[5] Although we acknowledge the McDonald radiological criteria is standard in adult neurology and is likely to be introduced into paediatric demyelination criteria soon, it is not established in the diagnosis of MS in children at present.[1] Thirdly, some studies described single-centre cohorts, whereas others were multi-centre cohorts, which could affect recruitment. And finally, whereas some recent studies are prospective, most studies are retrospective follow-up studies (including this study), which is methodologically weaker.

When we compare the CDMS and non-MS patients, there were two clinical differentiating characteristics on univariate analysis. Having a preceding infection was protective of MS, and cerebellar signs were found to be predictive of MS in our cohort; however, using multivariate analysis only 'preceding infection' was found to discriminate between MS and non-MS.

The risk of CDMS after ADEM in our cohort was 8% (three of 36). This is lower than previously reported rates of between 10% and 29% in studies prior to the 2007 consensus,[6–8] but comparable with the rates of 0% to 17% in more recent studies complying with the 2007 consensus.[5,14,15,26] Therefore children in NSW, Australia, are at a lower risk of developing MS if their first ADS is ADEM, as would be expected.

The risk of CDMS after CIS in our cohort was 19% (10/52) despite a mean follow-up of 5.8 years (range one to 11.9 years), which is low compared to the reported rates of between 33% and 46% from paediatric studies internationally.[14,15,26]

The risk of CDMS after CIS-ON ($n = 24$) was 17% (four of 24). This is comparable to two recent studies reporting rates of between 17%[27] and 19%,[28] but much lower than the 36% reported in a Canadian study, although this study included patients with ON in the context of a polysymptomatic presentation.[4]

The risk of CDMS after CIS-TM was 18% (three of 17). This is similar to the 13% reported in a Canadian study[29] but high compared to the 3% reported in a recent Dutch study,[13] which may be partly because our study diagnosed TM using clinical criteria as an isolated clinical spinal cord syndrome, whereas the Dutch study classified patients with clinical TM plus asymptomatic abnormal brain MRI as having a polyfocal ADS.[13]

We performed a multivariate analysis of both clinical and radiological findings comparing the CDMS and non-MS patients in our cohort. There were three MRI characteristics that were most significant; the strongest predictor was the presence of lesions in the corpus callosum and this characteristic has been proposed in two previous paediatric MS MRI criteria.[9,20]

Having a combination of well- and poorly defined lesions was our second most common predictor of MS. This is biologically logical as MS is a chronic disorder often with asymptomatic periods prior to the first ADS, and there are typically active and inactive lesions in the CNS. Previously the KIDMUS group proposed that the 'sole presence of well-defined lesions' was typical of MS (as opposed to ADEM),[9] and Callen et al. similarly suggested that 'lesion distribution pattern that is not diffuse bilateral' was also typical of MS.[10] Therefore based on these two studies, as well as a number of others that categorise describe the MRI lesion characteristics of ADEM as opposed to MS patients,[6,30] it is commonly accepted that MS patients are more likely to have well-defined lesions as opposed to the lesions commonly seen in ADEM, which are 'diffuse' or poorly defined.

The third highest predictor of MS was having contrast-enhancing lesions. This criterion has formed part of the adult MS MRI criteria for the last decade,[31] and although it has not previously been proposed as a criterion for paediatric MS, Verhey et al. reported this finding as being hazardous to MS with HR 11.88 (CI 6.47–21.82).[20] It has been argued that contrast-enhancing lesions can be found in any patient with an acute CNS demyelinating event because of a breakdown in the blood-brain barrier secondary to inflammation.[20] However, our study suggests that contrast enhancement is more common in MS compared to non-MS. We believe that the second and third findings are similar to the McDonald 2010 criteria[12] – having 'a combination of asymptomatic contrast-enhancing and non-enhancing lesions', which implies having both active and inactive lesions.

Asymptomatic MRI brain lesions during CIS-ON appears to increase the risk of CDMS,[4,27,28] and we have further reproduced that association in this study ($p < 0.05$).

Likewise asymptomatic lesions in our CIS-TM patients were associated with an increased risk of CDMS. This concept of 'asymptomatic' lesions is an established theme in adult MS according to the McDonald 2010 criteria[12] and an emerging theme in paediatric MS risk stratification.

When we tested the proposed paediatric and established adult MRI MS criteria on the baseline scans, the Callen ADEM vs MS criteria[19] had the best combined sensitivity (69%) and specificity (85%) for the cohort as a whole. However, when we applied the McDonald 2010 MRI MS criteria to presentations of CIS alone as recommended by Polman et al. (baseline scans only),[12] the McDonald 2010 outperformed the Callen criteria with a sensitivity of 70% and specificity of 91% applied to a baseline scan.

The McDonald 2010 criteria when applied in its entirety (baseline and serial MRI scan) have a high sensitivity (91%) and specificity (93%) in our total cohort (including ADEM patients). These results confirm the findings of a Canadian study that found the McDonald 2010 MRI MS criteria to have a sensitivity of 100% and a specificity of 86% when applied to a paediatric cohort presenting with an ADS.[32] However, we found it difficult to apply the McDonald 2010 DIT criterion, 'the presence of asymptomatic contrast enhancing and non-enhancing lesions'[12] to children presenting with ADEM because of the difficulty in deciding if a lesion is asymptomatic in the context of encephalopathy. Polman et al.[12] warned that the application of the McDonald 2010 MRI MS criteria to the baseline MRIs of children presenting with ADEM would be inappropriate because the MRIs of these children often contain a combination of contrast-enhancing and non-enhancing lesions.

In conclusion, this is the first follow-up study of CNS demyelination to examine the risk of MS in Australian children. Despite the long follow-up, the rate of MS is the lowest yet reported in paediatric demyelination. It would be useful to perform a similar study in multiple Australian centres to examine the 'latitude hypothesis', as has been conducted in adults. Furthermore, we confirmed using multivariate analysis that radiological features are more predictive of MS than clinical features, and our data support the use of McDonald 2010 radiological criteria, particularly when applied to children with CIS.

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Declaration of conflicting interests

None declared.

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