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Conversion of clinically isolated syndrome to multiple sclerosis: a prospective multi-center study in Eastern India

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Abstract

Background: In White populations more than 60% of clinically isolated syndrome (CIS) convert to multiple sclerosis (MS) on a long-term follow-up; several predictors for conversion have been identified.
Objective: This study aimed to determine the conversion rate and the predictors of conversion from CIS to MS (McDonald 2010) among Indians. The other objective was to evaluate the diagnostic accuracy of the new McDonald 2017 criteria in prediction of a second clinical attack.
Methods: Clinical and demographic data of CIS cohorts were collected. Baseline investigations included cerebrospinal magnetic resonance imaging (MRI) with contrast and cerebrospinal fluid (CSF) testing for oligoclonal band (OCB). Follow-up clinical and MRI examinations were performed annually for at least 24 months.
Results: Of the 82 subjects (age range 15–58 years), 36 (43.9%) converted to MS; 31/82 (37.8%) converted in 24 months. The predictors for conversion were earlier age of onset, CSF-OCB, cerebral MRI T2 lesion count, and periventricular and juxtacortical location of lesions. Twenty-two (26.83%) CIS fulfilled the McDonald MS 2017 criteria at baseline.
Conclusion: In this first prospective study of CIS in India, the risk factors for conversion are similar but the conversion rate to MS is lower than that in the western nations.

Keywords: Clinically isolated syndrome, McDonald criteria, cerebral MRI, oligoclonal band, multiple sclerosis, Barkhof's criteria, India

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory, demyelinating disorder of the central nervous system (CNS). The disease develops in genetically susceptible population as a consequence of environmental exposure. In approximately 85% of individuals the disease starts with a single clinical event, the "clinically isolated syndrome" (CIS).[1,2] When a second clinical demyelinating event affecting a different CNS site occurs at a later date, the diagnosis becomes clinically definite MS (CDMS).[3] Prospective studies in western countries have demonstrated that 60–70% of CIS patients develop CDMS in the next 20 years.[1,4] There is a wide variability in the data regarding the time to conversion from CIS to MS in different studies. In some of the studies the conversion time was short with median value of 11 months,[5,6] and 85–90% converted in 2–3 years.[5,7,8] On the other hand, there are studies that reported longer conversion time. Brownlee et al. observed that with a mean follow-up of more than 5 years only 45% of CIS patients transformed to CDMS.[9] Others reported that after 2-year follow-up, 10–50% converted to MS.[10,11]

CIS is a single demyelinating event and one cannot be absolutely certain about its conversion to MS. Treatment with disease-modifying drug (DMD) in a non-converting CIS is debatable and, particularly in resource-constrained nations, this imposes huge economic burden to the individual and to the society. On the other hand, treatment with DMD for MS

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gives the best result if instituted early, soon after the first clinical event. So determination of the predictors for conversion is essential in a case of CIS. Several studies have attempted to determine the predictors for conversion from CIS to MS.[12–15] The principal predictors identified in western literature were (i) number of T2 lesions in baseline cranial magnetic resonance imaging (MRI) scan, (ii) younger age at CIS onset, and (iii) oligoclonal band (OCB) in cerebrospinal fluid (CSF).

MS is a disease occurring predominantly among people of Northern European ancestry where the prevalence is over 100 per 100,000. The disease is rare in India with an estimated prevalence of 5–20 per 100,000.[16] A recent epidemiological survey carried out in South India revealed that the prevalence of MS is around 8/100,000.[17] It is possible that the natural history of MS among Indians is quite different from that in Europeans.

Objectives

1. To determine the rate of conversion from CIS to MS and explore the clinical and the investigational variables that predict the risk of conversion from CIS to MS in this prospective multi-center study in Eastern India. In this paper, MS means fulfilment of McDonald 2010 MS diagnostic criteria.[18]
2. To evaluate the diagnostic accuracy of the newly introduced McDonald 2017 criteria in the prediction of second clinical attack in cases of CIS.

Materials and methods

Kolkata, the capital of the state of West Bengal and one of the principal cities of India, is located in the eastern part of the country. The current population of the city is around 5.2 million within its municipal limits. The majority of the population are Bengali Hindus, although people from all the Indian communities reside in this cosmopolitan city. The CIS cohort was recruited from seven neurological centers in Kolkata during the period January 2009 to April 2016, and the prospective study continued till August 15, 2018. The study was approved by the Institutional Ethics Committee of National Neurosciences Centre Calcutta.

Inclusion criteria were as follows:

1. Subjects of either sex, between ages 15 to 60 years, diagnosed as CIS.
2. Availability of MRI (1.5 T, standard protocol) scans within 2 months of onset.
3. Subjects willing to provide written informed consent to participate in the study as per plan.

Exclusion criteria included the following:

1. Clinical event attributable to other diseases (i.e., infectious, neoplastic, congenital, metabolic, or vascular disease).[19]
2. Neuromyelitis optica (NMO), or a history of a progressive disease course from onset (i.e., primary progressive MS).
3. Already diagnosed cases of MS.

The standard diagnostic criteria, i.e., those for CIS,[1] MS (McDonald 2010),[18] and MS (McDonald 2017),[20] were followed in this study.

Baseline study

Careful history and comprehensive physical examination were undertaken in all the CIS cohorts. General information included age, gender, occupation, and monthly family income. Expanded Disability Status Scale (EDSS) was used to express the level of disability at baseline.[21] Approximately 6 months later after the clinical recovery, EDSS was again performed. All the subjects were thoroughly investigated within 1 month of symptom onset, prior to the administration of pulse methylprednisolone therapy. Appropriate investigations were carried out to exclude the "CIS mimics." Serum aquaporin-4 IgG (AQP4-IgG) and visual evoked studies were done. Routine analysis of CSF was performed and presence of OCB determined by the method of isoelectric focusing. In all the cases, cerebral and spinal cord MRI with contrast (1.5 T) was undertaken as per protocol and the data recorded on a structured format (Appendix 1).[22]

Diagnosis and follow-up

The CIS cohort was followed up on an annual basis when a thorough clinical examination and MRI as per protocol were performed. If a subject developed a new clinical event in between, he or she was examined as soon as possible and MRI carried out. The subjects were followed up for at least 24 months. However, in those who converted to MS before 24 months, the follow-up with serial neuroimaging ended there. None of our cohort participants received DMD.

Potential predictive factors for conversion to MS

The putative predictive factors recorded in the baseline data included gender, age, family income, presenting clinical features, OCB in CSF, and cerebrospinal MRI findings (number and site of T2

hyper-intense lesions, presence of contrast enhanced lesions, fulfillment of Barkhof criteria).[8,23]

Statistical methods

Data have been summarized by routine descriptive statistics, namely mean and SD for numerical variables that are normally distributed, median and interquartile range (IQR) for skewed numerical variables, and counts and percentages for categorical variables. Ninety-five percent confidence intervals (95% CI) have been presented where deemed relevant. Numerical variables were compared between groups by Student's independent samples t test, if normally distributed, or by Mann–Whitney U test, if otherwise. Fisher's exact test or Pearson's Chi-square test were employed for intergroup comparison of categorical variables. Statistical significance was inferred for $p < 0.05$. Odds ratios (ORs) with 95% CI were calculated for putative predictors through univariate analysis. Predictors showing statistically significant difference between converters and non-converters were then entered simultaneously into a logistic regression (LR) model with conversion to MS as the binary outcome. MedCalc version 15.8 (Mariakerke, Belgium) software was used for statistical analysis.

Application of McDonald 2017 criteria to CIS cohorts

All the studied cases were clinically followed up for over 24 months. The newly introduced McDonald 2017 criteria were retrospectively applied to the CIS cohort to evaluate their diagnostic accuracy in prediction of second clinical attack in cases of CIS. True positives (TP) are those who fulfill diagnostic criteria of MS McDonald 2017 at baseline and have second attack on follow-up, whereas false positives (FP) when they do not. False negatives (FN) are defined when baseline McDonald 2017 negative cases later have second attack; on the other hand true negatives (TN) are those who do not. The following values are calculated with 95% confidence intervals:[24]

$$\text{Sensitivity}: [\text{TP}/(\text{TP}+\text{FN})] \times 100$$

$$\text{Specificity}: [\text{TN}/(\text{TN}+\text{FP})] \times 100$$

$$\text{Positive predictive value (PPV)}: [\text{TP}/(\text{TP}+\text{FP})] \times 100$$

$$\text{Negative predictive value (NPV)}: [\text{TN}/(\text{TN}+\text{FN})] \times 100$$

$$\text{Accuracy}: [(\text{TP}+\text{TN})/(\text{TP}+\text{TN}+\text{FP}+\text{FN})] \times 100$$

Results

One hundred and five consecutive CIS patients were recruited in the study. Twelve were lost to follow-up and 11 declined to undergo serial neuroimaging studies. Ultimately, 82 subjects (age range 15–58 years; mean ± SD, 34.9 ± 10.66) fulfilled the requirements and completed the study. None of these cases developed a different disorder apart from MS on follow-up. There were 36 males and 46 females. Of the 82 CIS cohorts, 36 (43.9%) converted to MS. Twenty-four (29.3%) had their second clinical event; the rest satisfied the diagnostic criteria based upon the radiological parameters. The median time to conversion was 12 months. The median follow-up period for MS non-converter was 29.5 months (IQR 24–38) with range 24–84 months. The mean age of the 36 CIS converters was lower than that of the 46 non-converters ($p = 0.001$) but there was no difference in the gender distribution. Baseline presentations of CIS converters included optic neuritis in seven, myelitis in 13, infratentorial demyelination in 14, and hemispheric demyelination in three. Incidentally, 31 (37.80%) CIS converted to MS in 24 months; 19/31 had second clinical attack.

All apart from one of the 36 (97.2%) CIS converters had T2-weighted cerebral lesions at baseline. On the other hand, only six (13.04%) out of 46 CIS non-converters had cerebral T2 lesions. The spinal T2 lesions of MS converters involved less than two vertebrae (short segment). Seventy-two of the 82 cases had CSF-OCB estimation by isoelectric focusing. Table 1 presents a statistical comparison of the baseline features of the converters ($n = 36$) versus the non-converters. Table 2 compares the baseline features of those who converted in 24 months ($n = 31$) against the non-converters.

Univariate comparison (Table 1) indicates that presence of T2 lesions in the baseline cerebral MRI is most strongly associated with future conversion to MS. Furthermore, location of T2 lesions in juxtacortical, periventricular, corpus callosum and infratentorial regions in baseline cerebral MRI are strong predictors of conversion, as is the presence of CSF-OCB. Presence of optic nerve lesion, however, appears to reduce risk of conversion. Subgroup analysis with those who converted in 24 months (Table 2) indicates that the same above mentioned factors apply as predictors.

The variables included in the LR analysis were age, total lesion count (from MRI brain; i.e. not

Table 1. Comparison of baseline profile of converters versus non-converters in the CIS cohort.

Parameter	Converters ($n = 36$)	Non-converters ($n = 46$)	p value[a]
Age (years)			
Range	15.0–51.0	18.0–58.0	0.001
Mean ± SD	30.7 ± 9.21	38.2 ± 10.63	
Gender distribution			
Male/female	13 (36.11%)/ 23 (63.89%)	23 (50.00%)/ 23 (50.00%)	0.264
Average monthly family income (INR)			
<10,000	8 (22.22%)	17 (36.96%)	0.020
10,000–30,000	13 (36.11%)	13 (28.26%)	
30,000–60,000	6 (16.67%)	14 (30.43%)	
>60,000	9 (25.00%)	2 (4.35%)	
Duration of follow-up (months)			
Range	1.0–74.0	24.0–84.0	<0.001
Mean ± SD	17.3 ± 16.95	34.2 ± 14.14	
Median (IQR)	12.0 (5.5–24.0)	29.5 (24.0–38.0)	
EDSS Score			
Range	1.5–8.5	2.5–8.5	0.598
Mean ± SD	4.6 ± 2.27	4.7 ± 2.38	
Median (IQR)	3.5 (3.0–7.0)	3.0 (3.0–8.0)	
CSF oligoclonal band[b]			
Present in	11 (30.56) Not done in 6; absent in 19	4 (8.70%) Not done in 4; absent in 38	0.012
MRI brain lesions			
Present in	35 (97.22%)	6 (13.04%)	<0.001
Median (IQR)	12.0 (2.0–22.0)	0.0 (0.0–0.0)	<0.001
Juxtacortical lesions			
Present in	24 (66.67%)	3 (6.52%)	<0.001
Median (IQR)	4.0 (0.0–10.0)	0.0 (0.0–0.0)	<0.001
Periventricular lesions			
Present in	26 (72.22%)	2 (4.35%)	<0.001
Median (IQR)	2.5 (0.5–6.0)	0.0 (0.0–0.0)	<0.001
Corpus callosum lesions			
Present in	11 (30.56%)	0	<0.001
Median (IQR)	0.0 (0.0–1.0)	—	0.018
Infratentorial lesions			
Present in	17 (47.22)	1 (2.17)	<0.001
Median (IQR)	0.0 (0.0–2.0)	0.0 (0.0–0.0)	<0.001
Optic nerve lesions			
Present in	7 (19.44%)	26 (56.52%)	<0.001
Spinal cord lesions			
Present in	13 (36.11%)	18 (39.13%)	0.822
Gadolinium enhanced brain lesions			
Present in	6 (16.67%)	2 (4.35%)	0.130

CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; INR = Indian rupees; IQR = interquartile range; MRI = magnetic resonance imaging.

[a]p value in the last column is from Student's unpaired t test for age, Chi-square test for income distribution, Fisher's exact test for other categorical variables and Mann-Whitney U test for other comparisons.

[b]CSF oligoclonal band data was not available for 10 cases.

Table 2. Comparison of baseline profile of converters (in 24 months) versus non-converters in the CIS cohort.

Parameter	Converters in 24 months ($n = 31$)	Non-converters ($n = 46$)	p value[a]
Age (years)			
Range	15.0–51.0	18.0–58.0	0.001
Mean ± SD	29.9 ± 9.36	38.2 ± 10.63	
Gender distribution			
Male/female	12 (38.71%)/ 19 (61.29%)	23 (50.00%)/ 23 (50.00%)	0.360
Average monthly family income (INR)			
<10,000	6 (19.35%)	17 (36.96%)	0.034
10,000–30,000	12 (38.71%)	13 (28.26%)	
30,000–60,000	6 (19.35%)	14 (30.43%)	
>60,000	7 (22.59%)	2 (4.35%)	
Duration of follow-up (months)			
Range	1.0–34.0	24.0–84.0	<0.001
Mean ± SD	12.1 ± 8.59	34.2 ± 14.14	
Median (IQR)	11.0 (5.0–20.0)	29.5 (24.0–38.0)	
EDSS Score			
Range	1.5–8.5	2.5–8.5	0.537
Mean ± SD	4.6 ± 2.23	4.7 ± 2.38	
Median (IQR)	3.5 (2.5–7.0)	3.0 (3.0–8.0)	
CSF oligoclonal band at baseline[b]			
Present in	9 (29.03%) Not done in 6; absent in 16	4 (8.70%) Not done in 4; absent in 38	0.013
MR brain lesions			
Present in	31 (100.0%)	6 (13.04%)	<0.001
Median (IQR)	12.0 (1.0–25.0)	0.0 (0.0–0.0)	<0.001
Juxtacortical lesions			
Present in	20 (64.52%)	3 (6.52%)	<0.001
Median (IQR)	4.0 (0.0–10.0)	0.0 (0.0–0.0)	<0.001
Periventricular lesions			
Present in	21 (67.74%)	2 (4.35%)	<0.001
Median (IQR)	2.0 (0.0–6.0)	0.0 (0.0–0.0)	<0.001
Corpus callosum lesions			
Present in	10 (32.26%)	0	<0.001
Median (IQR)	0.0 (0.0–0.1)	—	0.017
Infratentorial lesions			
Present in	14 (45.16%)	1 (2.17%)	<0.001
Median (IQR)	0.0 (0.0–0.2)	0.0 (0.0–0.0)	0.002
Optic nerve lesions			
Present in	6 (19.35%)	26 (56.52%)	0.002
Spinal cord lesions			
Present in	12 (38.71%)	18 (39.13%)	1.000
Gadolinium enhanced brain lesions			
Present in	5 (16.13%)	2 (4.35%)	0.111

CSF = cerebrospinal fluid; EDSS = Expanded Disability Status Scale; INR = Indian rupees; IQR = interquartile range; MRI = magnetic resonance imaging.

[a]p value in the last column is from Student's unpaired t test for age, Chi-square test for income distribution, Fisher's exact test for other categorical variables and Mann–Whitney U test for other comparisons.

[b]CSF oligoclonal band data was not available for 10 cases.

considering optic nerve or spinal cord lesions), juxtacortical lesion count, periventricular lesion count, corpus callosum lesion count, infratentorial lesion count, and presence of CSF-OCB. Gender and gadolinium enhancement of lesions were not included as these showed no statistically significant difference between converters and non-converters upon univariate analysis.

Overall model quality was good with Nagelkerke's R^2 value of 0.7024 (indicating that over 70% of the variability is accounted for by the variables selected). The power of the model's predicted values to discriminate between positive and negative cases was quantified by the area under curve value which, at 0.932, was close to 1 and thus indicated high discriminating power. The cases that convert have been correctly predicted to the extent of 87.80%. The LR indicated that age, total T2 lesion count (from MRI brain), juxtacortical lesion count and periventricular lesion count are significant predictors upon multivariate analysis. The total T2 lesion count is the strongest predictor. Corpus callosum lesion count and infratentorial lesion count do not appear to be statistically significant. Repeating the LR analysis for converters in 24 months, presence of periventricular lesions was the most important predictor for conversion with an adjusted OR of 56.13 (95% CI 1.49–2113.96). However, if the number of lesions at individual sites was factored in rather than presence or absence, then this no longer remains a significant predictor.

Barkhof et al. introduced a set of MRI criteria to predict the conversion from CIS to CDMS.[8,23] We judged the diagnostic performance of each of these criteria, and their combinations, in our CIS cohort of 82 subjects. This is summarized in Table 3. Individually each of these four criteria or combination of any two, combination of any three, or presence of all four showed statistically significant difference between converters and non-converters. However, the best combination of diagnostic indices in our series was offered by Barkhof's criterion 3, i.e. at least one juxtacortical lesion.

Twenty-two cases (26.83%) fulfilled the McDonald 2017 MS criteria at baseline, whereas 56 cases did not. Four CIS cases were undetermined because of lack of CSF-OCB data. Of the 22 McDonald 2017 positives, six and nine had second clinical attacks after 12 and 24 months, respectively. Of the 56 McDonald 2017 negative cases, six and eight had second attacks after 12 and 24 months, respectively. After 1 year, sensitivity of McDonald 2017 was 50% (95% CI, 39.65–62.25%), specificity 75.76% (95% CI, 60.08–94.32%), PPV 27.27% (95% CI, 21.62–33.95%), NPV 89.29% (95% CI, 70.81–111.17%), and accuracy 71.79% (95% CI, 56.93–89.38%). After 2 years, McDonald 2017 showed sensitivity of 52.94% (95% CI, 41.98–65.91%), specificity of 78.69% (95% CI, 62.40–97.97%), PPV of 40.90% (95% CI, 30.43–50.92%), NPV of 85.71% (95% CI, 67.97–106.71%), and accuracy of 73.08% (95% CI, 57.95–90.98%).

Discussion

The conversion rate from CIS to MS after 2 years in our study is lower than that observed in the western

Table 3. Odds ratios and diagnostic indices of the four Barkhof's criteria applied to the present series.[14]

Barkhof's criterion	OR (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
1. Presence of 9 or more T2 brain lesions	27.50 (5.76–131.20)	55.56% (38.10–72.06%)	95.65% (85.16–99.47%)	90.91% (70.84–98.88%)	73.33% (60.34–83.93%)
2. At least one infratentorial lesion	36.00 (4.46–290.57)	44.44% (27.94–61.90%)	97.83% (88.47–99.94%)	94.12% (71.31–99.85%)	69.23% (56.55–80.09%)
3. At least one juxtacortical lesion	44.00 (9.08–213.15)	66.67% (49.03–81.44%)	95.65% (85.16–99.47%)	92.31% (74.87–99.05%)	78.57% (65.56–88.41%)
4. At least 3 periventricular lesions	45.00 (5.58–362.75)	50.00% (32.92–67.08%)	97.83% (88.47–99.94%)	94.74% (73.97–98.87%)	71.43% (58.65–82.11%)
Any 2 positive	25.36 (6.55–98.21)	63.89% (46.22–79.18%)	93.48% (82.10–98.63%)	88.46% (69.85–97.55%)	76.79% (63.58–87.02%)
Any 3 positive	93.00 (5.32–1625.42)	50.00% (32.92–67.08%)	100.00% (92.29–100.0%)	100.00% (81.47–100.0%)	71.87% (59.24–82.40%)
All 4 positive	27.74 (1.54–499.45)	22.22% (10.12–39.15%)	100.00% (92.29–100.0%)	100.00% (63.06–100.0%)	62.16% (50.13–73.19%)

countries, since the 2-year conversion rate in the latter ranges from 55% to 85%.[5,7,10,25–28] However, our rate of conversion is higher than that observed in a study from China,[29] where conversion rate was only 25% after a mean follow-up of 38 months.

White matter lesions in cerebral MRI at baseline in CIS imparts fourfold higher risk of conversion to MS compared to normal MRI, after 2 years of follow-up.[11] In CIS presenting with optic neuritis or myelitis in our study, presence of cerebral T2 lesions in baseline MRI was found to be a predictor of future conversion to MS. Earlier age at CIS onset, total cerebral T2 lesion count and location of T2 lesions in the juxtacortical or in the periventricular regions are strong predictors for conversion in our study. These predictors have also been observed in the western literature.[11,13,14,30,31] It was reported earlier that $\geq$1 periventricular lesion in CIS is significantly more sensitive than $\geq$2 or $\geq$3 for predicting second clinical attack, with only a slight reduction in specificity.[32,33] Incidentally, the median periventricular count was 2.5 in our CIS converters. In case of converters in 24 months, presence of periventricular lesions was the most important predictor for conversion. It is the periventricular involvement per se rather than the lesion count is what matters in conversion. In the western literature,[5,7,25] corpus callosum and infratentorial lesions are also noted to be the important predictors; but that is not revealed in our study upon multivariate analysis. This is probably because our sample size could not provide enough corpus callosal and infratentorial lesions for determining statistical significance. However, regarding the corpus callosal lesions, our observation coincides with some previous reports.[8,33]

Tintore et al. observed that fulfillment of any three combined or all four criteria proposed by Barkhof et al. has high predictive value regarding conversion.[8,13] This observation was also made in our study. We also found OCB in CSF samples to be a predictor for conversion from CIS to MS, but that was not as strong as the MRI T2 lesions. This finding is in keeping with the earlier observations.[13] We also concur with the earlier study that gender did not influence conversion to MS.[13]

There have been several revisions of the McDonald criteria, namely, 2001, 2005, 2010, and of late 2017. With each revision more and more cases of MRI-only MS were identified with absence of further clinical attacks. Our observation concurs with that noted earlier that using McDonald 2010 criteria about one-third of the cases were MRI-only MS.[9] Using McDonald revised 2017 even more such cases of MS with less active disease course can be captured. For occurrence of second attack McDonald revised 2017 showed higher sensitivity but lower specificity compared to McDonald 2010.[24] In an earlier study the sensitivity, specificity, PPV, NPV, and accuracy of McDonald 2017 for second attack after 2 years were 67%, 47%, 31%, 80%, and 52%, respectively.[24] In comparison, our study revealed higher PPV, NPV, and accuracy of McDonald 2017 for second clinical attack after 2 years.

This study has its share of limitations. Our sample is not very large. Accrual of a large CIS cohort is quite a challenge in a country where the disease is rare. Data regarding CSF-OCB was available in 72 of the 82 cases, either because OCB was not tested at all or because the old method of gel electrophoresis was performed in some cases and hence not taken into consideration. Although not definite, serum vitamin D level might play a role in conversion,[12] but this was not investigated in our cases. Our CIS cohorts were recruited till April 2016, hence we followed the McDonald 2010 MS criteria.

In conclusion, we can say that we have conducted a prospective multi-center study of CIS cohorts with serial MRI scan of brain and spine to determine the natural history of this illness and the predictors for conversion to MS in our setting. None of our CIS cohorts received DMD. To our knowledge this is the first prospective study of CIS with serial neuroimaging in India. We propose that all CIS cases should have a comprehensive baseline investigation including cerebrospinal MRI and CSF-OCB testing. In those where predictors for conversion are present, follow-up MRI is required at frequent intervals to capture MS early. Early accurate diagnosis of MS ensures the best timing of DMD administration with maximal benefit.

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Conflict of interests

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Supplemental Material

Supplemental material is available for this article online.

References

1. Miller DH, Chard DT and Ciccarelli O. Clinically isolated syndromes. *Lancet Neurol* 2012; 11: 157–169.
2. Thompson AJ, Baranzini SE, Geurts J, et al. Multiple sclerosis. *Lancet* 2018; 391: 1622–1636.
3. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983; 13: 227–231.
4. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008; 131: 808–817.
5. Çinar BP and Özakbaş S. Prediction of conversion from clinically isolated syndrome to multiple sclerosis according to baseline characteristics: a prospective study. *Noro Psikiyatr Ars* 2018; 55: 15–21.
6. Schwenkenbecher P, Sarikidi A, Bönig L, et al. Clinically isolated syndrome according to McDonald 2010: intrathecal IgG synthesis still predictive for conversion to multiple sclerosis. *Int J Mol Sci* 2017; 18: 1–12.
7. Gaetani L, Fanelli F, Riccucci I, et al. High risk of early conversion to multiple sclerosis in clinically isolated syndromes with dissemination in space at baseline. *J Neurol Sci* 2017; 379: 236–240.
8. Barkhof F, Filippi M, Miller DH, et al. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. *Brain* 1997; 120: 2059–2069.
9. Brownlee WJ, Swanton JK, Altmann DR, et al. Earlier and more frequent diagnosis of multiple sclerosis using the McDonald criteria. *J Neurol Neurosurg Psychiatry* 2015; 86: 584–585.
10. D'Alessandro R, Vignatelli L, Lugaresi A, et al. Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study. *J Neurol* 2013; 260: 1583–1593.
11. Korteweg T, Uitdehaag BM, Knol DL, et al. Interobserver agreement on the radiological criteria of the international panel on the diagnosis of multiple sclerosis. *Eur Radiol* 2007; 17: 67–71.
12. Kuhle J, Disanto G, Dobson R, et al. Conversion from clinically isolated syndrome to multiple sclerosis: a large multicentre study. *Mult Scler* 2015; 21: 1013–1024.
13. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain* 2015; 138: 1863–1874.
14. Alroughani R, Al Hashel J, Thussu A, et al. Predictors of conversion to multiple sclerosis in patients with clinical isolated syndrome using the 2010 revised McDonald criteria. *ISRN Neurol* 2012; 2012: 792192.
15. Spelman T, Meyniel C, Rojas JI, et al. Quantifying risk of early relapse in patients with first demyelinating events: prediction in clinical practice. *Mult Scler* 2017; 23: 1346–1357.
16. Browne P, Chandraratna D, Angood C, et al. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. *Neurology* 2014; 83: 1022–1024.
17. Pandit L and Kundapur R. Prevalence and patterns of demyelinating central nervous system disorders in urban Mangalore, South India. *Mult Scler* 2014; 20: 1651–1653.
18. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* 2011; 69: 292–302.
19. Miller DH, Weinshenker BG, Filippi M, et al. Differential diagnosis of suspected multiple sclerosis: a consensus approach. *Mult Scler* 2008; 14: 1157–1174.
20. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol* 2018; 17: 162–173.
21. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an Expanded Disability Status Scale (EDSS). *Neurology* 1983; 33: 1444–1452.
22. Chong HT, Ramli N, Lee KH, et al. Magnetic resonance imaging of Asians with multiple sclerosis was similar to that of the West. *Can J Neurol Sci* 2006; 33: 95–100.
23. Tintoré M, Rovira A, Martínez MJ, et al. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. *Am J Neuroradiol* 2000; 21: 702–706.
24. van der Vuurst de Vries RM, Mescheriakova JY, Wong YYM, et al. Application of the 2017 revised McDonald criteria for multiple sclerosis to patients with a typical clinically isolated syndrome. *JAMA Neurol* 2018; 75: 1392–1398.
25. Jafari N, Kreft KL, Flach HZ, et al. Callosal lesion predicts future attacks after clinically isolated syndrome. *Neurology* 2009; 73: 1837–1841.
26. Dalton CM, Chard DT, Davies GR, et al. Early development of multiple sclerosis is associated with progressive grey matter atrophy in patients presenting with clinically isolated syndromes. *Brain* 2004; 127: 1101–1107.
27. Young J, Quinn S, Hurrell M, et al. Clinically isolated acute transverse myelitis: prognostic features and incidence. *Mult Scler* 2009; 15: 1295–1302.
28. Eran A, Garcia M, Malouf R, et al. MRI in predicting conversion to multiple sclerosis within 1 year. *Brain Behav* 2018; 8: 1–6.
29. Liu Y, Duan Y, Yu C, et al. Clinical isolated syndrome: a 3-year follow-up study in China. *Clin Neurol Neurosurg* 2011; 113: 658–660.
30. Morrissey SP, Miller DH, Kendall BE, et al. The significance of brain magnetic resonance imaging

abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: a 5-year follow-up study. *Brain* 1993; 116: 135–146.
31. Sailer M, O'Riordan JI and Thompson AJ. Quantitative MRI in patients with clinically isolated syndromes suggestive of demyelination. *Neurology* 1999; 52: 599–606.
32. Brownlee WJ, Miszkiel KA, Altmann DR, et al. Periventricular lesions and MS diagnostic criteria in young adults with typical clinically isolated syndromes. *Mult Scler* 2017; 23: 1031–1034.
33. Arrambide G, Tintore M, Auger C, et al. Lesion topographies in multiple sclerosis: a reappraisal. *Neurology* 2017; 89: 1–6.

Appendix 1 Cerebro-spinal magnetic resonance imaging data of clinically isolated syndrome cohort.

Brain MRI findings	Number of lesions
Total number of lesions	
Cerebral atrophy	Yes / No
Location / Distribution	
Supra-tentorial	
Periventricular	
Deep white matter	
Juxta-cortical	
Corpus callosum	
Infra-tentorial	
Cerebellum	
Midbrain	
Pons	
Medulla	
Appearance of lesions	
Gadolinium enhancement (total no)	
Large (>5 mm)	
Oval / Ovoid	
Confluent	
Perpendicular	
Hypo-intense on T1	
Black hole on T1	
Spinal MRI features	**Number of lesions**
Total number of lesion	
Size (no. of vertebral segments)	
Large lesions (>2 vertebral segments)	Yes / No
Location	
Cervical	
Thoracic	
Cervico-thoracic	
Thoraco-lumbar	
Lumbar or sacral	
Entire spine	
Cross-section appearance	
Central	
Lateral	
Complete cross-section	
T1-weighted images	
Gadolinium enhancement	
Hypo-intense lesions	
Black holes (syrinx-like)	Yes / No
Swelling	Yes / No
Atrophy	Yes / No