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Early predictors of conversion in patients with clinically isolated syndrome: a preliminary Egyptian study

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Abstract

Background: Clinically isolated syndrome (CIS) is the first neurologic episode of multiple sclerosis (MS). Clinical presentation, neurophysiological studies, and magnetic resonance imaging (MRI) are used to predict risk of conversion to MS. There is little information regarding the risk factors of CIS conversion to MS so far in the Egyptian patients. This study aimed to evaluate the predictors of early conversion of the Egyptian patients with CIS to MS.

Methods: A longitudinal prospective study was conducted on 43 Egyptian patients diagnosed as CIS according to the McDonald criteria (2010). The CIS patients underwent clinical assessment of disability using Expanded Disability Status Scale (EDSS), brain imaging by magnetic resonance imaging (MRI), and visual evoked potential (VEP) at baseline and after 1-year follow-up.

Results: Eight patients (19.6%) with CIS converted to clinically definite MS after 1 year. A logistic regression analysis revealed that the CIS patients with initial clinical presentation with optic neuritis and higher MRI brain lesion number were associated with early conversion to MS ($p = 0.003$, $p = 0.002$, respectively). The total MRI brain T₂ lesion number that predicts early conversion to MS was four lesions with sensitivity (100%) and specificity (85.7%).

Conclusions: The patients with CIS that early presented with optic neuritis and higher MRI brain lesion number are at higher risk for conversion to clinically definite MS.

Keywords: Clinically isolated syndrome, Predictors of conversion, Multiple sclerosis

Background

Clinically isolated syndrome (CIS) refers to a monophasic clinical episode with patient-reported symptoms and objective findings reflecting a focal or multifocal inflammatory demyelinating event in the central nervous system (CNS), developing acutely or sub acutely, with a duration of at least 24 h, with or without recovery, and in the absence of fever or infection, similar to a typical multiple sclerosis relapse (attack and exacerbation) but in a patient not known to have multiple sclerosis (Thompson et al. 2018).

A number of risk factors for conversion to clinically definite MS (CDMS) have been studied, including demographic characteristics, MRI lesions, cerebrospinal fluid (CSF) oligoclonal bands, and more recently vitamin D levels (Kuhle et al. 2015).

Many experts recommended the initiation of a disease-modifying therapy after the initial demyelinating event particularly in patients at high risk for subsequent attacks rather than waiting for dissemination in time based on MRI or clinical outcomes (Frohman et al. 2006). The common problem in early treatment of those patients is that it is difficult to predict which individuals are most at risk for early relapse. It was suggested that early relapse is predictive of worse long-term outcomes (Weinshenker et al. 1989; Amato et al. 1999). To our knowledge, the early predictors for conversion to clinically definite MS in patients with CIS have not been well studied before in Egyptian patients. This study aimed to evaluate those potential predictors of increased risk of conversion within the first year.

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Methods

Patients

This study is a longitudinal prospective study conducted on 43 patients diagnosed as clinically isolated syndrome according to McDonald's criteria (2010) (Polman et al. 2011). The CSF oligoclonal bands could not be assessed in our cohort as the McDonald's criteria (2010) was applied in this study. The ethical committee of faculty of medicine, Fayoum University has approved the study. Written informed consent was obtained from all patients and controls. The patients were recruited from Neurology Out-patient Clinic, Fayoum University from July 2014 to July 2015. The age of patients ranged from 19 to 55 years.

Methods

All the patients underwent full medical and neurological examination at baseline and after 1 year follow-up including history taking obtained by interviewing the patients, with special emphasis on the following: clinical presentation of the attacks, number of the attacks, and clinical evaluation of disability using Expanded Disability Status Scale (EDSS), and all the patients with CIS underwent visual evoked potential (VEP) evaluation. P 100 latency and amplitude were measured.

Magnetic resonance imaging of the brain and the cervical spinal cord with contrast was performed at baseline and after 1-year follow-up on 1.5-T superconductive magnetic utilizing spine echo (SE) pulse sequence. The following measures were evaluated manually including the whole T₂ hyperintense lesions number, spinal T₂ lesions number, and the whole gadolinium (Gd)-enhancing lesions number. The patients underwent clinical and radiological re-evaluation for early detection of conversion to clinically definite MS after 1 year follow-up. The main endpoint of this study relies mainly on follow-up of the CIS patients in a prospective way.

The patients were divided into two groups according to conversion to MS

- Group Ia (patients who converted to clinically definite MS)
- Group Ib (patients who did not convert to clinically definite MS)

Statistical analysis

Statistical package for social science (SPSS) version 19 was used for data management and analysis. The Mann-Whitney test was used for comparison of quantitative nonparametric variables including clinical presentation with either optic neuritis or transverse myelitis, percentage of patients with delayed P₁₀₀ or not. Independent Student's *t* test used to compare measures of two independent groups of quantitative parametric data. Logistic regression test was used to assess the association between

categorical-dependent and categorical-independent variables and detection of risk ratio. The level $p < 0.05$ was considered the cut-off value for significance.

Results

Eight patients (19.6%) of the CIS group were converted to clinically definite MS (group Ia) after 1-year follow-up, as regards to their initial clinical presentation, six patients (75%) of the converters (group Ia) presented with optic neuritis and two patients (25%) presented with spinal cord disorder.

It was found that the mean age at onset was lower in CIS patients who converted to CDMS (26.9 ± 4.4) versus (30.3 ± 4.5) with tendency to reach significant level ($p = 0.06$). Although females constituted the majority of cases, there was no significant difference between converters and non-converters on the basis of gender. As regards the clinical presentation, there was no statistically significant difference between the two groups whether they initially presented with optic neuritis or spinal cord disorder as shown in Table 1.

Although the patients that converted to CDMS showed significant higher EDSS as well as delayed P100 latency scores than non-converters after 1-year follow-up, there was no significant difference at baseline between the two groups as illustrated in Tables 1 and 2.

In respect to radiological parameters, it was found that the converters showed higher MRI T₂ lesion number than non-converters (group Ib) at baseline and after 1-year follow-up. However, there was no statistically significant difference in total Gd-enhancing T₁ lesion number between the two groups at baseline as shown in Tables 1 and 2.

Multivariate logistic analysis showed that initial clinical presentation with optic neuritis (OR = 1.3, $p = 0.003$), higher MRI T₂ lesion numbers (OR = 1.6, $p = 0.002$) were independent predictors of CIS conversion to clinically definite MS after 1-year. It was shown that the number of total T₂ lesion that predict early conversion of CIS patients for MS was four supratentorial lesions with sensitivity (100%) and specificity (85.7%) as shown in Fig. 1.

Discussion

Clinically isolated syndrome is a term describing the first neurological episode that could be suggestive of multiple sclerosis. This may create a diagnostic and therapeutic dilemma given the difficulty in predicting who will be converting to CDMS. Clinical presentation in combination with MRI of the brain and CSF analysis can be used in CIS patients to detect the patients who at risk for clinically definite MS (Alroughani et al. 2012). It was found in this study that eight patients (19.6%) of CIS after 1-year follow-up were converted to clinically definite MS in concordance to these results, those of Martignelli et al. (2014) which that stated that only 19% of

Table 1 Comparison between the converters and non-convertors at baseline of the study as regard clinical, radiological, and neurophysiological data

Clinical data	Group 1a (convertors) (n = 8)	Group 1b (non-convertors) (n = 35)	p value
Age (years)	26.9 ± 4.4	30.3 ± 4.5	0.06
Sex			
Male	0 (0%)	9 (26%)	0.2
Female	8 (100%)	26 (74%)	
Clinical presentation (%)			
Optic neuritis	6 (75%)	19 (54%)	
Spinal cord disorder	2 (25%)	16 (46%)	0.05
EDSS	2.25 ± 1.07	1.9 ± 0.91	0.4
Patients with delayed P ₁₀₀ latency (%)	2 (25%)	20 (57%)	0.2
MRI T ₂ lesion number	7.4 ± 3.5	2.3 ± 2.2	< 0.001*
Gd-enhancing lesions			
No enhancement	5 (62.5%)	22 (62.9%)	0.6
Contrast enhancement	3 (37.5%)	13 (37.1%)	

EDSS Expanded Disability Status scale, MRI magnetic resonance imaging
* = $p < 0.05$

their CIS patients had converted to clinically definite MS in the first year of follow-up, and those of Zhang et al. (2016) which found that 22% of patients with CIS converted to clinically definite MS in first year follow-up and 52% patients converted to clinically definite MS at 5-year follow-up.

It was shown that the CIS patients that converted to MS were younger (below 30 years old) than non-convertors in this study with tendency to reach to a significant level. Similar to this result, Alroughani et al. (2012) found that the mean age of the convertors was less than 30 years and independently associated with a higher risk of developing a second event within 2 years of onset. It was postulated that the African American patients had more rapid disease progression than non-white race/ethnicity and was associated with a higher risk of early second event which has been associated with poorer long-term prognosis (Mowry et al. 2009).

Although most of the convertors were females, there was no statistically significant difference in gender between the two groups, in agreement with this result, some studies (Alroughani et al. 2012; Dobson et al.

2012) that stated that there was no effect of gender on the conversion rate of CIS.

In respect to clinical presentation, it was found that most of convertors (75% of the patients) were initially presented with optic neuritis, and that the multivariate logistic analysis showed that optic neuritis presentation was an independent predictor for conversion after 1-year follow-up in this study. There was a conflict of results in the literature, as Kuhle et al. (2015) found that 31% of the convertors presented with optic neuritis and only 20% presented with spinal cord syndrome, while on the other side, some researchers (Alroughani et al. 2012; Miller et al. 2005) reported that optic neuritis was associated with a lower risk of developing MS than other types of clinically isolated syndrome. This conflict could be attributed to geographical variation in clinical presentation and length of follow-up.

In this study, it was found that there was no significant difference in disability assessed by EDSS between the convertors and non-convertors at baseline while the CIS patients that converted to CDMS showed significant worse EDSS scores after 1-year. It was suggested that

Table 2 Comparison between the converters and non-convertors after 1-year follow-up as regard clinical, radiological and neurophysiological data

Clinical data	Group 1a (convertors) (n = 8)	Group 1b (non-convertors) (n = 35)	p value
EDSS	3.44 ± 1.67	0.77 ± 0.87	< 0.001*
Patients with delayed P ₁₀₀ latency (%)	2 (25%)	5 (14%)	0.007
MRI T ₂ lesion number	8.9 ± 2.8	2.3 ± 2.2	< 0.001*

EDSS Expanded Disability Status scale, MRI magnetic resonance imaging
* = $p < 0.05$

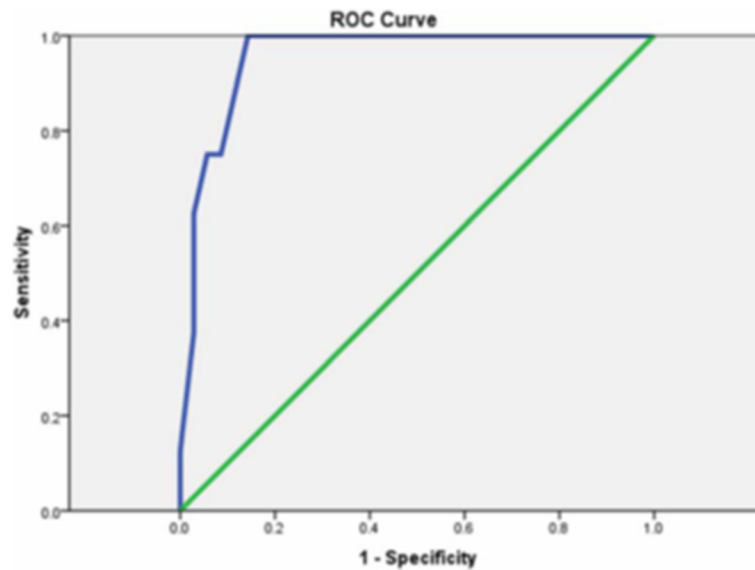


Fig. 1 Sensitivity and specificity test for MRI T₂ lesion number in prediction of conversion of CIS

the EDSS scores of the first attack may have no significant role in predicting early conversion for CDMS. Bi et al. (2016) studied the characteristics of the CIS patients and their risk factors for progression to MS or neuromyelitis optica (NMO), and it was shown that the average EDSS score of the NMO group was higher than that of the MS group, suggesting that the NMO disability was higher than that of MS. Therefore, the diagnosis of NMO should be paid attention to when the EDSS score of CIS was higher at their initial presentation.

It was suggested that the neurophysiological studies could predict conversion for CDMS in CIS patients as Swanton et al. (2006) study showed that 64% of CIS patients had VEP abnormal rate, and 24% of the patients had somatosensory evoked potential abnormal rate suggesting that the evoked potential studies were of great value for the prediction of CIS conversion. In this study, there was no significant difference in VEP results between converters and non-converters at baseline while, the converters showed significant delayed p100 latency than non-converters after 1-year. In agreement with these results, Bi et al. (2016) stated that the individually evoked potential was not predictable for CIS transformation. But the combination of two or three evoked potential anomalies may be helpful in prediction of CIS prognosis.

Conventional MRI has a well-established role in the initial assessment of patients with CIS. The risk for conversion to CDMS is greater in patients presenting with abnormal T₂-weighted images. It was found that 50 to 70% of the patients with CIS may have asymptomatic abnormal T₂-weighted images at their initial presentation (Miller et al. 2012). Several studies (Kuhle et al. 2015;

Alroughani et al. 2012; Miller et al. 2012) had postulated that the number of MRI lesions at baseline was a strong predictor to MS conversion in the CIS patients as those who had ≥ 9 T₂ lesion were at a higher risk for conversion. In this study, it was found that the patients that had converted to CDMS have a significant higher T₂ lesion numbers at baseline and after 1-year follow-up. Moreover, the multivariate regression analysis had confirmed that higher MRI lesion number is an independent predictor of conversion.

Interestingly, it was found that the number of total MRI brain T₂ lesion at the baseline that predict early conversion of CIS patients to MS was four lesions with sensitivity (100%) and specificity (85.7%). While Martinelli et al. (Martinelli et al. 2014) stated that the number of MRI T₂ lesions at baseline appeared to be predictive of CDMS was nine lesions. For patients with fewer than nine lesions, the conversion rate to CDMS was 50 vs. 66% for the patients with nine or more lesions. This difference in results could be attributed to the small numbers of patients and short duration of follow-up.

Although the previous studies (Brex et al. 1999; Pestalozza et al. 2005; Zivadinov et al. 2013) had postulated that the increased risk of conversion for MS was associated with the presence of gadolinium-enhancing lesions, there was no statistically significant difference in the total T₁ lesion number between the converted and non-converted groups in this study. Accurate estimation of the incidence of Gd-enhancing lesions at CIS presentation is difficult because of inconsistent administration of contrast across studies. Gd-enhancing lesions may only be present in subjects with abnormal T₂-weighted images (Brex et al. 1999). The presence of at least one Gd-enhancing lesion is

predictive of time to CDMS in monofocal, but not in multifocal presentations (Nielsen et al. 2009).

This study had some limitations including a short-duration follow-up and small number of participants. Moreover, there is a lack of application of McDonald's criteria 2017 in this study as this manuscript was submitted to the Egyptian journal of neurology before the publication of McDonald's criteria 2017. It is highly recommended to have a further estimation of the CSF oligoclonal bands in the patients with CIS to fulfill dissemination of time to determine who will convert to CDMS according McDonald's criteria 2017 in the upcoming studies.

Conclusions

It was concluded that the patients with CIS that initially presented with optic neuritis and higher MRI brain lesion number are at higher risk for conversion to clinically definite MS, and initiation of disease-modifying therapy should be considered as early as possible to overcome the worse long-term outcomes.

Abbreviation

CDMS: Clinically definite multiple sclerosis; CIS: Clinically isolated syndrome; CNS: Central nervous system; CSF: Cerebrospinal fluid; EDSS: Expanded Disability Status Scale; Gd: Gadolinium; MRI: Magnetic resonance imaging; MS: Multiple sclerosis; NMO: Neuromyelitis optica; SE: Spine echo; SPSS: Statistical package for social science; VEP: Visual evoked potential

Ethics approval reference

The research has been approved in the ethical committee, Faculty of medicine, Fayoum University on March 25, 2014, with reference number (1) and code (D-8).

Authors' contributions

HAS is responsible for conception of the work, analyzing, interpreting the data, and approving the final revision of the work. SSS is responsible for analyzing and interpreting the data of the work. LID is responsible for drafting the work, analyzing, interpreting the data, and communicating with the journal during the manuscript submission, peer review, and publication process. MAT is responsible for collecting data and writing the article. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Faculty of Medicine, Fayoum University Ethical Committee had approved the study; written informed consent were obtained from all the patients and control volunteers before the study initiation.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no conflicts of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 29 November 2017 Accepted: 25 June 2018

Published online: 17 July 2018

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