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Study of Profile of Patients with Clinically Isolated Syndrome and their Conversion to Multiple Sclerosis

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ABSTRACT
Clinically isolated syndrome can convert to multiple sclerosis on long-term follow up. It was observed that various predictors are involved in the disease conversion. This study aimed to determine the conversion rate and the predictors of conversion form CIS to MS. The present study was conducted in the Department of Neurology, Bangur Institute of Neuroscinces, Kolkata during the period of Jan 2013 to Dec 2014. Based on the inclusion and exclusion criteria a total of 49 patients were included in this study. Demographic, clinical and radiological data was recorded patients converted from CIS to MS. The predictors for the conversion of CIS to MS was compared and analyzed. Male was more in CIS and MS. 3 optic neuritis, 1 myelitis, 2 multifocal and 5 OCBs were progressed to CIS to MS. Patients with 4-8 and >= MRI lesions were converted CIS to MS. OCBs was positive for 5 patients who are progressed CIS to MS. In this prospective study 6 patients progressed to CIS to MS. In the predators optic neuritis, OCBs and MRI lesions 4-8 and >=9 were progressed CIS to MS.

INTRODUCTION

Clinically Isolated Syndrome (CIS) is a term that describes a first clinical episode with features suggestive of Multiple Sclerosis (MS). People with onset of MS and relapse rate is about 85%[1,2]. This relapse consists of an episode of neurological disturbance known as a CIS. Typically progressive and debilitating, MS is the leading cause of non-traumatic neurological impairment in young adults, usually affecting those in the 20-40 year age range, with a male to female ratio of 1:2 in most populations[3-5]. It usually occurs in young adults and affects optic nerves, the brainstem or the spinal cord. Although patients usually recover from their presenting episode, CIS is often the first manifestation of MS. The most notable risk factors for MS are clinically silent MRI lesions and CSF oligoclonal bands., weak or uncertain risk factors include vitamin-D deficiency, Epstein-Barrvirus infection, smoking, HLA genes and miscellaneous immunological abnormalities. Diagnostic investigations including MRI aim to exclude alternative causes and to define the risk for MS. MRI findings incorporated into diagnostic criteria in the past decade enable MS to be diagnosed at or soon after CIS presentation. The course of MS after CIS is variable: after 15-20 years, a third of patients have a benign course with minimal or no disability and a half will have developed secondary progressive MS with increasing disability. Prediction of the long-term course at disease onset is unreliable. Disease-modifying treatments delay the development from CIS to MS. Their use in CIS is limited by uncertain long-term clinical prognosis and treatment benefits and adverse effects, although they have the potential to prevent or delay future tissue damage, including demyelination and axonal loss. MS represents a spectrum of demyelination that depends on disease duration and clinical categorization. Most of the patients present with the relapsing-remitting form of the disease. The earliest clinical presentation of Relapsing-Remitting MS (RRMS) is the CIS. Predicting which CIS patients are at high risk for MS is complicated by the disparity between clinical attacks and the extent of axon pathology. Clinical findings in combination with brain MRI and CSF analysis can be used in CIS patients to evaluate their risk for Clinically Definite MS (CDMS). Application of the McDonald criteria also allows an earlier MS diagnosis by using new MRI lesions in define dissemination in time. Early immune-modulatory therapy for selected CIS patients may eventually prevent future axon pathology and progression of disability in this lifelong disease[6]. With this background the present study aimed to study of profile of patients with CIS and their conversion to MS.

MATERIALS AND METHODS

Study Period and Centre: This study was conducted for two years (Jan2013-Dec2014). The study center is Department of Neurology, Bangur Institute of Neuroscinces, Kolkata. The study was approved by Institutional Research Committee and Institutional Human Ethics Committee.

Inclusion Criteria:

- Age between 20-45 years
- Patients with first clinical event if CIS
- Not lost the follow up
- Clinical criteria (Optic neuritis, myelitis, internuclear ophthalmoplegia, brainstem. cerebellar symptoms, dysarthria and sensory symptoms)
- MRI criteria [1GD enhancing lesion, >T2 lesions of which (1 infratentorial lesion, 1 jutracortical lesion, 3 periventricular lesions)]

Exclusion Criteria:

- Patients with progressive symptoms at onset and not satisfy the CIS definition
- CIS due to infection, secondary inflammatory disorders, vascular disorders.
- Co-morbid conditions like diabetes, hypertension, recent head injury, trauma
- Vitamin-D deficiency
- Patients who had symptoms or signs suggestive of other disorders like acute disseminated encephalomyelitis, neuromyelitis optica and vasculitis

Procedure: The study population was selected on the basis of inclusion and exclusion criteria. A total of 49 patients included in this study. Their demographic, clinical data was recorded. They were observed for 2 years with the follow up study. Data was recorded each visit and analyzed the conversion of patients from CIS-MS.

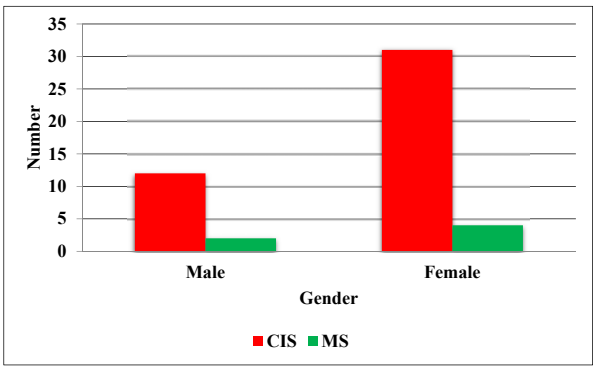
Statistical Analysis: The data was expressed in number, percentage, mean and standard deviation. Statistical Package for Social Sciences (SPSS 16.0) version used for analysis. Chi-square test applied to find the statistical significant. $p<0.05$ ($p<0.05$) considered statistically significant at 95% confidence interval.

RESULTS AND DISCUSSIONS

The study results showed that out of 49 patients 6 were converted to MS. In CIS and MS male number is more compared to females (Graph-1). In the optic neuritis 3 showed MS and 35 in CIS. In 6 myelitis patients 1 progressed to MS. Patients with brainstem/cerebellar problems were not converted to

MS stage. In multifocal 2 patients showed to MS changes and 1 had CIS. 5 CIS and 5 MS were observed in OCBs (Table-1). In MRI 0 and 1-3 lesions patients not progressed to MS. 3 patients converted MS who had 4-8 lesions. 3 patients with more than 9 lesions were progressed to MS (Table-2). In 6 patients 5 showed OCBs positive (Table-3).

Myelitis formed second major presentation of CIS in our study, 6 out of 49(12.24%) patients. This is in comparison with other Indian studies data. Acute onset of motor weakness was the next common initial presentation seen in 27-31% of Indian patients as evidenced by P. Syal[7] and the one previous study from our institute by G. Gangopadhyay[8]. Over a 2 year period, out of 49 patients, 6(12.24%) converted to MS from CIS in our study. In comparison to other studies conversion from CIS to MS. Over 80% of CIS patients with MRI lesions go on to develop MS, while approximately 20% have a self-limited process, PA. Brex[9] EM. Frohman[10] and Alroughani *et.al.,* studies showed that average 60.8% with CIS converted to MS after 10.1+4.2 months. Our study results are lower than that described from west. Majority of those patients who progressed to MS from CIS belonged to Optic neuritis group. 6 out of 49 patients converted to MS from CIS, 3 of these patients were from optic neuritis presentation. Multifocal involvement as CIS presentation formed the second majority who converted to MS . 2 patients out of 49 had multifocal presentation. 1 patient of Myelitis as initial presentation converted to MS from CIS, fulfilling the Mcdonald's criteria. Although a large number of our convertors presented with optic neuritis (77.5%) and the rate of conversion of CIS to MS was approximately 12.24%, a presentation with optic neuritis was not significant. Miller *et al.* found that optic neuritis was associated with a lower risk of developing MS than other types of CIS. Although females formed the majority who formed the MS converted group-females constituted the majority of the cohort, there was no difference between convertors and non-convertors on the basis of gender in our study. This finding is similar in comparison to the Kuwait study done by R. Alroughani[16]. A multivariate regression analysis revealed that high number of lesions in MRI (p=0.001), multifocal type of CIS presentation p=0.003) and positive CSF OCBs (p=0.001) as shown in table predicted the conversion of CIS to McDonald MS. MRI lesions in CIS-MRI lesions were found in 39/49(79.59%) patients of CIS. Within the optic neuritis group, MRI lesions were found in 73.68% patients, 100% each in myelitis, multifocal and in the brainstem/cerebellar group. Magnetic resonance imaging studies from India in patients with MS by Syal *et.al.,* showed positive findings in 86.9% of cases[17]. Gangopadhyay *et.al.,* found 69.56% of their patient to have a positive MRI in either the brain or spinal cord[18]. Another study by Mani[19] showed anabnormal brain MRI in 24 of 25 patients and an abnormal spine MR1 in 15 of 16 patients. The site of involvement in these studies is no different from those reported from the west. The most important and the strong predictor to MS conversion from CIS was the number of MRI lesions at base line. All those 3 out of 6 patients who progressed to MS from CIS had >= 9 lesion on MRI at base line. This in analogous to other studies from Indian and western data, as evidenced by Tintore *et al.* who studied 156 CIS patients for a median period of 7 years and found high risk of conversion in those patients with 3-4 Barkhof criteria. And those with 1-3 lesions behaved in a monophasic pattern. With respect to the radiological parameters, CIS patients who converted to MS had >9 lesions and 4-8 lesions than the nonconvertor cohort, while those with 0 lesions and 1-3 lesions continued to behave as a monophasic condition. Thus the number of MRI T2 lesion at base line forms the most important predictor in the assessment of risk and time to development of CDMS. The number of MRI lesions at baseline was a strong predictor to MS conversion from CIS in this study, which is in similar comparison to studies by, R. Alroughani[11] predictors of Conversion to MS in Patients with CIS using the 2010 Revised McDonald Criteria. In our study 3/6 patients from MS cohort had 9 or more lesions and fulfilled the McDonald's criteria with respect to DIT (Dissemination In time) following second clinical event. Among the remaining 3 patients with 4-8 lesions, 2 showed new Gd enhancing lesions and 1 showed new T2 lesion fulfilling McDonald's criteria. These results are consistent with other Western data and Indian studies. As in the study by, R. Alroughani[11] most of our CIS patients also converted radiologically at their second and third MRI follow ups within the studied period. The applicability of DIT/DIS criteria has certainly influenced the high proportion of radiologically convertors in a 2 year study. Chard[20]. found that 15% of patients developed radiological definite MS using the previous McDonald criteria when CIS patients were



Graph-1:Gender distribution of patients converted CIS to MS

Table-1: Clinical and radiological predictors of CIS conversion to MS

Clinical presentation	CIS cohort (n=43)		MS cohort (n=6)		
	Number	%	Number	%	p-value
Optic neuritis	35	71.42	3	6.12	0.084
Myelitis	5	10.20	1	2.04	0.724
Brainstem/Cerebellar	2	4.08	0	0.00	0.590
Multifocal	1	2.04	2	4.08	0.003*
OCBs	5	33.33	5	83.33	0.001*

Table-2: Number of lesions in MRI patients converted from CIS to MS

Number of lesions in MRI	CIS cohort (n=43)		MS cohort (n=6)		
	Number	%	Number	%	p value
0 lesions	10	20.40	0	0.00	0.00
1-3 lesions	19	38.77	0	0.00	0.00
4-8 lesions	14	28.56	3	6.12	0.001**
>=9 lesions	0	0.00	3	6.12	0.001**

Table-3: Characteristics of six patients converted from CIS to MS

S.No	Age (Years)	sex	Clinical feature	OCBs	No of MRI lesions
1.	26	F	Multifocal	+ve	>=9 lesions
2.	25	M	Optic neuritis	+ve	>=9 lesions
3.	22	F	Optic neuritis	+ve	4-8 lesions
4.	23	F	Myelitis	+ve	>=9 lesions
5.	28	M	Multifocal	+ve	4-8 lesions
6.	22	F	Optic neuritis	-ve	4-8 lesions

prospectively followed for 6 years. G'omez-Moreno[21] applied the revised 2010 McDonald criteria on 67 CIS patients with baseline MRI performed within the first 3 months after onset. After at least 24 months, follow up, the overall conversion rate was 74%. They concluded that the DIT criterion using a single MRI could improve the accuracy of early MS diagnosis in that group of patients with typical CIS and gadolinium enhancing and nonenhancing lesions. In our study of 49 patients, 45 of them were positive for VEP. Since demyelinating type of VEP abnormality was the diagnostic inclusion criteria 38/38 patients of optic neuritis had positive finding, 2/6 patients of Myelitis, 3/3 patients of Multifocal and 2/2 of cerebellar/ brainstem had VEP abnormality. VEP variable did not show any statistical significance in predicting conversion risk to MS. Visual evoked potentials are sensitive for detecting clinically silent lesions in the anterior visual pathway[22]. Abnormal VEPs (specifically consisting of a delayed but well-preserved waveform) can be used in combination with findings on a neurological examination to fulfill MS diagnostic criteria for DIS. However, abnormal pattern reversal on VEPs, while highly sensitive to demyelination, are not specific to MS. As evidenced from our study in the predictors of conversion to MS from CIS 3/6 patients who converted to MS had optic neuritis as initial manifestation, 2 had multifocal presentation and 1 belonged to the myelitis group. Statistical significance was the multifocal presentation which was detected to have high propensity to convert to MS. But this is contradictory to the findings by Miller *et al.* Which showed spinal cord/myelitis variant had high propensity to convert to MS from CIS subgroups.

Amongst the converters from CIS to MS the mean age at onset was significantly lower and even though the younger age was not independently associated with the high risk of developing MS. This result is not consistent with the other study reports. The other risk factors such as gender and age had no predictive value. Our study results are in agreement with other studies EM. Mowry[23] and C. Confavreux[24]. The major limitations of this study is less sample size and follow up period.

CONCLUSION

In this study 12.24% of patients from CIS cohort converting to MS over a period of 2 years. The three most important variables, found to be important and independent risk predictors of conversion to MS from CIS found out using the multiple logistic analysis-the multifocal subtype of CIS, the presence of higher number >=9/4-8 lesions on MRI and the presence of CSF OCBs. The various other factors such as age, sex and other subtypes of CIS did not show any predictive value. Currently frequent MRI scans at early intervals and regular follow up during the initial years after the CIS facilitate early and accurate diagnosis of definite MS.

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