Patterns of Clinically Isolated Syndrome in Patients Attending Multiple Sclerosis Clinic in Baghdad Teaching Hospital

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Abstract

Clinically isolated syndrome (CIS) "is the first demyelinating event that is suggestive of multiple sclerosis and that makes patients at risk for further relapses". Eighty five percent of patients with multiple sclerosis, their onset is with (CIS). It is difficult to predict whether a given individual will develop multiple sclerosis following a (CIS).

To determine pattern of (CIS) presentation among Iraqi patients and study factors associated with risk for conversion to clinical definite multiple sclerosis (CDMS). A record base study of thirty five patients labeled as (CIS) attending multiple sclerosis clinic in Baghdad Teaching Hospital was conducted during the period from 1/1/2011 to 1/12/2011. For each patient a study protocol sheet was done and filled from the database in the multiple sclerosis clinic, each patient was assessed clinically at least one time .The following information were studied: Patients gender , age at presentation , pattern of presentation , residual deficit after their 1st attack , disability depending on Expanded Disability Status Scale (EDSS), duration to convert to (CDMS) if they develop another attack after their diagnosis as (CIS), and their baseline MRI (1Tesla).

The mean age for the studied sample is (**34.20±8.38**), with (9 male) and (26 female). A (28.6%) of the patients have multifocal and (71.4%) have monofocal presentation. Fifteen patients (42.9%) have residual deficit after their 1st attack , eleven patients (31.4%) converted to (CDMS), the mean time for conversion to definite multiple sclerosis is (23±15) months, six patients (17.14%) have normal brain MRI at their 1st presentation while the remainder have abnormal MRI. Conversion to (CDMS) is more in patient with multifocal presentation, residual deficit after 1st episode and positive baseline MRI findings.

Key words: clinical isolated syndrome, pattern of presentation.

أنماط المتلازمة المعزولة السريرية في المرضى العراقيين

الخلاصة:

ان المتلازمة المعزولة السريرية هي الحدث الأول من مرض تصلب الاعصاب اللويحي المتعدد ، مما يجعل المرضى المصابين بها عرضة لانتكاسات أخرى. حيث ان ٨٥٪ من المرضى الذين يعانون من مرض تصلب الاعصاب اللويحي المتعدد، تكون بداية المرض مع المتلازمة المعزولة السريرية.

لتحديد الانماط السرسرية لدى المرضى العراقيين المصابين بالمتلازمة المعزولة سريريا ودراسة العوامل المرتبطة بزيادة خطورة التحول الى مرض تصلب الاعصاب اللويحي المنتشر.

أجريت دراسة بأثر رجعي ل ٣٥ مريضا شخصوا على انهم مصابين بالمتلازمة المعزولة السريرية يراجعون عيادة تصلب الاعصاب في مستشفى بغداد التعليمي حيث اجريت الدراسة للفترة من ٢٠١١/١/١ إلى ٢٠١١/١٢/١. وتمت دراسة المعلومات التالية: عمر وجنس المريض لدى الاصابة بالعرض الاول للمتلازمة، ونمط الاصابة ان كانت متعددة او احادية، والعجز المتبقي بعد العرض الاول ،نسبة العجز اعتمادا على مقياس الاعاقة المستخدم لمرضى تصلب الاعصاب المتعدد (EDSS) ،الفترة التي استغرقها المرضى الذين تحولوا الى مرض تصلب الاعصاب المتعدد ، وصورة الرنين المغناطيسي (MRI) للدماغ لكل مريض عند تشخيصه. خمسة وثلاثين مريضا شخصوا كمصابين بالمتلازمة المعزولة السريرية مسجلين في عيادة تصلب الأعصاب المتعدد في مستشفى بغداد التعليمي، متوسط العمر لعينة الدراسة هو (٣٤.٢٠ ± ٨.٣٨)، عينة الدراسة متكونة من (٩ ذكور) و (٢٦النساء). إن المرضى الذكور، والمصابين بأعراض متعددة ، والمرضى الذين تبقى لديهم نسبة من العجز بعد العرض الأول والمرضى الذين كانت صورة الرنين المغناطيسي لديهم غير طبيعية كانوا أكثر عرضة للتحول لمرض تصلب الأعصاب المتعدد . كان المرضى الذين أصيبوا بالتهاب العصب البصري اقل عرضة للتحول إلى تصلب الأعصاب المتعدد واحتاجوا وقتا أطول للتحول. المرضى الذين لديهم أعراض متعددة والذين أصيبوا بالأعراض الناجمة عن الإصابة الهرمية كان العجز (EDSS) لديهم أعلى و بشكل ملحوظ في السنوات اللاحقة من هذا المرض. المرضى الذين كانت صورة الرنين المغناطيسي الأولية طبيعية كان العجز لديهم أقل اعتمادا على مقياس(EDSS) للعجز بالمقارنة مع المرضى الآخرين.

Introduction

Increasing availability of magnetic resonance imaging (MRI) technology improved the diagnosis of central nervous system (CNS) demyelinating disorders, and this with the arrival of Food and Drug Administration (FDA)-approved disease-modifying drugs (DMD) for multiple sclerosis (MS) starting in 1993 increased the importance of early diagnosis and treatment[1]. Long-term follow-up studies of patients presenting with an isolated clinical syndrome characteristic of MS led to the identification of baseline risk factors for conversion to clinically definite multiple sclerosis (CDMS) [1]. Subsequent studies of clinically isolated syndrome (CIS) patients revealed that early treatment with (DMD) may be beneficial in delaying a second demyelinating attack [2]. A clinically isolated syndrome" refers to a first acute episode suggestive of CNS demyelination, and it may be the first presentation of multiple sclerosis" [3]. About 85% of people with MS have their disease onset with a relapse ,this relapse known as CIS [4].To be termed CIS this relapse should last at least 24 hours and occur in absence of fever or infection, with no clinical features of encephalopathy [5]. Data on overall incidence of CIS are lacking, but one may extrapolate CIS incidence rates based on MS incidence. However, because not all CIS represent MS, one should assume that CIS incidence rates are higher than MS incidence [1]. According to Benamer H study (Frequency and clinical patterns of multiple sclerosis in Arab countries), MS prevalence is 42 per 100000, the mean age of onset is (26.6-30 years), and female to male ratio is 1.1/1 to 3/1 in Arab countries [6]. In the United States, overall MS incidence of 7.5 per 100,000. The incidence was 10.4 per 100,000 women compared to 4.5 per 100,000 men. Incidence rates are similar in European countries, with an increased incidence noted in northern latitude countries [7].

The sex ratio of both MS and CIS is about 2.5 (women and girls) to 1(men and boys). The usual age group of CIS is that of MS: 70% of patients present between 20 and 40 years (mean 30 years), but patients can present older and younger ages. Childhood onset of MS is almost invariably with CIS [8].

Clinical Presentation

CIS is by definition, always isolated in time (i.e., monophasic) [9]. Clinically, it's isolated in space (i.e, monofocal) with signs indicating a lesion in the optic nerve (a common presentation in many reported CIS studies), spinal cord, brainstem or cerebellum, or (rarely) a cerebral hemisphere. However, some patients with

CIS have clinical dissemination in space (i.e, multifocal). Clinically multifocal CIS presentations (e.g. optic neuritis with an extensor planter response or simultaneous optic neuritis and internuclear ophthalmoplegia) are less common than monofocal presentations [9].

Review of a large database of patients with CIS found that 21% presented with optic neuritis, 46% with long tract symptoms and signs, 10% with a brainstem syndrome, and 23% with multifocal abnormalities [4, 9].

The international panel of the experts in multiple sclerosis defined five types of CIS: [5].

Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion

Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion

Type 3 CIS: clinically monofocal, MRI may appear normal, no asymptomatic MRI lesions

Type 4 CIS: clinically multifocal, MRI may appear normal, no asymptomatic MRI lesions

Type 5 CIS: no clinical presentation to suggest demyelinating disease (without symptoms, headache, dizziness), but MRI is suggestive [5].

- Factors associated with conversion into (CDMS):

Many risk factors for the development of CIS to MS have been investigated:

1. Genetic

In patients with CIS with MRI lesions, positive HLADRB*1501 status has been associated with higher lesion load and conversion to MS [9]. However, a new study done in 2011 did not show an association between susceptibility gene and disease course or conversion to CDMS [10].

2-Vitamin D

New studies try to clarify the role of vitamin D deficiency as a risk factor for conversion to MS after CIS and assess whether vitamin D treatment affect conversion of CIS to MS [9].

3- Epstein-Barr virus (EBV)

Tow studies show that past infection with EBV is associated with increase CIS risk and conversion to MS [9, 11].

4- Clinical features

Younger age at presentation, female gender [12] and greater number of functional systems affected at presentation are associated with higher risk for conversion to CDMS [13].

The different presentations of CIS are associated with different disease courses and prognosis [7]. In patients with ON follow-up studies have reported conversion to CDMS between 10% and 85% of patients. In patients with spinal cord CIS, conversion to MS has been reported to vary between 41% and 61%.The proportion of patients with brainstem syndromes who develop MS varies between 53% and 60%.[9].

The probability of a second episode during the study period was 16·7% in North American Optic Neuritis Treatment Trial (ONTT), 38% in Controlled High Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS), and 45% in Early Treatment of Multiple Sclerosis study (ETOMS) in the untreated groups. [9,14,15].

In ETOMS, the chance of developing CDMS was greater in patients with a polysymptomatic onset than in those with a monosymptomatic onset and there was no difference between the various symptoms evident at onset [15].

ON is the best-studied CIS, one of the longest follow-up studies of patients with optic neuritis was done in Sweden where 86 patients with acute monofocal unilateral ON were recruited between 1969 and 1981 and followed up until a diagnosis of MS was made, of the 86 patients, 33 developed MS, three died, and 50 continued to have isolated ON [16]. In this group, the estimated 15 year risk of MS was 40 % [17]. In 60% of patients, MS occurred within 3 years. Patients who were young and those with onset in winter also had a high risk of MS. [18].

5-CSF

CSF examination helps to predict conversion to MS in patients with negative MRI or with MRI showing few lesions (i.e. MRI does not meet McDonald criteria for dissemination in space). In patients with negative MRI the presence of oligoclonal bands (OCBs) increase the risk of conversion to MS from 4% to 23% [19].

5-MRI findings

The predictive value for conversion to clinically definite MS of four studies is provided in (table 1-1) [4].

Study	Normal MRI	Abnormal MRI
Brex et al[20]	19%	88%
Optic Neuritis Study Group[21]	22%	56%
Mimneboo et al[22]	24%	72%
Tintore et al[23]	8%	63%

Adapted from Lancet Neurol 2005; 4: 281–88.

From these findings it's warranted to conclude that the long-term risk for CDMS is 60-80% when lesions present on MRI and 20% when MRI is normal [3,14].

Regarding the features of the lesions two factors are important and are associated with risk of conversion to CDMS and these are:

Number of the lesions (0,1-9,10 or more), and the number of Barkhof criteria (0,1-2,3-4) both these factors identify patients with low, medium, and high risk for conversion to CDMS respectively [4,14].

Taking lesion location into account CIS with at least one infratentorial regions at onset of CIS have increased risk of conversion, the risk being slightly higher in those with brainstem than in those with lesion in the cerebellum [4,14].

Patients and Methods

A record base study of 35 patients (9 males and 26 females) labeled as CIS in MS clinic in Baghdad Teaching Hospital were followed in the period between 1/1/2011 to 1/12/2011.

Inclusion criteria

Only patients labeled as CIS at their 1st diagnosis in the MS clinic of Baghdad Teaching Hospital were included and even those convert to CDMS after their 1st diagnosis as CIS. All the patients were on regular treatment with subcutaneous Betaferon (patients who were with normal MRI on presentation receive treatment after their MRI become abnormal on subsequent visit to MS clinic).

Methods

a. Demographic features of the studied group:

A-Age (age of patients when developing their 1st symptoms):

Patients were classified into 2 groups depending on their age:

1- Those <40years
2- Those ≥40 years

B-Gender:

b. The studied factors:

The following clinical information was provided:

1-Duration to convert to CDMS

Patients were categorized into those who converted into CDMS below 1 year and those who converted into CDMS above

1year we use this cut point as it is the point used by most authors to assess the optimal response to treatment.

2-Clinical presentation

Patients were classified into:

a- Monofocal: when patient presentation is isolated in space with signs indicating a lesion in the optic nerve, spinal cord, brainstem or cerebellum, or (rarely) cerebral hemisphere.

b- multifocal: when patient presented with multifocal CIS presentations (e.g. optic neuritis with an extensor plantar response).

3-Residual deficit

Patients are divided into: those who remained with a deficit after the 1st attack and those who did not.

4-Patient disability

We used the (EDSS) to classify patients into those with EDSS score <3, and those with EDSS ≥ 3 depending on the definition of benign MS, each patient EDSS has been assessed at least one time.

5-Regarding MRI

Each patient have baseline MRI (1 Tesla), and we classified patients into 2 groups:

a- Patients with normal MRI

b- Patients with positive MRI (abnormal) findings according to Barckoff criteria for the diagnosis of MS.

Barkhof criteria include (1) one gadolinium-enhancing lesion or at least nine total T2 lesions, (2) one juxtacortical lesion, (3) one infratentorial lesion, and (4) three periventricular lesions. Three of these four are currently required for the diagnosis [20, 21].

All the above data was collected from patient sheets and assessed at least in a single follow up visit.

Patients were classified as having CDMS according to McDonald's criteria 2005.

Alternative diagnoses were ruled out by appropriate tests according to local standards. Diagnosis of CDMS was confirmed by an experienced neurologist.

Statistics

Analysis of data was carried out using the available statistical package of SPSS-18 (Statistical Packages for Social Sciences-version 18 "PASW" Statistics). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of difference of different means (quantitative data) was tested using analysis of variance (ANOVA) for more than two groups and using independent student t-test for difference between two means, while different percentages (qualitative data) were tested using Pearson Chi-square test (χ^2-test). Statistical significance was considered whenever the P value was less than 0.05.

Results

Table 1: The demographic distribution of the studied group

Age at diagnosis (years)	No (%)
18-25years	5(14.3)
25--29	5(14.3)
30--34	5(14.3)
35--39	9(25.7)
40--44	8(22.9)
≥45yeras	3(8.6)
Mean±SD (Range)	34.74±8.63 (17-53)
Gender :	
Male <40years	5(55.6)
≥40years	4(44.4)
Female <40 years	15(57.7)
≥40years	11(42.3)
Duration to convert to CDMS (months)	23±15 (3-72)

Figure (1) shows categorization of patients according to their pattern of presentation were 10 (28.6%) patients presented with multifocal and 25 (71.4%) presented with monofocal presentation.

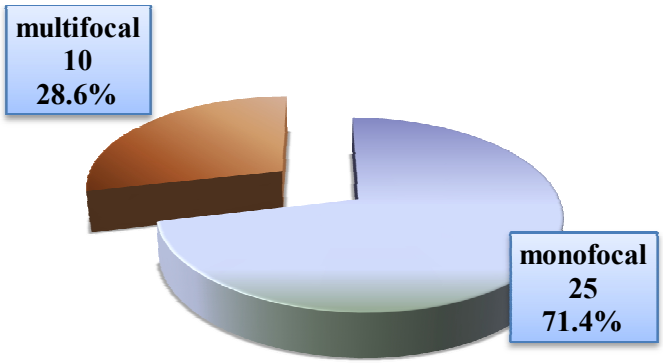

Figure (2): The distribution of patients whether remain CIS or converted to CDMS. Eleven patients (31.4%) were converted to CDMS.

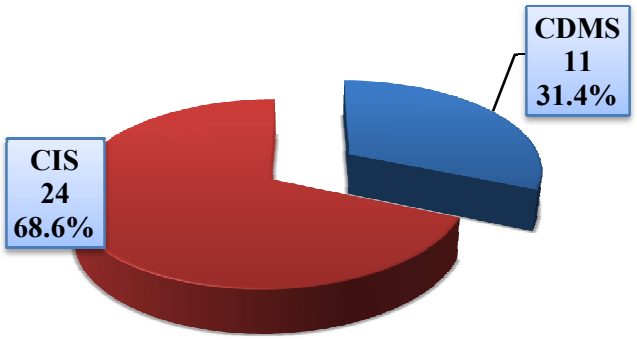

Table 2: study conversion to CDMS in correlation to gender and age of patients. There were 4 (44.4%) of male patients out of 9 males converted to CDMS and 7 (26.9%) of females out of 26 female patients converted to CDMS (P value =0.329) , also 6 (30.0%) of patients below 40years and 5 (33.3%) of patients ≥ 40 years were converted to CDMS (P value =0.833).

Variable	Patients with		P value
	CDMS No(%)	CIS No(%)	
Gender Male (n=9)	4(44.4)	5(55.6)	0.329
Female (n=26)	7(26.9)	19(73.1)	
Age <4o years (n=20)	6(30.0)	14(70.0)	0.833
≥40years (n=15)	5(33.3)	10(66.7)	
Mean age±SD (Range)	38.55±9.28(21-53)	36.29±8.74(21-49)	

Table 3 study the effect of pattern of presentation on subsequent conversion to CDMS were 7 patients (28.0%) out of 25 patients with monofocal compared to 4 patients (40.0%) out of 10 patients with multifocal presentation converted to CDMS (P value=0.490).

Pattern of presentation	CDMS No (%)	CIS No(%)	Total	P value
Monofocal	**7 (28.0)**	**18(72.0)**	**25**	
Mutifocal	**4 (40.0)**	**6(60.0)**	**10**	**0.490**
Total	**11**	**24**	**35**	

Figure (3) show the distribution of patients according to the persistence of deficit of the 1st attack. There were 20 (57.1%) of patients have persistent deficit and 15 (42.9%) have no deficit after their 1st attack of presentation.

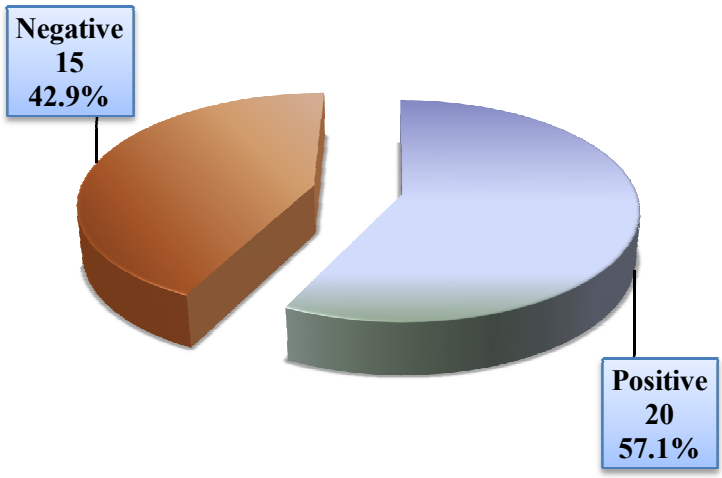

Table 4: study the effect of deficit persistence and conversion to CDMS. There 7 patients (35.0%) of patients with residual deficit convert to CDMS compared to 4 patients (26.7%) with no deficit converted to CDMS ,this is statistically not significant (P= 0.599).

Variable	Patients			
	Convert to CDMS	Remain CIS		
	No (%)	No (%)	Total	P value
Residual deficit: yes	7(35.0)	13(65.0)	20	0.599
No	4(26.7)	11(73.3)	15	
Total	11	24	35	

Table 5: show distribution of the studied group according to MRI findings. Two patients (33.3%) out of 6 patients with normal MRI, 5 patients (22.7%) out of 22 patients with 1 site lesion , and 4 patients out of 7 patients with more than 1 site lesions on brain MRI convert to CDMS , this is statistically not significant (P= 0.231).

	Patients		P value
	Converted to CDMS(%)	Remain CIS(%)	
MRI findings Normal	2(33.3)	4(66.7)	0.231
One site	5 (22.7)	17(77.3)	
More than one site	4(57.1)	3(42.9)	
Total	11	24	

Figure (4): The distribution of patients according to EDDS

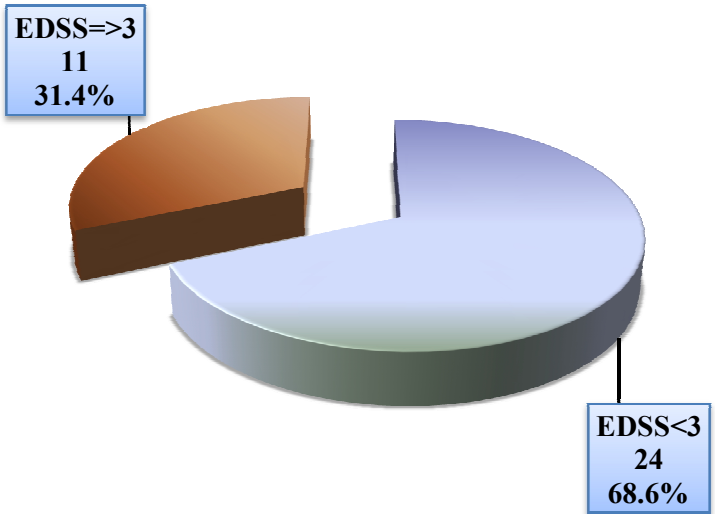

Table 6: shows correlation between EDSS and presentation of patients (monfocal Vs multifocal), specific symptom at presentation (ON, pyramidal ……etc.), residual deficit , and MRI findings. Patients with multifocal presentation have higher EDDS compared to monofocal presentation (statistically significant, P=0.030), patients with residual deficit have higher EDDS compared to those without deficit (statistically significant, P=0.017), and patients with positive MRI have higher EDDS compared to patients with normal MRI (statistically not significant, P=0.292)

	EDSS score (Mean±SD)	P value
Type of presentation :		
Monofocal	1.84±1.04	0.030*
Multifocal	2.80±1.36	
Residual deficit:		
Positive	2.53±1.15	0.017*
Negative	1.57±1.07	
MRI findings:		
Normal remain CIS	1.13±0.25	0.292
Normal convert to CDMS	1.00	
One site remain CIS	2.32±1.33	
One site convert to CDMS	2.00±0.79	
More than one site remain CIS	2.33±1.04	
More than one site convert to CDMS	2.75±1.50	

***P value significant.**

Discussion

The course of MS after CIS is variable: after 15-20 years, a third of patients have benign course with minimal or no disability and a half have developed secondary progressive MS with increasing disability [9]. In this study males show higher percentage to convert to CDMS compared to females.

The sex ratio in this study is approximately similar to all studies done in Arab countries were females more often affected than males, at a ratio ranging from 1.1:1 to 3:1 [6]. Worldwide studies showed female predominance at onset of 1st episode of MS patients in ratio 3:1 [7, 8].

Studies about the effect of gender on developing 2nd episodes after the 1st one are controversial; with some show that male sex are higher risk to convert to CDMS [22], and others show no significant trend of increased risk in men [7], and others show no effect of sex [23] and others show female to be a risk factor for conversion to CDMS [9, 24].

Regarding age at presentation in this study there was no difference in risk for conversion to CDMS and age at presentation. This is contradictory to Nilsson et al [25], Mawry et al [12], and to Ruet et al [26].This contradictory can be explained by our small study group and small number of patients who convert to CDMS.

In this study 2/3 of patients presented with monofocal presentation and 1/3 presented with multifocal.

The percentage of mono and multifocal presentation in CIS patients differ in different studies, in Confavreux et al, [27] 23% of CIS patients presented with multifocal presentation, and in Savic et al, patients with monofocal presentation represent (43,18%) and those with multifocal presentations (52,27%) in the studied group [28].

In this study patients with multifocal presentation convert to CDMS in higher percentage compared to patients with monofocal presentation.

This is similar to Gomi et al, where chance of developing CDMS was greater in patients with a multifocal onset than in those with monofocal onset [15], and contradictory to Confavreux et al where no difference in the predictive value of unifocal or multifocal presentation [27].

Regarding persistence of deficit after 1st attack, in our study patients with deficit after their 1st relapse have higher percentage of conversion to CDMS compared to those with no deficit after their 1st relapse although this is statistically not significant.

This is similar to Weinshenker et al, Kurtzke et al, and Miller et al, where patients with residual deficit have higher risk to convert to CDMS and worsening disability [29-31] and contradictory to Gomi et al where no difference between the various symptoms was evident [15].

Regarding MRI findings, in this study patients with abnormal baseline MRI have higher percentage to convert to CDMS in comparison to patients with normal base line MRI, although this is statistically not significant.

This similar to Brex et al where (19%) with normal MRI compared to (88%) with abnormal MRI [32], ONTT group where (22%) with normal MRI compared to (56%) with abnormal MRI converted to CDMS[24], Minneboo et al where (24%) with normal MRI compared to (72%) with abnormal MRI [33], and to Tintore et al were (8%) with normal brain MRI compared to (64%) with abnormal brain MRI converted to CDMS. [19].

Regarding EDSS patients with multifocal mode of presentation have higher EDSS compared to patients with monofocal presentation this is statistically significant.

Patients with normal baseline MRI have lower EDSS compared to patients with abnormal baseline MRI this is statistically not significant.

This is similar to Brex et al, [32] Minneboo et al, [33] and to finding of ONTT, [24]in

all these studies patient with abnormal baseline MRI have higher risk to deteriorate to EDSS≥3 compared to patients with normal MRI at presentation.

Conclusion

1- Gender and age at presentation have no statistical significance for conversion to CDMS.

2-Pattern of presentation (monofocal Vs multifocal), persistence of deficit after 1st attack, and abnormal baseline MRI show higher percentage to convert to CDMS although this is statistically not.

3-Patints with multifocal presentation have higher disability measured by EDDS than those with monofocal presentation on their subsequent years of the disease following their 1st attack.

4-Those patients with abnormal MRI findings have higher disability measured as EDSS $\geq$ 3.

5-Further studies are needed to confirm the applicability of factors found in this study to be associated with conversion to CDMS.

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