Disability and prognosis of relapsing remitting multiple sclerosis, is it different in Iraqi patients?

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ABSTRACT

الأهداف: تقييم العوامل التي تؤثر على التنبؤ المستقبلي لمرض التصلب العصبي المتعدد الانتكاسي المتقطع بين المرضى العراقيين.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في عيادة التصلب العصبي المتعدد، مستشفى بغداد التعليمي، بغداد، العراق، واستمرت خلال الفترة من مارس 2008م إلى يناير 2010م. شملت الدراسة 500 مريضاً (270 أنثى، و230 ذكر) ممن تتماشى صفاتهم مع معايير ماكدونالد لتحديد مرض التصلب العصبي المتعدد الانتكاسي المتقطع، وبلغ معدل أعمارهم 45.58 عاماً. لقد قمنا بمراجعة وتحليل التاريخ المرضي للمرضى، بالإضافة إلى نتائج مؤشر حالة الإعاقة الممتد.

النتائج: أشارت نتائج الدراسة إلى ظهور الأعراض السريرية الأحادية في 70% من المرضى، وقد كان الشلل النصفي (48%) من أكثر الأعراض السريرية شيوعاً، وتلاه التهاب الأعصاب البصرية (24%). تمثلت العوامل التي يمكن أن تعجل في ظهور أو تفاقم أعراض المرض في كل من: تقدم العمر وقت بداية المرض، وتأثر النظام الهرمي والمصرة في بداية المرض، وزيادة عدد الانتكاسات في السنتين الأولى من المرض. ولم يكن لعاملي العمر، أو نوعية العرض السريري تأثيراً كبيراً على إعاقة الوظائف اليومية الهامة.

خاتمة: أثبتت الدراسة أنه يمكن تلخيص العوامل التي يمكن أن تعجل في ظهور أو تفاقم أعراض التصلب العصبي المتعدد الانتكاسي المتقطع فيما يلي: تقدم العمر وقت بداية المرض، وتأثر النظام الهرمي والمصرة في بداية المرض، وزيادة عدد الانتكاسات في السنتين الأولى من المرض.

Objective: To assess the prognostic factors of relapsing remitting multiple sclerosis (RR-MS) in Iraqi patients.

Methods: This retrospective study of patients with RR-MS was carried out at the MS Clinic in Baghdad Teaching Hospital, Baghdad, Iraq between March 2008 and January 2010. Patients history and extended disability status scale scores were reviewed using the clinic database.

Results: Five hundred patients (270 female, and 230 male) fulfilled the McDonald criteria for RR-MS, their mean age was 45.58 years. Mono symptoms were found in 70% of patients. Hemiplegia (48%) was the most common clinical feature followed by optic neuritis (24%). Poor prognostic indicators were older age at onset, pyramidal and sphincter involvement at the beginning of the illness, and more relapses in the first 2 years of the illness. There were no significant effects of gender or symptom type as prognostic indicators on the residual disability of the studied patient.

Conclusion: Older age at onset, pyramidal and sphincter involvement at the beginning of the illness, and more relapses in the first 2 years of the illness were poor prognostic indicators.

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Multiple sclerosis (MS) is a chronic heterogeneous inflammatory and degenerative disease of the CNS. It is a demyelinating and axonal degenerative disease of the central white matter. It is the most common cause of disability in young adults after trauma. The wide variety of clinical manifestations depends on the extent and the anatomical sites of demyelinating plaques. The functional prognosis of the disease is poor in the late phases of the disease.[1] After 10 years from the disease onset, around 75% of patients develop moderate to severe functional disability.[2] Iraq as a part of the Middle East area is considered as a MS medium risk prevalence area.[2] The expanded disability status scale (EDSS) was developed by John Kurtzke in 1983;[3] and it is a widely used prognostic method for assessment of functional outcome of MS. The

Table 1 - The demographic features and relapse details of 500 Iraqi patients with relapsing remitting multiple sclerosis.

Variables	n	(%)
Gender		
Male	230	(46)
Female	270	(54)
Age at study (years)		
Minimum	29	
Maximum	62	
Mean±SD	45.58±8.43	
Age at CDMS onset		
Minimum	18	
Maximum	52	
Mean±SD	30.92±7.71	
Type of symptoms		
Poly symptomatic	150	(30)
Mono symptomatic	350	(70)
Number of relapses in first 2 years		
Minimum	0	
Maximum	6	
Mean±SD	2.3±1.6194	
Number of relapses per first 2 years with EDSS above 4.5		
0-2	80/200	(40)
2-6	280/300	(93)
Total 0-6	360/500	(72)

CDMS - clinical definite multiple sclerosis, SD - standard deviation

EDSS scale ranges from 0-10, grades between 0-4.5 represent the independent ambulatory patients, while EDSS between 5-9 refers to impaired ambulation.[3] The objective of this study is to assess the clinical parameters of MS, and to determine their relation to prognosis of the disease in Iraqi patients.

Methods. This retrospective study reviewed the files of 500 patients (270 females and 230 males) with relapsing remitting (RR) MS according to the McDonald criteria.[4] The study was carried out between March 2008 and January 2010, in the MS Clinic at Baghdad Teaching Hospital in the center of Baghdad, Iraq. This is the main MS clinic in Iraq located in Baghdad Teaching hospital, and part of Baghdad University. The inclusion criteria were patients with RR-MS at onset and on every other day treatment with subcutaneous beta interferon (1b). The exclusion criteria were a progressive onset disease course, patients with less than 5 years onset, and patients non complaint with interferon therapy. The Al-Kindy College of Medicine/University of Baghdad (linked with Baghdad teaching hospital) ethical committee approved the study. Patient consent was taken to use their clinical data in this work. The study was primarily based on examination of the patient at the last visit and review of their file sheets registered in the MS clinic. Each patient disease course and EDSS score were recorded. We also recorded the following: gender, age at onset, first symptom type (poly symptomatic or mono symptomatic), specific symptoms (cerebellar, brainstem, sphincter, pyramidal, optic), number of relapses in the first 2 years of the illness, EDSS score at first inclusion in the MS clinic (EDSS 1), and EDSS score after 5 years (EDSS 2).

Data were translated into a computerized database structure. Statistical analyses were computer assisted using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 14. Frequency distribution for selected variables was carried out first. A *p*-value less than 0.05 was considered statistically significant. Chi square test was used to test the significant association between discrete variables, and Pearson correlation to test the relation between 2 continuous variables. The statistical significance of difference in the mean of a normally distributed quantitative variable between 2 groups was assessed by independent sample t-test.

Results. Five hundred patients with clinically definite MS were enrolled in the study, 270 females, and 230 males. **Table 1** illustrates demographic features and relapse numbers. The patients' mean age at the time of study was 45.58 years, the minimum age at enrollment was 29, and the maximum age was 62 years old. The mean age at clinically definite multiple sclerosis (CDMS) onset was 30.92, with a minimum age of 18, and a maximum age of 52 years. **Table 1** also shows type of symptoms (poly symptomatic or mono

Table 2 - The correlation between the gender and EDSS scores in 500 Iraqi patients with relapsing remitting multiple sclerosis.

EDSS	Female			Male			Total (Female + Male)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
EDSS 1	270	5.1852	2.3252	230	5.0217	2.1610	500	5.1100	2.2299
EDSS 2	270	6.2037	2.1134	230	5.8913	1.9185	500	6.0600	2.0118

EDSS - expanded disability status scale, SD - standard deviation

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Table 3 - Percentage of specific clinical parameters at onset and their correlation with the EDSS at onset (EDSS 1) and at last visit (EDSS 2) in 500 Iraqi patients with relapsing remitting multiple sclerosis.

Clinical parameters	n (%)		EDSS 1		EDSS 2	
			Mean	SD	Mean	SD
Cerebellum	10	(2)	1.5000	0.64334	4.0000	0.4710
Brainstem	50	(10)	5.5000	2.5981	5.9000	2.3822
Sphincter	80	(16)	6.0000	2.0000	6.9375	1.6570
Hemiplegia	240	(48)	5.5208	2.0720	6.3542	1.7537
Optic	120	(24)	3.8333	2.0487	5.1250	2.3848

EDSS - expanded disability status scale, SD - standard deviation

symptomatic), with a mean EDSS 1 of 4.5 in poly symptomatic patients, and 5.04 in mono symptomatic patients. The EDSS 2 results showed a mean score of 6.33 in poly symptomatic, and 6.15 in mono symptomatic patients. With regard to relapses, **Table 1** shows the mean number of relapses during the first 2 years was 2.3, and ranged from no relapses to 6. Forty percent of patients with 2 or fewer relapses in the first 2 years had an EDSS 2 score above 4.5, and 93% with more than 2 relapses per first 2 years had an EDSS 2 above 4.5. **Table 2** shows the correlation between gender and EDSS, and shows there is no significant gender difference in EDSS 1 and EDSS 2. **Table 3** shows the percentage of the first clinical manifestation in the present study and correlation with EDSS score at onset and at the last visit. Results showed that EDSS 2 was 6.93 in patients with sphincteric symptoms, and 6.35 in hemiplegic symptoms, with p=0.004, other symptoms showed no significant correlation with high grades of EDSS. **Table 4** shows the correlation between age at onset of CDMS and EDSS 2 and shows significantly higher mean EDSS 2 scores in the older age groups.

Discussion. The present study reveals that gender has no effect on prognosis, and this result is in agreement with studies by Moreira et al,[5] and Tremlett

et al,[6] who also found no poor prognostic effect for male gender. However, our results are in contrast to Niscot,[7] and Simone et al,[8] who reported that female gender was associated with better prognosis. They attribute a better prognosis in females to hormonal changes and the effects of sex chromosomes on the immune system, the blood brain barrier, and parenchymal CNS cells, as well as a more predominant progressive course in male patients. Vlahiotis et al[9] found that females were more educated and had better awareness of their disease management. Male gender is commonly believed to be a risk factor for poor prognosis in RR-MS, and other studies also showed no significant trend of increased risk among men.[10,11]

Our study results also showed a significant correlation between age older than 40 years at onset and higher EDSS residual disability. This is in agreement with studies by Pfleger et al,[12] and Lau et al.[13] Poor prognosis of older late onset MS is related to more commonly progressive types of MS in older patients,[14] and also related to age decrease in CNS remyelination.[15] Such a repair defect is a key player in the occurrence and aggravation of an irreversible neurologic disability in MS. On the other hand, the influence of age on the occurrence of the progressive phase of the disease may also reflect age-related changes in immune function.[16,17]

Our study results showed no significant correlation between the type of symptoms, whether mono or poly symptomatic, on the residual disability measured by EDSS of patient with RR-MS. This is in contrast with studies by Pfleger et al,[12] and Ramsaransing et al,[18] who found that a mono regional onset predicted a better prognosis compared with a poly regional onset. Our study results also showed that onset of hemiplegia or sphincter involvement had a higher EDSS than other presentations. This is consistent with Ramsaransing et al's study,[18] which suggested that manifestations of sphincteric symptoms at onset are associated with poor prognosis status. Also, Stankoff et al's[16] study agrees with the result of poor outcome of pyramidal symptoms.

Table 4 - Correlation between age at onset of CDMS and EDSS 2 in 500 Iraqi patients with relapsing remitting multiple sclerosis.

Age at CDMS	n	Mean	SD	Std Error	EDSS 2		Minimum	Maximum
					95% confidence interval for mean			
					Lower bound	Upper bound		
1-19	10	4.0000	0.47100	0.14900	3.66307	4.33693	4.00	4.00
20-29	140	2.5714	1.17436	0.31386	1.8934	3.2495	1.00	6.00
30-39	150	4.6000	1.78486	0.46085	3.6116	5.5884	1.50	7.50
40-49	190	6.7895	1.26179	0.28947	6.1813	7.3976	4.50	9.00
50-59	10	7.0000	0.57700	0.18246	6.58724	7.41276	7.00	7.00
Total	500	4.9000	2.22004	0.31396	4.2691	5.5309	1.00	9.00

CDMS - clinical definite multiple sclerosis, EDSS - expanded disability status scale, SD - standard deviation, Std Error - standard error of deviation

In our study, relapse plays an important role on subsequent disability in patients with RR-MS. Results showed that more relapses in the first 2 years of the illness were associated with poor prognosis and higher EDSS, and this is similar to the results Scalfari et al.[19] Kremenchutzky et al[20] suggested that relapses have no impact on long-term disability progression after a certain degree of disability is reached or when the disease duration is more than 2 years. The role of relapses on later functional outcome is proven by many studies showing that early axonal damage was more abundant in the active lesions than in chronic lesions, leading to irreversible neurological damage manifested as incomplete clinical recovery with resultant subsequent cumulative deterioration in functional abilities.[20]

Limitations of the present study included difficulty in performing follow up MRI scanning due to the limited number of devices in Iraq. Also, the security situation in Iraq led to a loss of contact with a high number of patients, and hence leading to involvement of only half of the number of patients registered in the MS clinic.

In conclusion, the poor prognostic indicators were older age at onset, pyramidal and sphincter involvement at the beginning of the illness, and more relapses in the first 2 years of the illness. There were no significant effects of gender and symptom type as prognostic indicators of residual disability. Future case control studies are needed to assess the brain and spinal cord MRI findings in correlation with clinical presentations and prognosis.

References

1. Ropper AH, Brown RH. Multiple Sclerosis and Allied Demyelinative Diseases. In: Victors M, Ropper AH, editors. Adams and Victor's Principles of Neurology. 8th ed. New York (NY): McGraw-Hill Professional; 2005; p. 771-796.
2. Bohlega S. Multiple sclerosis in Arabs. *Neurosciences (Riyadh)* 2003; 8 Suppl: 90.
3. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 1444-1452.
4. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". *Ann Neurol* 2005; 58: 840-846.
5. Moreira MA, Felipe E, Mendes MF, Tilbery CP. [Multiple sclerosis: descriptive study of its clinical forms in 302 cases]. *Arq Neuropsiquiatr* 2000; 58: 460-466. Portuguese.
6. Tremlett H, Zhao Y, Rieckmann P, Hutchinson M. New perspectives in the natural history of multiple sclerosis. *Neurology* 2010; 74: 2004-2015. Review.
7. Niscot A. Gender and sex hormones in multiple sclerosis pathology and therapy. *Front Biosci* 2009; 14: 4477-4515. Review.
8. Simone IL, Carrara D, Tortorella C, Liguori M, Lepore V, Pellegrini F, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. *Neurology* 2002; 59: 1922-1928.
9. Vlahiotis A, Sedjo R, Cox ER, Burroughs TE, Rauchway A, Lich R. Gender differences in self-reported symptom awareness and perceived ability to manage therapy with disease-modifying medication among commercially insured multiple sclerosis patients. *J Manag Care Pharm* 2010; 16: 206-216.
10. Eriksson M, Andersen O, Runmarker B. Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis. *Mult Scler* 2003; 9: 260-274.
11. Myhr KM, Riise T, Vedeler C, Nortvedt MW, Gronning R, Midgard R, et al. Disability and prognosis in multiple sclerosis: demographic and clinical variables important for the ability to walk and awarding of disability pension. *Mult Scler* 2001; 7: 59-65.
12. Pfleger CC, Flachs EM, Koch-Henriksen N. Social consequences of multiple sclerosis: clinical and demographic predictors - a historical prospective cohort study. *Eur J Neurol* 2010; 17: 1346-1351.
13. Lau KK, Wong WW, Sheng B, Yu IT, Fung BH, Li HL, et al. The clinical course of multiple sclerosis patients in Hong Kong. *J Neurol Sci* 2008; 268: 78-82.
14. Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. *J Am Geriatr Soc* 2001; 49: 168-171.
15. Sim FJ, Zhao C, Penderis J, Franklin RJ. The age-related decrease in CNS remyelination efficiency is attributable to an impairment of both oligodendrocyte progenitor recruitment and differentiation. *J Neurosci* 2002; 22: 2451-2459.
16. Stankoff B, Mrejen S, Tourbah A, Fontaine B, Lyon-Caen O, Lubetzki C, et al. Age at onset determines the occurrence of the progressive phase of multiple sclerosis. *Neurology* 2007; 68: 779-781.
17. Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, UBC Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology* 2009; 73: 1616-1623.
18. Ramsaransing G, Maurits N, Zwanikken C, De Keyser J. Early prediction of a benign course of multiple sclerosis on clinical grounds: a systematic review. *Mult Scler* 2001; 7: 345-347.
19. Scalfari A, Neuhaus A, Degenhardt A, Rice GP, Muraro PA, Daumer M, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain* 2010; 133: 1914-1929.
20. Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: observations on the progressive phase of the disease. *Brain* 2006; 129: 584-594.