Prognostic Indicators in Patients with Relapsing Remitting Multiple Sclerosis

Ali Kadim Karim *,Nawfal Madhi Sheaheed **,Abdulraheem Taha *, Zeki Noah Al-Musawi ******

ABSTRACT:

BACKGROUND:

Multiple sclerosis is an inflammatory demyelinating disease of the central nervous system affecting nearly 2 million people worldwide. Multiple sclerosis typically begins in early adulthood and has a variable prognosis.

OBJECTIVE:

To determine the factors that affects the prognosis in Iraqi patients with relapsing remitting multiple sclerosis.

PATIENTS AND METHODS:

This study includes fifty patients with relapsing remitting MS and was conducted from March 2007 to July 2008 in Baghdad Teaching Hospital MS clinic. A study protocol sheet was done and filled from the patient's database in the MS clinic. The prognostic indicator of residual disability depends on the Expanded Disability Status Scale (EDSS).

RESULTS:

The mean age for the study sample was 45.58 years, with 27 male and 23 female. High percentage of patients presented as monosymptomatic (70%), most of the symptoms was spinal (48%). The mean value for relapses was 2.3 with maximum number of 6. The study shows that there is no significant effect of gender as a prognostic indicator on the residual disability of patient with relapsing remitting MS. There is significant correlation between the age at CDMS and the EDSS in the first visit (EDSS1).

CONCLUSION:

We concluded that the older age at onset, pyramidal and sphincteric involvement at the beginning of the illness and more relapses in the first 2 years of the illness all are associated with poor prognosis.

KEY WORDS: relapsing remitting multiple sclerosis, prognostic indicator.

INTRODUCTION:

In 1983, Poser et al. proposed a new set of criteria for diagnosing MS that combined findings from the clinical examination and patient history with the results of MRI, CSF testing, and VEP [1-6]. Diagnostic criteria for clinically definite MS require documentation of two or more episodes of symptoms and two or more signs that reflect pathology in anatomically noncontiguous white matter tracts of the CNS [6].

* Baghdad Teaching Hospital, Baghdad.
** Baghdad Teaching Hospital, Baghdad.
*** Baghdad Teaching Hospital, Baghdad.
**** Professor of Neurology at Al-Kindi College of Medicine, Baghdad University; Consultant Neurologist, Neurosciences Hospital, Baghdad.

Although there is significant variability between patients, average time from disease onset to difficulty with walking is 8 years; walking with a cane is 15 years; and wheelchair-bound is 30 years. These observational studies were performed before the use of disease-modifying therapies, so these estimates may be different in patients receiving treatment [7]. Certain clinical features suggest a more favorable prognosis, including optic neuritis (ON) or sensory symptoms at onset; fewer than two relapses in the first year of illness; and minimal impairment after 5 years [6]. Older age at onset, initial symptoms involving cerebellar, spinal, or pyramidal systems and higher initial clinical activity are all unfavorable prognostic factors. Prognostic

radiologic measures include brain and spinal cord atrophy and gadolinium-enhancing lesions [7]. Patients with truncal ataxia, action tremor, pyramidal symptoms, or a progressive disease course are more likely to become disabled. Importantly, some MS patients have a benign variant of MS and never develop neurologic disability. The likelihood of having benign MS is thought to be <20%. Mortality as a direct consequence of MS is uncommon, although it has been estimated that the 25-year survival is only 85% of expected. Death can occur during an acute MS attack, although this is distinctly rare. More commonly, death occurs as a complication of MS (e.g., pneumonia in a debilitated individual). Death also results from suicide [6]. The objective of this study is to define groups of prognostic factors in the natural history of relapsing remitting MS and to study the effects of such factors.

PATIENTS AND METHODS:

A retrospective randomized study conducted in the MS clinic of neurology department of Baghdad teaching hospital in the period from March 2007 to July 2008 and 50 patients sheets were reviewed and examined carefully. Patients whom started this disease course as a relapsing remitting form were involved while patients with other disease course were excluded, except those patients who started as relapsing remitting disease (RRD) and progressed to secondary progressive form with a hope to find factors that may affect such prognosis at least in our population. The study primarily based on review of patients file sheets that are registered in the MS clinic. EDSS score was used to assess the severity of the disease. Number of relapses in the first 2 years of the illness. EDSS score at first inclusion in the MS clinic (EDSS1). EDSS score at last follow-up (EDSS2). The data were transferred to a corresponding data sheets. Data were translated into a computerized database structure. An expert statistical advice was sought for. Statistical analyses were computer assisted using SPSS version 14(Statistical Package for Social Sciences). Frequency distribution for selected variables was done first. P value less than 0.05 level of significance 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 two continuous variables. The statistical significance of difference in mean of a normally distributed quantitative variable between 2 groups was assessed by independent sample t-test.

RESULTS:

The study was performed on fifty clinically definite MS patients with relapsing remitting course. (Table 1) shows the number, the mean and the standard deviation (SD) for the age, gender, and the age at CDMS and their percentages. The minimum age at enrollment in the MS clinic was 29 years old and the maximum one was 62 years old. The minimum age at CDMS was 18 years old and the maximum one was 52 years old. (Table 2) shows the high percentage of pyramidal symptoms among the patients. (Table 2) also shows that there is significant correlation between sphincteric and pyramidal symptoms and their effect the residual disability (EDSS2) while the other symptoms are not. (Table 3) shows highly significant correlation between the numbers of relapses in the first 2 years of the illness and the residual disability (EDSS2).

Table 1: The demographic distribution of the study group.

Parameter		No. / %				
Number		50				
AGE	Minimum	29				
	Maximum	62				
	Mean	45.58				
	SD	8.43				
Gender	Male	23/46%				
	Female	27/54%				
Age at CDMS*	Minimum	18				
	Maximum	52				
	Mean	30.92				
	SD	7.71				
	FEMALE			MALE		
	N	mean	SD	N	mean	SD
EDSS1	27	5.1852	2.3252	23	5.0217	2.1610
EDSS2	27	6.2037	2.1134	23	5.8913	1.9185

* CDMS Clinically Definite MS

Table 2: the distribution of patient according to the specific symptoms and the correlation between specific symptoms and EDSS

Specific symptoms	No.	%	EDSS1		EDSS2	
			mean	STD*	mean	STD
Cerebeller	1	2.0%	1.5000	.	4.0000	.
Brain stem	5	10.0%	5.5000	2.5981	5.9000	2.3822
Sphenicter	8	16.0%	6.0000	2.0000	6.9375	1.6570
Pyramidal	24	48.0%	5.5208	2.0720	6.3542	1.7537
Optic	12	24.0%	3.8333	2.0487	5.1250	2.3848

*STD: standard deviation.
P value for sphinecteric and pyramidal symptoms= (<0.05)

Table 3: The correlation between the relapses and the EDSS2.

parameter	Mean	standard Deviation	Minimum	Maximum	Chi-Square	df	p
relapses	2.3000	1.61940	.00	6.00	25.600	6	.000
EDSS2	6.2100	2.03312	1.50	9.00	27.480	12	

DISCUSSION:

Our study reveals that gender has no effect on the prognosis and this is may be due to small sampling. Lević Z, Dujmović I et al have been dealing with the prognostic relevance of gender; the results of different studies were controversial[8]. In some reports, female sex was associated with better prognosis, but in others the results were opposite, females were at a higher risk of transition to a worse disease state [8]. Arnaud N study shows that sex dimorphism may be explained by sex chromosome effects and effects of sex steroid hormones on the immune system, blood brain barrier or parenchymal central nervous system (CNS) cells[9]. D. A. Cottrell et al reveal that gender had no discernible effect on the rate of progression through early levels of the EDSS scale, but time from onset of multiple sclerosis to EDSS 10 was significantly more rapid in men than in women [7]. Out of the 10 studies [10-19] that considered , two showed that men with RRMS were at significantly greater risk after adjusting for other factors and 3 showed a no significant trend of increased risk among men. The remaining 5 studies [10-19] found no effect for sex [20]. In the case of mortality rate in MS, no significant difference between the sexes was found [21]. In our study the results show there is significant

correlation between the age at onset and the residual disability, in which patients older than 40 years have poor prognosis. Poser S et al show that the mean age at onset was significantly less in the benign MS, on average being 5.4 years younger than in the non-benign MS. Those older than 40 at onset were more likely to have progressive disease from onset. Overall these data support the findings of others indicating that onset after age 40 are generally associated with an unfavorable course [22-26]. Male gender tend to have older age of onset, tendency for a more progressive course, more frequent onset of disease with motor, cerebellar, or sphincter symptoms [27]. Tremlett H et al confirmed the above findings as well as the lack of female preponderance in primary progressive MS independent of age of onset [28, 29]. The survival time is certainly longer for young patients, but the prognosis as judged from the disruption of the normal pattern of life from an early age may indeed be worse [30] The shorter survival among patients with a high age at onset may be a reflection of the shorter life expectancy among older patients, independently of the disease; Thus the age effect on life expectancy may represent a real biological effect of the disease. Older age at onset was associated with a worse prognosis in all studies but Trojano M et al [16] showed that the strength of the association varied depending on how older age at onset was defined and how disability was defined. When continuous measures of age at onset were used the risk of developing secondary progressive MS (SPMS) per decade ranged from 10% to 34 %[12, 14, 15, and 18]. Varying the definition of disability from development of SPMS to "severely impaired or lost walking" changed the odds ratio from 2.12 to 1.09 in the same population of patients. Thus, age at onset does not seem to be a robust predictor of disability [21]. Some evidence suggests that age also influences disease course, as patients with late onset MS more frequently have primary progressive disease than patients with an earlier onset [31, 32]. Several mechanisms could be involved in this age-related neurodegenerative course of the disease. An age related decrease in CNS remyelination has been observed in experimental models [33] and such a repair defect is a key player in the occurrence and aggravation of an irreversible neurologic disability in MS. McAlpine D et al have suggested that manifestations of optic neuritis or sensory symptoms at onset [34, 35] is associated with benign status, whereas pyramidal symptoms at onset have been associated with a poor outcome[34,36,37,38,39]. Similarly initial sensory symptoms have been considered favourable by some, but not by others [40]. In our study relapses play an important role on the subsequent disability in patient with relapsing remitting MS in which more relapses in the first years of the illness are associated with poor prognosis. A relapse was defined as a period of at least 24 hours in which new symptoms develop, or existing ones deteriorate, with objective evidence from clinical examination for a change, and against background course stability for at least 1 month [6]. There is evidence that relapses are strongly correlated with active MRI lesions, either with the appearance of new ones, enlargement of old ones or with gadolinium enhancement. A high number of relapses in the first and second years, a short relapse-free interval between the first two attacks, polysymptomatic onset and time to early disability are additional,but less important factors [41,42]. Relapses are considered to be the clinical expression of acute inflammatory lesions in which focal disruption of the blood-brain barrier is followed by an immunological cascade in which migration of inflammatory cells into the CNS precipitates demyelination through complement damage as well as other immunological mechanisms. The onset of functional impairment is commonly acute or subacute and caused by demyelination, conduction block and in some cases axonal damage. Complete or partial resolution of disability usually occurs over weeks or months [43-46] and is thought to involve an element of resolution of oedema and inflammation, remyelination, axon sodium channel redistribution, and lesion repair. This suggests that relapses play an important role in determining subsequent prognosis and in development of disability, although other studies have failed to confirm this association [47, 48].

CONCLUSION:

Gender has no effect on the residual disability (EDSS) in patient with relapsing remitting MS. Older age at onset is associated with poor prognosis. Type of symptoms whether mono or polysymptoms have no effect as a prognostic factor in patient with relapsing remitting MS. The EDSS score is influenced greatly if the presenting symptoms were pyramidal or sphincter involvement.

Recommendations: recording the EDSS score in each visit of patient to the MS clinic at least once

time every 2 months. Disease modifying therapy should be used if it is indicated in order to decrease the number of relapses in relapsing remitting course of MS for which that have worse effect on the prognosis.

REFERENCES:

1. McDonald. W. I., Compston, A., Edan, G., Goodkin, D. E., Hartung, H. P., Lublin F. D., et al. Recommended Diagnostic Criteria for Multiple Sclerosis: Guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. Annals of Neurology 2001;50:121-27.
2. Picone MA, Cook SD. Multiple sclerosis. In: Kirshblum S,Campagnolo DI, DeLisa JA, editors. Spinal cord medicine. Philadelphia:Lippincott Williams & Wilkins; 2002: 527-36.
3. Polman, C. H., Reingold, S. C., Edan, G., Filippi, M., Hartung, H, Kappos, L., et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Annals of Neurology. 2005; 58: 840-46.
4. Poser, C., Paty, D., Scheinberg, L., McDonald, W., Davis, F., Ebers, G., et al.. New diagnostic criteria for multiple sclerosis: Guidelines for research protocols. Annals of Neurology. 2001; 13:227-31.
5. Schumacher, G. A., Beebe, G. W., Kibler, R. F., Kurland, L. T., Kurtzke, J. F., McDowell, F., et al.. Problems of experimental trials of therapy in multiple sclerosis: Report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. Annals of New York Academy of Sciences. 1965; 122:552-68.
6. Swanton, J. K., Fernando, K., Dalton, C. M., Miszkiel, K. A., Thompson, A. J., Plant, G. T., et al. Modifi cation of MRI criteria for multiple sclerosis in patients with clinically isolated syndromes. Journal of Neurology, Neurosurgery, and Psychiatry, 2006;77: 830-33.
7. Cottrell DA, Kremenchutzky M, Rice GP, Koopman WJ, Hader W, Baskerville J, Ebers GC. The natural history of multiple sclerosis: a geographically based study. 5. The clinical features and natural history of primary progressive multiple sclerosis. Brain 1999; 122, 625–39.
8. Lević Z, Dujmović I et al. Prognostic factors for survival in multiple sclerosis. Multiple Sclerosis 1999; 5:171-78.
9. Arnaud Nicot. Gender and sex hormones in multiple sclerosis pathology and therapy. Frontiers in Bioscience 2009; 14: 4477-515.
10. Eriksson M, Andersen O, Runmarker B. Long-term follow up of patients with clinically isolated syndromes, relapsing-remitting and secondary progressive multiple sclerosis [published correction appears in *Mult Scler*. 2003;9:641]. *Mult Scler*. 2003; 9:260-74.
11. Myhr KM, Riise T, Vedeler C, 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. Riise T, Gronning M, Fernandez O, et al. Early prognostic factors for disability in multiple sclerosis, a European multicenter study. *Acta Neurol Scand*. 1992; 85:212-18.
13. Simone IL, Carrara D, Tortorella C, et al. Course and prognosis in early-onset MS: comparison with adult-onset forms. *Neurology*. 2002; 59:1922-28.
14. Kantarci O, Siva A, Eraksoy M, et al; Turkish Multiple Sclerosis Study Group
15. (TUMSSG). Survival and predictors of disability in TurkishMSpatients. *Neurology*. 1998; 51:765-72.
16. Bergamaschi R, Berzuini C, Romani A, Cosi V. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. *J Neurol Sci*. 2001; 189:13-21.
17. Trojano M, Avolio C, Manzari C, et al. Multivariate analysis of predictive factors of multiple sclerosis course with a validated method to assess clinical events. *J Neurol Neurosurg Psychiatry*. 1995; 58:300- 6.
18. Poser S. Multiple sclerosis: an analysis of 812 cases by means of electronic data processing. *Schriftenr Neurol*. 1978; 20:1-93.
19. Amato MP, Ponziani G, Bartolozzi ML, Siracusa G. A prospective study on the natural history of multiple sclerosis: clues to the conduct and interpretation of clinical trials. *J Neurol Sci*. 1999; 168:96-106.
20. Moreira MA, Felipe E, Mendes MF, Tilbery CP. Multiple sclerosis: descriptive study of its clinical forms in 302 cases. *Arq Neuropsiquiatr*. 2000; 58:460-66.

21. Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. *N Engl J Med*. 2005; 353:375-81.

22. Annette Langer-Gould, Rita A. Popat, Stella M. Huang, Kristin Cobb, Paulo F, Michael K. Gould, Lorene M. Nelson: Clinical and DemMultivariate analysis of predictive factors and models of outcome. *Brain* 1991; 114:1045–56.

23. Visscher BR, Liu K-S, Clark VA, *et al*. Onset symptoms as predictors of mortality and disability in multiple sclerosis. *Acta Neurol Scand* 1984; 70:321–28.

24. Hawkins S A, McDonnell G V. Benign multiple sclerosis? Clinical course, long term follow up, and assessment of prognostic factors. *J Neuro Neurosurg Psychiatry* 1999; 67:148–52.

25. Pittock SJ, McClelland RL, Mayr WT, et al. Clinical implications of benign multiple sclerosis: a 20-year popographic Predictors of Long-term Disability in Patients with Relapsing-Remitting Multiple Sclerosis. Arch Neurol/Vol 63, DEC 2006:1686-91.

26. Sumelahti ML. Occurance, survival and prognostic factors of multiple sclerosis in Finland. Acta Universitatis Tamperensis 874. University of Tampere: Tampere 2002.

27. Leibowitz U, Alter M. Clinical factors associated withincreased disability in multiple sclerosis. *Acta Neurol Scand* 1970; 46:53–70.

28. Poser S, Bauer HJ, Poser W. Prognosis of multiple sclerosis. Results from an epidemiological area in Germany. *Acta Neurol Scand* 1982; 65:347–54.

29. Weinshenker BG, Rice GPA, Noseworthy JH, *et al*. The natural history of multiple sclerosis: a geographically based study. 3. ulation-based follow-up study. Ann Neurol 2004; 56:303–06.

30. Tremlett H, Paty DW, Devonshire V. The natural history of primary progressive MS in British Columbia, Canada. Neurology 2006; 65:1919–23.

31. Kantarci O. and Wingerchuk D. Epidemiology and natural history of multiple sclerosis: new insights Current Opinion in Neurology 2006;19:248–54.

32. Lyon-Caen O, Izquierdo G, Marteau R, et al. Late onset multiple sclerosis. A clinical study of 16 pathologically proven cases. Acta Neurol Scand 1985; 72:56–60.

33. Polliack ML, Barak Y, Achiron A. Late-onset multiple sclerosis. J Am Geriatr Soc 2001; 49:168–71.

34. 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; 22:2451–59.

35. McAlpine D. The benign form of multiple sclerosis: a study based on 241 cases seen within three years of onset and followed up until the tenth year or more of the disease. Brain 1961; 84:186–203.

36. 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;7:345–47.

37. Kurtzke JF, Beebe GW, Nagler B, Kurland LT, Auth TL. Studies on the natural history of multiple sclerosis: 8. Early prognostic features of the later course of the illness. J Chronic Dis 1977; 30:819–30.

38. Thompson AJ, Hutchinson M, Brazil J, Feighery C, Martin EA. A clinical and laboratory study of benign multiple sclerosis. Q J Med 1986; 58:69–80.

39. Ramsaransing GS, De Keyser J. Benign course in multiple sclerosis: a review. Acta Neurol Scand 2006; 113:359–69.

40. Sayao AL, Devonshire V, Tremlett H. Longitudinal follow-up of "benign" multiple sclerosis at 20 years. *Neurology* 2007; 68:496-500.

41. Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. Neurol Sci 2000; 21:S831-S38.

42. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003; 126:770–82.

43. Weinshenker BG, Bass, B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain; 1989;112:1419–28.

44. George C. Ebers. Prognostic factors for multiple sclerosis: the importance of natural history studies. J Neurol 2005; 252 [Suppl 3]: III/15–III/20.

45. Bethoux F, Miller DM, Kinkel RP Recovery following acute exacerbations of multiple sclerosis: from impairment to quality of life. Mult Scler 2001;7:137–42.
46. Nos C, Sastre-Garriga J, Borras C, Rio J, Tintore M, Montalban X Clinical impact of intravenous methylprednisolone in attacks of multiple sclerosis. Mult Scler 2004;10:413–16.
47. Ozakbas S, Cagiran I, Ormeci B, Idiman E ,Correlations between multiple sclerosis functional composite, expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis. J Neurol Sci .2004; 218:3–7.
48. West T, Wyatt M, High A, Bostrom A, Waubant E .Are initial demyelinating event recovery and time to second event under differential control? Neurology 2006;67:809–13.
49. Fog T, Linnemann F, The course of multiple sclerosis in 73 cases with computer-designed curves. Acta Neurol Scand .1970;47(Suppl):3–175.