Right-Sided clinical findings are worse prognostic factor in Multiple Sclerosis patients?

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ABSTRACT

الأهداف: دراسة أهمية جانب النتائج السريرية في التنبؤ بحالة مرضى التصلب المتعدد (MS).

المنهجية: في دراستنا قمنا بتسجيل 361 مريضا MS. تم إجراء هذه الدراسة بأثر رجعي. في الفحوصات العصبية، تم تسجيل النتائج السريرية على أنها اليمين واليسار والثنائية. استخدمنا مقياس اتساع مدى الإعاقة (EDSS)، درجة شدة التصلب المتعدد (MSSS)، مؤشر التقدم (PI) للحالة العصبية.

النتائج: في الهجوم الأول ، كانت هناك اختلافات في EDSS، PI و MSSS للنتائج على الجانب الأيمن بين فترات السكون والهجوم (p=0.057, p=0.008, p=0.017). في النتائج السريرية على الجانب الأيمن، كانت قيمة PI و MSSS أعلى من القيم الأخرى في فترات السكون والهجوم (p=0.002, p=0.045). في الهجوم الأخير، وجدنا اختلافات ثابتة في قيم EDSS و EDSS بين فترات السكون والهجوم في النتائج السريرية على الجانب الأيمن فقط (p=0.042, p=0.027). في العرض الأول، كانت قيمة PI في العلامات السريرية الثنائية أقل (p=0.016).

الخلاصة: كانت النتائج السريرية على الجانب الأيمن عوامل تنبؤ ضعيفة في جميع مراحل التصلب المتعدد، في حين أن النتائج الثنائية لم تكن عاملاً تنبؤيًا ضعيفًا في المرحلة المبكرة من التصلب المتعدد.

Objectives: To investigate the importance of the side of clinical findings in predicting the prognosis in multiple sclerosis (MS) patients.

Methods: In our study we enrolled 361 MS patients. This study as retrospective was performed. On neurological examinations, clinical findings were recorded as right, left and bilateral. We used the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Severity Score (MSSS), Progression Index (PI) for neurological status.

Results: At the first attack, there were differences in the EDSS, PI and MSSS of right-sided findings between remission and attack periods (p=0.057, p=0.008, p=0.017 respectively). In the right-sided clinical findings, the value of PI and MSSS were higher than the others between in remission and attack periods (p=0.002, p=0.045 respectively). At last attack, we found statically differences in EDSS, MSSS values between remission and attack periods in only right-sided clinical findings (p=0.042, p=0.027 respectively). In the first presentation the PI value in bilateral clinical signs was lower (p=0.016).

Conclusion: Right-sided clinical findings were poor prognostic factors in all stages of MS, whereas bilateral findings were not poor prognostic factor in the early-stage MS.

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In the literature, there are many studies that investigate prognostic factors in patients with multiple sclerosis patients.[1,2] Most of these studies are related to biomarkers.[3,4] Many previous studies have described differences in brain modulation of immune function by right and left hemispheres.[5,6,7] In animal studies, researchers showed that each hemicortex modulated lymphocyte reactivity in different ways.[5] However, asymmetry of cell-mediated immunity in peripheral system has been demonstrated in some cancer cases.[8-10] Using the tuberculin test, it was reported that cell-mediated immune hypersensitivity response in the left side was higher than right side in high-school students.[11] The right neocortex suppressed functions of immune

system, whereas the left neocortex induced functions of immune system.[12] Despite researchers reported asymmetry of cell-mediated immunity in peripheral system in various cancer types. We believe that our study is important in terms of leading the studies investigating the central asymmetry of cell-mediated immunity for other studies, including MS. Therefore, our aim in this study is to investigate the importance of right/left/bilateral-sided clinical findings for predicting the prognosis in MS.

Methods. This study was performed as retrospectively at Neurology Department, Istanbul Medeniyet University, Goztepe Research and Educational Hospital, Istanbul, Turkey. We recorded MS patients (n=361) between 2001 and 2016. In accordance with the 2010 McDonald criteria, we included aged 18-70 years with diagnosed of relapsing-remitting MS (RRMS), primary progressive MS(PPMS), or secondary progressive MS (SPMS) patients.[13,14] We considered the patients under 14 years of age as pediatric onset and excluded from the study. The patients of MS were divided into relapse and remission periods. We considered the onset of symptoms as the duration of the disease. We tought that the first presentation sign is very important to evaluate prognosis of MS. The exclusion criteria were a history of neurodegenerative diseases or other neuroinflammatory diseases. The institutional ethics committee approved our study protocol. Ethics Approval Letter signed and stamped by Ethics Committee is presented.

Gender, age at onset of MS, family history of MS, MS type, MS drug treatment, education, existence of other disorders, duration of MS, and existence of MS lesions in supratentorial, infratentorial, and brainstem or spinal areas were recorded, in addition to the existence of CSF oligoclonal bands. We noted visual and sensorial evoked potentials from hospital charts. On neurological examinations, findings were classified as right unilateral, left unilateral, or bilateral in both attack and remission periods.

To evaluate disability, the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Severity Score (MSSS), Progression Index (PI) were used[14-16] in both attack and remission periods. PI used (PI=EDSS/time from onset in years) in order to evaluate disability for the disease duration. As it is generally considered that very slow PI (0.20 or less) has at least approximately as good prognostic value.

The Extended Disability Situation Scale (EDSS) was also used and if the EDSS score is 0-3.5, it is considered mild or if the EDSS score is 4-9.5 it is considered moderate / severe MS. To determine MSSS (Multiple Sclerosis Scale Score) can be use a program from http://www-gene.cimr.cam.ac.uk/MSgenetics/GAMES/MSSS. The score is from 0 to10 -low is good, high is bad. At all visits, right optic neuritis, left optic neuritis, right pyramidal sign, left pyramidal sign, right sensory sign, left sensory sign, right cerebellar sign, left cerebellar sign, intestinal bladder sign, and brainstem sign were checked. Bilateral pyramidal signs, bilateral sensory signs, bilateral cerebellar signs, bilateral optic neuritis, intestinal bladder signs and brainstem signs were accepted as bilateral clinical findings. The other clinical findings were accepted as right or left sided clinical findings. We tried to control patients with at least 6 months intervals. There were also patients who came more frequently or later than this range. We used the neurological disability of the first and last lateralized clinical findings in order to obtain a more accurate result when performing the statistical analysis of the patients.

Statistical analysis. We used the Number Cruncher Statistical System 2007 (Kaysville, Utah, USA) program. We applied that statistical methods (mean, standard deviation, median, frequency, odds, minimum, maximum) for descriptive analysis. For comparing 2 groups of parameters we used Mann–Whitney U test in the quantitative data which does not conform to a normal distribution. We used the Kruskal–Wallis test for comparisons of 3 groups not having normal distribution. To compare for intra-group of parameters not having normal distribution we used the Wilcoxon signed-ranks test. We used Spearman's correlation analysis to assessment interparameter relationships. We reported data as mean ± standard deviation. if $p<0.05$ was considered significant.

Results. In our study, 251 (69.5%) participants were females, and 110 (30.5%) were males. The patients were aged 19–69 years, the mean age was 40.65±9.97 years. **Table 1** shows the patients' demographic features. The duration of the disease ranged from 1 to 43 years, mean 10.98±7.94 years. Age of onset of the disease ranged from 14 to 58, mean 30.42±8.70 years. Regarding family medical history, MS was found in first-degree relatives in 5.5% (n=20) of cases and present in second-degree relatives in 1.4% (n=5) of cases. There was no family history of MS in 93.1% (n=336) of cases.

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Additional diseases were present in 64.7% (n=234) of cases. Depression was observed in 13.6% (n=49) of MS patients. The average follow-up was 4.97±3.80 months.

The EDDS ranged from 0 to 8.5, with a mean of 2.34±2.00. The PI measurements ranged from 0 to 6.5, with an average of 0.52±0.62. The MSSS ranged from 0 to 97, with a mean of 44.50±26.66.

In the attack periods, right optic neuritis was observed in 1.5% (n=27) of cases, and left optic neuritis was detected in 2.0% (n=38) of subjects. The right pyramidal signs were present in 2.5% (n=49) of cases, and the left pyramidal signs were present in 4.4% (n=82) of cases. The right sensory signs were detected in 4.8% (n=90) of cases, and the left sensory signs were detected in 0.8% (n=14) of cases. The right cerebellar signs, left cerebellar signs, intestinal bladder signs, and brainstem signs were detected in 0.8% (n=14), 0.9% (n=16), 0.2% (n=4), and 1.8% (n=33) of cases, respectively.

In the remission periods, right optic neuritis was observed in 13.9% (n=258) of cases, and left optic neuritis was observed in 14.4% (n=267) of cases. The right pyramidal signs were observed in 27.6% (n=512) of cases, and the left pyramidal signs were detected in 13.7% (n=254) of cases. The right sensory signs, left sensory signs, right cerebellar signs, left cerebellar signs, intestinal bladder signs, and brainstem signs was detected in 13.6% (n=252), 12.1% (n=225)12.1% (n=225), 12.4% (n=231), 38.4% (n=714), and 20.9% (n=388) of cases, respectively.

Table 1 - The demographic features of multiple sclerosis patients.

Age (year)	**n** (%)
Min-Max (Median)	19-69 (40)
m±SD	40.70±10.05
Gender n (%)	
Female	251 (69.5)
Male	110 (30.5)
Duration of illness(year)	
Min-Max (Median)	1-43 (8)
m±SD	10.98±7.94
Age of onset of illness(year)	
Min-Max (Median)	14-58 (29)
m±SD	30.42±8.70
Educationstatus n (%)	
Noliterate	14 (3,8)
Primaryschool	170 (47.1)
High school	95 (26.4)
License	74 (20.5)
Graduate	8 (2.2)
Familyhistory n (%)	
MS absent	336 (93.1)
First degreerelative	20 (5.5)
Second degreerelative	5 (1.4)

The rates of infratentorial, supratentorial, spinal, and brainstem lesions were 8.4% (n=157), 27.0% (n=501), 15.2% (n=283), and 8.5% (n=158), respectively. Regarding MS types, the incidence of RRMS was 80.6% (n=1497), whereas that of SPMS and PPMS was 12.7% (n=236) and 6.7% (n=124), respectively.

Gender and family history were not prognostic indicators (p>0.05). According to the EDSS, older age was associated with a worse prognosis (p<0.01), although this relationship was not confirmed by the MSSS or PI. In evaluations of the EDSS, PI, and MSSS during the first attack periods in MS patients, only the PI was lower in patients with bilateral clinical signs than those with right- or left-sided clinical signs (p=0.016), as shown in **Table 2**.

At the time of the first attack, the difference in the EDSS between remission and attack periods was not statistically significant among patients with right/left/bilateral clinical findings (p>0.05). It was the only remarkable reduced measurement at the right-sided clinical signs (p=0.057). When the EDSS of patients was compared according to the side of clinical signs, there was no difference among patients with right unilateral, left unilateral, or bilateral clinical findings (p>0.05). During the last attack, we found statistically significant difference in the EDSS in patients with only right-sided clinical signs between remission and attack periods (p=0.042) (**Table 3**).

At the time of the first attack, PI values were lower in those with bilateral clinical signs than other sided clinical sign values during the attack period (p=0.001). The difference in PI values between remission and attack periods was statistically significant in patients with right-sided clinical signs (p=0.008) and bilateral-sided clinical signs (p=0.036). The differences between the remission and attack periods measurements are statistically significant compared to the groups. The difference in PI values between remission and attack periods in patients with right-sided clinical signs was higher compared to the difference in PI values between remission and attack periods in patients with left and bilateral sided clinical signs. (p=0.002). At the last attack, for PI values we found no significant difference between remission and attack periods (**Table 3**).

During the first attack, MSSS values of patients with left-sided clinical findings were higher than patients with other sided clinical findings in the remission periods (p=0.007). The difference in MSSS values

Table 2 - Evaluating of EDSS, PI and MSSS only at the first attacks in MS patients.

EDSS n=78	Right sided n=11	Left sided n=6	Bilateral sided n=53	[a]*p*-value
Min-Max(Median)	1-6.5 (2)	1-5 (2.3)	0-7 (1.5)	0.347
Mean±SD	2.59±1.43	2.75±1.47	2.50±2.26	
PI				
Min-Max(Median)	0.2-3.3 (1)	0.1-2 (1)	0-5 (0.3)	0.016*
Mean±SD	1.33±1.07	1.13±0.75	0.65±0.87	
MSSS				
Min-Max(Median)	18-96 (67)	32-90 (37)	0-96 (31)	0.214
Mean±SD	56.64±26.45	52.80±26.96	41.5±32.71	

[a]Kruskall Wallis Test, *p<0.05

between remission and attack periods was statistically significant in those with right-sided clinical findings (p=0.017). The difference in PI values between remission and attack periods in patients with right-sided clinical signs was higher compared to the difference in PI values between remission and attack periods in patients with left and bilateral sided clinical signs (p=0.045). At the time of the last attack, MSSS values of patients with only right-sided clinical findings there was a significant difference between in remission and attack periods (p=0.027), as shown in **Table 3**.

In patients with infratentorial lesions, EDSS values were higher than those of patients without infratentorial lesions in both remission and attack periods (p=0.029, p=0.016, respectively). Not detected significant difference in EDSS values of infratentorial lesion of patients between remission and attack periods (p=0.035).

In patients with spinal lesions, EDSS and MSSS values were higher in those without spinal lesions in both remission (p=0.022; p=0.027, respectively), attack periods (p=0.002; p=0.008 respectively). There was no significant difference for PI values in patients with spinal lesions between remission and attack periods (p=0.009).

In patients with brainstem lesions, EDSS and MSSS values were higher in patients with brainstem lesions than in those than without brainstem lesions in both remission (p=0.006; p=0.016, respectively), attack periods (p=0.012; p=0.030, respectively). The PI values were also high in the remission period in patients with brainstem lesions (p=0.012).

In patients with supratentorial lesion, we found no statistically significant difference for the EDSS, PI, or MSSS values (p>0.05). In terms of lateralized clinical findings, we found no difference in the EDSS, PI, or MSSS values (p>0.05) of patients with RRMS, PPMS, SPMS.

In MS patients with additional diseases and disorders, such as collagenous tissue disease, and depression, we found no difference in the EDSS, PI, or MSSS values (p>0.05) compared with patients with MS without these diseases.

Discussion. Asymmetrical modulation of the immune system, peripheral system, and central nervous systems has been reported.[17] In an animal study, Shen et al[18] reported that interleukin-6 played an important function in asymmetrical brain immunomodulation in brain. Previous studies reported peripheral asymmetry of cell-mediated immunity in various diseases.[11,18] Clinical research studies also reported differences in immunomodulatory effects of right and left hemispheres, in addition to immune asymmetry mediated by peripheral cells in some diseases.[18,19] In the present study, neurological disability as assessed by the EDSS, PI, and MSSS was worse in patients with right-sided clinical findings at the time of the first attack as compared with that of patients with other sided clinical findings. In addition, right-sided clinical findings were worse for EDSS and MSSS at the last attack as compared with that of patients with other sided clinical findings. In light of these data, we conclude that right-sided clinical findings were worse as compared with those with left-and bilateral-sided clinical findings in earlier and later stages of MS.

As can be seen from **Table 3**, in the first attack, neurological disabilities in patients with right lateralized findings were poor for EDSS, PI and MSSS (p<0.05); in the last attack, neurological disabilities in patients with right lateralized findings were poor for EDSS and MSSS (p<0.05). Therefore, we can say that right lateralized findings were poor prognostic factor. Although, neurological disabilities in patients with bilateral lateralized findings were not poor for EDSS, PI

Table 3 - Evaluation of EDSS, PI and MSSS Value of Side of Clinical Findings in the Remission and Attack Periods at the first and last attacks.

		The First attack side of clinical findings				The Last attack side of clinical findings			
		Right (n=36)	Left (n=39)	Bilateral (n=183)	[a]*P*-value	Right (n=8)	Left (n=7)	Bilateral (n=259)	[a]*P*-value
EDSS									
Remission	Min-Max(Median)	0-4.5 (1)	0-7 (1.5)	0-8 (1.5)	0.123	1-3.5 (2)	1-6.5 (2)	0-8 (1.5)	0.139
	Mean±SD	1.47±1.22	2.24±1.75	2.29±2.04		2.14±1.03	3.29±2.27	2.12±1.88	
Attack	Min-Max(Median)	0-4 (2)	0-7 (2)	0-8.5 (2)	0.860	1-5.5 (2.5)	1-5 (3)	0-8.5 (2)	0.191
	Mean±SD	1.93±0.91	2.40±1.80	2.46±2.08		2.88±1.60	2.93±1.48	2.34±1.92	
[b]*p*-value		0.057	0.660	0.224		0.042*	1.000	0.058	
Difference (Attack-Remission)	Min-Max(Median)	-2.5-3 (0.5)	-5-7 (0)	-6.5-6 (0)	0.630	0-2 (1)	-5-2 (0)	-6.5-7 (0)	0.331
	Mean±SD	0.46±1.35	0.15±2.19	0.18±2.40		1.00±0.87	-0.36±2.39	0.22±2.24	
PI									
Remission	Min-Max(Median)	0-2 (0.3)	0-3.5 (1)	0-6.5 (0.5)	0.126	0.3-3 (1)	0.3-6.5 (0.7)	0-5.5 (0.5)	0.078
	Mean±SD	0.66±0.70	0.93±0.79	0.75±0.89		1.29±0.86	1.47±2.23	0.75±0.78	
Attack	Min-Max(Median)	0-3 (1)	0-4 (0.6)	0-6.5 (0.3)	0.001**	0.3-5 (0.8)	0.2-1.5 (0.4)	0-6.5 (0.4)	0.350
	Mean±SD	1.16±0.89	1.06±1.02	0.62±0.79		1.30±1.56	0.63±0.47	0.79±0.90	
[b]*p*-value		0.008**	0.712	0.036*		1.000	0.068	0.804	
Difference (Attack - Remission)	Min-Max(Median)	-1.8-2.5 (0.5)	-3.1-2.4 (0)	-5.5-5 (0)	0.002**	-1.6-2 (0.1)	-5-0 (-0.1)	-5.5-5 (0)	0.385
	Mean±SD	0.50±1.04	0.11±1.21	-0.13±1.04		0.02±1.17	-0.85±1.85	0.04±1.08	
MSSS									
Remission	Min-Max(Median)	0-81 (32)	10-93 (50)	0-94 (36)	0.007**	30-88 (50)	12-92 (50)	0-94 (36.5)	0.432
	Mean±SD	35.29±21.69	53.90±26.1	41.83±26.07		57.00±25.85	48.33±32.95	43,29±25,77	
Attack	Min-Max(Median)	8-90 (50)	10-93 (42)	0-93 (36)	0.066	30-93 (70.5)	12-88 (50)	0-93 (37)	0.071
	Mean±SD	50.69±24.53	52.24±25.92	43.13±26.93		68.13±22.00	49.86±30.73	45,92±26,83	
[b]*p*-value		0.017*	0.581	0.450		0.027*	0.593	0.153	
Difference (Attack - Remission)	Min-Max(Median)	-45-73 (19)	-61-83 (-2)	-91-81 (0)	0.045*	0-50 (9)	-42-25 (0)	-91-83 (0)	0.290
	Mean±SD	15.40±33.13	-0.84±34.66	1.55±31.80		16.57±17.33	-3.33±21.59	3.20±33.48	

[a]Kruskall Wallis Test, [b]WilcoxonSignedRanks Test, *p<0,05, **p<0,01, EDSS - Expanded Disability Status Scale, PI - Progression Index, MSSS - Multiple Sclerosis Severity Score

and MSSS in the first and last attacks (p>0.05), except for PI in the first attack (p=0,036). Therefore, we can say that bilateral findings were not poor prognostic factor. Also, the poor do not mean to be good. We can not say that bilateral findings are a good prognostic factor.

The right lateralized findings were poorer prognostic signs in both the first attack and last attack than the other lateralized signs, however, left and bilateral lateralized signs do not have this feature statistically. The left common carotid artery intima-media thickness (CCA-IMT) is greater than right.[20] Non-lacunar cerebro-vascular ischemic events were also reported to be more common in the left hemisphere than right hemisphere.[21] The patho-physiological mechanism of strokes in the more often left hemisphere, still unclear the left CCA-IMT was higher than the right. In a previous study, Algraet al[19] indicated that the risk of sudden death is increased in the left-sided brain infarctions. Therefore, the left hemisphere appears to be more sensitive than the right hemisphere to hemodynamic stress and endothelial dysfunction. In the present study, we demonstrated that neurological disabilities were worse in those with clinical findings affecting the left hemisphere as compared with those of patients with findings affecting the right hemisphere in early and later stages of MS.

Previous research demonstrated that the production of cytokines differs between hemispheres, and the

levels of interleukin-1 and interleukin-6 of the right neocortex were higher than left neocortex of animals.[12] In central nervous system infections, trauma, ischemia, and convulsions, the production of these 2 cytokines increased.[22] After partial resection of the left fronto-parietal cerebral neocortex, immunoglobulin production, natural killer cell activity, T-cell activity mitogen-induced T-cell responses, and synthesis of modulating factors are reduced.[23] Similarly of this report, Bardos et al[24] reported that natural killer cells were controlled by the left-brain neocortex. Therefore, we thought that the right hemisphere may have a more important function than the left hemisphere in suppression of immune function disorders. As a result, the left hemisphere maybe more vulnerable to CNS immune disorders.

In the current study, the presence of bilateral-sided clinical findings was not an indicator of a poor prognosis in patients with early-stage MS. Thus, we concluded that compensatory mechanisms may be more effective in the presence of bilateral involvement than unilateral involvement. Consistent with previous studies, we found the prognosis of patients with infratentorial, spinal, and brainstem lesions was poorer than that of patients without these lesions.[25,26] The presence of epilepsy, collagenous tissue disease, and depression had adverse effects on MS, in accordance with findings of recent studies.[27,28]

The present study has a number of limitations due to its retrospective design. There were some published clinical reports investigating the presence of peripheral asymmetry of cell-mediated immunity.[8,9] In the literature, there is not any clinical report investigating central immune asymmetry in terms of clinical findings. The study also benefits from a large number of patients. The findings can shed light on new studies regarding the differences of immunity between both hemispheres. Despite we did not evaluate any relationship between dominant and non-dominant sides and the side affected we believe that our study is important in terms of leading the studies investigating the central asymmetry of cell-mediated immunity for other studies, including MS.

In conclusion, we suggest that the presences of bilateral-sided clinical signs are not a poor prognostic factor in the early stage of MS. The presence of infratentorial, spinal, and brainstem lesions served as prognostic indicators of the extent of neurological disability. Neurological disabilities associated with clinical findings in the left hemisphere were worse in early and later stages of MS. Early observation of the presence of right-sided clinical signs can aid clinicians in selecting patients for early immunomodulatory or immunosuppressant treatments.

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Statistics

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as the use of *P* values, which fails to convey important information about effect size. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the computer software used.