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Prediction of Conversion from Clinically Isolated Syndrome to Multiple Sclerosis According to Baseline Characteristics: A Prospective Study

Klinik İzole Sendromdan Multipl Skleroza Dönüşümü Temel Özelliklere Bağlı Olarak Öngörebilme

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ABSTRACT

Objective: Clinically isolated syndrome (CIS) is a clinical state that proceeds with inflammation and demyelination, suggestive of multiple sclerosis (MS) in the central nervous system in the absence of other alternative diagnoses. The purpose of this study was to determine in a prospective cohort, the predictor factors in conversion from CIS to MS on the basis of clinical, magnetic resonance (MR) imaging and cerebrospinal fluid (CSF) findings.

Methods: Forty-one CIS patients were included in this study and followed up for at least two years.

Results: Clinically, polysymptomatic or sensorial involvement, good prognostic factors and complete response to pulse therapy were found to be of prognostic value in conversion to MS. A greater presence of oligoclonal bands in CSF was identified in the converted group (92.8%). In terms of localization, presence of callosal lesion (71.4%), periventricular lesion (97.1%), Gd-enhanced lesion (48.6%), black hole (54.2%) and brainstem lesion (57.1%) was statistically significant in terms of conversion to MS.

Conclusion: A carefully performed neurological assessment of symptoms and signs, and evaluation of lesions on MR combined with CSF findings are important for identifying the risk of conversion to MS. This information may be useful when considering treatment in CIS patients instead of waiting for conversion to MS.

Keywords: Clinically isolated syndrome, multiple sclerosis, prognosis, conversion

ÖZ

Amaç: Klinik izole sendrom, diğer alternatif tanıların yokluğunda multipl sklerozu (MS) düşündüren, santral sinir sisteminin inflamasyonu ve demiyelinizasyonu ile giden bir klinik durumdur. Bu çalışmada amacımız; klinik izole sendrom (KİS)'dan MS'e dönüşümü etkileyen öngörü etmenlerini klinik, MR görüntüleme ve beyin omurilik sıvısı (BOS) bulguları temelinde tanımlamaktır.

Yöntem: Çalışmaya 41 KİS hastası alındı ve en az iki yıl süreyle takip edildi.

Bulgular: Klinik olarak, polisemptomatik ve duyusal tutulum, iyi prognostik faktörler ve puls tedaviye tam yanıtın, MS'e dönüşümde prognostik değere sahip oldukları bulundu. BOS'ta oligoklonal bant (OKB) varlığı, MS'e dönen grupta daha fazla saptandı (%92,8). Beyinde lezyon lokalizasyonları incelendiğinde; korpus kallosum (%71,4), periventriküler lezyon (%97,1), beyin sapında lezyonu varlığı (%57,1), kara delik (%54,2) ve kontrast tutan lezyon varlığı (%48,6), MS'e dönüşümde anlamlı olarak değerlendirilmiştir.

Sonuç: Hastanın semptom ve bulgularının nörolojik değerlendirmesinin dikkatlice yapılması ve MR'daki lezyonların ve BOS bulgularının değerlendirilmesi, KİS'ten MS'e dönüşüm riskinin tanımlanmasında oldukça önemlidir. Bu bilgiler, KİS hastalarında MS'e dönüşümü beklemeden tedavi planlanmasında kullanılabilir.

Anahtar kelimeler: Klinik izole sendrom, multipl skleroz, prognoz

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INTRODUCTION

Clinically isolated syndrome (CIS) is the clinical state that proceeds with inflammation and demyelination in the central nervous system, suggestive of multiple sclerosis (MS) in the absence of other alternative diagnoses (1, 2). It is referred to as the "first clinical event" if MS develops. It may present in the form of isolated optic neuritis (ON) or isolated partial medulla spinalis and brainstem involvement, or may be polyregional or supratentorial at onset. MS begins as CIS in 85% of cases (3, 4). Considering the benefits of early treatment, identification of the risks for conversion of CIS to MS is of very great importance (5, 6).

Diagnosis of MS is based on the presence of clinical attacks, including dissemination in time and space. Magnetic resonance (MR) imaging is the most frequently used tool for evaluating patients presenting with a clinical picture of CIS suggestive of MS (2, 7). However, brain and spinal cord MR

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play a key role in demonstrating dissemination in time and space for a diagnosis of MS according to the original (8) and revised (9) criteria of the International Panel (IP). In CIS patients, number and volume of lesions on T2-weighted MR scans at follow-up visits (10–12) and presence of gadolinium (Gd)-enhanced lesions (13–15) are associated with a risk of conversion to MS. While normal brain MR images and cerebrospinal fluid (CSF) indicate a low risk for MS development, presence of abnormal findings is consistent with a risk of MS of 80–90% (3, 16). Although CSF findings have low specificity (17), well-defined CSF findings are also important for diagnosis of MS.

The aim of this study was to evaluate the impacts of clinical, neuroimaging and CSF features, the factors most likely to verify the probable outcomes, on conversion from CIS to MS.

MATERIALS AND METHODS

Patient Selection

Patients presenting to the Department of Neurology of Dokuz Eylül University and admitted to the neurology clinic due to unique neurological event (CIS) were included in the study.

Clinical Factors and Outcome Measures

Clinical features that potentially affect conversion to MS were classified as localization of involvement, presence of polysymptomatic involvement, and poor and good prognostic factors. Poor prognostic factors were defined as the presence of motor, brainstem and cerebellar signs and sphincter involvement at onset, while good prognostic factors were defined as sensorial onset and optic neuritis (18–21). Lumbar puncture (LP) was performed in order to analyze the CSF IgG index and presence of oligoclonal band (OCB) in CSF. IgG index results higher than 0.7 were considered significant. Presence of OCB in CSF was studied using the isoelectric focusing method. Initial MR scanning was performed during the attack period. Scanning was performed according to our hospital's standard protocol before pulse methylprednisolone (MP) therapy. This protocol included the sequences of brain T1 and T2 axial, flair sagittal, proton density, and T1 with Gd, as well as the sequences of spinal cord T1 axial and sagittal, T2 axial and sagittal, and T1 with Gd. In order to evaluate conversion to MS, MR was performed initially and then every 6 months, the first occasion being on the 6th month. Number of lesions, localization of lesions, presence and number of black holes, presence and number of lesions that enhanced Gd, and presence and number of lesions on cervical and thoracic MR images were evaluated with brain MR imaging.

All patients were monitored until the last patient had completed 24 months of follow-up. The endpoint for the study group was set at diagnosis of definite MS according to Poser's or McDonald's 2005 criteria. Patients with a second clinical event were regarded as clinically definite multiple sclerosis (CDMS) according to Poser's criteria (naturally, this group also met the definite MS criteria according to McDonald 2005). Patients with new/active lesion (s) detected at control MR were regarded as definite MS according to McDonald's 2005 criteria (these cases do not meet the diagnosis of CDMS according to Poser's criteria). If these patients experienced an event regarded as an attack before the relevant MR imaging, they were regarded as MS according to Poser's criteria.

A CSF IgG index higher than 0.7 or presence of OCB in the CSF were identified as "positive CSF". If the initial MR met the Barkhof-Tintore criteria (10) the condition was identified as "positive MR". In addition, neuromyelitis optica (NMO) IgG antibody was analyzed in the patients with no lesions specific for MS at brain MR and with lesions longer than 2 segments at spinal MR imaging. NMO IgG-positive patients and patients with lesions longer than 2 spinal segments with no MS-specific brain lesions were excluded.

CIS patients with or without conversion to MS were compared on the basis of characteristics of attack, duration of treatment for attack, and results of laboratory analyses and radiological imaging.

Statistical Analysis

Statistical analysis of the study data was performed on SPSS (Statistical Package for Social Sciences) Windows 16.0 software. In addition to descriptive statistical methods (mean, standard deviation, and frequency), the Chi-square test was used for the comparison of the rates in categorical variables, the p value calculated for the Fischer test was used when needed. The means of independent two groups that were not distributed normally were compared using the non-parametric Mann-Whitney U test. The means of more than two groups were compared using Kruskal Wallis analysis of variance, again a non-parametric test. Wilcoxon's test was used to compare the means of two dependent groups. The direction and level of correlation between variables were identified using Pearson's correlation analysis. The probability of event was calculated with patients' initial characteristics using the Cox proportional regression method. Statistical significance for all results was set at a p value less than 0.05. Kaplan-Meier analysis was used for variables affecting time to conversion. A log-rank value less than 0.05 was considered significant.

RESULTS

Forty-one patients presenting to the neurology clinic with a diagnosis of CIS between June 2009 and June 2010 were included in the study. The mean follow-up period was 12.8±8.5 months (range 3–35 months, median; 12, IQR: 6–16.5). Thirty-five (85.4%) of the 41 patients converted to MS, the other 6 remaining CIS at the end of the study. The rates of conversion of CIS to MS according to the initial clinical characteristics are shown in Table 1. The mean time for conversion of CIS to MS in the entire study group was 9.82±5.08 months (3–29 months). Fourteen (40%) of the patients converted to MS by means of a new attack (Poser's MS). The mean time to conversion to MS in this group was 11.0±6.17 months (range 3 to 29 months). Twenty-one (60%) CIS patients were considered to have converted to MS based on the presence of new/active lesions detected at brain MR images (McDonald's MS). Mean time to conversion to MS in these patients was 9.0±4.12 months (range 6 to 18 months). In terms of gender, 85.7% of the patients who converted to MS and 66.6% of the cases that remained CIS were female (p=0.038). All the study group were followed up for at least 24 months. Mean length of follow up in the patients who remained CIS was 28.5±2.71 months (range 25 to 35 months). One patient with transverse myelitis was monitored for clinical signs of recurrent myelitis.

Table 1. Rates of conversion of CIS to MS depending on initial clinical syndrome

Localization	Conversion rate (%)
Optic neuritis	85.7
Brainstem	72
Transverse myelitis	90.9
Supratentorial	100
Polyregional	87.5

The clinical features that may affect conversion to MS are summarized in Table 2. Polysymptomatic involvement had a significant effect on conversion to MS (p=0.032). Additionally, patients with sensorial involvement and good prognostic features (sensorial onset and optic neuritis) converted to MS more frequently. In addition, when the probability of an event was calculated using patients' initial features with Cox proportional regression, presence of initial sphincter involvement increased the risk of conversion to MS 1.23-fold (Table 2).

Table 2. Comparison of the factors that are likely to affect transformation in the patients who remained as CIS and those were converted to MS

	Remained as CIS (%)	Converted to MS (%)	p	HR	95% CI of HR		P for HR
Polysymptomatic	33.3	60	0.032	0.89	0.57	2.62	0.529
Motor involvement	66.6	54.3	NS	0.74	0.37	1.46	0.382
Sensorial involvement	50	65.7	0.038	0.91	0.45	1.85	0.795
Brainstem involvement	50	28.5	NS	0.85	0.41	1.77	0.665
Cerebellar involvement	0	5.7	NS	1.45	0.35	6.11	0.610
Optic nerve involvement	33.3	25.7	NS	0.99	0.46	2.13	0.988
Sphincter involvement	0	11.4	NS	1.23	0.43	3.51	0.704
Poor prognostic factor (The presence of motor, brainstem and cerebellar signs and sphincter involvement at onset)	83.3	71.3	NS	0.94	0.51	2.64	0.605
Good prognostic factor (Sensorial onset and optic neuritis)	17	28.5	0.043	1.19	0.56	2.12	0.812
Need for 10-day pulse therapy	0	17.1	NS	1.02	0.44	1.65	0.651
Complete response to pulse therapy	0	22.8	0.031	0.96	0.63	2.72	0.782

NS: Not significant, CIS: Clinically isolated syndrome, MS: Multiple sclerosis, HR: Hazard ratio.

Table 3. MRI variables that affect transformation to MS

Localization of Lesion	Remained as CIS (%)	Transformed to MS (%)	P	HR	95% CI of HR		P for HR
Periventricular	83.3	97.1	0.032	2.39	0.32	17.91	0.396
Corpus callosum	16.7	71.4	0.015	2.67	1.23	5.78	0.013
Cerebellar	16.7	25.7	NS	1.28	0.60	2.76	0.524
Brainstem Infratentorial	33.3 50	57.1 57.1	0.001 NS	1.97	0.98	4.00	0.059
Spinal	83.3	67.6	NS	0.92	0.45	1.91	0.829
≥2 spinal	50	48.6	NS	1.17	0.43	3.19	0.753
Black hole	33.3	54.2	0.003	1.65	0.84	3.25	0.145
≥2 black holes	33.3	42.8	0.000	1.96	0.80	4.79	0.138
Gd-enhancing lesion	16.7	48.6	0.027	1.97	0.99	3.92	0.054
≥2Gd-enhancing lesions	0	34.3	0.045	2.97	1.33	6.62	0.008

NS: Not significant, CIS: Clinically isolated syndrome, MS: Multiple sclerosis, Gd: Gadolinium, HR: Hazard ratio.

Thirty-three (80.5%) of the 41 patients met initial Barkhof-Tintore criteria at MR images. Results of the evaluation of MR parameters are given in Table 3. In terms of localization, presence of periventricular, juxtacortical, brainstem and corpus callosum lesions were identified as triggering factors for conversion to MS. The presence of black holes, particularly more than one, at initial MR images also affected conversion to MS. Presence of more than one Gd-enhancing lesion was also identified as an effective factor. Presence of lesion in the brain stem increased the probability of conversion 1.97-fold compared to absence of such lesions, while presence of Gd-enhancing lesion also increased the probability of conversion to MS 1.97-fold. Gd lesions numbering two or more increased the probability of conversion to MS 2.97-fold compared to absence of such lesions, while presence of lesion in the corpus callosum increased the probability of conversion 2.67-fold compared to absence of such lesion.

When the two groups (remaining as CIS or converted to MS) were compared in terms of meeting Barkhof-Tintore criteria at initial MRI, significantly higher rates were determined in patients who converted to MS (p=0.004). A similar result was observed for McDonald's 2010 criteria (18) (p=0.013). Of the patients who converted to MS, 85.7% met the Barkhof-Tintore criteria at their initial MR images, while only 50% of the patients that remained CIS met those criteria. Of the patients who converted to MS, 42.9% met the MR parameters in the McDonald 2010 criteria, while 17.7% of the patients who remained CIS met these parameters. Results from both comparisons were statistically significant. MR was negative in 14.3% of the patients who converted to MS. Detailed investigation of the group that converted to MS and with negative MR revealed that 50% of these presented with a clinical picture of transverse myelitis. Additionally, 50% of those with polyregional onset and 33% of those with optic neuritis had negative initial MR findings. MR was initially positive in patients with brainstem and supratentorial onset and who converted to MS.

Results of the analysis of CSF changes are shown in Figure 1. Presence of OCB seems to be of predictive value in terms of conversion to MS (p=0.049). No significant relation was obtained in terms of IgG index being higher than 0.7 or 1.0. However, the difference between the groups in terms of the parameter defined as positive CSF (presence of OCB in CSF and/or IgG index higher than 0.7) was statistically significant (p=0.035). OCB was determined in CSF in 28 (68.3%) of the 41 patients. The rate of conversion to MS was 92.8% in the CIS patients with OCB in CSF, 88.8% in those with IgG index >0.7, and 83.3% in those with IgG index >1. The conversion rate of patients with positive CSF was 89.1%. In addition, an IgG index greater than 0.7 increased the risk of conversion to MS 0.997-fold (p for HR=0.992). Presence of OCB in CSF increased the risk of conversion 2.16-fold (p for HR=0.052).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of MR images and CSF characteristics for conversion to multiple sclerosis were calculated. The sensitivity,

Table 4. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of localization of lesions at MRI for transformation to MS

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Juxtacortical	82.8	50	90.6	33.3	78
Periventricular	82.7	16.6	87.1	50	80.4
Infratentorial	57.1	50	86.9	16	56
Corpus callosum	71.4	83.3	96.1	3.3	73.1
Black hole	54.2	66.6	90.4	20	56
Gd-enhancing lesions	48.5	83.3	94.4	21.7	53.6
Spinal lesion	66.6	16.6	81.4	8.3	56

Table 5. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of CSF findings for transformation to MS

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
OCB in CSF (+)	74.2	66.6	92.8	30.7	73.1
IgG index ≥ 0.7	68.5	50	88.8	21.4	65.8
IgG index ≥ 1	42.8	50	83.3	13	43.9
Positive CSF	94.2	33.3	89	50	85.3

OCB: Oligoclonal band, CSF: Cerebrospinal fluid, IgG: Immunoglobulin G.

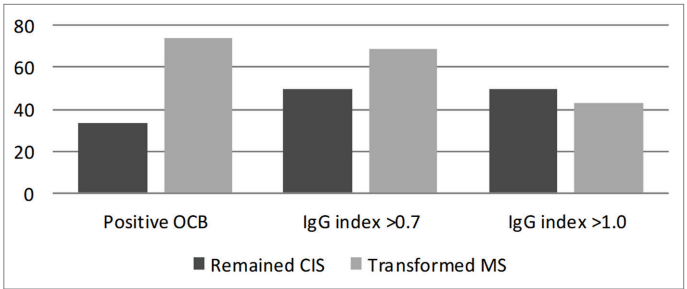

Figure 1. Ratio of CSF parameters in subjects remaining as CIS and in those transformed into MS. MS: Multiple sclerosis, CIS: Clinically isolated syndrome, CSF: Cerebrospinal Fluid, OCB: Oligoclonal band, IgG: Immunoglobulin G.

specificity, PPV, NPV, and accuracy of the Barkhof-Tintore MRI criteria were 78.9%, 50%, 90.9%, 37.5%, and 80.4%, respectively. The sensitivity, specificity, PPV, NPV, and accuracy of MR lesions are given in Table 4. Corpus callosum and Gd-enhancing lesions emerged as the most specific, while periventricular and juxtacortical lesions were the most sensitive. PPV was highest in callosal lesions (96.1%). The sensitivity, specificity, PPV, NPV, and accuracy of CSF findings in the MS conversion group and in the group that remained CIS are given in Table 5. Positive CSF findings had the highest sensitivity. PPV was quite high in all four parameters.

In terms of conversion time to MS, sensorial involvement was negatively correlated with early conversion. Patients with sensorial involvement converted to MS later than patients without sensorial involvement in their first clinical event (11.2 and 7.7 months, respectively, p=0.049). Time to conversion to MS was 9.15 months in subjects with OCB in CSF and 12.66 months in those without. The difference was not significant (p=0.20). Times to conversion to MS with IgG indices higher or lower than 0.7 were 11.2 months and 7.27 months, respectively (p=0.092).

In terms of impact of meeting McDonald 2005 MR criteria (Barkhof-Tintore) at onset on the time to conversion, this was 9.63 and 12.6 months in subjects meeting or not meeting these criteria, respectively. The difference between the groups was not significant (p=0.42). Time to conversion to MS was not significantly different between patients with or without periventricular (p=0.34), juxtacortical (p=0.37), brainstem (p=0.06), cerebellar (p=0.27), callosal (p=0.17), spinal (p=0.47) or Gd-enhanced (p=0.62) lesions. Time to conversion was 8.21 months in subjects with black hole and 12.25 months (p=0.041) in those without black hole at initial MR images. The difference between the groups was significant (p=0.041). Mean time to conversion to MS was 12.25 months for subjects without black hole, 12 months for those with a single black hole, and 7.2 months for those with more than one black hole. A significant difference was observed between the three groups (p=0.013). The difference derived from early conversion to MS in the group with more than one black hole.

MR characteristics and presence of OCB were evaluated together in terms of conversion to MS. Patients with OCB in CSF and meeting the Barkhof-Tintore criteria were compared with patients who did not meet either of or both these criteria. Mean time to conversion to MS was 5.7±0.94 months in the group that met both criteria, and 11.8±5.73 months in the other group. The difference was highly significant (p=0.006). Patients without OCB in CSF and not meeting Barkhof-Tintore criteria were compared with the patients meeting either of these criteria. Mean time to conversion to MS was 15.5±5.5 months in the patients in whom both parameters were negative, and 8.93±4.98 months in the other group that did not meet either or both of these criteria (p=0.002). Positive CSF and MR were demonstrated in 31 (75%) of the 41 CIS patients. However, both OCB and MR were positive in 26 (63.4%) of the 41 patients. In addition, 82.8% of the 35 CIS patients converted to MS. Since positive CSF and positive MR are potential variables for conversion of CIS to MS, CSF and MR findings were combined for analysis. Table 6 details the rate of conversion to MS when MR characteristics were combined with positive

Table 6. Rates of conversion to MS in the event of various accompanying MRI findings in CIS patients with positive CSF and positive MRI

Positive CSF+Positive MRI+	Conversion to MS (%)
+ periventricular lesion	93.5
+ juxtacortical lesion	93.1
+ corpus callosum lesion + infratentorial lesion	95.8 90.9
+ black hole	94.7
+ Gd-enhancing lesion	93.7

MS: Multiple sclerosis, CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging, Gd: Gadolinium.

Table 7. Rates of conversion to MS if accompanied by various MRI findings in CIS patients with positive CSF or positive MRI

Positive CSF or positive MRI +	Conversion to MS (%)
Juxtacortical lesion	90
Corpus callosum lesion Infratentorial lesion	96 86.9
Black hole Gd-enhancing lesion	90 94
Spinal lesion	85
Juxtacortical + corpus callosum lesion Corpus callosum + Gd-enhancing lesion Corpus callosum lesion+ black hole	95.3 100 100

MS: Multiple sclerosis, CSF: Cerebrospinal Fluid, MRI: Magnetic resonance imaging, Gd: Gadolinium.

Table 8. Time to the transformation to MS according to the presenting clinical features in patients with positive CSF and positive MRI

Positive CSF + positive MRI +	Transformation time (ay)	P
Polysymptomatic	9.2 ± 1.3	0.39
Optic neuritis	9 ± 1.7	0.39
Transverse myelitis	9.1 ± 1.3	0.43
Brainstem	7.7± 1.1	0.05
Supratentorial	16.2 ± 4.9	*

*Since all patients with supratentorial onset, in whom both CSF and MRI were positive, transformed into MS, no p value could be calculated.
CSF: Cerebrospinal fluid, MRI: Magnetic resonance imaging.

CSF. The rate of conversion to MS was 87.1% in the presence of either positive CSF or positive MR. The rate of conversion to MS was calculated when the presence of lesions in significant localizations was combined with either CSF positivity or MR positivity. The rate of conversion to MS in the patient group is set out in Table 7.

CIS cases with optic neuritis, transverse myelitis or supratentorial or polysymptomatic onset converted to MS at a rate of 100% in 2 years in the event of positive CSF and positive MR (meeting Barkhof-Tintore criteria). Cases with brainstem onset converted to MS at a rate of 77% in 2 years in case of positive CSF and positive MR. Time to conversion to MS was investigated according to the type of clinical onset in CIS cases with positive CSF and positive MR. Since all CIS cases with supratentorial onset converted to MS, no p value could be calculated. Time to conversion to MS in CIS patients is given in Table 8.

DISCUSSION

Early diagnosis and prompt investigation of therapeutic options, and the reduction of attacks and/or progression in MS, as in many other chronic autoimmune diseases, will lower the risk of sequelae. Due to the high possibility of successful treatment in the early period, it is important to diagnose MS in the earliest period, and even during the first clinical event (CIS). However, it is also difficult to diagnose MS during the first attack, although most of these patients develop MS (1).

This study investigated clinical, CSF and MR criteria that are considered to be effective in converting CIS to MS in cases presenting with first clinical events suggestive of MS. Of the study cases with CIS, 85.4% matched the criteria that would provide dissemination in time and space, and converted to definite MS. In one study that monitored CIS patients for 20 years, 63% of patients converted to MS (22). In the present study, MS was determined in 60% of 41 CIS patients according to the McDonald criteria and in 40% of CIS patients according to the Poser criteria. Dalton et al. (2002) monitored 95 CIS patients for 3 years; 58% were diagnosed with MS according to the McDonald 2001 criteria and 38% were diagnosed with MS according to the Poser criteria, in agreement with the present study (23). Analyzing the rate of conversion according to the clinical pictures among CIS patients, it was notable that all cases with supratentorial onset converted to MS. Lower rates of conversion (61% for transverse myelitis, and 60% for brainstem) have been reported previously compared to those in the present study (22, 24). The rate for ON determined in the present study is consistent with the studies cited above.

Consistent with previous studies conducted with CIS patients (25), polysymptomatic and polyregional involvement emerged as a more significant risk factor in converting CIS to MS than monosymptomatic and monoregional involvement. These findings may be regarded as evidence of dissemination in time and space in the diagnosis of MS. These data may be interpreted as meaning that despite representing different concepts, polyregional involvement and polysymptomatic onset have the same significance in this context.

Our findings show that sensorial involvement plays a determining role in the conversion of CIS to MS. Sensorial involvement, both in general and in the present study, also occurs among good prognostic criteria (18, 20, 21). Presence of good prognostic criteria (sensorial onset and optic neuritis) was determined as a significant variable in converting CIS to MS in this study. We therefore conclude that the effects of sensorial involvement and good prognostic criteria on converting CIS to MS can be evaluated together. However, sphincter involvement in the first clinical event was shown to increase conversion to MS.

In the present study, the rate of conversion to MS was 91% for patients with a clinical picture of acute transverse myelitis (TM), which was higher than that reported in previous studies (26). In addition, one of the reasons for the more frequent conversion to MS among patients presenting with TM in our study compared to the levels cited in the literature may be that patients with long-term TM were excluded at the beginning of the study. However, the level of recurrent TM, which was reported at 8% in the same study, was similar to that determined in the present study. In one study, 58 patients presenting with acute TM and with normal brain MR images were monitored for 5 years, and 29% converted to MS (27). Although the present study determined a higher rate of conversion to MS (50%) in TM patients that did not match MR criteria, this might have resulted due to the limited number of patients. However, this may be evidence that brain MR is a strong risk factor in conversion from CIS to MS only if brain MR images during the first clinical event is suggestive of MS. Moreover, it also indicates that a normal brain MR is not a low risk factor, as might be anticipated. Compared with other types of onset, our study also determined that absence of lesions at brain MR images in patients with ON indicates a low risk in terms of conversion to CDMS (18). However, presence of normal MR is known not to prevent development of CDMS. One study determined higher accuracy rates, similarly to the present study, in terms of definite diagnosis of MS based solely on abnormal MR findings in case of Barkhof (13), Paty (28) and Fazekas (29) criteria and OCB together (30). High specificity is therefore more important than high sensitivity for the diagnosis of such a lifelong disease as MS.

In untreated relapsing-remitting MS, new lesions are observed at brain MR imaging performed at any time, at a level of 50%. Some of these new lesions are converted to a permanent axon transection area (31). The rate of conversion of new lesions to black holes is approximately 30% in typical MS patients (31, 32). One study reported that evidence of CNS tissue

degradation, such as black holes, was highly associated with disability in MS (31, 33, 34). The presence of black holes at initial MR images indicates that the disease has a silent background. In the present study, the presence of more than one black hole at initial MR images was identified as a significant risk factor for converting CIS to MS. Presence of more than one Gd-enhanced lesion was also determined as a significant factor. In conclusion, the disease has probably begun much earlier in CIS patients with black holes. CIS may be expected to be converted to MS via an attack (Poser MS) or a new/active lesion (McDonald MS). A similar inference also applies to Gd-enhanced lesions. Moreover, impairment of the blood-brain barrier is also associated with a risk for conversion to MS. These findings indicate that MR is important both for diagnosis of MS and in predicting conversion of CIS to MS. Detailed evaluation of the localizations of lesions at MR revealed a statistically significant difference between the groups that remained as CIS and those that converted to MS in terms of presence of periventricular, callosal and brainstem lesions. The periventricular region is frequently involved in MS, and the presence of ovoid lesions larger than 2 mm poses a risk in terms of conversion to MS. Brain MR examinations demonstrated that lesions in the corpus callosum have high specificity and quite significant PPV in terms of the risk for MS development. Comparing our data with those of Barkhof et al.'s 1997 study, our findings demonstrated that the presence of periventricular and juxtacortical lesions and black holes has lower specificity despite exhibiting higher sensitivity and PPV, whereas the presence of corpus callosum lesions and lesions that uptake contrast agent has lower sensitivity despite exhibiting higher specificity and PPV (13). One study demonstrated the prognostic role of MR imaging in CIS patients, and reported conversion to CDMS at a rate of 60–80%; however, initial MR images were observed to be normal in approximately 10–20% of converted patients (10). Despite high rates of conversion in the present study, initial MR images, consistent with the literature, were normal in 14.3% of the patients who converted to MS. Again, when the groups were compared in terms of MR characteristics, the rate of meeting Barkhof-Tintore criteria was significantly higher in the group that converted to MS. However, 80.5% of those who converted to MS met the Barkhof-Tintore criteria at their initial MR. The sensitivity, specificity, PPV, and NPV of Barkhof-Tintore MR criteria in this study were 78.9%, 50%, 90.9%, and 37.5%, respectively. However, in contrast to the present research, a study conducted with 74 CIS patients reported that Barkhof-Tintore criteria exhibited high specificity, but low sensitivity for dissemination in space (13).

When the CIS patients in our study were evaluated on the basis of McDonald 2010 MR criteria, approximately half (42.9%) were diagnosed on the basis of initial MR findings containing evidence of dissemination in time and space. These findings once again show the increasing importance of the 2010 criteria and early diagnosis. Gd-enhancement seems to be associated with an increase in disability, and a correlation was determined between meeting the Barkhof-Tintore criteria and disability (35). Again, the same study identified the presence of infratentorial lesions as a predictor for conversion of CIS to MS. However, in our study, the presence of infratentorial lesion as a risk factor was not statistically significant.

In addition to MR, the presence of an intrathecal OCB is also a relatively consistent finding in MS. One study compared OCB-negative and -positive patients, and determined lower EDSS in OCB-negative cases. The rate of disability or progression also differed statistically significantly (36). These data conflict with the result of a study performed previously in our clinic in 2009 (37). In that study, the finding that presence of OCB in CSF was higher in female patients, and associated with low EDSS, was interpreted as suggesting that the greater the typical characteristics of MS, the better the prognosis. Evaluating the present study in the light of the relevant literature, we concluded that presence of OCB is a significant risk factor for converting CIS to MS. However, it may not be a poor prognostic factor for MS, and may even positively affect prognosis.

Evaluating clinically isolated syndrome patients in terms of CSF findings, the presence of OCB was identified as a factor with predictive value for conversion to MS. However, no significant correlation was determined depending on whether the IgG index was higher than 0.7 or 1.0. When only the presence of OCB in CSF was investigated, positive CSF was found to exhibit high sensitivity, but low specificity. Two previous studies reported that presence of OCBs in CSF has higher specificity and sensitivity in early diagnosis of conversion to CDMS compared to MR (36, 38). However, our findings show that presence of OCB has higher specificity, despite exhibiting low sensitivity. This may be due either to a difference between study designs, or to the fact that presence of OCB is lower in Turkish population compared to Northern Europe and North America. Low prevalence leads to low sensitivity and high specificity.

CONCLUSION

This study investigated the time to conversion to MS in terms of clinical, laboratory and MR characteristics. In terms of the characteristics of clinical onset, time to conversion to MS was significantly longer in CIS patients with supratentorial onset. Compared with other symptoms, time to conversion to MS was significantly longer in patients with sensorial symptom at the onset. These data again show that sensorial onset is one of the good prognostic factors. Again, patients who presented with ON, one of the good prognostic factors, converted to MS in either the very early or very late phases. Combining these data with the fact that 100% of patients with ON and with positive CSF and MR findings converted to MS, we concluded that patients with ON convert to MS in a shorter time if they also meet the typical criteria of MS at the onset. Among the MR characteristics, presence and number of black holes highly significantly reduces time to conversion to MS. Since the pathogenesis of black holes is known to be associated with axonal loss, this finding is not a conspicuous evidence for the disease having started earlier than assumed. The fact that presence of OCB and positive MR, which are highly important in the diagnosis of MS, affect the time to conversion of CIS to MS is not unexpected. In the event that both of these are negative, the conversion time is considerably prolonged. However, if one of them is positive, the conversion time is significantly shortened. The present study highlights the effect of the presence of OCB and positive MR, either separately or in combination, on time to conversion to MS.

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Informed Consent: Written informed consent form was obtained from all patients.

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