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RESEARCH ARTICLE

Isolated Optic Neuritis and Definite Multiple Sclerosis Conversion Features

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ABSTRACT

Objective: Identifying the factors associated with the development of multiple sclerosis (MS) in isolated optic neuritis (ION) is vital for early treatment decisions.

Materials and Methods: In this study, we investigated definite MS conversion properties in patients with ION based on neurological, laboratory, magnetic resonance imaging (MRI), visual evoked potential (VEP), cerebrospinal fluid (CSF) examinations according to McDonald criteria 2005 and 2017.

Results: Twenty-six of 41 patients (63.4%) with ION developed definite MS according to McDonald criteria 2005, and 32 patients (78%) developed it according to McDonald criteria 2017. We found that the risk of MS development after ION increased in the first 2 years (34.1%) according to McDonald Criteria 2005. VEP examinations revealed that prolonged latency in the P100 response supported the MS diagnosis. In the cranial MRI, the presence and excessiveness of white matter lesions were critical factors in predicting conversion from ON to MS. In addition, oligoclonal band (OCB) detection in the CSF helps predict MS conversion.

Conclusion: Identifying the prognostic factors to understand MS development in ION and other clinically isolated syndromes (CIS) is essential when selecting patients for early treatment and considering early treatment options. The 2017 McDonald criteria provide a more rapid diagnosis of MS, but atypical clinical manifestations and misleading MRI findings must be carefully considered.

Keywords: Multiple sclerosis, oligoclonal band, optic neuritis

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, neurodegenerative disease of the central nervous system (CNS).[1] In about 85% of MS cases, there is an onset of an isolated episode of focal neurological deficit called clinically isolated syndrome (CIS).[1] In practice, determining when a CIS patient will get MS diagnosis is essential. A lot of studies have researched clinical and paraclinical baseline variables of CIS that could provide information for predicting conversion to MS.[1,2]

Acute isolated optic neuritis (ION) is a demyelinating, inflammatory CIS characterised by sudden onset of unilateral visual loss, predominantly affecting young people.[2] ION is often the first manifestation of MS, may convert to neuromyelitis optica (NMO), or can be diagnosed with another CNS disease. ION is highly associated with MS, and 50% of cases develop MS after 15 years.[3] Defining the factors to determine MS conversion in CIS is important because MS carries a high risk of developing neurological disability.

This study investigated the clinical, laboratory, and MRI characteristics of patients with ION associated with the development of definite MS according to the McDonald criteria 2005 and 2017 revision.[4] According to the 2017 revision, compared to 2005, patients can get MS diagnosis after a single clinical episode if they have existing cranial magnetic resonance imaging (MRI) lesions in typical CNS areas and an asymptomatic contrast-enhancing lesion that fulfils the dissemination criteria in space

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and time.[4] Approximately 2/3 of patients with CIS fulfil these MS diagnosis criteria during their lifetime.[5] Identifying baseline laboratory and MRI findings associated with an increased risk of early development of MS can help clinicians consider the benefit–risk ratio of early disease-modifying treatment.

MATERIALS and METHODS

We retrospectively reviewed the records of 41 patients (32 females and nine males) between 18 and 46 years who experienced an ION between 2005 and 2009 and were evaluated according to McDonald criteria 2005 in Okmeydani Educational and Research Hospital. We investigated MS conversion properties based on laboratory cranial MRI (imaging within one month of symptom onset and follow-up MRI after at least 3–6 months), visual evoked potential (VEP), and cerebrospinal fluid (CSF) examinations. The 2005 and 2017 revisions of the McDonald diagnostic criteria for MS were applied to the recorded data, and conversion rates to clinically definitive MS (CDMS) were described. None of the patients had any other neurological or ophthalmological diseases at presentation. All secondary optic neuritis cases were excluded. Clinical, laboratory, and imaging findings were investigated for all patients. Laboratory examinations included complete blood count and biochemical and vasculitis tests. All patients were evaluated for MS via CSF serology (cells, protein, glucose and oligoclonal bands (OCB)), VEP, brain and spinal cord MRI. VEP latencies were recorded using the method described by Brusa et al.[1] The CSF was analysed using isoelectrofocusing methods. Detection of OCB was considered positive if more than one band was not detected in the serum but was present in CSF.[6] All patients initially underwent 1.5/3 Tesla signal brain MRI after the onset of visual symptoms. A second MRI was performed at least 3 months later. Both MRIs included T2-weighted fast spin–echo/proton density-weighted sequences and T1 with and without gadolinium. An intravenous bolus of 0.1 mmol/kg gadolinium-DTPA was administered before imaging. The number of high-signal lesions on T2-weighted images and contrast-enhancing lesions upon examination were recorded. We retrospectively reviewed the periods of pulse steroid treatment. We examined the correlation between treatment periods and conversion to MS according to McDonald criteria 2005 and 2017.[4] All follow-up examinations were performed at least 3 months later. A relapse was defined as the appearance of new symptoms or the worsening of old symptoms for at least 24 h without an infection.[1] At follow-up, conversion to MS and time to conversion to CDMS were evaluated clinically and radiologically.[4] The study protocol was planned, and written informed consent was obtained from patients. The study was completed following the Helsinki Declaration and was confirmed by the institutional review committee (2009/number: 267).

The Statistical Package for the Social Sciences (SPSS) 25.0 program was used for statistical data analysis. Categorical measurements were summarised as numbers and percentages, with continuous measurements as means and standard deviations (median and minimum/maximum where appropriate). The Shapiro–Wilk test was used to determine whether the parameters in the study showed a normal distribution. The Mann–Whitney U and Kruskal–Wallis tests were used for non-normally distributed parameters, and $p<0.05$ was considered statistically significant.

RESULTS

There were 41 patients (32 females and nine males) with a mean age of 50.1±8.05 years (33–64 years). The mean age at symptom onset was 29.8±8.5 years (18–46 years). According to the baseline clinical and radiological parameters, 27 (65.8%) patients fulfilled the 2017 criteria for MS diagnosis. At least three months later, MRI scans and additional clinical and paraclinical data showed that 26 patients (63.4%) developed ION according to McDonald criteria 2005, and five patients developed CDMS according to the 2017 criteria.

Fourteen patients (34.1%) converted to MS within two years, seven patients (17%) converted to MS between 2 and 4 years, and five patients (12.2%) converted to MS over the 4-year follow-up period according to McDonald criteria 2005. We found a statistically significant increase in the risk of developing MS within 2 years of presentation according to the 2005 criteria ($p=0.014$).

Twenty-seven of 41 (65.8%) patients fulfilled the 2017 criteria based on CSF and baseline MRI. Twenty-two of 27 (81.4%) patients fulfilled the criteria based on the CSF. Only three of the 27 (11.1%) patients fulfilled the 2017 criteria based on radiological evidence for dissemination, and two of the 27 (7.4%) patients fulfilled the criteria according to CSF and radiology.

According to the follow-up MRI, four additional patients fulfilled the 2017 criteria according to new radiological evidence, and one fulfilled the criteria according to CSF and radiological evidence.

One of the 41 subjects presented with bilateral ON and converted to MS according to both criteria. The sample was divided based on the left (10 patients, 24%) or right (30 patients, 73.2%) eye involvement. Sixteen of 30 patients presenting with right ON and nine of 10 presenting with left ON converted to CDMS according to McDonald criteria 2005. Moreover,

Table 1. VEP results and the number, percent of patients with MS diagnosis according to Mc Donald citeria 2005 and 2017

	Mc Donald criteria 2005 (n=25)		Mc Donald criteria 2017 (n=31)	
	n	%	n	%
Right eye VEP response (n=30)				
Normal (n=6) (20%)	0		1	3.6
Long P100 latency (n=21) (70%)	15	60	18	58
No response (n=3) (10%)	1	4	3	9.6
Left eye VEP response(n=10)				
Normal (n=1) (10%)	0		0	
Long P100 latency (n=6) (60%)	6	24	6	19.3
No response (n=3) (30%)	3	12	3	9.6

VEP: Visual evoked potential

Table 2. OCB results and the number and percent of patients with MS diagnosis according to Mc Donald citeria 2005 and 2017

	Mc Donald criteria 2005 n=26		Mc Donald criteria 2017 n=32	
	n	%	n	%
OCB				
Not performed (n=5)	4	15.4	4	12.5
Negative (n=10)	0		2	6.2
Positive (n=26)	22	84.6	26	81.3

OCB: Oligoclonal band

22 of 30 patients presenting with right ON and nine of 10 patients presenting with left ON converted to CDMS according to McDonald criteria 2017. According to both criteria, the conversion to MS was statistically significant in groups with prolonged P100 latency ($p<0.05$). The VEP examination results are summarised in Table 1.

Initial MRIs were normal in 12 (29%) patients, and 29 (71%) had one or more demyelinating lesions but did not meet the 2005 McDonald criteria for dissemination in space. Over an at least 3-month follow-up period, three of 12 subjects (25%) with normal MRI and 23 of 29 patients (79.3%) with abnormal MRI converted to MS. Five of 11 patients (45.4%) with fewer than three typical demyelinating T2 and FLAIR lesions on MRI converted to MS. All 18 patients with three or more lesions on MRI converted to CDMS according to McDonald criteria 2005. According to the baseline clinical and radiological parameters, 27 (65.8%) patients fulfilled the 2017 criteria for MS diagnosis. According to follow-up MRI, four additional patients fulfilled the 2017 criteria according to new radiological evidence. The presence or excessiveness of brain lesions using T2-weighted and FLAIR sequences on MRI was a statistically significant strong predictor of MS conversion according to both criteria ($p<0.05$).

Thirty-six of 41 patients had CSF testing performed during the acute disease course. OCB was detectable in 26 patients (63.4%), and 22 of them (84.6%) get MS diagnosis according to McDonald criteria 2005. All 26 patients converted to MS according to McDonald criteria 2017. Thus, according to both criteria, monosymptomatic ON (MON) patients with OCB in CSF have a significantly higher risk of MS development than MON patients without OCB ($p<0.05$). The findings of the CSF examination are summarised in Table 2.

Table 3. The number and percent of patients converted to definite MS according to Mc Donald criterias 2005 and 2017 with different treatment periods

	Mc Donald criteria 2005 n=26		Mc Donald criteria 2017 n=32	
	n	%	n	%
Pulse steroid treatment periods				
≤5 days (n=18)	11	42.3	12	37.5
7 days (n=12)	10	38.4	11	34.4
10 days (n=11)	5	19.3	9	28.1

Table 4. MS conversion properties according to Mc Donald criteria 2017

	MS diagnosis negative according to McDonald criteria 2017 (n=9)	MS diagnosis positive according to McDonald criteria 2017 (n=32)	p
Age (year) median (min-max)	50 (39–68)	50 (33–64)	0.78
Age of disease onset (year) median (min-max)	28 (20–45)	28 (15–46)	0.70
Disease duration (month) median (min-max)	51 (36–120)	84 (36–204)	0.039
1st MR lesion number median (min-max)	1 (0–6)	2 (0–6)	0.001*
2nd MRlesion number median (min-max)	1 (0–6)	3 (0–6)	0.001*
Pulse steroid treatment periods (day) median (min-max)	5 (5–10)	6 (5–10)	0.72

*: p<0.05, Mann-Whitney U test

Table 5. MS conversion properties according to McDonald criteria 2005

	None (n=15)	<2 year (n=14)	2-4 year (n=7)	>4 year (n=5)	p
Age (year) median (min-max)	50 (39–68)	50(33–61)	52 (43–64)	50 (38–58)	0.56
Age of disease onset (year) median (min-max)	31 (20–45)	30 (16–46)	30 (19–43)	34 (15–28)	0.39
Disease duration (month) median (min-max)	59 (36–120)	77 (36–120)	113 (62–167)	156 (118–202)	0.001*
1st MR lesion number median (min-max)	1 (1–3)	2 (1–3)	2 (2–3)	2 (1–3)	0.001*
2nd MRlesion number median (min-max)	2 (1–3)	3 (2–3)	3 (2–3)	3 (2–3)	0.001*
Pulse steroid treatment day number median (min-max)	7 (5–10)	7 (5–10)	6 (5–10)	5 (5–10)	0.43

*: p<0.05, Kruskal-Wallis H test

We retrospectively reviewed the pulse steroid treatment periods of all 41 patients. These 41 patients were divided into three groups according to treatment period. Eighteen patients received treatment for 5 days, and 23 received treatment for 7 or 10 days. We did not find a significant correlation between pulse steroid treatment period and conversion to MS according to both criteria (p<0.05). The findings for treatment periods and MS conversion properties are summarised in Table 3. In Tables 4 and 5, MS conversion properties are summarised according to McDonald 2005 and 2017 criteria.

DISCUSSION

ION due to an inflammatory demyelinating lesion of the optic nerve is frequently the first manifestation of MS,[3] and it occurs in over 50% of MS patients at any time during the disease course.[7] ION is the first symptom in approximately 20% of MS patients,[5] and one study found 42.2% converted to MS over 10 years.[8] Jacobi et al.[9] found that 73% of CIS patients converted to MS at the 2-year follow-up according to McDonald criteria 2005.

We found that MS development risk significantly increased within the 2 years following presentation. This is inconsistent with studies showing that the risk of transformation to MS increases with time. In these studies, the 2 and 5-year risks of converting to MS after ION were 27% and 45%, respectively, and 10-year risks have been found to be 14–38%.[3,10,11] Studies have reported that the risk of early conversion to MS increases at 2 years in brainstem/cerebellar CIS.[12,13]

In CIS patients, the most valuable prognostic factor for conversion to MS is the number of MRI T2 lesions.[14,15] Approximately 85% of CIS patients converted to MS within 2 years, and the majority (approximately 78%) got MS diagnosis within 1 year. An increased amount of MRI lesions is the strongest independent risk factor for determining early development of MS in patients with CIS to satisfy the dissemination in space (DIS) criteria.[13] We found similar results to those in the literature.

In recent studies, OCB was positive in approximately 70% of patients with CIS and in over 90% of patients with MS.[16–18] The presence of OCB has a specificity of 94% and a sensitivity of 91% and for developing definite MS after CIS.[19]

A high percent of accuracy (86%) and sensitivity (77%) in the diagnosis of MS after CIS has been defined in the 2005 McDonald revision criteria.[20,21]

The critical change in the McDonald 2017 revision is that OCB can be taken as an agent for dissemination in time (DIT), so after the first clinical event and a single brain MRI, MS can be diagnosed.[22,23] Some studies show that by applying the 2017 criteria, the sensitivity for conversion to MS, which ranged from 68 to 100%, increased.[24–29]

The prolonged latency that reflects the slowing of conduction velocity through the demyelinated segment of the optic nerve in VEP provides high sensitivity and specificity for detecting abnormalities in visual functions.[30] This study found the conversion to MS statistically significant in groups with prolonged P100 latency and no response.

One study showed accelerated recovery of visual function and a reduced risk of conversion to MS with intravenous methylprednisolone (IVMP) within the first 2 years in CIS patients compared to oral prednisone or placebo.[31] However, at 10 years, an increased risk of recurrence of ION was found in the oral prednisone group compared to the intravenous-treated group.[31] In acute MS relapse, clear differences were not found in the efficacy and safety between oral and intravenous steroids.[32,33]

Another study declared that acute steroid therapy in ION only hastens recovery but does not predict conversion to CDMS.[3,34] In addition, early treatment of CIS patients found beneficial in delaying development of definite MS.[35] However, in our study, we didn't found an association between the treatment periods with IVMP and risk of conversion to MS.

One of the limitation of this study is existence of a small number of participants. In several studies, prognostic factors for MS conversion in larger cohorts of CIS patients have been investigated. Still, in our study, we aimed to analyse the baseline and follow-up data of patients with ION specifically.

CONCLUSION

In patients with ION, we found higher MRI brain lesion numbers, OCBs in the CSF and abnormal VEP (i.e. prolonged P100 latency or no response), which were strongly predictive of CDMS. Thus, initiation of disease-modifying therapy should be considered as early as possible. Similar to literature, in this study the McDonald 2017 revision enables a more rapid diagnosis of MS. Conversely, atypical clinical presentations and fallacious MRI findings should be attentively considered to avoid misdiagnosis or overdiagnosis.

Disclosures

Ethics Committee Approval: The study was approved by the Okmeydanı Training and Research Hospital Pharmaceutical Research Local Ethics Committee (No: 267, Date: 18/06/2009).

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