Journal of Clinical Neuroscience 21 (2014) 583–586

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Risk of multiple sclerosis after optic neuritis in patients with normal baseline brain MRI

Inês Brás Marques [a,*], Fernando Matias [a], Eduardo Duarte Silva [b], Luis Cunha [a], Lívia Sousa [a]

[a] Department of Neurology, Coimbra University Hospital, Praceta Mota Pinto, Coimbra 3000-075, Portugal
[b] Department of Ophthalmology, Coimbra University Hospital, Portugal

ARTICLE INFO

Article history:
Received 23 August 2012
Accepted 8 June 2013

Keywords:
Clinically isolated syndrome
Demyelinating diseases
Multiple sclerosis
Optic neuritis

ABSTRACT

When assessing and managing a patient with optic neuritis (ON), the risk of future development of multiple sclerosis (MS) is an important issue, as this can be the first presentation of the disease. Although the presence of lesions on baseline brain MRI is the strongest predictor of MS conversion, some patients with normal imaging also develop MS. We aimed to estimate MS risk in patients with ON and a normal baseline MRI and identify individuals with higher risk of conversion. We performed a retrospective study including patients with idiopathic ON and normal baseline brain MRI who presented to our hospital over an 8 year period. Of a total of 42 patients, 10 converted to MS: five during the first follow-up year, seven during the first 2 years and all of the patients within the first 5 years, with a 5 year MS conversion rate of 23.8%. MS conversion rates were significantly higher in patients with history of previous symptoms suggestive of demyelination ($p = 0.002$), cerebrospinal fluid oligoclonal bands unmatched in serum ($p = 0.004$) and incomplete visual acuity recovery ($\leqslant 6/12$) after 1 year ($p = 0.002$). Lower conversion rates were found in patients with optic disc edema ($p = 0.022$). According to these results, a significant proportion of patients with idiopathic ON and a normal baseline brain MRI will develop MS, with a higher risk during the first 5 years. Therefore, in the presence of factors in favor of MS conversion, close follow-up, including semestral medical consultations and yearly brain MRI, can be recommended. Early immunomodulatory treatment may be individually considered as it can delay conversion and reduce new lesion development rate.

1. Introduction

Optic neuritis (ON) is the first presentation of multiple sclerosis (MS) in approximately 20% of patients [1,2] and the estimated risk of MS conversion after ON is 30% at 5 years, 38% at 10 years and 50% at 15 years [3]. Therefore, when assessing and managing a patient with isolated ON without an identifiable etiology, the possibility of future development of MS has to be considered. Determining which patients have a higher risk of conversion to MS is important, as studies suggest that there may be a benefit from early immunomodulatory treatment in patients with clinically isolated syndrome (CIS), including ON [4–10]. Although the presence of one or more lesions on baseline brain MRI has been identified as the strongest predictor of MS conversion [3,11–16], there are patients with normal baseline MRI who also develop MS and predictors of conversion are still to be determined in this subgroup of patients.

We aimed to estimate the risk of developing MS and identify subjects with higher risk of conversion in a population of patients with idiopathic ON and normal baseline MRI.

2. Methods

We performed a retrospective study of patients with idiopathic ON and normal baseline MRI presenting to Coimbra University Hospital, Portugal, between 2003 and 2010. Patients were found by a search for "Optic Neuritis" (International Classification of Diseases, Ninth Revision, Clinical Modification code 377.3) through the hospital database. Clinical charts of all patients were reviewed and demographic, clinical, paraclinical and treatment data were systematically collected.

The diagnosis of ON was based on clinical criteria, including subacute visual acuity loss, ocular pain exacerbated by eye movements, dyschromatopsia and relative afferent pupillary defect. Detection of conversion to clinically definite MS was based on the occurrence of another clinical event suggestive of demyelinating disease, excluding ON recurrence, during follow-up. MS diagnosis was performed according to the McDonald criteria approved at the time of the diagnosis.

* Corresponding author. Tel.: +351 2 3940 0448; fax: +351 2 3982 2637.
E-mail address: inesmbmarques@gmail.com (I.B. Marques).

0967-5868/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jocn.2013.06.013

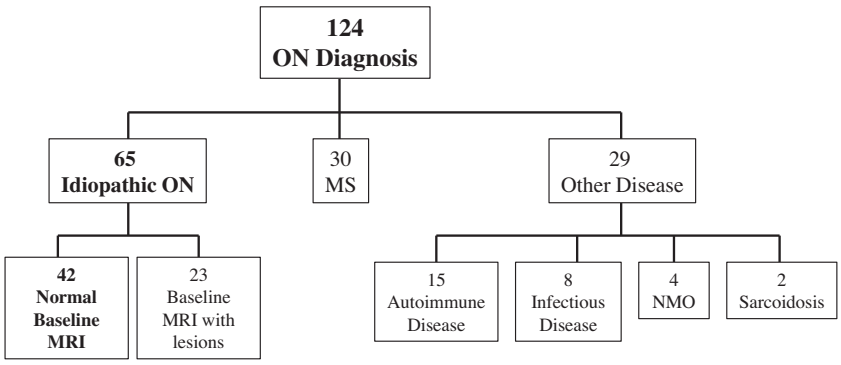

Fig. 1. Distribution of patients according to optic neuritis etiology. MS = multiple sclerosis, NMO = neuromyelitis optica, ON = optic neuritis.

Exclusion criteria included ON attributable to a disease other than MS, previous diagnosis of MS and the presence of lesions on baseline brain MRI.

All patients were evaluated by a neurologist and an ophthalmologist and a detailed clinical history, ophthalmologic examination and complete neurological examination was performed at the time of the first examination in our hospital. Visual acuity testing was performed using the Snellen chart and expressed as a fraction using the metric system. Reversal pattern visual evoked potentials (VEP) and cerebrospinal fluid analysis (CSF), including oligoclonal band (OB) testing using isoelectric focusing with immunoglobulin G immunoblotting, were performed during the first week after symptom onset in the majority of patients. In VEP evaluation, P100 wave latency was considered prolonged when it was higher than 115 milliseconds and P100 wave amplitude was considered reduced when less than 50% of the value of the contralateral eye. Gadolinium-enhanced 1.5 Tesla MRI (5 mm slices with a 2.5 mm gap) was performed within the first month after ON onset in all patients.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as the mean with standard deviation (SD), or medians. Categorical variables were expressed as absolute and relative frequencies (percentages). The independent sample *t*-test was used for comparison of means, Pearson's chi-squared test was used for comparing proportions and a logistic regression model was used to test for the independent significance of variables significant in the univariate analysis. All reported *p* values were two-sided and considered statistically significant if less than 0.05.

3. Results

A total of 124 patients with a diagnosis of ON were identified in the hospital database (Fig. 1). Thirty patients were excluded from the study because of previous MS diagnosis and 29 patients were excluded as they were ultimately diagnosed with another disease. Among the 65 patients with idiopathic ON, 23 were excluded because of the presence of lesions suggestive of demyelinating disease in baseline brain MRI. Therefore, a total of 42 patients with idiopathic ON and normal baseline MRI were identified.

The majority of patients were female (78.6%) and Caucasian (100%) with a mean age at ON onset of 29.6 years (SD: 8.4 years, range: 14–54 years). The mean follow-up time was 5.3 years (SD: 2.3 years). ON was unilateral in 88% of patients and retrobulbar in 71.4%. Visual acuity was reduced in all patients, ranging from only light perception to 6/7.5, and all patients had a central or paracentral visual field defect. Neurological examination revealed 28.6% of patients had abnormalities not related to ON, including hyperreflexia in 10 patients, nystagmus in three patients and mild ataxia in one patient. Thirty-one percent of patients reported a history of previous symptoms suggestive of demyelination, including previous episodes of sensory symptoms (paresthesia and/or hypoesthesia) in 11 patients and a remote episode of imbalance of a few weeks duration with spontaneous recovery in two patients. VEP were performed in 85.7% of patients with 29 patients with prolonged latency of the P100 wave and seven patients with prolonged latency and decreased amplitude of the P100 wave. CSF analysis was performed in 95.2% of patients, with 12 patients with more than two CSF OB unmatched in serum. Baseline brain MRI had evidence of optic nerve involvement in 76% of the patients, including optic nerve sheath gadolinium-enhancement (71%) and optic nerve sheath dilatation (43%). Treatment with high-dose intravenous methylprednisolone (1 g/day) was given to 83% of patients over 3 to 7 days. Recovery after 1 year of follow-up was evaluated based on visual acuity re-evaluation with 52.4% achieving total recovery (returning to visual acuity levels previous to ON), and 47.6% achieving incomplete visual acuity recovery with improvement equal or inferior to 6/12 (Table 1).

Table 1
Distribution of patients according to visual acuity values at optic neuritis (ON) diagnosis and after 1 year of follow-up

		Visual acuity after 1 year of follow-up					
		6/60	6/18	6/15	6/12	6/7.5	6/6
Visual acuity at ON diagnosis	<1/60	1	-	-	-	-	2
	1/60	1	-	-	-	-	3
	2/60	-	-	-	-	-	1
	6/60	-	2	1	-	-	3
	6/30	-	1	3	-	-	-
	6/18	-	-	-	1	1	-
	6/15	-	-	-	1	-	3
	6/12	-	-	-	-	1	2
	6/10	-	-	-	-	7	2
	6/7.5	-	-	-	-	-	6

ON recurrence occurred in 31% of patients, including eight patients with one recurrence and five patients with multiple (two to six) recurrences.

A total of 10 patients developed clinical conversion to MS, five during the first year after ON, two during the second year, one during the third year and two during the fifth year of follow-up. The mean time to MS diagnosis was 2.2 years (SD: 1.6 years, median: 1.5 years) and the 5 year conversion rate was 23.8%. MS conversion rate within 5 years of ON diagnosis was calculated for the variables collected (Table 2).

A statistically significant increase in MS conversion rate was associated with a history of previous symptoms suggestive of demyelination, OB in CSF unmatched in serum and incomplete visual recovery after 1 year. Patients presenting with optic disc

Table 2
Multiple sclerosis conversion rates according to demographic, clinical, paraclinical and treatment variables

Patient characteristics		Patients, n	MS conversion rate (%)	*p* value	Odds ratio	95% CI
Sex	Female	33	24.2	0.9	-	-
	Male	9	22.2			
ON	Unilateral	37	21.6	0.365	-	-
	Bilateral	5	40			
Fundoscopy	Disc edema	12	0	0.022	0.67	0.51–0.86
	Retrobulbar ON	30	33.3			
Other abnormalities on NE	Yes	12	33.3	0.359	-	-
	No	30	20			
Previous symptoms suggestive of demyelination	Yes	13	53.8	0.002	10.1	2–51
	No	29	10.3			
Oligoclonal bands in CSF	Positive	12	58.3	0.001	11.7	2.2–61.3
	Absent	28	10.7			
Treatment	IV methylprednisolone	35	25.7	0.517	-	-
	No treatment	7	14.3			
Visual acuity recovery after 1 year	Incomplete	20	45	0.002	17.2	1.9–153.7
	Complete	22	4.5			
Recurrence	Yes	13	30.8	0.478	-	-
	No	29	20.7			

CSF = cerebrospinal fluid, IV = intravenous, MS = multiple sclerosis, NE = neurological examination, ON = optic neuritis.

edema had significantly lower MS conversion rates. No statistically significant differences in MS conversion rate were found related to patient sex, ON laterality, the presence of other neurological examination abnormalities, corticosteroid treatment, or ON recurrence.

Among patients who ultimately converted to MS, the abnormalities detected in the neurological examination were mild ataxia and hyperreflexia, and the reported previous symptoms suggestive of demyelination were imbalance and sensory symptoms. All patients with MS conversion had P100 wave prolonged latency and in three patients P100 wave amplitude was also diminished. Visual acuity recovery was incomplete in all but one of the patients who developed MS. Four patients with ON recurrence (one to two recurrences) converted to MS.

Although patients with MS conversion were slightly older at ON diagnosis (32.9 ± 7.4 years) than patients without conversion (28.63 ± 8.5 years), this difference was not statistically significant ($p = 0.163$).

4. Discussion

This study emphasizes that a significant proportion of patients presenting with isolated ON and a normal baseline brain MRI will develop MS, especially in the first follow-up years. We found a 23.8% 5 year risk of developing MS, a value in accordance with previous reports, which estimate MS conversion rates between 10% and 30% in these patients [3–9]. The Optic Neuritis Treatment Trial [3], the largest study on MS risk after ON, included 191 patients with ON without baseline brain MRI lesions, with a conversion risk in this subgroup of 16% at 5 years, 22% at 10 years and 25% at 15 years, suggesting higher risk of MS development in the first 5 years and very low probability of conversion after 10 years of follow-up. In our study, we also found a higher MS conversion rate during the first years after ON, with 70% of conversions occurring during the first 3 years and 100% during the first 5 years.

We identified a higher MS conversion rate in patients with previous history of symptoms suggestive of demyelination, a feature estimated to be present in one-third of the patients presenting with a first demyelinating event and increasingly being considered to be useful in predicting conversion to MS [17,18].

The Poser criteria for MS diagnosis [19], used between 1983 and 2001, considered OB a laboratory support for MS diagnosis, but the diagnosis of laboratory supported definite MS in patients with OB implied the presence of other clinical or paraclinical evidence. In the subsequent 2001, 2005 and 2010 McDonald Diagnostic Criteria for Relapsing Remitting MS [20–22], MRI assumed a preponderant value in MS diagnosis, and the presence of OB was no longer considered in the diagnostic criteria. Nevertheless, in clinical practice, the presence of OB in CSF continues to be a factor in favor of MS diagnosis in the appropriate clinical context and a useful tool for predicting the prognosis of patients presenting with CIS. Higher MS conversion rates in patients who have OB in CSF has also been reported in other studies, with an estimated two-fold increase in MS risk in patients with OB, independent of the presence of lesions in the MRI [23].

None of the patients with baseline optic disc edema developed MS, reinforcing the idea that this feature may be associated with a lower risk of developing MS, as already reported in the Optic Neuritis Treatment Trial [3]. In patients with MS, ON is classically retrobulbar in the majority of patients [3,24], which is explained by the fact that the intraocular optic nerve is composed of unmyelinated axons and the optic nerve myelin sheath only begins after the retinal ganglion cell axons pass through the lamina cribrosa, surrounding only the retrobulbar portion of the optic nerve [25]. Although mild diffuse optic disc edema can be seen in one-third of patients with demyelinating lesions because of transudation of fluids from injured axons and disc vessels, optic disc edema is more common and obvious when there is blockage of orthograde axoplasmic flow by mechanical or ischemic processes [25]. For this reason, the presence of optic disc edema is less suggestive of future development of MS than retrobulbar ON.

In patients with MS, axonal loss is reported in the early stages of the disease, including CIS, and is associated with irreversible damage and incomplete recovery [26–29]. Studies with optic coherence tomography have demonstrated axonal loss in the retinal nerve fiber layer in patients with MS in the early stages of the disease [30–32]. This early axonal loss is probably the reason why most of our patients with subsequent MS conversion had incomplete recovery after the first clinical presentation of the disease. Therefore, we believe that incomplete recovery must be regarded as a warning signal of increased risk for MS conversion.

Contrary to other studies [3,7,33,34], we did not find an association between MS risk and sex, age or ON recurrence.

This study suggests that previous symptoms suggestive of demyelination, OB in CSF unmatched in serum, incomplete visual acuity recovery and retrobulbar ON are factors predicting MS conversion. When these factors are present, close follow-up, including semestral medical consultations and yearly brain MRI, can be recommended, at least during the first 5 years. Early

immunomodulatory treatment may be considered as it can prevent or delay conversion, reduce the development of new subclinical lesions and improve the clinical outcome [4–10]. Treatment decision must be individualized and reserved for high risk patients, as some patients will never develop MS.

There are some limitations that need to be acknowledged and addressed regarding the present study, including the small size of the sample and retrospective nature. We also recognize that the population of patients with ON is possibly underrepresented as various factors may affect patient selection, including coding errors in the hospital database and the fact that some patients never present for medical evaluation, especially when there is spontaneous recovery. MS conversion rate may also have been underestimated as only clinical MS conversion was considered and new silent subclinical lesions, that would allow MS diagnosis according to the current MS diagnosis criteria [22], may have been missed.

Conflicts of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

[1] Balcer LJ. Optic neuritis. N Engl J Med 2006;354:1273–80.
[2] Frohman EM, Frohman TC, Zee DS, et al. The neuro-ophthalmology of multiple sclerosis. Lancet Neurol 2005;4:111–21.
[3] Optic Neuritis Study Group. Multiple sclerosis risk after optic neuritis: final optic neuritis treatment trial follow-up. Arch Neurol 2008;65:727–32.
[4] CHAMPS Study Group. Interferon beta-1a for optic neuritis patients at high risk for multiple sclerosis. Am J Ophthalmol 2001;132:463–71.
[5] Beck RW, Chandler DL, Cole SR, et al. Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol 2002;51:481–90.
[6] Kinkel RP, Kollman C, O'Connor P, et al. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;66:678–84.
[7] Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001;357:1576–82.
[8] Kappos L, Polman CH, Freedman MS, et al. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;67:1242–9.
[9] Comi G, Martinelli V, Rodegher M, et al. Effect of glatiramer acetate on conversion to clinically definite multiple sclerosis in patients with clinically isolated syndrome (PreCISe Study): a randomised, double blind, placebo-controlled trial. Lancet 2009;374:1503–11.
[10] Comi G, De Stefano N, Freedman MS, et al. Comparison of two dosing frequencies of subcutaneous interferon beta-1a in patients with a first clinical demyelinating event suggestive of multiple sclerosis (REFLEX): a phase 3 randomised controlled trial. Lancet Neurol 2012;11:33–41.
[11] O'Riordan JI, Thompson AJ, Kingsley DP, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998;121:495–503.
[12] Morrissey SP, Miller DH, Kendall BE, et al. The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis: a 5-year follow-up study. Brain 1993;116:135–46.
[13] Korteweg T, Tintoré M, Uitdehaag B, et al. MRI criteria for dissemination in space in patients with clinically isolated syndromes: a multicentre follow-up study. Lancet Neurol 2006;5:221–7.
[14] Jacobs LD, Kaba SE, Miller CM, et al. Correlation of clinical, magnetic resonance imaging, and cerebrospinal fluid findings in optic neuritis. Ann Neurol 1997;41:392–8.
[15] Söderström M, Jin YP, Hillert J, et al. Optic neuritis. Prognosis for multiple sclerosis from MRI, CSF and HLA findings. Neurology 1998;50:708–14.
[16] Brex PA, Ciccarelli O, O'Riordan JI, et al. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002;346:158–64.
[17] Morrow SA, Fraser JA, Nicolle D, et al. Predicting conversion to MS – the role of a history suggestive of demyelination. Can J Neurol Sci 2010;37:488–91.
[18] Gout O, Lebrun-Frenay C, Labauge P, et al. Prior suggestive symptoms in one-third of patients consulting for a "first" demyelinating event. J Neurol Neurosurg Psychiatry 2011;82:323–5.
[19] Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–31.
[20] McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;50:121–7.
[21] Poman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–6.
[22] Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302.
[23] Tintoré M, Rovira A, Río J, et al. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? Neurology 2008;70:1079–83.
[24] Marshall D. Ocular manifestations of multiple sclerosis and relationship to retrobulbar neuritis. Trans Am Ophthalmol Soc 1950;48:487–525.
[25] Martin TJ, Corbett JJ. Neuro-ophthalmology: the requisites. 1st ed. St Lois: Mosby; 2000.
[26] Trapp BD, Peterson J, Ransohoff RM, et al. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338:278–85.
[27] Filippi M, Bozzali M, Rovaris M, et al. Evidence for widespread axonal damage at the earliest clinical stage of multiple sclerosis. Brain 2003;126:433–7.
[28] Rocca MA, Mezzapesa DM, Falini A, et al. Evidence for axonal pathology and adaptive cortical reorganization in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. Neuroimage 2003;18:847–55.
[29] Wattjes MP, Harzheim M, Lutterbey GG, et al. High field MR imaging and 1H-MR spectroscopy in clinically isolated syndromes suggestive of multiple sclerosis: correlation between metabolic alterations and diagnostic MR imaging criteria. J Neurol 2008;255:56–63.
[30] Costello F, Coupland S, Hodge W, et al. Quantifying axonal loss after optic neuritis with optical coherence tomography. Ann Neurol 2006;59:963–9.
[31] Trip SA, Schlottmann PG, Jones SJ, et al. Optic nerve atrophy and retinal nerve fibre layer thinning following optic neuritis: evidence that axonal loss is a substrate of MRI-detected atrophy. Neuroimage 2006;31:286–93.
[32] Trip SA, Schlottmann PG, Jones SJ, et al. Retinal nerve fiber layer axonal loss and visual dysfunction in optic neuritis. Ann Neurol 2005;58:383–91.
[33] Nilsson P, Larsson EM, Maly-Sundgren P, et al. Predicting the outcome of optic neuritis: evaluation of risk factors after 30 years of follow-up. J Neurol 2005;252:396–402.
[34] Mowry EM, Pesic M, Grimes B, et al. Clinical predictors of early second event in patients with clinically isolated syndrome. J Neurol 2009;256:1061–6.