THE RISK OF MULTIPLE SCLEROSIS DEVELOPING IN PATIENTS WITH ISOLATED IDIOPATHIC OPTIC NEURITIS IN BRAZIL

MARCO AURÉLIO LANA-PEIXOTO * — *MARIA INÊS VILHENA LANA-PEIXOTO* *

SUMMARY — We studied 88 patients with isolated idiopathic optic neuritis (IION) in order to evaluate the rate of progression to multiple sclerosis (MS) in Brazil. The patients were reassessed from one month to nine years after the development of the HON (mean follow-up was 4.6 years). There were 52 men and 36 women with ages ranging from three to 59 years (mean 24.3 years). Bilateral optic neuritis occurred in 19 patients whereas sequential involvement of the fellow eye after an interval longer than four weeks occurred in other 19 patients. Recurrences in the same eye occurred in seven cases. Nine patients (10.8%) developed clinically definitive MS — 13.9% of the women and 7.7% of the men with IION. The median age at the time of diagnosis of MS was 25 years. The mean interval between HON and the emergence of other MS signs varied from one month to five years — median one year. Sixty-seven percent of these, patients developed signs of spinal cord involvement. Our findings when compared to published series in different countries are closer to figures reported in Japan than those in the West.

Risco de desenvolvimento de esclerose múltipla em pacientes com neurite óptica idiopática isolada no Brasil.

RESUMO — O risco de progressão da neurite óptica idiopática isolada (NOH) para esclerose múltipla (EM) ainda não está bem definido, com taxas variáveis dependendo de critérios de diagnóstico, tempo de follow-up, fatores genéticos, raciais e, possivelmente geográficos. Com o propósito de estudar a taxa de desenvolvimento de EM em pacientes com NOIÍ, um grupo de 88 pacientes (52 homens e 36 mulheres) com NOII foi seguido por período de 1 mês a 9 anos (média 4,6 anos). Em 19 pacientes a neurite óptica foi bilateral, ou seja, ocorreu simultaneamente ou em intervalo até 4 semanas nos dois olhos; enquanto em outros 19 pacientes ela foi seqüencial, afetando o olho contralateral após intervalo maior que um mês. Recorrências afetando o mesmo olho foram observadas em 7 pacientes. Nove pacientes (10,8%) com NOII desenvolveram sinais de EM entre 1 mês e 5 anos após o primeiro episódio de neurite óptica, o intervalo mediano sendo 1 ano. Estes pacientes representavam 13,9% das mulheres e 7,7% dos homens com NOII e a mediana das idades foi 25 anos. Dois terços dos pacientes que desenvolveram EM apresentaram envolvimento predominantemente medular. Nossos achados, em relação à taxa de progressão da NOII para EM assim como à predileção por envolvimento espinal, se assemelham mais aos dados publicados no Japão que em países ocidentais.

It has been well established that optic nerve involvement almost always occurs in the course of multiple sclerosis (MS). The lesions may be either clinically evident 33 or silent and only disclosed through electrophysiological [12]~14 methods or autopsy studies 30. Conversely it has been demonstrated that a high proportion of patients who present isolated idiopathic optic neuritis (IION> goes on to develop demyelinating lesions outside the anterior optic pathways 3,4,6,8,9,n,i3,i5,i6,i8,i9,2i,26,32,34,36,37,40,48,52,54. The estimated risk of manifest MS developing in patients with HON is variable, the rates ranging from 11.5% [20] to 85% 31 in the literature. Several factors such as

* Associate Professor of Neurology, Department of Neurology, Federal University of Minas Gerais.

Dr. M. A. Lana Peixoto — Institute Hilton Rocha - Av Anel da Serra 1335 - 30210 Belo Horizonte MG - Brasil.

patient selection, diagnostic criteria, length of the follow-up, genetic predisposition, sex race and the geoghaphic location where the cohorts were studied may account for these differences. Series from different countries suggest that racial and geographic factors may also play an important role in the risk of conversion of HON to MS. Many studies in Europe [3,6,16,31,33,36,37,41,47,49,53], United States [46] and Australia [29,45] showed that the risk is over 50%. On the other hand progression rates in Israel [18] and Japan [17] were estimated in 32% and 8.3% respectively. To trie best of our knowledge, in addition to a series from Chile [2] in which only one out of 23 patients with HON (4.3%) developed MS in a mean follow-up period of 9.7 years, no other study in Latin America was conducted.

In order to evaluate the conversion rate of HON to MS in Brazil, a MS presumptively low prevalence country, a group of patients was observed during a mean follow-up period of 4.6 years. The results of this investigation are herein reported and discussed.

PATIENTS AND METHODS

Between 1980 and 1989 136 patients with a presumable diagnosis of optic neuritis were examined by one of us (MALP) at the Neuro-Ophthalmology Department of the Institute Hilton Roeha, a national referral hospital for eye diseases in Belo Horizonte, Brazil. AH patients had full ophthalmic and neurologic examinations to rule out eye or CNS disorders. Patients with family history of visual failure, history of heavy tobacco or a alcohol comsuption, use of toxic substances, evidence of diabetes, hypertension, dietary deficiency, neurosyphilis, ischemic optic neuropathy, optic nerve vasculitis or compression, uveitis and retinal disorders were excluded. Patients with previous history of diplopia or any evidence of motor or sensation deficit, motor incoordination or sphincter disturbance were also discarted.

The diagnosis of optic neuritis according to the, criteria of Perkin and Rose [41] was then confirmed in 100 patients. Nine of them had history, or signs of neurologic disease in addition to optic neuritis and were therefore discarded. Three patients who developed optic neuritis in the course of or immediately after measles or mumps were also excluded. The remaining 88 patients were considered to present HON and are the subject of this study.

Patients were said to have bilateral optic neuritis when both eye were involved simultaneously or within four weeks of each other. Recurrent optic neuritis was defined as attacks of optic neuritis involving one or other eye at an interval greater than four weeks. When the recurrent episode affected the other eye the term sequential optic neuritis was employed [41].

The period of follow-up was taken as the time from the original attack of optic neuritis to the time of the last reassessment, or in patients developing MS, to the time of development of other signs of CNS involvement. This period ranged from one month to 9 years (mean 4.6 years). Clinically definite or probable MS was diagnosed according to the criteria of Poser et al. [42] and the onset was dated to the first symptom that the patient could recall.

RESULTS

In 88 cases of HON there were 52 men and 36 women, the sex ratio being 1.4:1.0. The age at onset ranged from 3 to 59 years and the mean age was 24.3 years. Seventeen patients were 14 or less years old at the time of the optic neurits, 10 of them were 6 or less years old.

There were 19 patients (21%) with bilateral optic neuritis and 19 others with sequential involvement of the fellow eye after an interval longer than four weeks. Recurrent episodes affecting the same eye was observed in seven patients (7.9%). Most of the recurrences occurred in the first two years following the initial episode. The median age of patients with bilateral optic neuritis was 16 years whereas of patients with recurrences was 38 years.

Nine patients (10.2%) developed clinical evidence of demyelination elsewhere in the CNS and were regarded as fulfilling the criteria for diagnosis of definite MS (Table 1). There were five out of 36 women (13,9%) and four out of 57 men (7.7%), with age ranging from 17 to 49 years at the time of diagnosis of MS; the median age being 25 years. Three of these patients had presented bilateral simultaneous optic neuritis (cases 5, 6 and 8), whereas

Case	Sex	Age	Eye	Recurrences	Interval IION - MS	Developing signs
1	M	23	OS	OD	2 months	Paraparesis; paresthesiae in lower limbs
2	M	18	OS	OS	3 years	Paresthesiae in lower limbs weakness of rt. hand
3	M	40	OD	OD	1 year	Paresthesiae in lower limbs
4	F	26	OS	OS	5 years	Paresthesiae in lower limbs; sphincter dysfunction
5	M	27	bilat.		1 year	Ataxia of limbs; ataxic gait
6	F	49	bilat.		1 year	Paraparesis; sensory level at T_4; sphincter dysfunction
7	F	25	OD		3 years	Paraparesis; ataxia of limbs, ataxic gait; sensory loss
8	F	17	bilat.		1 month	Diplopia; internuclear ophthalmoplegia
9	F	20	OD	OS	5 years	Paralysis of rt. hand and face; ataxia of limbs; ataxic gait

Table 1 — Optic neuritis patients developing multiple sclerosis.

sequential involvement of the fellow eye after an interval longer than four weeks occurred in two patients (cases 1 and 9), and recurrence in the same eye in other three patients (cases 2, 3 and 4). In just one patient (case 7), optic neuritis occurred in a single eye and Showed no recurrence until the time of the diagnosis of MS. In case 4 there were three episodes of recurrence in the same eye before clinical signs of MS developed.

The interval between IION and the emergence of other MS signs varied from one month to five years, with a mean of 26 months and a median of one year. In six out of nine patients (67%) who progressed to MS there was predominant involvement of the spinal cord. Incoordination of the limbs and ataxic gait were the most marked clinical signs in two patients, whereas diplopia and internuclear opthalmoplegia occurred in one case.

COMMENTS

Multiple sclerosis in Brazil is presumably very rare although epidemiological studies have not been published to date. The risk of developing MS following HON is even less known in this country. A similar situation occurs throughtout Latin America and to the best of our knowledge, the only study on the progression of HON to MS in this continent comes from Chile 2 where just one among 23 patients with HON manifested MS in a mean follow-up period of 9.7 years. The present investigation shows that nine of 88 patients (10.2%) who were first seen with HON eventually developed MS. This figure is much higher than the Chilean study but our sample is larger and derived from a private hospital usually attended by middle class or well-to-do people who are generally more attentive and have easier access to health care. Yet this rate may even be underestimated if one considers some relevant methodological points. First of all, although some of our patients had a follow-up time as long as 10 years, for many others this period was shorter than one year. It has been well recognized that the longer the follow-up the greater the chance of conversion 13.16,33,34,36. Secondly, it is possible that some patients who developed MS were lost for follow-up and have not notified us about the disease. It is also to be noted that as many as 17 patients (27.3%) were 14 or less years old. Some authors 39 have found a very small risk or development of MS in this age group although others 44 have demonstrated, on clinical grounds and by magnetic resonance imaging (MRI), conversion rates as high as those of adults. If children were excluded from our series the progression rate would increase to 9 of 61 patients (14.7%).

As gender is concerned as risk factor for the development of MS our analysis shows that 13.5% of the women and 7.7% of the men progressed to MS. The greater risk in the women is in agreement with other studies [3,8,15,46]. Some authors reported a risk 3.4 times greater *in* women than in men [46].

Bilaterality and recurrences have also been considered as risk factors [8,9,17,52]. In the present investigation MS developed in five of 38 patients (13.2%) who had simultaneous or sequential optic neuritis or in four of 52 (8%) who had unilateral involvement. Three of these last patients had had recurrent episodes of HON coming before MS. This positive influence of recurrence has not been confirmed by other autors [16,19,46].

The longest interval between HON and the onset of clinical signs of lesions elsewhere was five years in our study. Most patients who converted to MS had clinical signs one year after onset of the HON. Although the majority of investigations demonstrate that the risk of progression to MS is greater in the first years following HON [6,10,16,19,29,40,45,48,54], reassessment after extended follow-up and life table analysis have revealed an actual increment of the risk as time goes on [13,46]. Rizzo and Lessell [46] observed no decline in the risk of developing MS after the first several years

Author	Date	Country	Number of cases	Follow-up mean (range)	% Definite MS	% Prob/ Possible MS
Rose [47]	1970	England	91	? (0.5 - 7)	55	—
Sandberg-Wolheim [48]	1975	Sweden	60	13.3 (0.5 - 6)	36	—
Compston et al.[9]	1978	England	146	? (0.8 - 3.5)	25	15
Cohen et al.[8]	1979	USA	60	7.1 (5 - 12)	28	7
Nikoskelainen et al.[36]	1981	Finland	48	? (7 - 10)	—	56/19
DeLeersnyder et al.[10]	1981	France	14	1.07 (0.25 - 3)	21	—
Isayama et al.[17]	1982	Japan	84	5.2 (1 - 11.8)	8.3	—
Stendal-Brodin and Link [52]	1983	Sweden	30	11 (6 - 20)	33	—
Kinnunen [19]	1983	Finland	214	5.1 ?	19	—
Landy [29]	1983	Australia	110	?	56	—
Mapelli et al.[32]	1985	Italy	54	9.2 (5 - 16)	25	—
Hely et al.[15]	1986	Australia	82	4.8 (0.5 - 22)	32	—
Rizzo et al.[46]	1988	USA	60	14.9 (5 - 20.5)	58	—
Sanders et al.[49]	1989	Netherland	48	? (0.5 - 3.5)	60	—
Alvarez et al.[2]	1989	Chile	23	9.7	4.3	—
Present series		Brazil	88	4.6 (0.1 - 9)	10.2	—

Table 2 — Prospective studies on the correlation between IION and MS in different countries.

of follow-up. Conversely, they report, through life table analysis, that 74% of the women and 34% of the men in their cohort would have developed MS within 10 years after their initial attack of HON, and that after 20 years of follow-up 91.3% of the women and 44.8% of the men would be expected to develop MS. It is conceivable that as follow-up of subjects in our cohort extends or if life table analysis is used the rate of conversion may increase. At the present time however, among all published prospective studies, our figure is only smaller than those in Chile and Japan (Table 2). It is still uncertain if geographical factors may influence the prognosis of HON. Distinct study designs and particular methodological aspects are always to be considered to account for the different results 26. However dissemination rates in different MS prevalence zones seem relate directly to the prevalence of MS in those areas. In general, series in Northern-European countries 3,36,47,49 show the greatest progression rates whereas they have been variably reported in the United States 4,8,33,40,46,54 and Australia 15,29,45 in Israel is, Japan 17 and Chile 2 dissemination to MS is unfrequent.

In Japan a prospective study of 84 patients with HON showed a conversion rate of 8.3% in a mean follow-up period of 5.2 years 1?. This rate is very close to ours and it turns to be another point of similarity of MS in eastern countries and Brazil. It is known that MS in Japan 22,25.50,5i, Korea 27, India 7,35 and China 5 has a low prevalence rate, a higher frequency of visual symptoms at the onset and a predominant involvement of the optic nerves and spinal cord. In Brazil the disease presents similar clinical features 28. An example of this tendency is the occurrence of spinal cord signs in six of our nine patients (67%) who developed MS. In the Japanese group spinal cord involvement was present in 85.7% of the MS patients 1?. Asian and Latin American countries may share common factors influencing the expression of the disease and the progression of HON to MS.

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