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ORIGINAL ARTICLE

Late onset multiple sclerosis

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KEYWORDS
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Long onset multiple sclerosis clinical course

Abstract
Introduction: Late onset multiple sclerosis (LOMS) is an unusual entity , poorly characterized and diff cult to diagnose.
Objective: To study a series of patients with LOMS (presentation of the f rst symptom of disease after the age of 50 years).
Patients and methods: In this retrospective study we review demographic characteristics, f rst onset symptom, diagnostic delay, disability at the time of diagnosis (EDSS), disease course and f ndings in CSF, VEP and MRI studies.
Results: We included 18 patients (12 F and 6 M) with LOMS (4.8% of the total). The most frequent f rst symptoms were motor de f cits (33%), multisystem de f cits (33%) and cerebellum disorder (16%). Clinical course (all the cases with a minimal follow-up of 5 years after the diagnosis): primary progressive-MS (62%), secondary progressive MS (22%), relapsing-remitting MS (16%). The initial EDSS score was higher than 4 points in one third of patients and diagnosis delay was over 5 years in two thirds of cases. The cerebral MRI study was abnormal and compatible with MS in all patients and ful f lled the Barkhof criteria in 12 cases (67%). IgG oligoclonal bands were positive in 64% of patients in the CSF study and VEP were abnormal in 73%. The most frequent wrong diagnoses were cerebrovascular disorders and spondyloarthritic cervical myelopathy.
Conclusions: LOMS course is often primary , progressive and motor and multisystem symptoms are the most frequent. The diagnosis is usually delayed and when it is made patients have a high disability score. The f ndings of cerebral and spinal MRI, CSF and VEP studies are of high diagnostic yield. Cerebrovascular disorders and spondyloarthritic cervical myelopathy are the most important entities in the differential diagnosis of LOMS.

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PALABRAS CLAVE
Esclerosis múltiple de inicio tardío;
Factores demográficos;
Resonancia magnética;
Líquido cefalorraquídeo;
Potenciales evocados visuales;
Formas clínicas evolutivas de esclerosis múltiple

Esclerosis múltiple de comienzo tardío

Resumen
Introducción: La esclerosis múltiple de comienzo tardío (EMCT) es una entidad infrecuente y no bien caracterizada, que suele plantear dificultades diagnósticas.
Objetivos: Estudio retrospectivo de una serie hospitalaria de EMCT (primer síntoma a partir de los 50 años).
Pacientes y métodos: Se estudiaron factores demográficos, síntomas iniciales, retraso diagnóstico, grado de discapacidad en el momento del diagnóstico, formas clínicas evolutivas y hallazgos en estudios de LCR, PEV y RM.
Resultados: Se incluyeron 18 pacientes (12 mujeres y 6 varones) con EMCT (4,8% del total de la serie estudiada). Los síntomas iniciales mas frecuentes fueron déficits motores (33%), de afectación de múltiples sistemas (33%) y cerebelosos (16%). Las formas clínicas evolutivas (todos los casos con un seguimiento mínimo de 5 años tras el diagnóstico) fueron: EM-PP (62%), EM-SP (22%) y EM-RR (16%). La EDSS en el momento del diagnóstico era superior a 4 en un tercio de los pacientes; el retraso diagnóstico superó los 5 años en dos tercios de los casos. El estudio de RM cerebral resultó anormal y compatible con EM en todos los pacientes y cumplía criterios de Barkhof en 12 (67%). Las BOC resultaron positivas en el 64% de los pacientes en los que fueron determinadas; los PEV estaban alterados en el 73% de los casos estudiados. Los diagnósticos erróneos previos mas frecuentes fueron patología cerebrovascular y mielopatía espondiloartrósica cervical.
Conclusiones: La EMCT suele manifestarse con déficits motores o de múltiples sistemas, que progresan desde su inicio; se diagnostica con retraso, cuando hay ya un grado de discapacidad importante. El estudio de RM cerebral y medular en conjunción con los PEV y BOC en el LCR facilita su diagnóstico. Patología cerebrovascular isquémica y mielopatía cervical son los diagnósticos erróneos más habituales.

Introduction

Multiple sclerosis (MS) is a disease of unknown aetiology, in which inflammatory, autoimmune, and degenerative processes all take part. The symptoms of MS generally debut between the ages of 20 and 40 years, and women are affected twice as often as men.[1,2] MS tends to follow a course of episodes of neurological impairment (relapses) that remit either totally or partially (relapsing-remitting forms or RRMS) or that cause neurological impairment that progresses from the time of onset (primary progressive forms or PPMS) or after an initial period of relapses (secondary progressive forms or SPMS). Twenty per cent of all MS cases are PPMS and the remaining 80% are RRMS, half of which go on to become SPMS.[1,2] Although there is no general consensus, MS is currently thought to be late onset (LOMS) if the first symptoms of the disease present starting after 50 years of age.[3-9] The diagnosis and clinical management of LOMS is baffling, given that there are several different diseases that can present similar symptoms,[7] including ischaemic cerebrovascular disease, the frequency of which increases with age, and cervical myelopathy of spondyloarthritic origin, considered to be the number one cause of paraesthesia over the age of 50. Another confounding factor is the presence of preferentially subcortical hyperintense lesions on T2-weighted and FLAIR sequences of magnetic resonance imaging studies (MRI), which also become more common in the elderly and are particularly striking in patients with vascular risk factors.[10,11] We have conducted a study of the cases of LOMS diagnosed in our centre.

Patients and methods

All patients diagnosed with MS using Poser's criteria[12] at the "Complexo Hospitalario de Santiago de Compostela" (CHUS) and who manifested the first symptom of the disease when they were 50 years old or older (LOMS) were studied. Demographic data, clinical syndrome at the time of onset, score on the Expanded Disability Status Scale proposed by Kurztke[13] (EDSS) at the time of diagnosis, MRI findings at the time of diagnosis, presence or absence of oligoclonal IgG bands (IgG OCB) in CSF, presence or absence of alteration (specified in terms of the P100-wave latency delay) in the visual evoked potentials (VEP) study, and the clinical course type were all evaluated.

The cases of LOMS in this study were selected from all the patients diagnosed with MS at the CHUS from 1991 to 2005; all were examined at least once by MRI (0.5 T facility up until 1999 and 1.5 T from that time onward) and, in accordance with a clinical protocol, all were examined so as to rule out infectious diseases (syphilis, Lyme disease, HIV, and, in certain cases, HTLV-1 and brucellosis), B_{12} and folic acid deficiency, sarcoidosis, vasculitis, and connective

Table 1 Summary of magnetic resonance studies (MRI with T1-weighted, T2-weighted and FLAIR sequences ("fluid attenuation inversion recovery") and intravenous gadolinium (iv Gd)

Magnetic resonance imaging study	Nº of patients	9 or more HI	< 9 HI	One or more juxtacortical HI	Three or more periventricular HI	One or more infratentorial HI	Gd uptake	Black holes
T1-weighted MRI of the brain	18							13 (72%)
T2-weighted /FLAIR MRI of the brain	18	11 (61%)	7 (39%)	8 (44%)	12 (67%)	13 (72%)		
T1-weighted MRI of the brain - iv Gd	12						1 (8%)	13 (72%)
T2-weighted spinal MRI	10		7 (70%)					

HI lesions: hyperintense lesions.

tissue diseases. The patient follow-up in this study ranged between 5 and 19 years from the time of diagnosis.

Results

A review was carried out on the clinical history of 368 patients with MS, of whom 18 (4.8%) presented the first symptom of the disease after the age of 50. Of these, 12 were female (F) and 6, male (M), which makes for a F:M ratio of 2:1. The mean age of onset of LOMS (first relapse or beginning of neurological dysfunction documented in the medical history) was 55.5 years, with a range of 50 to 66 years. As for age at the time of diagnosis, 12 patients were between 50 and 55, 4 patients were between 56 and 60, one patient was over the age of 60, and another patient was 76 years old (this paradigmatic case will be summarized later on).

The initial neurological presentation consisted of motor impairment in 6 patients (33%), multisystem involvement in 6 (33%), cerebellar involvement in 3 (16%), sensory impairment in one (5%), optical neuritis in one (5%), and the brainstem was affected in one patient (5%).

The MRI scan of the brain was abnormal and compatible with MS in all 18 patients. In 7 of the 10 patients examined (70%), there were spinal cord lesions. The results are explained in detail in table 1. Despite the fact that the studies were not homogeneous (gadolinium (Gd) was not injected in all cases, nor was the spinal cord studied in all cases), 12 patients would have met Barkhof's criteria (these criteria had not been described when many of the patients underwent MRI studies).

The CSF was analyzed in 11 patients, 7 of whom (64%) presented oligoclonal bands (OCB). In 15 patients, VEP were studied and in 11 of these 15, the potentials were altered (73%).

With a follow-up period of at least 5 years since the time of diagnosis, the clinical evolution was documented as: PPMS in 11 patients (62%), SPMS in 4 (22%), and RRMS in 3 (16%). The diagnosis was made during the first 5 years after presentation of the initial symptom in 12 patients (66%), between 6 and 10 years in 5 (28%), and in one case (6%), the diagnosis was established more than 10 years after symptomatic debut. The score on the EDSS at the time of diagnosis was 4 points or less in 12 patients (67%), between 4.5 and 6 in 4 (22%), and greater than 6 in 2 (11%). In 6 patients, mistaken diagnoses had previously been made of idiopathic trigeminal neuralgia (one case), cervical myelopathy (2 cases), and cerebrovascular disease (3 cases).

The oldest patient was 76 years old at the time of onset and was transferred to our centre due to acute paraesthesia. She had high blood pressure, as well as dyslipidaemia and had suffered several episodes of paroxysmal atrial fibrillation. One year prior to admission, she had presented hemiparesia on the left side with minimal residual impairment and 10 years earlier, she had had hemiparesia on the right side of her body that left no sequelae; she was taking carbamazepine for trigeminal neuralgia that had begun 11 years previously. At the time of admission, the patient presented transverse spinal cord syndrome with mid-thoracic level for all sensory modalities, intense paraesthesia with bilateral Babinski's sign, and sphincter dysfunction. The spinal MRI was normal. In the MRI of the brain, several hyperintense areas can be seen in the encephalic white matter (fig. 1). IgG OCB were detected in the CSF that were not present in serum and VEP were normal. The patient was treated with methylprednisolone IV (1 g/day/5 days) and after one week was able to walk unaided. She was diagnosed with RRMS.

Discussion

Advanced age is no longer considered to be a diagnostic exclusion criterion for MS. We currently have greater insight into LOMS, albeit based only on retrospective studies of hospital series. A case has been published of a female patient who was 82 when she presented the first symptom of MS.[14] In some publications, the term very late onset has been used to refer to cases in which the disease debuts in the seventh decade of life.[15]

The percentage of patients with LOMS in our series (4.8%) was very similar to that of the University of British Columbia study (Vancouver, Canada), one of the largest series in the literature with 132 cases (4.7% of the total patient

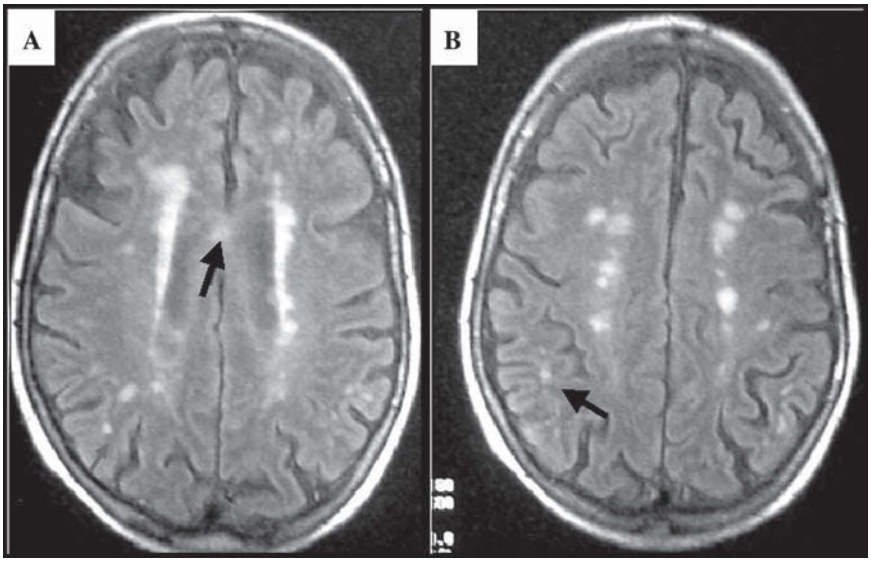

Figure 1 MRI of the head (FLAIR sequence) of the eldest patient in the series (76 years): several hyperintense areas are seen in the white matter, many of which are located periventricularly and with the largest axis perpendicular to the lateral ventricles; the arrows point to other lesions in the corpus callosum (A) and juxtacortical lesions (B).

population).[8] It is also very much in line with the series of Polliack et al., consisting of 30 cases (4.6% of the total) belonging to the Sheba Medical Centre of Tel-Hashomer (Israel).[5] Nevertheless, it must be remembered that this percentage has varied in other series from 1.1%[6] to 12.7%.[17] In the Mayo Clinic series (Rochester, USA), which was reported in 1983, the percentage of LOMS was 9.4% in a total of 838 patients [3] and in the most recent publication, from the Alfried Krupp Hospital of Essen (Germany), the incidence was 8% out of a total of 645 patients. [9] We have found no clear reason to account for these variations and, in light of the data presented, we cannot attribute them to a geographic factor or to being seen at departments specializing in MS, although some of them may have a particular power of attraction for special cases. LOMS is also more common in women. In our series, the proportion of 2:1 in favour of females was similar to that of the usual presentation of MS and was slightly higher than that of other series, 1.4:1[9] or 1.7:1.[5]

Pyramidal type motor impairment or a polysymptomatic presentation (generally a combination of motor and sensory impairment and sphincter dysfunction) were the most common form of debut (66% of the cases). These data were also found in other studies. [3-6,8,9] They are explained by the greater tendency of LOMS to affect the spinal cord, particularly in PPMS, which in our series accounted for 61% of the cases and reaches figures of up to 83% in some studies. Isolated sensory symptoms are rare in LOMS.[18]

MRI has become the diagnostic technique with the greatest specificity and sensitivity for diagnosis, as well as the most useful technique for following up on patients with MS. As age increases, the white matter lesions in the brain due to microangiopathy , known as leukoaraiosis, become more common, and this may cause the study to lose specificity. De Seze et al. [19] conducted an MRI study in patients with LOMS and found that Barkhof's criteria[20] were the most useful in this form of the disease, albeit less specific than in forms that present in the more usual way . We should point out that, despite the preponderance of PPMS, two thirds of our patients met Barkhof's criteria; the scant presence of Gd-enhanced lesions should also be highlighted, which might indicate a predominance of the degenerative component over the inflammatory component in LOMS.[21]

The presence of IgG OCB in CSF with simultaneous absence of the same in serum points towards intrathecal synthesis of these antibodies; this finding is not specific to MS, but does support its diagnosis and may be highly valuable in progressive forms and in doubtful or atypical cases, as occurs in LOMS. The relatively low positivity in our series (64%) contrasts with the rates of more than 90% for all forms of MS, which have been put forth in consensus works.[22] This might also be attributed to methodological problems in the first few years when the isoelectric focus technique was implemented. In other series of LOMS such as the French series, the percentage of patients with OCB was also relatively low (74%), though other series have reported 98% rates, clearly greater than the 92% found in juvenile onset forms of MS. [9] In PPMS forms, an OCB positivity rate or increased IgG index has been reported in 83% of the cases.[23]

Increased P100-wave latency in the VEP study is considered indicative of demyelination in the optic pathway and has been used to support the diagnosis of MS. We found altered VEP in 73% of the patients with LOMS, a percentage similar to that of other series.[6,9]

One important characteristic of LOMS is the delay in making the diagnosis. One third of our cases had more than 5 years of evolution when they were diagnosed and one third scored more than 4 on the EDSS. Older age, co-morbidity of vascular disease (the case we described with fibrillation is a clear example of a diagnostic delay of 11 years) and the

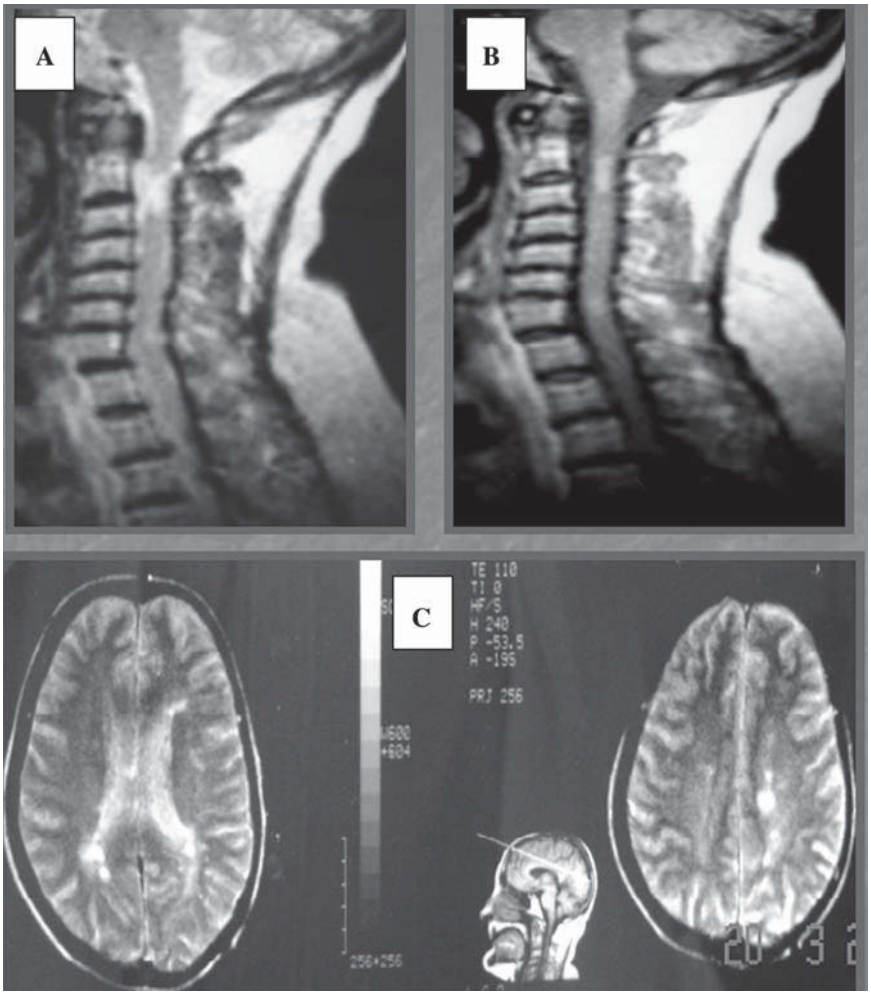

Figure 2 A. Sagittal image of the T2-weighted MRI study of the spine: cervical arthrosis and a hyperintense area in the spine at the C2 level can be seen. B. Sagittal image of the T2-weighted MRI study performed 4 years later: new hyperintense areas are seen in the cervical spinal cord. C. Axial image of the T2-weighted MRI brain study: multiple hyperintensities in the periventricular white matter and semioval centres.

predominance of progressive forms are three fundamental determining factors. In the California series of PPMS, the mean EDSS at the first visit was 5.5[23] and in the German LOMS series, it was 3.5.[9] Although the list of differential diagnoses to be considered with LOMS is very long, [7] cerebrovascular disease (especially subcortical arteriosclerotic leukoencephalopathy) and cervical spondyloarthritic myelopathy are at the head of said list. Vasculitis, intoxications, B_{12} deficiency, sarcoidosis, degenerative ataxias, metabolic diseases such as adrenoleukodystrophy, chronic infections (syphilis, Lyme disease, HTLV-1, HIV), spinal vascular fistulae, and paraneoplastic syndromes[3] should also be considered. In addition to clinical suspicion, the results of brain and head MRI studies, CSF and VEP studies will be very useful, not forgetting the appropriate laboratory studies to confirm/rule out the previously listed conditions.[7] Figure 2 illustrates how a patient is misdiagnosed with cervical spondyloarthritic myelopathy after a fall and 4 years later, a new MRI study, which included a brain study, helps to confirm the diagnosis of MS.

Although LOMS is a rare condition [24] and difficult to diagnose if the proper methodology is not followed (consisting of a computerized tomographic study and brain and spinal MRIs in suspected cases of vascular disease), it is wise to bear it in mind and to be aware of its existence, since at the very least, the relapsing forms can benefit from immunomodulating treatment. Its prognosis is not necessarily worse than that of earlier onset forms of the disease.[8]

The present study of patients with LOMS, the first to our knowledge to be published in Spain, has certain limitations, including the fact that we do not provide data regarding cognitive impairment and incidence of depression, as well as the lack of data on the progression of disability. Nevertheless, it reflects the changes in clinical practice in the last two decades with respect to the study of MS patients. The relatively low number of patients, the variability in the time of follow-up, and the conditions of neurological care have been the reasons determining these shortcomings.

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