FACULTAD DE MEDICINA
UNIVERSIDAD DE CANTABRIA

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

**Lesiones pseudotumorales
como forma de presentación de la esclerosis múltiple:
investigación dirigida a su significado pronóstico**

**Pseudotumoral lesions
as a presentation form in multiple sclerosis:
research into its prognostic meaning**

Autor/a: Marta López Vicente

Director/es: Jon Infante Ceberio

Vicente González-Quintanilla

Santander, Junio 2022

Index

1. Abstract

Pseudotumoral lesions are considered an atypical manifestation of demyelination of the central nervous system. Due to their scarce frequency in patients with multiple sclerosis (MS), they usually constitute a diagnostic challenge.

Our aim was to study the characteristics of patients with pseudotumoral lesions in a first clinical episode, contributing to the description of this form of MS and its prognostic implication.

Patients with pseudotumoral forms of MS were identified in the database of the monographic outpatient clinic of the Marqués de Valdecilla University Hospital; and demographic, clinical, analytical and radiological (MRI) variables were analysed retrospectively in patients with these lesions.

Of the 450 patients included in the database, 14 (57% male) with a mean age of 33.64 years, presented with pseudotumoral lesions. The most frequent form of presentation was motor (71%) or sensory (71%) deficits, followed by cerebellar or brainstem symptoms. The majority (85%) required hospitalization, although only 3 cases required diagnostic biopsy. The most frequent location for lesions was periventricular. At follow-up, 11 patients (78%) met RRMS criteria and 3 met CIS criteria (21%). In addition, 10 patients started disease-modifying treatment.

Our results are in line with previous studies, providing further information on the particularities of these lesions, both clinically and radiologically. Future research is needed to better understand both this form of MS and its prognostic significance.

Keywords: pseudotumoral lesions (PL), multiple sclerosis (MS), magnetic resonance imaging (MRI).

2. Resumen

Las lesiones pseudotumorales se consideran una manifestación atípica de la desmielinización del sistema nervioso central. Su escasa frecuencia en pacientes con esclerosis múltiple (EM) constituye habitualmente un reto diagnóstico.

Nuestro objetivo es estudiar las características de los pacientes con dichas lesiones en un primer episodio clínico, contribuyendo a la descripción de esta forma de EM y su implicación pronóstica.

Se identificaron pacientes con formas pseudotumorales de EM en la base de datos de la consulta monográfica del Hospital Universitario Marqués de Valdecilla, y se analizaron variables demográficas, clínicas, analíticas y radiológicas (RMN) retrospectivamente en los pacientes con estas lesiones.

De los 450 pacientes incluidos en la base de datos, 14 pacientes (57% varones) con una media de edad de 33.64 años debutaron con lesiones pseudotumorales. La forma de presentación más frecuente fue déficit motor (71%) o sensitivo (71%), seguido de clínica cerebelosa o del tronco del encéfalo. La mayoría (85%) requirió hospitalización, aunque sólo en 3 casos biopsia diagnóstica. La localización más frecuente de las lesiones fue periventricular. En el seguimiento 11 pacientes (78%) cumplieron criterios de EMRR y 3 de CIS (21%). Además, 10 pacientes iniciaron tratamiento modificador de la enfermedad.

Nuestros resultados se sitúan en línea con estudios previos, aportando mayor información sobre las particularidades de dichas lesiones, clínica y radiológicamente. Se precisan futuras investigaciones para comprender mejor tanto esta forma de EM como su significado pronóstico.

Palabras clave: lesiones pseudotumorales, esclerosis múltiple (EM), resonancia magnética (RMN).

3. Background

Multiple sclerosis (MS) is the most common non-traumatic disabling disease in young adults and the most prevalent chronic inflammatory disease of the central nervous system (CNS), affecting more than 2 million people worldwide[1,2]; but the underlying etiology of the disease remains uncertain[3–6].

3.1. Pathogenesis

Current knowledge about the disease suggests that this disorder would develop in a genetically susceptible individual who is exposed to a triggering specific external agent and/or to an endogenous antigen, though such agent is rarely (if ever) identified[1,7]. This fact would be responsible for promoting the redundant autoimmune cascade in which oligodendroglia, myelin, axons, and neurons are damaged. Physiopathologically, these different mechanisms result in multiple focal areas of inflammation and demyelination, which have been designated as "plaques"; as well as structural neuronal damage and atrophy[1,5,8–10].

In summary, MS is a complex and multifactorial disease; many genes modestly increase disease susceptibility, in addition to several well-defined environmental factors, that also have been suggested as triggering factors.

3.2. Epidemiology

Up to three-quarters of people affected by MS worldwide are reported as being females. Furthermore, concerning the individual risk of developing MS, individuals with an affected first-degree relative have a 2.5-5% risk of MS (compared to a risk of approximately 0.1-0.2% in the general population). Genomewide association studies have identified more than 200 gene variants that raise the risk of the disease, of which the most significant remains the HLA DRB1*1501 haplotype (with an odds ratio of approximately 3)[1,5,11–13].

Environmental risk factors such as geographic latitude, low vitamin D levels related to ultraviolet B light (UVB) exposure, tobacco exposure, obesity, especially in adolescence; and mononucleosis (resulted from infection with Epstein–Barr virus (EBV)) are also associated with an enhanced risk of multiple sclerosis. Other viruses have been suggested as potential causes, but none have been confirmed[3–5,7,12–16].

3.3. Clinical definition and MS phenotypes

Commonly, the age of MS onset varies from 20 to 40 years, however, onset at almost any age has been described. Nevertheless, disease onset ages earlier than 10 years or later than 50 years are considered rare conditions[1,5,17,18].

Clinically, MS is characterized typically by fully or partially reversible episodes of neurologic disability, usually lasting days or weeks. Typical presentation includes monocular visual loss due to optic neuritis, cerebellar or brainstem syndrome, limb weakness or sensory loss due to transverse myelitis[1,19–22].

Equally important is to emphasize that the clinical presentation of MS is variable about the location of the lesion. MS may also involve cognitive functions, mental confusion and deficits of symbolic functions (apraxia, agnosia, aphasia), in case of involvement of the frontal regions; and acute memory dysfunction, in case of involvement of the temporal regions[10,19,20,23].

Nevertheless, the clinical behaviours of MS are highly heterogeneous and have a decisive significance in both the progression of the disease and its prognostic implications[18,21,24].

As outlined in the latest consensus article on clinical phenotypes of MS (Lublin et al., Neurology 2014), a first major division can be established, related to the onset of the disease. Thus, a distinction is defined between **MS with relapses**, in which there is an absence of progression, and **progressive MS**, in which progression is responsible for the increase in disability among patients, regardless of the presence of relapses[21]

Focusing on MS with relapses, two clinical phenotypes are included within this entity[21]:

- **Clinically isolated syndrome (CIS):** is defined as the initial form of presentation of a demyelinating CNS disease such as MS, but in which no dissemination in time (DIT) had objectified (Table 1). An absence of any neurological background, fever or infection is essential for the diagnosis of this event. Its clinical course could include any of the clinical presentations described above, and it is commonly gradual and extends beyond 24 hours, but resolves spontaneously within days or weeks, with or without recovery[18,21,22].

  The review of the McDonald diagnostic criteria for MS carried out in 2011 (Polman et al., Annals of Neurology, 2011) established that the appearance of DIT and dissemination in space (DIS) on MRI (Table 1), in patients who had previously developed a CIS, implied the diagnosis of MS and, consequently, the exclusion of these patients from the CIS fenotype[25]. Accordingly, since the Clinical Classification Review (Lublin et al., Neurology 2014), CIS has been considered part of the relapsing-remitting MS phenotype as the initial disease event[21,22].

<table>
<tr><th colspan="2">DIS can be demonstrated by</th><th>DIT can be demonstrated by</th></tr>
<tr><td rowspan="4">≥1 T2-hyperintense lesions characteristic of MS in ≥ 2 of four areas of the central nervous system:</td><td>Periventricular</td><td rowspan="2">Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time</td></tr>
<tr><td>Cortical/Juxtacortical</td></tr>
<tr><td>Infratentorial</td><td rowspan="2">A new T2-hyperintense and/or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI</td></tr>
<tr><td>Spinal cord</td></tr>
</table>

Table 1: The 2017 McDonald Criteria for demonstration of DIS and DIT by MRI. Adapted from Thompson et al.; The Lancet Neurology 2018 [22].

- **Relapsing-remitting multiple sclerosis (RRMS)**: a phenotype characterized by a course consisting of flares and remissions (Figure 1), in patients where the presence of DIS and DIT has proven to be established (Table 2)[5,18,21,22]. The immense majority of MS patients start with this variety (≥ 85%)[3,18,26]

  The development of relapse or exacerbation of MS is evidenced by the appearance, reappearance or worsening of a symptom or neurological deficit persisting for more than 24 hours, with or without recovery; preceded by stability at least 1 month [5,18,21,22,25,27]. This event is commonly insidious, but fever or strong evidence of infection should not be present, as both are considered causes of "pseudo-exacerbations" that typically manifest as increasing weakness, lethargy, or even obtundation[21,27].

  Episodes of relapses or exacerbations are normally followed by variable periods of stabilisation or recovery. Even so, it may be the case that certain patients undergo some degree of persistent dysfunction during these periods, after acute events, nevertheless, they remain functional[18,21]. The duration of that period between relapses may vary, however, these occur usually with a frequency exceeding four weeks. In relapsing-remitting forms of MS, relapses generally occur at a rate of less than one per year[5,18].

Clinical presentation	**Additional data needed for MS diagnosis**	
≥ 2 clinical attacks and objective clinical evidence of ≥ 2 lesions, or; ≥ 2 clinical attacks and objective clinical evidence of 1 lesion and clear-cut historical evidence of a prior attack involving a lesion in a distinct anatomic location	None	
≥2 clinical attacks and objective clinical evidence of 1 lesion	DIS, demonstrated by:	An additional clinical attack implicating a different CNS site
		OR
		Demonstration of DIS by MRI
Clinical attack and objective clinical evidence of ≥2 lesions	DIT, demonstrated by:	A second clinical attack.
		OR
		Demonstration of DIT by MRI[a]
		OR
		Demonstration of CSF*-specific OCBs*
1 clinical attack and objective clinical evidence of 1 lesion	DIS, demonstrated by:	A second clinical attack implicating a different CNS site
		OR
		Demonstration of DIS by MRI[a]
	AND	
	DIS, demonstrated by:	A second clinical attack
		OR
		Demonstration of DIT by MRI[a]
		OR
		Demonstration of CSF*-specific OCBs*

*Table 2: The 2017 McDonald Criteria for diagnosis of multiple sclerosis in patients with an attack at the onset. [a]The MRI criteria for DIS and DIT are described in table 1 *CSF = Cerebrospinal Fluid *OCBs= Oligoclonal band. Adapted from Thompson et al.; The Lancet Neurology 2018[22].*

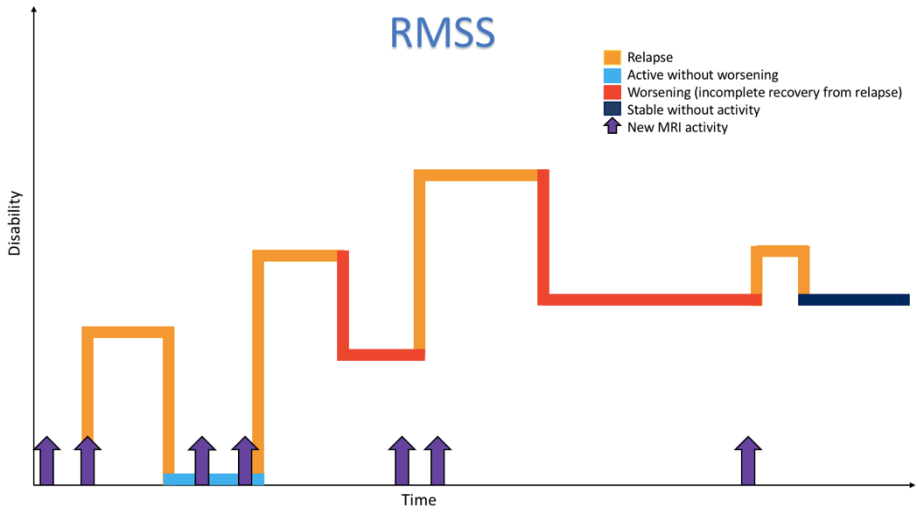

Figure 1: Disease course of RRMS. Adapted from the National Multiple Sclerosis Society[26].

From a strictly clinical perspective, "progression" denotes neurological deterioration with increased physical and cognitive dysfunction [18,21]. It is traditionally considered by clinical trials as a worsening of 0.5 points according to EDSS (Kurtzke's Expanded Disability Scale Score [28]) and persisting for a minimum of 6 months[29].

Likewise, two other clinical phenotypes are equally well defined within the entity of progressive MS[21].

- **Primary progressive MS (PPMS)**: progression is expected to occur from the onset of the clinical course, maintaining its great distinctiveness from secondarily progressive MS in the absence of relapses before the onset of progression (Table 3). Consequently, the clinical course is characterised by developing over a period of at least one year from the onset of progression; with no evidence of either period of remission/improvement or relapse.

  Individual patient progression differs from one patient to the other throughout the clinical course and it is possible the occurrence of overlapping relapses as well as periods of relative stability of the disease (Figure 2) [18,21,22,25]. Approximately 15% of MS patients undergo this clinical phenotype[3,18,22,26].

Primary progressive MS may be diagnosed in patients with:	
One year of disability progression (retrospectively or prospectively determined) independent of clinical relapse	
Plus 2 out of 3 of the following criteria:	≥1 T2-hyperintense lesions in ≥1 areas in the brain characteristic of MS (periventricular, cortical/juxtacortical or infratentorial)
	≥2 T2-hyperintense lesions in the spinal cord
	Presence of CSF-specific OCBs

Table 3: The 2017 McDonald Criteria for diagnosis of MS in patients with a disease course characterized by progression from onset (primary progressive MS). Adapted from Thompson et al.; The Lancet Neurology 2018[22].

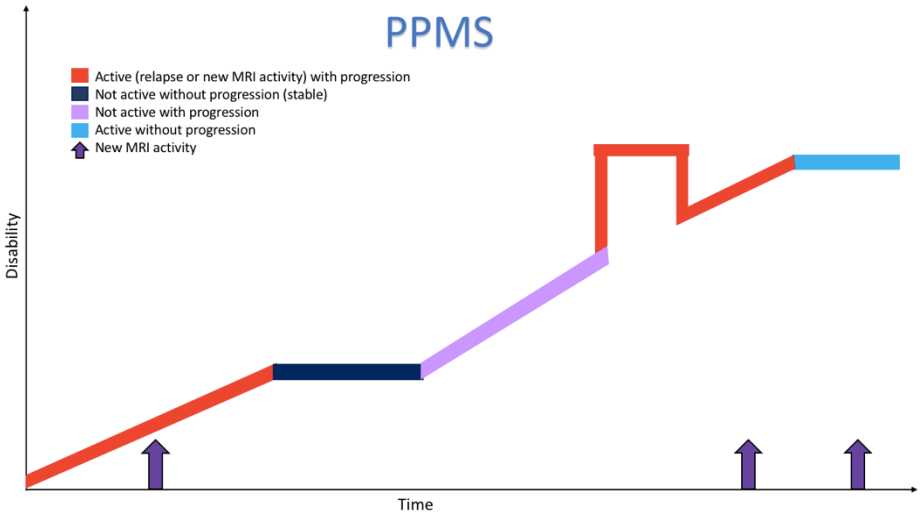

Figure 2: Disease course of PPMS. Adapted from the National Multiple Sclerosis Society[26].

- **Secondary progressive MS (SPMS)**: in this particular case, it is a retrospective diagnosis, due to the fact that it is characterised by the onset of progression, after an initial stage included in the MS with relapses phenotype (Figure 3)[18,21].

  The clinical course tends to be gradual and insidious, and progression to this phenotype spontaneously occurs in the majority of patients included in the RRMS clinical phenotype as a result of the absence of therapeutic intervention. Although duration time to the progressive phase is variable, research data suggest a median of approximately 10-20 years after RRMS onset for the conversion to the SPMS clinical phenotype for untreated patients (with a really wide range of about 50 years)[18,30,31].

  Moreover, data based on a cohort of patients who had not received treatment suggest that conversion to this clinical phenotype occurs in up to one-third of untreated patients within the first 8-10 years[31,32].

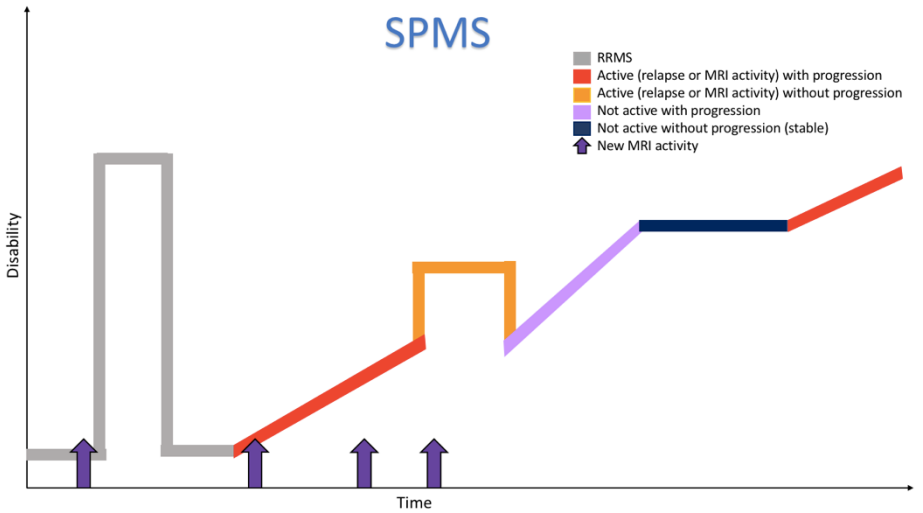

Figure 3: Disease course of SPMS. Adapted from the National Multiple Sclerosis Society[26].

3.4. Classification of clinical phenotypes by diseases´ activity, progression and worsening.

However, the latest re-evaluation of the MS clinical phenotypes (Lublin et al., Neurology 2014), establishes not only this major division between relapsing and progressive forms; but also considers the clinical and magnetic resonance imaging (MRI) activity of the disease. Hence, as Appendix 1 shows, within the different clinical phenotypes, active and non-active forms can be differentiated[21].

Clinical activity of the disease appears defined as relapses; whereas MRI activity, as it is described later, is defined by the detection of new enhanced lesions after gadolinium administration and/or enlarged T2 lesions. Regardless of which kind of activity is present, they are considered a potential disease modifier in any of the clinical phenotypes. In addition, other classifications are reflected in Appendix 1. The progressive phenotypes can be further characterized as with progression or without progression, and the RRMS phenotype can be further characterized as worsening or stable[18,21].

3.5. MRI findings

Once the clinical features of the disease have been described, the focus is placed on defining the **typical characteristics of the lesions detected by MRI.**

Since 2000, MRI has been the key diagnostic test when patients present a clinical episode suggestive of MS, and the most recent review of the McDonald diagnostic criteria for MS (Thompson et all., The Lancet Neurology 2018) allows for MS diagnosis with a single scan[22,33].

Inflammatory demyelination is easily visible on MRI. Therefore, the typical plaques that characterize multiple sclerosis are easily recognizable on MRI. Currently, **MRI sensitivity for identifying these demyelinating lesions is situated around 95% for those patients with clinically definite MS[34].**

As a consequence of this high sensitivity, MRI has become the most important paraclinical diagnostic tool for the diagnosis of the disease. Moreover, the appearance of new lesions is more frequent than new clinical relapses, so MRI is not only indispensable for the diagnosis of the disease, but also as a prognostic marker at the earliest stages of the disorder. In addition, the emergence of new immunomodulatory therapies for MS treatment provides MRI a new relevance for monitoring the response and efficacy of these therapies[34–41].

Furthermore, MRI findings that are consistent with multiple sclerosis have been observed in healthy people who underwent scanning for other purposes (for example a headache), referring to this situation as a radiologically isolated syndrome (RIS). RIS is not included in the latest re-evaluation of the MS clinical phenotypes (Lublin et al., Neurology 2014) as a phenotype of MS because the imaging findings alone are nonspecific, as later explained. However, research data suggests that MS develops in a meaningful number of patients with RIS; for which reason RIS patients with no obvious clinical signs or symptoms suggestive of MS should be followed prospectively[21,37,42,43].

3.5.1. T2-weighted sequences

MS plaques, whichever the evolutionary phase, generally behave **hyperintense in both proton density-weighted (PD) and T2-weighted** (**T2, T2-FLAIR or similar) sequences**, which is a very non-specific sign[23,44]. This hyperintensity translates an increase in the titular free water concentration. However, it is not possible to discriminate the contribution of oedema, demyelination, inflammation, axonal injury, gliosis or remyelination in the composition of the plaques. Consequently, the weak correlation between the mean lesion volume in T2-weighted sequences and the degree of neurological disability of the patient is partially explained[23,45,46].

Lesions detectable on T2-weighted sequences used to be numerous, small in size (at least 3 mm, and mostly smaller than 25 mm**), with nodular morphology** (Figure 4)[6,23,44,46,47]. Although most lesions are of this size, a confluence of them may occur, resulting in lesions with irregular borders showing the characteristic "ridge-like" outer margin (especially if they are located periventricular)[23,48,49].

In addition, although lesions could appear in any CNS region, the anatomical distribution of MS plaques is also characteristic, as they tend to develop in specific white matter areas such the **periventricular white matter** (especially the posterior one) **and juxtacortical white matter**, **the corpus callosum, the infratentorial parenchyma** (especially the pons and the cerebellum) **and the spinal cord** (preferentially the cervical segment)[6,23,44,49]**.**

At least one ovoid plaque with its major axis perpendicular to the anteroposterior axis of the cerebral hemispheres is defined in approximately 60-63% of MS patients. This particular arrangement is explained by the predisposition of the plaques to develop around the venules of the white matter surrounding the lateral ventricles, which trace a perpendicular trajectory to the ependymal surfaces. These ovoid plaques are defined as periventricular lesions and result in the radiological sign usually described as "**Dawson's fingers**" (Figure 4)[22,23,37,38,40,44,49,50].

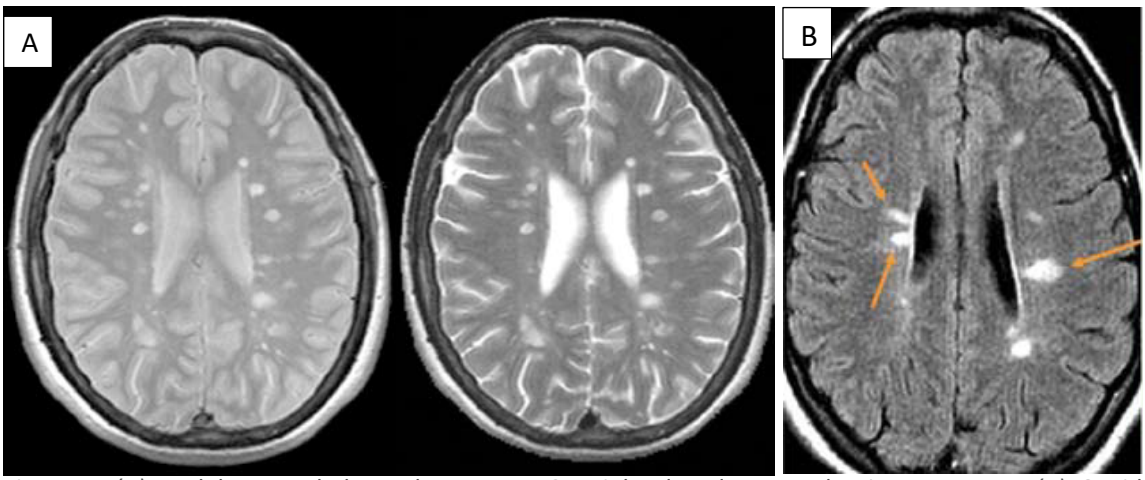

Figure 4: (A) Nodular morphology plaques on T2-weighted and proton-density sequences. (B) Ovoid morphology plaques, radiologically described as "Dawson´s fingers" (arrows); in T2-weighted sequence. Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

In particular, focal lesions predominantly located in the white matter surrounding the body and temporal horn of the lateral ventricles (periventricular lesions), are specific radiological discoveries, at least, in the early stages of the disease (Figure 5)[23]. This feature, initially, would facilitate to establish a differential diagnosis with other entities that usually diffusely affect the anterior white matter of the temporal lobes; such as congenital cytomegalovirus (CMV) infection and the inherited small vessel cerebrovascular disease called Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)[44,51,52].

Corpus callosum lesions are located preferably on its subependymal surface (lower margin) or its periphery, adopting a radial arrangement, perpendicular to the third ventricular wall (Figure 5)[22,23,40,44,50]. For this reason, these lesions are classified as periventricular by the review of the McDonald diagnostic criteria for MS carried out in 2017[22]. These lesions constitute a rare finding in non-MS processes, such as small vessel cerebrovascular disease due to corpus callosum resistance to ischemia[44,50]. Therefore, it is considered a sensitive and specific marker of early-stage disease, presenting in up to 50% of patients[6,50].

Juxtacortical lesions are predisposed to locate in intimate contact with the cerebral cortex, affecting the U-shaped fibers of the white matter adjacent to cortical grey matter; especially in the frontal and temporal lobes, but they could be located in all brain lobes and the cerebellum (Figure 5)[22,23,37,40,44]. Approximately half of the patients with clinically defined MS have at least one isolated U-fiber lesion, so they are also considered a specific marker for the initial diagnosis of the disease[50].

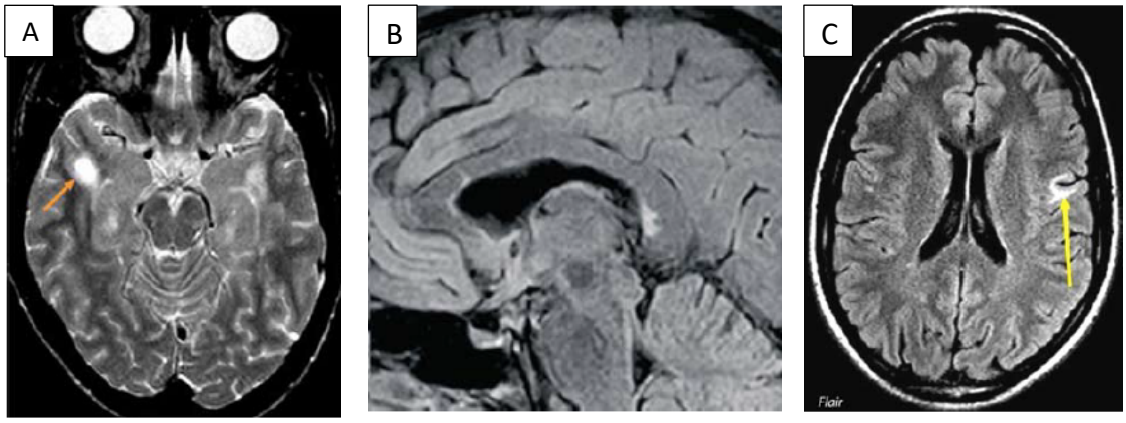

Figure 5: (A) Anterior temporal periventricular lesion on T2-weighted sequence. (B) Corpus callosum lesions predominantly affecting the subependymal surface on T2-Flair sequence. (C) Left frontal lobe juxtacortical lesion (arrow) affecting U-fibers on T2-Flair sequence. Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

Lesions typically described by clinical surveys as subcortical maintain their main difference from juxtacortical lesions by the fact that, although they are located in the cerebral hemispheric white matter, contact is not made with the cortex, nor with the ventricular surfaces, as opposed to the periventricular lesions[40].

Infratentorial lesions tend to locate in the cerebellum, especially in middle cerebellar peduncles and in the periphery of the pons (brainstem) (Figure 6). These lesions usually appear close to the surface [22,23,37,44,48]. Regarding lesions of the pons, most lesions are contiguous with the cisterns or include the floor of the fourth ventricle, the pontine surface or the pontine trigeminal root entry zone; myelin-rich regions. This special peripheral distribution of MS pons lesions distinguishes them, at first instance, from ischemic changes associated with small vessel cerebrovascular disease, because lesions of the latter commonly involve the central region of the pons as they correspond to a vascular border zone, supplied by different penetrating arteries[44,48].

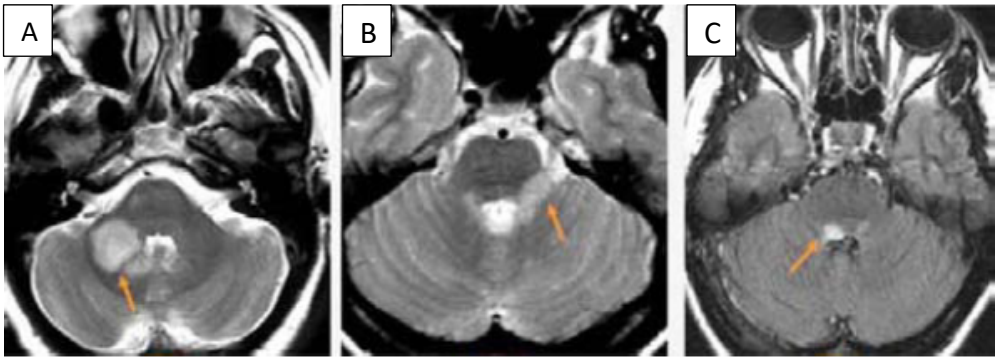

Figure 6: Infratentorial lesions, on T2-Flair sequences, located in the middle cerebellar peduncles (arrow in A), the periphery of the pons (arrow in B) and the floor of the IV ventricle (arrow in C). Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

On the other hand, although MS is a disease that shows a special predilection for the white matter, cortical lesions are occasionally described, thus reaching the grey matter (5-6% of lesions). However, their detection by classical T2-weighted sequences is difficult due to their small size and poor differentiation between the cerebrospinal fluid (CSF) of the cerebral convexity sulci[6,22,23,44,50].

At last, emphasize that research data objectified that the double inversion recovery (DIR) sequence improves the contrast of cortico-juxtacortical and infratentorial lesions (Figure 7); thereby increasing the sensitivity for their detection, in contrast with classical T2 weighted sequences[40,50,53].

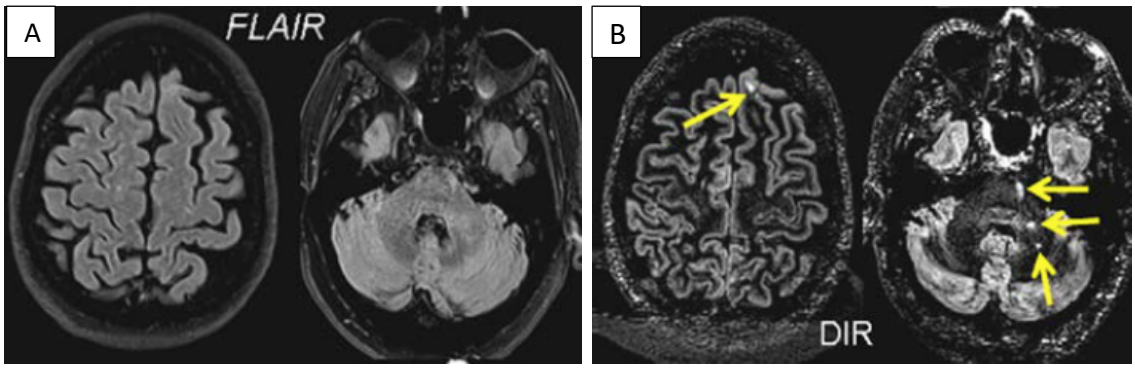

Figure 7: (A) Juxtacortical and infratentorial lesions detected in FLAIR sequences and (B) in DIR sequences (on the right). Note the higher sensitivity of the latter for the detection of these lesions (arrows). Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

3.5.2. T1-weighted sequences

Approximately 10-20% of MS plaques that appear hyperintense in T2-weighted, in T1-weighted sequences are **hypointense**[6,23,41].

It is important to underline that T1-weighted sequences together with the administration of intravenous paramagnetic contrast (gadolinium-containing compounds) enable the selective identification of lesions with inflammatory activity (Figure 5)[21,23,44,50]. This contrast enhancement is a constant radiological sign in actively demyelinating lesions during the initial phase of development (at least in recurrent forms), as during inflammation there is an increase in the permeability of the blood-brain barrier, leading to enhancement of the lesion, which typically lasts for 2-6 weeks. Thus, the absence of enhancement after contrast administration suggests non-active disease[21,23,44]. As shown in Table 1, the existence of contrast-enhancing and non-enhancing lesions in the same MRI study is sufficient to demonstrate DIT[22].

Therefore, regarding those plaques that are hypointense in T1-weighted sequences pre-contrast administration and hyperintense in T2-weighted sequences; whether they are active lesions, they display enhancement after contrast administration, and that hypointensity is the result of an oedematous component due to the inflammatory process; whereas in the case of chronic lesions, they do not show enhancement after said administration, and that hypointensity has been reported to be associated with areas of greatest myelin loss. The latter has been described as “black holes” but in addition to corresponding to a hypertensive lesion on T2-weighted sequences, a minimum of 6 months of persistence is necessary to be described as it [37,40,46].

Various enhancement patterns can be found, and although most enhancing lesions tend to show a nodular enhancement pattern[44,50,54]; incomplete ring enhancement is very specific to demyelinating lesions (Figure 8)[23,44]. The peripheral lesion area where no enhancement is found would coincide with the margin that abuts ventricles or grey matter, where the degree of inflammatory reaction is weaker[44].

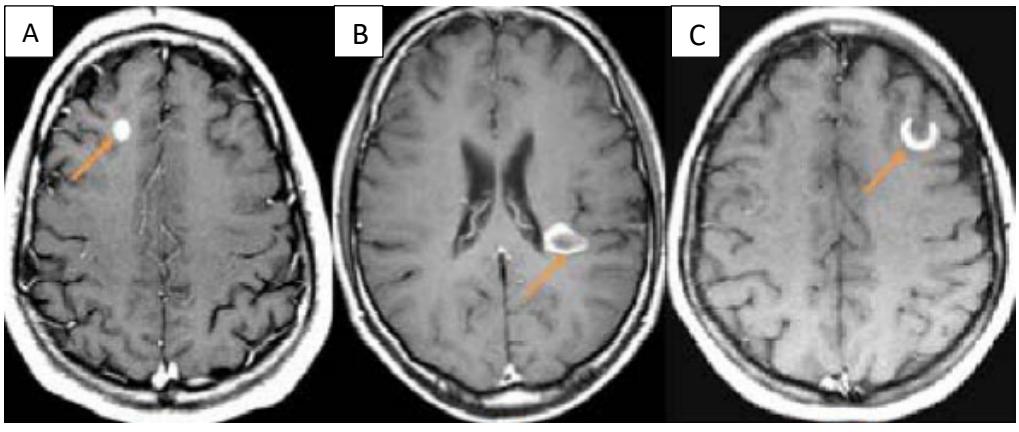

Figure 8: Gadolinium enhancement patterns of active lesions. T1-weighted images after gadolinium administration of gadolinium in three patients with active lesions. Inflammatory activity lesions may show nodular gadolinium enhancement (arrow in A), complete ring (arrow in B), and incomplete ring (arrow in C). Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

3.6. Other complementary explorations

3.6.1. Cerebrospinal fluid (CSF) examination

Although CSF examination has been de-emphasized in successive iterations of the McDonald Criteria, the latest revision of the 2017 MacDonald diagnostic criteria reinforces the role of CSF examination in the diagnosis of MS by including it within the criteria as a valuable test to substitute the need to satisfy the DIT criteria in certain clinical situations (Table 2)[22].

Under normal conditions, the immunoglobulin G (IgG) present in CSF is mainly derived from passive diffusion from plasma. Increased intrathecal synthesis of IgG is evidence of an altered immunological and inflammatory process in the CNS[55]. Although not specific to MS, the increased SIT is present in a high percentage of MS patients (almost 95%) and consequently; supports the diagnosis. Increased intrathecal synthesis of IgG can be measured qualitatively by the presence of oligoclonal bands (OCBs). Qualitative demonstration of two or more CSF-specific OCBs more reliably indicates intrathecal antibody synthesis than other tests, such as the IgG Index (quantitative measure). Importantly, analysis of paired CSF and serum samples is essential to confirm that OCBs are unique to CSF[22,55–58].

Finally, it should be considered that different CSF findings suggest diseases differing from MS, for instance significantly elevated proteins (>100 mg/dL); pleocytosis with >50 cells/mm3; or the presence of neutrophils, eosinophils or atypical cells[22,58].

3.6.2. Neurophysiological studies

The study of multimodal evoked potentials (MEPs) is another useful tool in the diagnosis and monitoring of MS. They have diagnostic and prognostic value in the detection of formed plaques and the recording of "silent" changes in the sensory pathways[58,59].

Research data suggest that the visual evoked potentials (VEPs) demonstrated the highest degree of abnormal findings, followed by somatosensory evoked potentials (SSEPs)[59]. Particularly useful are visual evoked potentials because they can be more sensible than MRI for manifesting lesions of the optical nerve[60]. In addition, some studies have shown the utility of electroretinography (ERG) in combination with VEPs for detecting optical nervous pathway abnormalities[61–63].

The latest review of the MacDonald criteria conducted in 2017, considered that data regarding the diagnostic sensitivity and specificity of MRI or VEPs, to demonstrate optic nerve lesions in patients without a clear history or clinical evidence of optic neuritis, were insufficient to support their incorporation into the criteria at that time. The high need for further studies to validate such tests in fulfilling DIS or DIT in support of the diagnosis of MS was recognized and identified as a high priority[22].

3.7. Disease-modifying therapies (DMTs)

Evidence over the years has shown how the clinical course of MS, mainly manifested by a gradual progression of functional and cognitive deterioration, is susceptible to modification if the disease is diagnosed and treated in its early stages[10,31,64,65].

Over the past decades, several DMTs have become available to decrease relapse frequency, reduce disability and restrict focal white matter lesion accumulation on MRI. Nevertheless, regrettably, nowadays no drug either completely prevents or reverses the progressive neurological deterioration, characterized mainly by impaired ambulation, loss of bladder control and slowing of cognitive processing [1,11,27,39,65,66].

3.8. Defining Pseudotumoral lesions

In this research, we focus on pseudotumoral demyelinating lesions (also called "tumefactive demyelinating lesions") in MS patients. These lesions have been considered an atypical manifestation of CNS demyelination[67–69]. Due to the possibility of mistaking the lesions for neoplasia, which often leads to the inevitable morbidity of subjecting patients to brain biopsies or other procedures, as well as delaying appropriate treatment; the lesions are termed "pseudotumoral"[68].

Pseudotumoral demyelinating lesions are infrequent but not exceptional in MS patients, even as the initial event of the disease with a prevalence in the range of 1.4–8.2% of multiple sclerosis patients[70,71]but they have been poorly investigated, and thus; usually constitute a diagnostic challenge, especially if it presents as the first clinical disease´s manifestation[69,72]. Moreover, pseudotumoral cases of MS have been described more frequently in female patients, particularly in the third and fourth decades of life[69–71,73].

Regarding neuroradiological features, they are usually large, show an atypical enhancement pattern, and could be associated with mass effect, and/or perilesional oedema[67,68,73]; which means they are commonly misinterpreted as due to a non-demyelinating cause, for example, a primary tumor of the CNS[68].

The usual definition of a pseudotumoral demyelinating lesion is a solitary large T2-weighted MRI 'margin to margin' size of 2 cm or more (Figure 9)[50,68,73–76]. The basis for a greater than 2 cm cut-off is based on cases, which came to brain biopsy, and so has real-world implications in that larger lesions are more likely to be biopsied. Evidence suggests that larger lesions generate more worries about the possibility of neoplasm, and lesions of up to 12 cm have been described[68].

Although pseudotumoral demyelinating lesions could appear anywhere within CNS, they are mainly located in the cerebral hemispheres, especially in frontal and parietal lobes; in subcortical and periventricular regions[37,68,72]. If active, they generally show an incomplete ring contrast enhancement pattern with the open part of the ring mostly towards either the deep or superficial grey matter (Figure 10)[23,50,69,72].

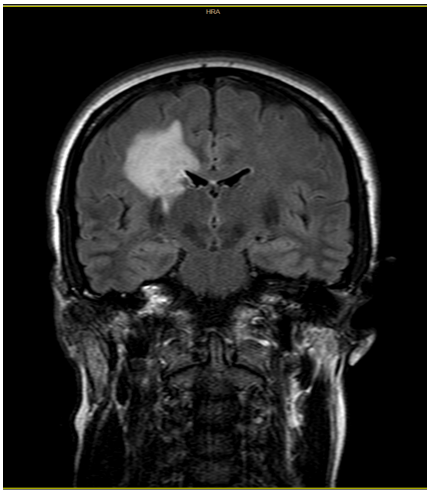

Figure 9: Pseudotumoral lesion with periventricular location, detected on T2-Flair sequence. Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

It has been suggested that approximately 70% of patients with pseudotumoral lesions fulfil the McDonald criteria at follow-up (median time to second attack: 4.8 years)[73]. However, concerning the evolution of the lesions on MRI, the usual reduction in size during MRI follow-up has been described[77].

Depending on the location and size of the lesion, clinical presentations are variable and include motor and sensory deficits, headache, cognitive abnormalities, visual disorders (hemianopia instead of optic neuritis), cerebellar and brainstem symptoms, mental confusion, if there is temporal regions involvement; impairment of symbolic functions (apraxia, aphasia, agnosia) if frontal regions are affected, and/or epileptic seizures if the cortex is involved[68,69,72,73]. However, hemiparesis had been suggested as the most frequent symptom described[68]. Consequently, symptomatic lesions present subacutely as any other mass lesion. Nevertheless, some lesions may be asymptomatic and detected as incidental findings on MRI scans performed for other medical reasons[68].

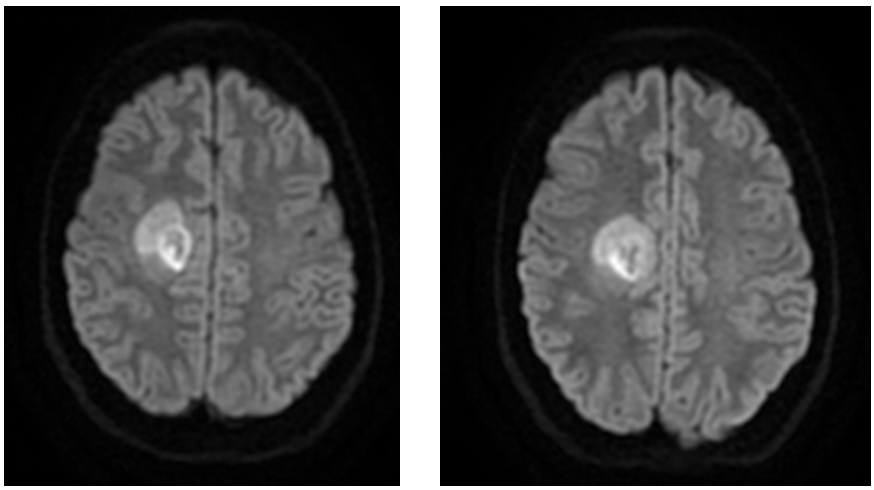

Figure 10: Pseudotumoral lesion detected on T1-weighted sequences after intravenous contrast administration, showing an incomplete ring-like enhancement pattern. Images provided by the image bank of the monographic MS consultation at the Marqués de Valdecilla University Hospital.

The great challenge of pseudotumoral demyelinating lesions, especially if the patient has not been diagnosed with MS previously, is the diagnosis. Differential diagnosis of these lesions includes brain neoplasms, abscesses and other CNS infections and infarction (Table 4)[68,72].

Differential diagnoses of cerebral pseudotumoral demyelinating lesion	Examples
Neoplasm	High-grade and low-grade astrocytomas
	Oligodendroglioma
	Metastases
	CNS lymphoma
Infection	Abscess – bacterial, fungal
	Tuberculoma
	Cryptococcoma
	Toxoplasmosis
	HIV
	Progressive multifocal leukoencephalopathy (PML)
Connective tissue disease	Behcet's disease
	Systemic lupus erythematosus
	Sjogren's syndrome
Drug-induced	Tacrolimus
Paraneoplasic	Gem cell cancer
Granulomatous disease	Sarcoidosis
Amyloidosis	Cerebral amyloid angiopathy/amyloidoma
Vasculopathy	Infarction
	Cerebral vasculitis (primary or secondary)
	Posterior reversible encephalopathy syndrome (PRES)
	Genetic – retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) because of TREX1 mutations

Table 4: Differential diagnoses of the cerebral pseudotumoral demyelinating lesion. Adapted from Todd A. Hardy; Current Opinion in Neurology 2019[68].

Diagnosis is helped by examining the CSF and the neuroradiological findings, but a brain biopsy is occasionally needed to reveal the real nature of the lesion[69,72,78]. In addition, the presence of other smaller lesions with typical features of MS plaques may be suggestive of the diagnosis[23].

The CSF examination is often problematic because the presence of an intracerebral mass can imply some risks during the procedure. The presence of intrathecal synthesis of immunoglobulins gives strong evidence for the diagnosis of MS, but this can also be observed in other diseases such as ADEM (Acute disseminates encephalomyelitis)[72].

Furthermore, given the low frequency of pseudotumoral MS forms, there are no studies that describe a large series and data about long-term prognosis or response to treatment are scarce.

We will discuss the demographic criteria, clinical findings, diagnosis approach, treatment and outcome of patients with pseudotumoral demyelinating lesions diagnosed with MS in the Hospital Universitario Marqués de Valdecilla and compare our findings with those published by other investigators.

4. Hypothesis

Current literary descriptions of pseudotumoral lesions as a form of MS presentation at the onset of the disease, are limited. MRI detection of these lesions is a real clinical challenge in terms of differential diagnosis, especially if they are detected at the same time as the first clinical episode of the disease.

The knowledge of the demographic data, main clinical findings, diagnosis approach, treatment received and outcome of patients with pseudotumoral demyelinating lesions may contribute to a better understanding of these forms of MS.

5. Objectives

Main objective:

To describe the characteristics of patients who develop pseudotumoral lesions as the initial manifestation of MS.

Secondary objectives:

- To describe the clinical features which most frequently appear in the first symptomatic episodes, conditioned by the presence of demyelinating pseudotumoral lesions.

- To collect other socio-demographic, analytic and complementary tests data that could lead to an increased risk of developing a pseudotumoral lesion as a form of presentation of multiple sclerosis.

- To report the radiological features of the demyelinating pseudotumoral lesions observed by the MRI studies.

- To evaluate the clinical and radiological evolution of patients over time.

6. Methodology

Our study was based on an exhaustive search through the MS database of the Neurology Department of the Marqués de Valdecilla University Hospital (Santander, Cantabria). Accordingly, cases of MS with radiological pseudotumoral behaviour were selected, with no temporal limit, finding the oldest case selected in 1996. The inclusion criteria applied were:

[1] Patients aged 18 years or older.

[2] MS diagnosis according to 2017 reviewed McDonald criteria[22].

[3] Detection of pseudotumoral brain lesions on MRI during the study of the first clinical flare suggestive of multiple sclerosis. Pseudotumoral lesions were defined as focal demyelinating lesions with a minimum diameter of 2 cm[73].

On the other hand, patients with pseudotumoral lesions on MRI but a final diagnosis different from MS were excluded.

A retrospective collection of data of patients that full-field these criteria were carried out from the MS outpatient in the Neurology Department of the Marqués de Valdecilla University Hospital.

The individual study of each patient required the systematic evaluation of different variables in a wide range of fields such as demography, clinical, analytical studies, radiology and other complementary studies.

Several demographic variables were systematically assessed for each patient including gender, age at the time of the study, cardiovascular risk factors such as hypertension, dyslipidemia, diabetes mellitus and obesity (considered as the detection of a BMI (body mass index) greater than or equal than 30[79]); exposure to smoking, personal history of autoimmune diseases, and another relevant personal history. In addition, family history of interest for our study was compiled, such as the family history of neurological diseases and multiple sclerosis, including for the latter, the degree of kindship if such family history was present.

Likewise, the clinical variables included in our study concerning the first clinical episode suggestive of multiple sclerosis were: age of symptoms onset, initial clinical presentation (it was assessed as dichotomous qualitative variables the presence or absence of visual deficit, sensory deficit, motor deficit, cerebellar symptoms, brainstem symptoms, spinal cord symptoms, ataxia, aphasia, apraxia, agnosia, cognitive impairment, headache and epileptic seizures) and the disability experienced during the clinical episode, which was measured using the Expanded Disability Status Scale (EDSS) score [28]. Furthermore, it was also analysed the necessity or not hospital admission during the first clinical flare, the number of days of hospital admission, whether this was necessary; and the clinical outcome from the flare (it was tested during the subsequent clinical appointment after the clinical episode and recorded as a dichotomous qualitative variable: partial recovery or complete recovery).

To conclude with the clinical variables related to the first clinical episode suggestive of multiple sclerosis, it was necessary to examine the need for treatment during that episode. Thus, the following variables were included: steroid treatment or not, the dose administered, the number of days of treatment, and the need or not to initiate disease modulating therapy (DMT) during that first episode.

However, it was also regarded as relevant to evaluate different analytical parameters gathered during the evaluation of that first clinical episode. Therefore, the analytical variables under study were: vitamin D levels (measured in nanograms/millilitre (ng/ml)); HLA alleles of the DRB1 locus, total cholesterol and LDL-cholesterol levels (measured in milligrams/decilitre (mg/dl)), the absolute number of lymphocytes (expressed as cells x 10^3/ microlitre (cells x 10^3/ul)), absolute levels of CD4 and CD8 lymphocytes (measured in cells/ul) CD4/CD8 ratio, C-Reactive Protein levels (measured in mg/dl); Glomerular Sedimentation Rate levels (measured in millimetres/hour (mm/h)); complement C3 and C4 levels (measured in mg/dl) and TSH levels (measured in international units/litre (mU/l).

In addition, as microbiological variables; serologies for hepatitis C (VHC), hepatitis B, Epstein-Barr virus (EBV), Brucella, Varicella Zoster virus (VVZ), Cytomegalovirus (CMV), Herpes virus, John Cunningham virus (JC virus), Rubella, Sarampion, Treponema pallidum and Mycoplasma Pneumoniae; were recorded.

As a consequence of the study, there was a need to study radiological variables, obtained by reviewing the MRI scans performed on the patients during the study of the first clinical flare. It was verified that the MRI scans in all cases were performed under the usual conditions of clinical practice, including at least axial and sagittal planes in T1-weighted, T2-weighted, FLAIR and T1-weighted sequences after the administration of gadolinium.

MRI findings recorded were evaluated by a neuroradiologist and included: the number of pseudotumoral lesions (PLs), largest diameter (measured in millimetres (mm)), lesion area (measured in cubic centimetres (cm^2)), lesion location (expressed as a qualitative polytomous variable: periventricular, juxtacortical, subcortical, infratentorial or medullary), enhancement after intravenous contrast (gadolinium) administration of that lesions, recording the contrast uptake pattern as a polytomous qualitative variable: nodular pattern, ring-like pattern or diffuse pattern; and in case the pattern was ring-like, collecting whether it was a complete or incomplete pattern[40].

A nodular pattern is characterized by a solid punctiform contrast uptake, whereas a diffuse one consists of heterogeneous and irregular contrast uptake and a ring-like one refers to a peripheral contrast uptake, which may be complete or incomplete[40].

Also, the presence or absence of bilaterality related to pseudotumoral lesions is recorded, as well as whether that lesions condition expansiveness or mass effect. For those cases where more than one lesion with a radiological pseudotumoral behaviour was identified, this list of variables was collected for the largest lesion.

Nevertheless, it was not only important to acquire MRI data about pseudotumoral lesions, but also radiological variables describing non-pseudotumoral lesions or typical demyelinating lesions of multiple sclerosis.

To this aim, the following variables were assessed: the total number of non-pseudotumoral lesions (expressed as a quantitative variable categorized by intervals: less than 10 lesions, 10-50 lesions and more than 50 lesions), localization and presence or absence of enhancement after contrast administration of these lesions, including both the number of enhancing lesions and their pattern of enhancement[40].

Moreover, variables concerning the request for other complementary tests during the study of this first clinical episode, such as lumbar puncture and cerebrospinal fluid study, brain biopsy and neurophysiological studies, were described.

Finally, it was considered essential to assess the clinical and radiological evolution of patients over time, after that first clinical episode. For this purpose, the following clinical variables were selected: time of evolution from the first outbreak to the last review, recorded in months; occurrence of relapses during that time, number of relapses, diagnosis of MS and clinical phenotype; establishment of disease-modulating treatment, collecting the name of the drug administered, and disability present at the last clinical review (it was measured with the Expanded Disability Status Scale (EDSS) score[28]. The development of a clinical relapse or exacerbation of MS is evidenced by the appearance, reappearance or worsening of a symptom or neurological deficit persisting for more than 24 hours and preceded by stability for at least 1 month [5,18,21,25,27].

For the same purpose, radiological variables were studied through the last control MRI performed, which were: the time elapsed from the first MRI until this last control one, the disappearance of pseudotumoral lesions, volume's variation of these lesions (expressed as a polytomous qualitative variable decrease, stability or increase), mass effect or expansivity conditioned by these lesions, variation in the enhancement shown by these lesions after intravenous contrast administration (expressed as a polytomous qualitative variable: decrease, stability or increase), appearance of new pseudotumoral lesions, recording both the number of these and if there is the enhancement of these lesions after intravenous contrast administration, in the case of the appearance of new lesions of this type. Furthermore, the location of new pseudotumoral lesions is recorded if they showed enhancement after intravenous contrast administration. In addition, the evolution of non-pseudotumoral lesions was also evaluated.

Statistical analysis

All data extracted from the database were analysed statistically. Incomplete data due to lack of reference in the clinical history were excluded. A descriptive analysis of the variables studied was performed. It was considered statistically significant if $p<0.05$. The SPSS software was used to perform the statistical analysis.

7. Results

7.1. Demographic data

Among the 450 patients registered in the database of the outpatient multiple sclerosis clinic of HUMV, 14 patients (3.11%) fulfilled all inclusion criteria and were included in our study. Of the 14 patients included, 6 patients (42.9%) were female and 8 patients (57.1%) were male.

Examining the first clinical episode suggestive of multiple sclerosis, the mean age at this onset episode was 33.64 (standard deviation (SD) $\pm$ 9.572 years); with a range of ages from 24 to 48 years.

Regarding cardiovascular risk factors, arterial hypertension (AHT), diabetes mellitus (DM), dyslipidemia (DLP) and obesity (BMI>30) were studied. Only 1 patient was hypertensive (7.1%), 4 patients were dyslipidemic (28.6%) and 3 patients presented a BMI higher than 30 (21.4%). Accordingly, no patients with diabetes mellitus were reported in the investigation (Table 5).

In addition, exposure to tobacco as a toxic habit was assessed, revealing that the majority of our patients were exposed to this habit (10 patients, 71.4%). The non-smoking group accounted for only 4 patients (28.6%) (Table 5).

Cardiovascular risk factors and exposure to tobacco		*Frequency*	*Percent*	***Stratification by gender***			
				Female		***Male***	
				Frequency	*Percent*	*Frequency*	*Percent*
Tobbaco	Yes	10	71.4%	4	66.7%	6	75.0%
	No	4	28.6%	2	33.3%	2	25.0%
AHT	Yes	1	7.1%	0	0.0%	1	12.5%
	No	13	92.9%	6	100%	7	87.5%
DLP	Yes	4	28.6%	2	33.3%	2	25.0%
	No	10	71.4%	4	66.7%	6	75.0%
DM	Yes	0	0%	0	0.0%	0	0.0%
	No	14	100%	6	100%	8	100%
BMI > 30	Yes	3	21.4%	2	33.3%	1	12.5%
	No	11	78.6%	4	66.7%	7	87.5%

Table 5: Description of the variables referring to cardiovascular risk factors and exposure to tobacco, and the corresponding stratification by gender for each of them.

Furthermore, no statistically significant differences were found for gender-stratified analysis of cardiovascular risk factors and tobacco exposure (Figure 11).

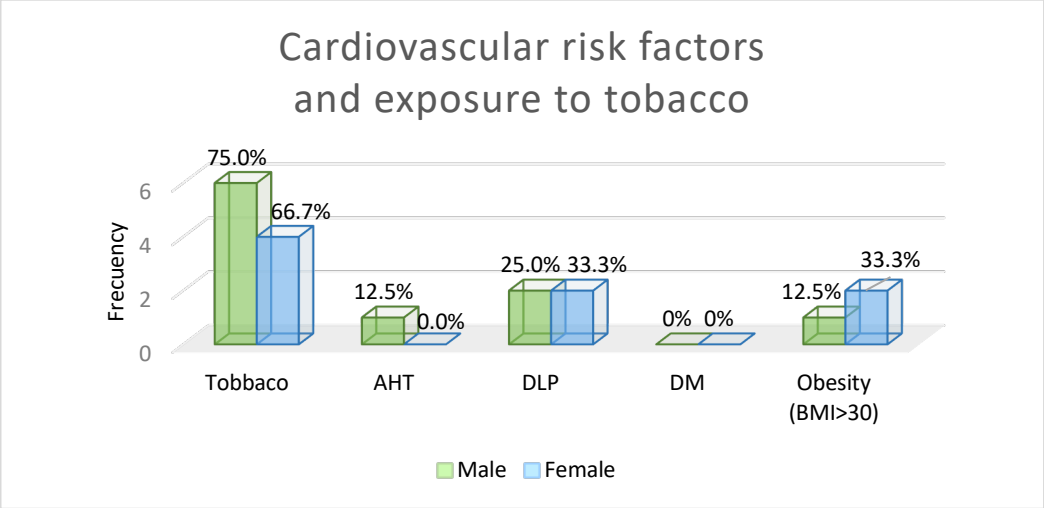

Figure 11: Representation of frequencies for the different cardiovascular risk factors and tobacco exposure, stratified by gender. Note that the percentages above each bar refer to the group of male or female, in each variable studied.

Concerning personal medical history, also the presence of autoimmune pathologies was considered; however, none of the patients suffered from such disorders. Besides, another relevant medical history from the patients' medical records was collected. Among the 14 patients included in the study, such data were available for 12 patients. Hence, regarding the latter, the most relevant were: 4 patients (33.33%) had migraines with aura, 4 patients (33.33%) had anxious syndrome, 2 patients (16.67% patients) had depressive syndrome, and 2 patients (16.67%) tension-type headaches. Others, such as tics, fibromyalgia, history of acute meningitis, herniated disc, arachnoid cysts or sleep apnoea-hypopnoea syndrome, were described in just a single patient (8.33%).

Furthermore, the identification of a family history of neurological diseases was considered relevant for our analysis. This kind of information was recorded for 12 patients (85.7%). Within the latter, 7 patients (58.3%) provided a family history of neurological diseases, while 5 patients lacked such a history (41.7%). Regarding the family history of neurological diseases found; MS was present in 2 patients (28.6%), although neither case involved a first-degree relative. Other family histories of neurological diseases described were: cerebrovascular accident (CVA), Alzheimer's disease, migraine and brain tumor (Table 6).

Family history of Neurological Diseases		*Frequency*	*Percent*	*Valid Percent*	***Neurological Disease***	*Frequency*	*Valid Percent*
Valid	Yes	7	50.0%	58.3%	MS	2	28.6%
					CVA	2	28.6%
					Alzheimer	1	14.3%
					Migraines	1	14.3%
					Brain tumor	1	14.3%
					Total	7	100%
	No	5	35.7%	41.7%			
	Total	12	85.7%	100%			
Missing	No data	2	14.3%				
Total		14	100%				

Table 6: Description of the variable referring to family history of neurological diseases presented by our patients.

7.2. Patients characteristics

Initial symptoms		*Frequency*	*Percent*
Motor deficit	Yes	10	71.4%
	No	4	28.6%
	Total	14	100%
Sensory deficit	Yes	10	71.4%
	No	4	28.6%
	Total	14	100%
Visual deficit	Yes	1	7.1%
	No	13	92.9%
	Total	14	100%
Spinal Cord deficit	Yes	0	0%
	No	14	100%
	Total	14	100%
Cerebellar symptoms	Yes	7	50%
	No	7	50%
	Total	14	100%
Brain stem symptoms	Yes	7	50%
	No	7	50%
	Total	14	100%
Headaches	Yes	4	28.6%
	No	10	71.4%
	Total	14	100%
Ataxia	Yes	3	21.4%
	No	11	78.6%
	Total	14	100%
Aphasia	Yes	1	7.1%
	No	13	92.9%
	Total	14	100%
Apraxia	Yes	0	0%
	No	14	100%
	Total	14	100%
Agnosia	Yes	0	0%
	No	14	100%
	Total	14	100%T
Epileptic Seizures	Yes	0	0%
	No	14	100%
	Total	14	100%
Cognitive deficit	Yes	0	0%
	No	14	100%
	Total	14	100%

Table 7: Description of variables referring to the type of initial symptoms presented by our patients during the first clinical episode suggestive of multiple sclerosis.

Regarding the type of initial symptoms presented by the patients studied, both motor and sensory deficits were the most frequent symptoms, being described in 10 patients (71.4%). As table 3 shows, other neurological manifestations reported in some patients were: cerebellar symptoms (7 patients, 50%), brain stem symptoms (7 patients, 50%), headaches (4 patients, 28.6%), ataxia (3 patients, 21.4%), aphasia (1 patient, 7.1%) and visual deficit (1 patient, 7.1%). Other neurological symptoms such as spinal cord deficits, cognitive deficits, apraxia, agnosia, or epileptic seizures were not identified in any patient (Table 7).

The disability experienced by patients during this first clinical episode was assessed using the EDSS. The scores compiled for the patients included in our research ranged from 1.5 points to 6 points, resulting in a median of 3 points.

7.3. Hospitalization and acute treatment

During this first clinical episode, 12 patients (85.7%) required hospital admission, with a mean length of admission of 8.75 $\pm$ 4.472 days. All patients who required hospital admission received steroid treatment. Also, one of the patients who did not require hospital admission received that treatment. Accordingly, 13 of the 14 patients (92.8%) included in our study require this treatment. In all cases, the drug administered was methylprednisolone, with a median dose of 1 gram per intravenous bolus (only a single patient out of these 13 patients; received a dose of 0.5 grams per intravenous bolus). The number of days treatment was provided, the data ranged from 3 to 7 days, with a mean of 4.54 $\pm$ 1.198 days. Instead, disease-modifying therapy (DMT) was not initiated in any of the patients during the clinical evaluation and management of this first clinical episode suggestive of MS.

Otherwise, on the first control appointment after that first clinical episode, partial recovery was observed in 9 patients (64.3%); whereas complete recovery was observed in 5 patients (35.7%).

7.4. Neuroimaging data

7.4.1. Pseudotumoral lesions data

Each of the 14 patients assessed underwent MRI in during this first clinical episode, and in every case, lesions with pseudotumoral radiological behaviour were identified. For most of them (12 patients, 85.71%), just one lesion with these characteristics were identified. In the remaining 2 patients (16.7%), 2 lesions of pseudotumoral characteristics were detected. For the latter, the lesion with the largest dimension was considered for the analysis.

Analysis of these lesions was carried out. Concerning their size, data revealed that their ranged from 21.85 mm to 48 mm, giving a mean lesion diameter of 33.36 $\pm$6.527 mm; and their area ranged from 4.97 cm^2 to 11 cm^2; with a mean lesion area of 7.10 $\pm$ 1,81 cm^2.

Pseudotumoral Lesions´ Locations	*Frequency*	*Percent*
Infratentorial	2	14.3%
Periventricular	9	64.3%
Subcortical	2	14.3%
Juxtacortical	1	7.1%
Total	14	100%

Table 8: Description of the variable referring to the locations of pseudotumoral lesions detected on patients studied.

For pseudotumoral lesions, several locations were described; being the periventricular region the most frequent in our patients (Table 8, Figure 12).

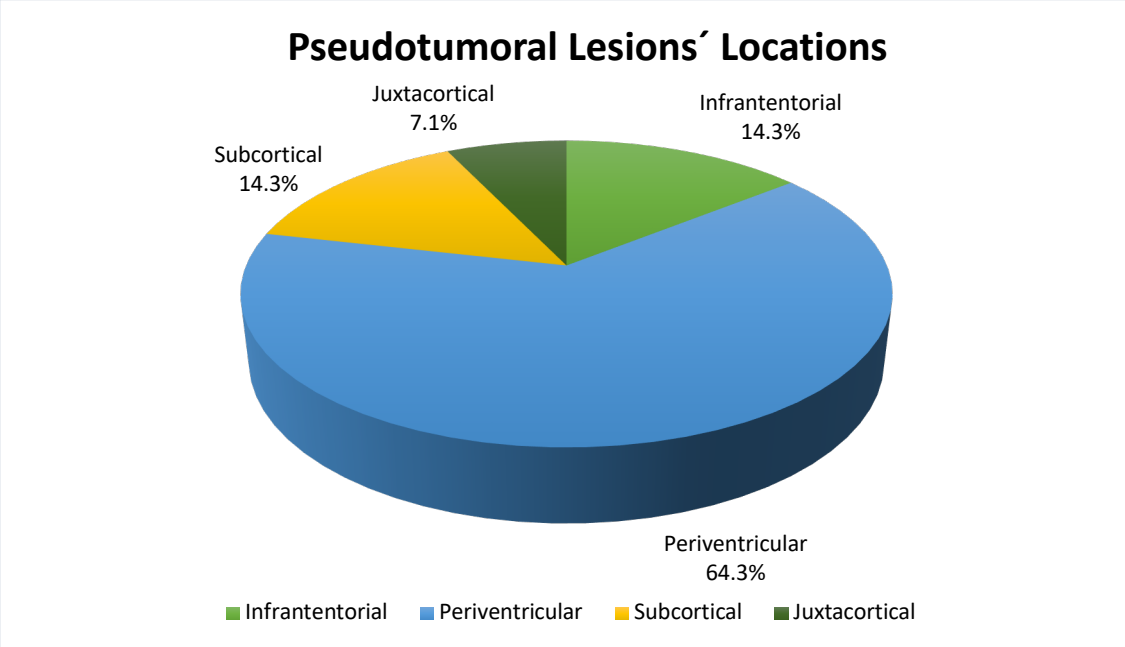

Figure 12: Representation of the percentages relating to frequencies for the different pseudotumoral lesions´ locations detected in our patients.

Although data were collected on the largest lesion for the two patients who presented 2 pseudotumoral lesions, it was examined whether the distribution of the lesions was bilateral, which was only found in one of the patients.

All pseudotumoral lesions (16 in total, as two patients showed 2 lesions with these characteristics) exhibited enhancement after intravenous administration of contrast (gadolinium). However, the pattern of enhancement detected was different: in 10 patients (71.4%) a ring-like pattern of enhancement was observed, while in the remaining 4 patients (28,6%) the pattern was nodular. Furthermore, in those patients who presented a ring-like enhancement pattern of the pseudotumoral lesions, 6 patients (60%) manifested an incomplete ring-like pattern, while 4 patients (40%) showed a complete ring-like pattern. In those cases where 2 pseudotumoral lesions were detected, both showed the identical type of enhancement pattern.

Finally, concerning pseudotumoral lesions, it became apparent that in 6 patients (42.9%) these lesions triggered mass effect or expressiveness, compared to 8 patients (57.1%) in whom this effect was absent.

7.4.2. Non-pseudotumoral lesions or typical MS plaques data

As well as pseudotumoral lesions were studied on MRI, data were simultaneously recorded for non-pseudotumoral lesions or typical demyelinating lesions usually described on MRI scans of MS patients. Classically, in clinical trials and clinical practice, the number of these lesions is described by intervals.

Number of non-pseudotumoral lesions		*Frequency*	*Percent*	*Valid percent*
Valid	0	1	7.1%	7.7%
	<10	3	21.4%	23.1%
	10-50	7	50.0%	53.8%
	>50	2	14.3%	15.4%
	Total	13	92.9%	100%
Missing	No data	1	7,1%	
Total		14	100%	

Table 9: Description of the variable referring to the number of non-pseudotumoral lesions detected in patients included in our research.

At the moment of the first clinical event, 1 patient showed no lesions at all (7.7%), 3 patients exhibited less than 10 lesions (23.1%), 7 patients had 10 to 50 lesions(53.8%) and 2 patients exceeded 50 lesions(15.4%). For one patient (7.7%), it was not possible to record data on these lesions due to the unavailability of the MRI images because of antiquity (Table 9, Figure 13).

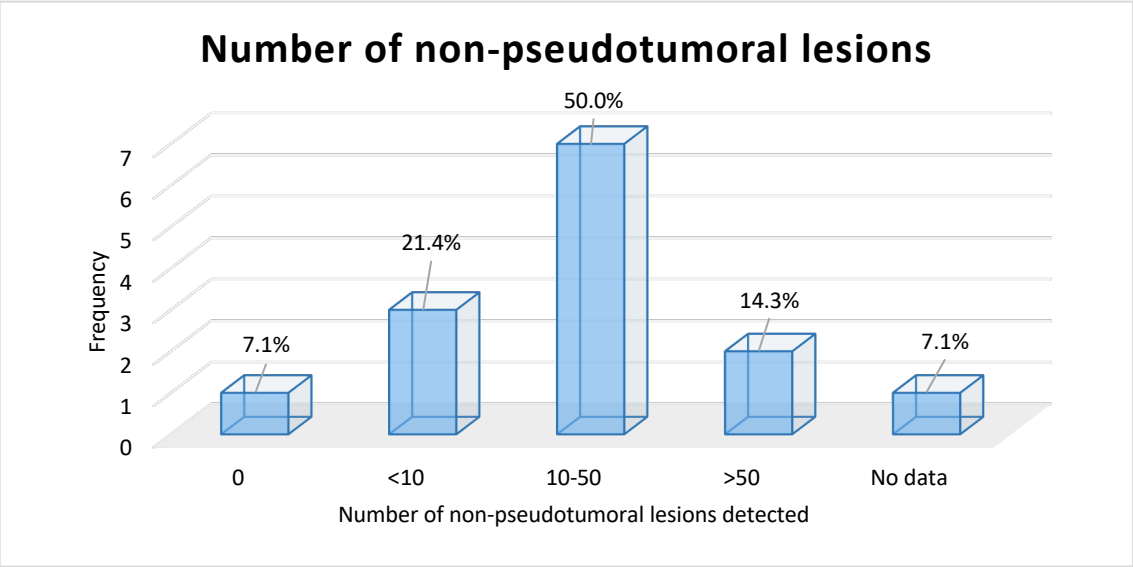

Figure 13: Representation of frequencies for the number of non-pseudotumoral lesions detected by MRI. Note that the number of that lesions was categorized by intervals (0 lesions, <10 lesions, 10-50 lesions and >50 lesions).

The different patients in our study for whom this data on non-pseudotumoral lesions could be obtained (13 patients, 92.9%) showed varied locations for these lesions, as expected (Table 10).

Non-pseudotumoral Lesions´ locations			*Frequency*	*Percent*	*Valid percent*
Juxtacortical	Valid	Yes	10	71.4%	76.9%
		No	3	21.4%	23.1%
		Total	13	92.9%	100%
	Missing	No data	1	7.1%	
	Total		14	100%	
Periventricular	Valid	Yes	10	71.4%	76.9%
		No	3	21.4%	23.1%
		Total	13	92.9%	100%
	Missing	No data	1	7.1&	
	Total		14	100%	
Subcortical	Valid	Yes	9	64.3%	69.2%
		No	4	28.6%	30.8%
		Total	13	92.9%	100%
	Missing	No data	1	7.1%	
	Total		14	100%	
Infratentorial	Valid	Yes	6	42.8%	46.2%
		No	7	50%	53.8%
		Total	13	92.9%	100%
	Missing	No data	1	7.1%	
	Total		14	100%	
Spinal cord	Valid	Yes	3	21.4%	23.1%
		No	10	71.4%	76.9%
		Total	13	92.9%%	100%
	Missing	No data	1	7.1%	
	Total		14	100%	
Optic Nerve	Valid	Yes	1	7.1%%	7.7%
		No	12	85.7%	92.3%
		Total	13	92.9%%	
	Missing	No data	1	7.1%	
	Total		14	100%	

Table 10: Description of the variable referring to the locations of non-pseudotumoral lesions showed in our patients.

A total of 10 patients presented with juxtacortical lesions (76.9%), 10 patients with periventricular lesions (76.9%), subcortical lesions were identified in 9 patients (69.2%), 6 patients had infratentorial lesions (46.2%), spinal cord lesions were identified in 3 patients (23.1%) and 1 patient showed lesions of the optic nerve (7.7%) (Figure 14).

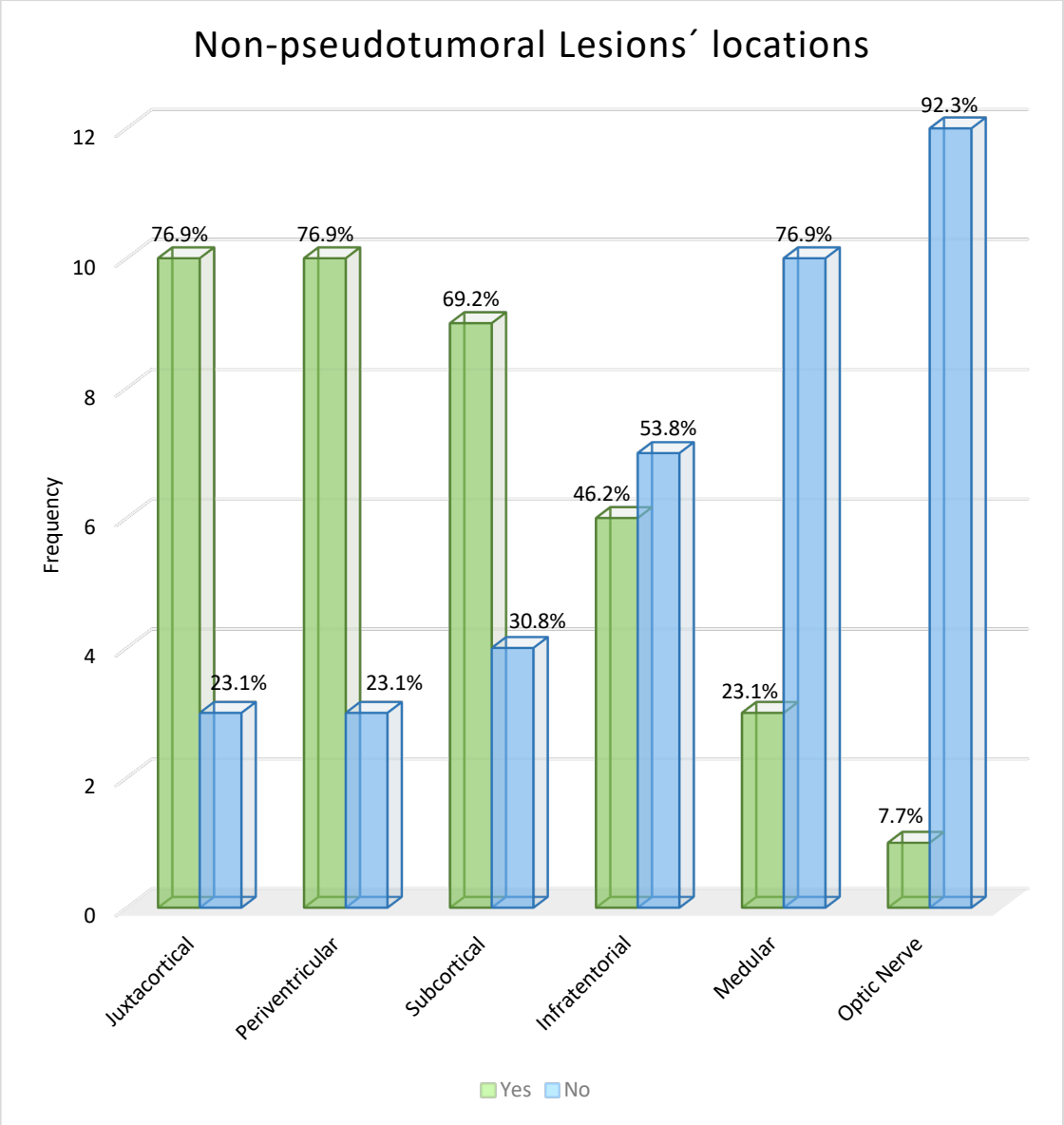

Figure 14: Representation of frequencies for the different non-pseudotumoral lesions´ locations described. Note that the percentages above each bar refer to the group of patients for whom data were available (13 patients).

Furthermore, among those patients who showed these typical MS lesions, enhancement of these was detected after administration of intravenous contrast (gadolinium) in 6 patients (42.6%), as opposed to 7 patients (53.8%) in whom this behaviour was not observed. Each of the 6 patients who presented with such enhancement of these lesions exhibited a nodular pattern of enhancement.

Additionally, the number of non-pseudotumoral lesions enhanced varied from 2 lesions to 18 lesions, leaving a mean and median number of non-pseudotumoral enhanced lesions of 5.33 $\pm$7.23 and 2 (Interquartile range (IQR) 2, 8) respectively.

7.5. Analytical data

Analytical parameters were recorded and analysed in all cases. The main results for all are detailed in table 11.

Analytical Parameters			*Mean*	*SD*	*Median*	*IQR*
Cholesterol (mg/dl)	Valid	14	193.360	38.326	199.50	161.25, 218.00
LDL- cholesterol (mg/dl)	Valid	14	119.140	32.607	122.00	100.00, 142.75
Absolute Number of Lymphocytes (Lymphocytes x 10^3/µl)	Valid	14	1.805	0.719	1.65	1.43, 1.80
Absolute Number of Lymphocytes TCD4 (Lymphocytes/µl)	Valid	11	926.090	413.381	970.00	615.00, 1277.00
Absolute Number of Lymphocytes TCD8 (Lymphocytes/µl)	Valid	11	452.436	171.911	484.00	429.00, 549.00
Complement component C3 (mg/dl)	Valid	11	110.584	18.980	110.64	104.00, 125.28
Complement component C4 (mg/dl)	Valid	12	175.103	527.825	23.13	16.13, 30.77
C-Reactive Protein (CRP) (mg/dl)	Valid	14	0.507	0.612	0.40	0.10, 0.42
Erythrocyte sedimentation rate (ESR) (mm/h)	Valid	10	11.800	17.306	2.00	1.75, 23.25
Vitamin D (ng/ml)	Valid	13	21.540	14.472	18.00	12.00, 28.50
TSH (mU/l)	Valid	14	1.750	0.963	1.49	1.13, 2.11

Table 11: Description of variables referring to the analytical parameters assessed in patients studied.

7.6. Serological data

Further, different serologies were also determined, so that the results for each of them are presented in table 12.

Serologies			*Frequency*	*Percent*	*Valid percent*
Anti-VHC	Valid	Positive	0	0.0%	0.0%
		Negative	12	85.7%	100%
		Total	12	85.7%	100%
Anti-HBs	Valid	Positive	4	28.6%	33.3%
		Negative	8	57.1%	66.7%
		Total	12	85.7%	100%
EBV IgG	Valid	Positive	11	78.6%	100%
		Negatve	0	0.0%	0.0%
		Total	11	78.6%	100%
VVZ IgG	Valid	Positive	11	78.6%	91.7%
		Negative	1	7.1%	8.3%
		Total	12	85.7%	100%
CMV IgG	Valid	Positive	4	28.6%	63.6%
		Negativo	7	50.0%	36.4%
		Total	11	78.6%	100%
Herpes IgG	Valid	Positive	5	35.7%	50.0%
		Negativo	5	35.7%	50.0%
		Total	10	71.4%	100%
Rubella IgG	Valid	Positive	6	42.9%	60.0%
		Negative	2	14.3%	20.0%
		Undetermined	2	14.3%	20.0%
		Total	10	71.4%	100%
Sarampion IgG	Valid	Positive	8	57.1%	80.0%
		Negative	2	14.3%	20.0%
		Total	10	71.4%	100%
Mycoplasma Pneumoniae IgG	Valid	Positive	6	42.9%	50.0%
		Negative	4	28.6%	33.3%
		Undetermined	2	14.3%	16.7%
		Total	12	85.7%	100%
Treponema Pallidum Antibodies (Ab)	Valid	Positive	0	0.0%	0.0%
		Negative	14	100%	100%
		Total	14	100%	100%
JC Virus Ab	Valid	Positive	2	21.4%	60.0%
		Negative	3	14.3%	40.0%
		Total	5	35.7%	100%
HIV-1/HIV-2 Anitigen (Ag) + Antibodies (Ab)	Valid	Positive	0	0.0%	0.0%
		Negative	14	100%	100%
		Total	14	100%	100%

Table 12: Description of variables referring to the serological variables assessed in patients studied.

7.7. HLA-DRB1 locus

Regarding the allelic distribution across our research population for the HLA-DBR1 locus, data were available for 11 patients (72.7%). For the latter, the allele 1 analysis of this locus yielded the following results: the HLA-DRB1*01 allele appeared in 2 patients (18.2%), the HLA-DRB1*04 allele in 5 patients (45.5%), and the HLA-DRB1*03, HLA-DRB1*07, HLA-DRB1*08, HLA-BRB1*11 alleles were present in 1 patient each (9.1% corresponding to each of them) (Figure 12).

Meanwhile, the results obtained for allele 2 of the same locus were as follows: the HLA-DRB1*15 allele was present in 8 patients (72.7%), the HLA-DBR1*04 allele in 2 patients (18.2%) and the HLA-DRB1*11 allele in 1 patient (9.1%).

Thereby the haplotypes identified in these patients for the HLA-DRB1 locus were: HLA-DRB1*04*15 (3 patients, 27.27%), HLA-DRB1*04*04 (2 patients, 18.18%), and HLA-DRB1*03*15, HLA-DRB1*08*15, HLA-DRB1*07*15, HLA-DRB1*11*15, HLA-DRB1*01*11, HLA-DRB1*01*15 (each of these was present in 1 patient, 9.09%).

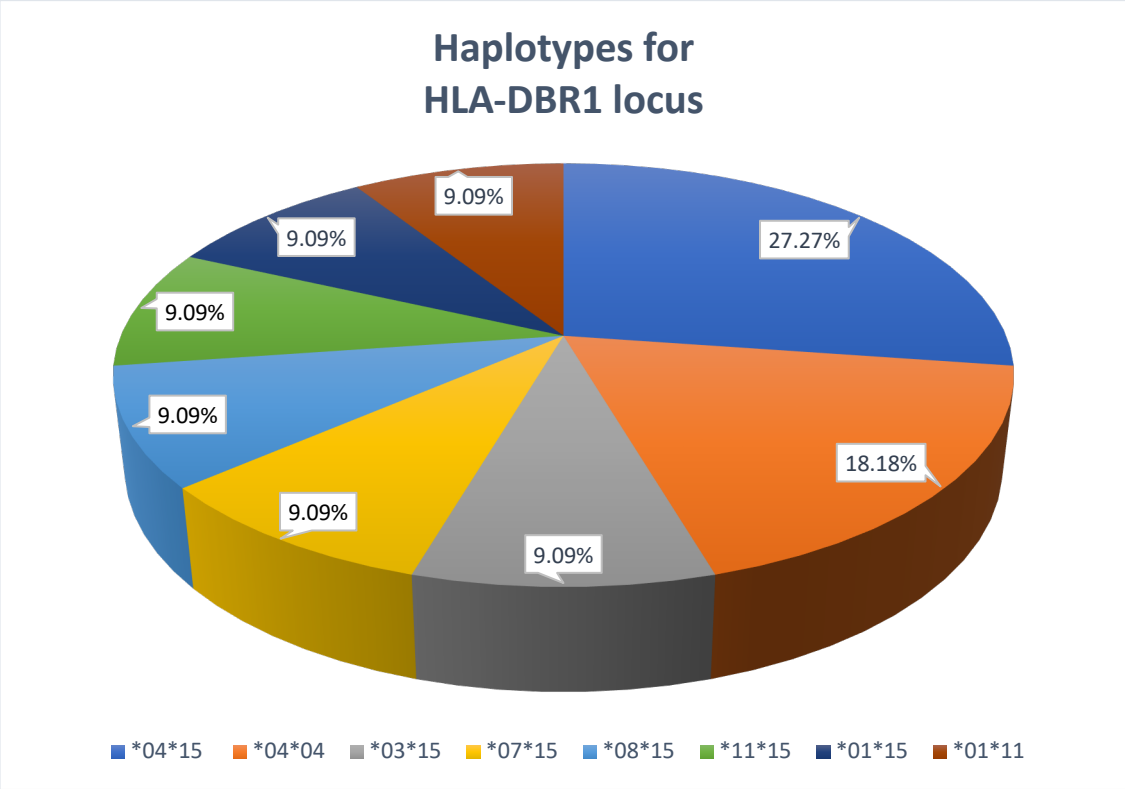

Figure 12: Representation of frequencies for the different haplotypes described for the HLA-DBR1 locus. Note that the percentages above each bar refer to the group of patients for whom data were available (11 patients).

7.8. CSF examination data

It was observed that in all patients included in our study (14 patients, 100%) a lumbar puncture was performed, revealing the presence of oligoclonal bands in 7 patients of them (50%).

Regarding the CSF study, data on protein levels were available in 12 of the 14 patients (71.4%). These data ranged from 24 mg/dl to 103 mg/dl, generating a mean for these protein levels of 53.93 mg/dl (± 24.806). Similarly, for the number of leukocytes per mm3 in CSF, data were available for 12 of the 14 patients (71.4%). In this case, the data ranged from 0 leukocytes/mm3 to 65 leukocytes/mm3, generating a mean of 13 leukocytes/mm3 (±20.374), however; the median was 3 leukocytes/mm3 (IQR 1.25, 21.25).

7.9. Neurophysiological test data

As part of the diagnosis procedure, neurophysiological studies were performed during the study of this first clinical episode suggestive of MS. Visual evoked potentials (VEP) were performed in 9 patients (64.3%), as opposed to 5 patients (35.7%) in whom no VEP was performed. Among the 9 patients who underwent this test, only 2 patients (22.2%) showed VEP alterations.

On the other hand, somatosensory evoked potentials (SSEP) were performed in only 4 patients (28.6%), compared to 10 patients (71.4%) in whom SSEP were not carried out. Only one patient (25%) of the 4 patients in whom this test was performed demonstrated alterations in the PESS.

Finally, electroneurography (ENG) was carried out in 6 patients (42.9%), compared to 8 patients (57.1%) who were not subjected to ENG. No abnormalities were observed in any of those 6 patients who underwent this test.

7.10. Brain biopsy data

Brain biopsy was only required for 3 of the 14 patients included in our study (21.4%). For all 3 patients, the delay in months from the onset of symptoms until the procedure was carried out was 1 month. Furthermore, none of the 3 patients suffered complications from the biopsy, and in none of the patients, a new biopsy was necessary after the first biopsy.

The results described for the 3 biopsies performed contributed to ruling out other possible entities and confirmed the suspected MS as the cause of the demyelinating pseudotumoral lesions.

7.11. Clinical evolution data

From the first clinical episode suggestive of MS, until the last clinical control for which data were available, the patients' evolution was evaluated. The mean duration of clinical follow-up was 63.79 months (± 82.905), however, the median was 31 months (IQR 12.75, 97.50).

By retrospectively reviewing the clinical history, we were able to account for the number of relapses that patients had suffered up to this last clinical review for which we possessed data. Hence, 4 patients (28.6%) reported relapses, compared to 10 patients (71.4%) in whom no such events were recorded. For these 4 patients in whom relapses were described, the mean number of relapses was 1.5 relapses (± 0.577).

Since that first clinical episode suggestive of MS and its subsequent evolution, 11 of the 14 patients (78.6%) included in the study fulfilled diagnostic criteria for RRMS, while the remaining 3 patients (21.4%) satisfied diagnostic criteria for CIS.

Examination of the disability experienced by the patient at the last clinical review for which data were available; revealed EDSS scores ranging from 0 points to 4 points, resulting in a median of 1.5 points (IQR 1, 3).

As for starting DMT during this clinical course, we detected 10 patients out of the 14 studied (71.4%) who had initiated such treatment. All of them corresponded to patients fulfilling the diagnostic criteria for RRMS. Only 1 patient (9.09%) of those 11 who fulfilled these criteria did not receive DMT. The different drugs registered for the 10 patients in our study were: dimethyl fumarate (2 patients, 20%), fingolimod (3 patients, 30%), natalizumab (2 patients, 20%), ocrelizumab (2 patients, 20%), and teriflunomide (1 patient, 10%) (Figure 13).

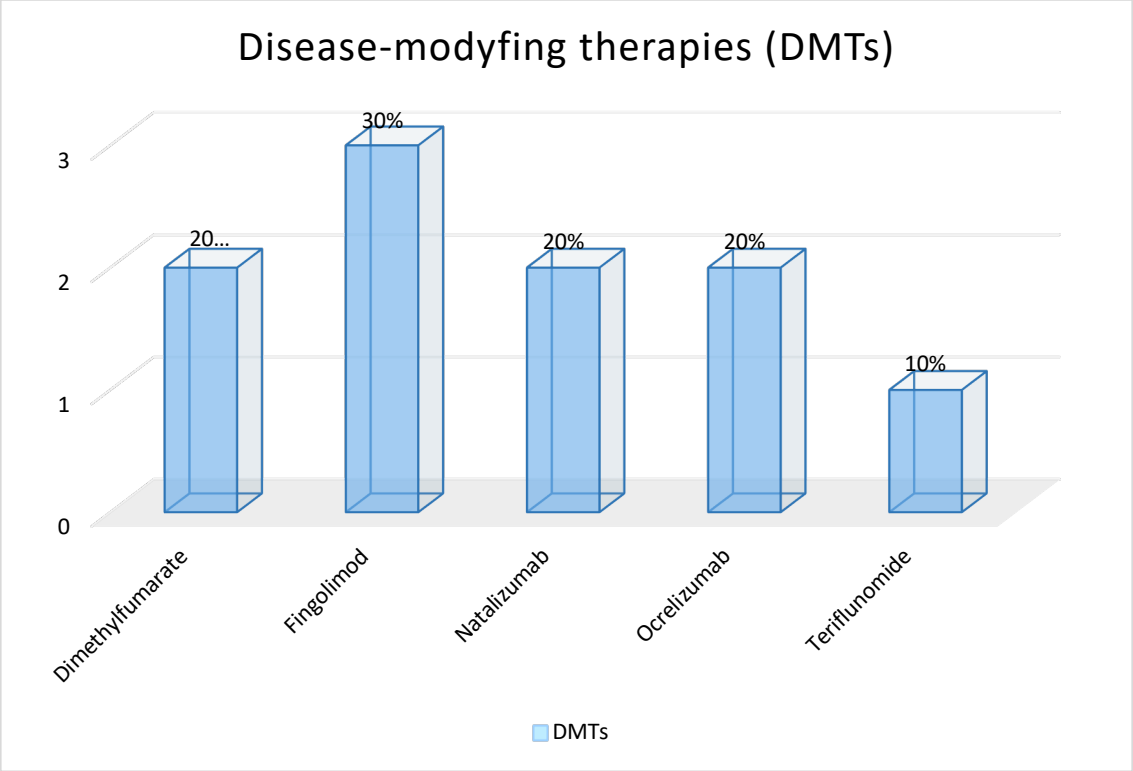

Figure 13: Representation of frequencies for the different DMTs administered to our patients. Note that the percentages above each bar refer to the group of patients who received any of these DMTs (10 patients).

7.12. Neuroimaging evolution data

Likewise, from the first MRI performed during that first clinical episode suggestive of MS to the last radiological control for which data were available, the time expressed in months was also different. Therefore, the mean time from that first MRI to the last control was 40.85 months (± 45.86); however, the median was 12 months (IQR 10.50, 61.50). For just 1 of the 14 patients no MRI control data were found (7.1%) so all data concerning these controls could only be studied in 13 patients (92.9%).

None of these patients showed complete disappearance of pseudotumoral lesions detected in their first MRI performed, however; all of them showed a decrease in the volume of the pseudotumoral lesions. In none of these patients, pseudotumoral lesions conditioned mass effect or expansiveness, and neither were any lesions enhanced after intravenous administration of contrast (gadolinium). Furthermore, the appearance of new pseudotumoral lesions was not described for any of the patients.

Concerning the evolution of non-pseudotumoral lesions or demyelinating lesions typical of MS, in addition to the patient for whom no control data were found, there was one patient who did not present lesions of this type in the first MRI; therefore, both were considered as missing data for the study of this variable. Accordingly, data for neuroimaging evolution of non-pseudotumoral lesions were accessible for 12 of the 14 patients in our study (85.71%).

Regarding the variations in the volume of these lesions, a decrease in volume was observed in 3 patients (25%), as compared to a constant volume in the remaining 9 patients (75%). The disappearance of old non-pseudotumoral lesions was described only for 1 of these 12 patients (8.33%), and only a single lesion was found to have disappeared.

Moreover, old non-pseudotumoral lesions that showed enhancement after intravenous contrast administration were detected in 3 of the 12 patients (25%), ranging in the number of enhanced lesions from 1 to 2 lesions, resulting in a mean of 1.33 old non-pseudotumoral enhanced lesions ($\pm$ 0.577). The location of these lesions was described as periventricular in 2 of the 3 patients (66.67%) and infratentorial in 1 patient (33.33%).

In this instance, new-onset non-pseudotumoral lesions were described in 4 of the 12 patients for whom data were available (33.33%). Although the number of these new lesions varied from 1 lesion to 10 lesions, the median was 1.5 new-onset non-pseudotumoral lesions. These lesions appeared with a periventricular location in 2 of these 4 patients (50%), with both juxtacortical and subcortical locations in 1 of these 4 patients (25%), and with multiple locations in the patient in whom 10 such new-onset lesions were described (25%). In addition, these lesions were reported to exhibit enhancement after intravenous administration contrast in 2 of the 4 patients (50%).

7.13. Other analysis

Although it is not the aim of the research, as the last step, Spearman's p coefficient was used to determine whether the size of the pseudotumoral lesion correlates with the main demographic (age), clinical (EDSS disability score and acute phase reactants) or radiological variables. In our population, a statistically significant correlation (r=0.78) was found between the largest diameter of the pseudotumoral lesion and disability on examination, measured by the EDSS scale (p=0.0484). A significant positive correlation (r=0.69) was also found between disability (EDSS) and major acute phase reactants such as ESR (p=0.0154).

Finally, using the Wilcoxon test, we analysed the existence of differences observed in the diameter of the pseudotumoral lesion between those individuals who subsequently developed MS and those who did not, those who received disease-modifying treatment and those who did not, and those with and without positive oligoclonal bands in CSF. Although no statistically significant differences were evident, a positive trend was observed between diameter and the presence of the variables studied (Figure 14).

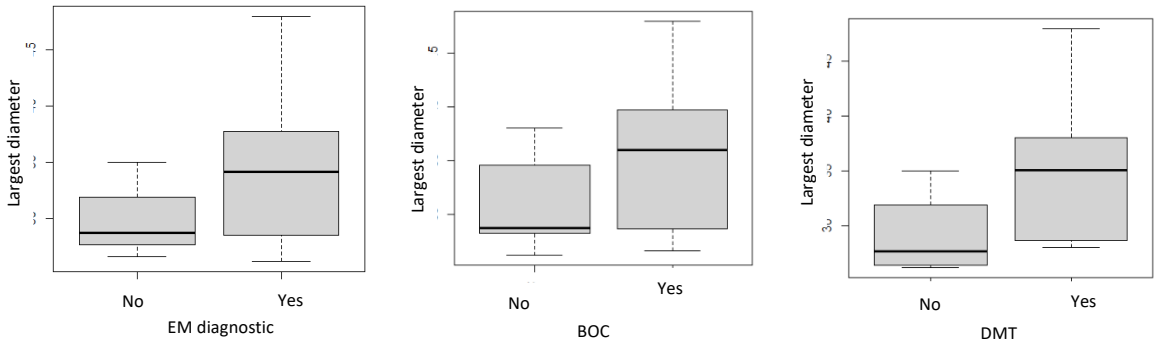

Figure 14: Relationship of pseudotumoral lesions´ largest diameter to MS diagnosis, presence of BOC and patients on DMT treatment.

8. Discussion

This research presents the main characteristics of patients with demyelinating pseudotumoral lesions followed in the MS Unit of the Hospital Universitario Marqués de Valdecilla. This form of presentation of the disease occurs infrequently and usually constitutes a diagnostic challenge, especially if it presents as the first clinical manifestation of the disorder [69,72], which may involve implications for the prognosis and treatment of these patients. Furthermore, descriptions and reviews in the literature are scarce, which justifies performing a study aimed at these patients. In this paper, we analyse the demographic, clinical, diagnostic and treatment characteristics and prognosis of our patients.

A total of 14 patients who met the inclusion criteria described above were assessed in our analysis. Considering that the prevalence described for these lesions in the literature ranges between 1.4 and 8.2%[70,73] and that the MS consultation database includes a total of 450 patients, the prevalence in our centre is 3.11% and, therefore; in concordance with expectations. Moreover, it constitutes one of the longest series described in the literature published to date.

8.1. Demographic research

Firstly, we will analyse our patients' demographic characteristics. The majority of patients were male (57.1%), which is a significant finding; considering that MS, like other autoimmune diseases, is more common in females[1]. Nevertheless, focusing on those patients who debut with pseudotumoral forms in the literature, although the female predominance is maintained, it is not so evident[69,70,73]. Furthermore, the relatively small number of cases, due to the monographic consultation of a single centre, could explain the slight differences in favour of the male gender in our results.

Concerning the age at the time of onset of the lesions, it was observed that pseudotumoral lesions can appear in practically any age group, showing a wide range of ages in our study (between 24 and 48 years). Anyway, the showed mean age of onset, less than 40 years (33.64 ± 9.572 years); is similar to that described in previous series, reflecting the fact that this form of presentation is more common among young people[69,71–73].

A variable rarely studied in previous research, and which our study has analysed, is the existence of cardiovascular risk factors in these patients. Their relevance is conditioned by their contribution to the differential diagnosis and because some of them, such as smoking, have been identified as negative prognostic factors in MS patients[80]. In our patients, as expected, the prevalence of the classical cardiovascular risk factors (AHT, MD, DLP, obesity as BMI > 30) was low, corresponding to the general population in young patients and with no significant differences among genders[81]. However, a high prevalence of patients with active smoking habits (71.4%) was found, with a slight predominance of males (75%) over females (66.7%). This particular finding is noteworthy because several studies have consistently reported that cigarette smoking is associated with a higher risk of developing MS[82].

The high prevalence in our study would raise a possible future line of research aimed at studying whether smoking exposure is also associated with a debut of the disease characterised by the presence of pseudotumoral lesions.

Furthermore, the existence of a previous autoimmune disease history was also analysed in our patients. Traditionally, patients suffering from an autoimmune disease have been considered to have an increased risk of developing another autoimmune condition, and also an increased risk of MS[83,84]. Nevertheless, although our patient sample was small, none of the individuals included presented a previous history of other autoimmune diseases. This finding confirms the results obtained by more recent studies with significant patient sample sizes, which have also found no association with other autoimmune diseases when it comes to MS. One example is the Danish National Registry research that studied 1403 patients diagnosed with MS between 2000 and 2004; and found no significant incidence versus controls, in the occurrence of autoimmune diseases other than MS (at least for females)[85].

Analysis of the personal history of interest, as in the case of cardiovascular risk factors, is another of the variables that have been rarely included in previous studies along this line of research. Our study, despite including a limited number of patients, showed a greater tendency to present pathologies in the psychiatric area, such as depressive or anxious disorders; and in the neurological area, such as different clinical modalities of headaches, among which migraine with aura was the most prevalent (33.33% of the 12 patients for whom such data were available).

The Global Burden of Disease Survey (GBD) published in 2017 reported migraine as the sixth most prevalent disease worldwide[2]. Furthermore, this pathology directly impacts 12-13% of the Spanish population, according to data from the Spanish Society of Neurology (SEN), which means that it is the most prevalent neurological disease in our country, affecting more than 5 million of the population[86,87]. Moreover, epidemiologically, MS and migraine share features that include a predominance of female involvement, and a tendency to affect them in their 20s and 40s[88].

Therefore, our research reinforces the idea of an association, despite a weak one, between MS and migraine, as the prevalence rates were found to be higher than in the general population. Current literature describes that up to two-thirds of MS patients suffer from headaches, most of them complaining of migraines[89–92]; consistent with our patients in whom the prevalence of migraine was twice that of tension-type headaches.

On the other hand, a family history of MS has been classically suggested as one of the risk factors for developing the disease, so the existence of affected first-degree relatives is estimated to increase the risk of developing MS in the future, compared to the general population[1,12,13]. Only 2 patients with a family history of MS were identified in our research, and neither of these cases involved affected first-degree relatives. However, the failure to identify this risk factor may simply be related to the reduced sample size of research.

Consequently, it could be interesting to examine whether this estimated risk for disease development when there is a family history of MS in first-degree relatives; remains similarly when it comes to estimating the risk of developing a pseudotumoral form of MS; in the case of first-degree relatives affected by this MS form.

8.2. Patients characteristics

Owing to their size, pseudotumoral lesions often involve symptomatic clinical episodes[69,72]. According to the literature published to date, it is suggested that motor deficits are the most frequent symptoms observed in patients presenting with these lesions[68,69,76,93], results that are consistent with those found in our patients, where 71.4% suffered from this type of symptomatology.

However, depending on the size and location of the lesions, a wide range of clinical symptoms such as sensory deficits, cognitive deficits, cerebellar and brainstem symptoms, and impairment of symbolic functions such as aphasia, apraxia, agnosia and ataxia; headaches and/or epileptic seizures have also been described[68,69,72,73].

All of them were included in our study for assessment. Our data reflect that sensory deficits were found in the same proportion as motor deficits (71.4%), and also cerebellar and brainstem symptoms were the second most described symptoms showing the same proportion in both cases (50%). The involvement of significant functions such as apraxia and agnosia were not identified in our research, with aphasia being identified in only 7.1% of patients. These data are similar to these objectivated by previous studies[69,71,73], as is the proportion of visual deficits (7.1%), with one particular exception, as sensory deficits were not described in the same proportion as motor deficits by some previous studies; although they are among the most frequently described symptoms[69,73].

However, regarding the remaining symptoms, our study did not identify epileptic seizures, which were found in previous studies[69,73]. Even so, due to the low proportion described in other series, this could be due to the mere fact of the low sample size included in our study. The same applies to cognitive deficits, which in previous studies were identified in a significant proportion of patients[69,73]. Nevertheless, in this case, it may be due to the fact that in our study cognitive deficits were interpreted as memory deficits, whereas other studies have included others such as confessional states, bradypsychia, aphasia or apraxia[69,73].

Finally, it should be noted that, although the presence of headaches has been described in the literature as one of the possible symptoms associated with these lesions[68,69,73]; the majority of studies carried out to date do not include this symptom for evaluation. Our study found that 28.6% of patients suffered from headaches, consistent with research conducted in 2011 by Takao et al, in which 12 patients with tumefactive demyelinating lesions were assessed and found headaches in 33% of the patients[93]. This particular finding could be related to the size of the lesions described so that further studies could analyse the relationship between lesion size and the presentation of persistent headaches in the first clinical episode.

The disability experienced by our patients during this first episode suggestive of MS was tested with the EDSS scale. This Kurtzke disability scale is the most widely used scale to evaluate the functional status of people with MS by assessing disability according to eight functional systems and is used as a reference in clinical trials and guidelines for MS diagnosis and treatment recommendations[28,94].

Our study suggests a wide variability in experienced disability ranging from 1.5 to 6 points for the EDSS score with a median of 3 points. These results are similar to those described by Lucchinetti et al; which analysed 168 patients with biopsy-confirmed inflammatory demyelinating disease of CNS, in which a median of 3.5 points on the EDSS scale was found at the first clinical episode[73]. A median of 3 points on the EDSS scale indicates that most patients presented at the time of diagnosis with moderate disability in one functional system, or mild disability in three or four functional systems while maintaining complete independence in ambulation[28].

8.3. Hospitalization and acute treatment

A novel feature of our research is the recording of the requirement for hospital admission during the first clinical episode in patients with these lesions, as to date, no previous series have described it. Hospital admission was required in 85.7% of our patients, with a mean length of stay of 8.75 ($\pm$4,472 days). This particular finding would suggest an increase in healthcare expenditure related to patients with these forms of the disease, compared to those who do not present these lesions, and in whom the entire study is done in an ambulatory setting.

During the acute phase management of this first clinical episode almost all patients received steroid treatment, and in addition to the 12 hospitalized patients, one patient received such treatment on an ambulatory care plan (92.7%). Moreover, the drug of choice in all cases was methylprednisolone, administered as intravenous boluses of 1000 mg daily (a single patient received a dose of 50 mg) and with a median treatment duration of 4.54 (1198) days. These results are similar to those described by previous studies[69,71,76]. One example is the research conducted by Sánchez et al, which retrospectively analysed 15 patients with these lesions, in which the steroid treatment with 1-2 intravenous methylprednisolone boluses of 1000 mg daily was necessary for all patients; and with a variable treatment period of 3-5 days[71]. DMT was not initiated in any of the patients in our study during the acute episode, a result that is consistent with previous studies[71].

Concerning recovery from this first clinical attack, and therefore; regarding response to steroid treatment during the acute phase, current literature results are variables. Although some studies, such as one carried out by Mauri-Fábrega et al found a full recovery in the 14 patients included in that study[69]; others such as that performed by Seewann et al., which included 69 patients with atypical inflammatory demyelinating lesions as suggested by MRI, had objectified that the proportion of patients who improve without partial recovery (50%), is higher than those who achieve full recovery (30%)[67]. Our study is consistent with the latter, as although slight, it shows a trend towards partial recovery (64.3%), and thus, improvement of clinical symptoms, rather than full recovery (35.7%).

Even so, these data suggest a good response to steroid treatment if it is administered in the acute phase of the disease, both in our study and previous ones.

8.4. Neuroimaging research

8.4.1. Pseudotumoral lesions research

Regarding imaging studies, as in the current literature[69–73,76,93], MRI was performed to evaluate the characteristics of the pseudotumoral lesions in all patients included in our study. These lesions were identified in all cases, with a tendency to appear as isolated masses (85.7%), since only 2 patients presented with 2 pseudotumoral lesions. This trend has been previously described in the current literature[23,50,69,71,73].

Data from previous studies define these lesions as greater than or equal to 2 cm (20 mm) in maximum diameter[50,68,73–76], in agreement with the diameters of the lesions in our patients (median lesion diameter 33.36$\pm$6.527 mm). However, our study includes the area of the lesions in their entirety, with a mean of 7.10 cm^2 (+/-1.81), which could be an added value in future research.

Over the last years, volumetry has gained importance in the field of MS research. In addition, technological developments with better and more powerful MRI equipment have made it possible to expand the possibilities of image analysis and consequently to identify prognostic markers in MS patients. In this sense, future lines of research will analyse the relationship between the lesion area and disease-specific variables.

Concerning the location of these lesions, the periventricular region was the most frequently observed in our patients (64.3%). This region has been described as one of the most preferred locations in the literature described to date[37,68].

However, it has also been reported that pseudotumoral lesions have a high tendency to be located in subcortical regions[37,72,75], even constituting the most frequent location in several previous studies. One example is the research carried out by In Hye Jeong et al, which evaluated 31 patients with this type of lesion, 38.7% of which were found in this location [76]. These data are in contrast to our findings, where only 14.3 % of the patients were found to show such location.

In addition, consistent with other earlier descriptions[71,76], infratentorial lesions were described, although to a very lesser proportion (14.3%).

Current literature describes that the presence of enhancement in T1-weighted sequences after intravenous administration of contrast (gadolinium) is constant for active pseudotumoral lesions. The most frequently described enhancement pattern is incomplete ring-like[23,50,69,72]. In agreement with this research, all the lesions described in our patients correspond to active lesions, as all showed this enhancement. Moreover, as in these previous studies[23,50,69,72], the ring-like pattern was the most frequently described (71.4%), and of those presenting this pattern, the incomplete pattern was the most prevalent (60%). However, our study also described a high proportion of patients with a complete annular pattern (40%).

This latter finding may have contributed to complicating the differential diagnosis with other pathologies, and may even delay the definitive diagnosis, or in some cases, require a brain biopsy.

For those patients in whom 2 pseudotumoral lesions were observed during the first clinical episode examination, both showed the same pattern of enhancement after intravenous contrast administration. This finding is consistent with the research carried out by Mauri-Fábrega et al, in which the same tendency to show a similar pattern of enhancement when several pseudotumoral lesions were objectified; was described[69].

Another radiological sign described in previous series was the appearance of a mass effect [50,72–74], described in 42.9% of patients in our study. The research performed by Atlintas et al, in which 54 patients with these lesions were studied, reported that the size of the lesion influenced the mass effect that they conditioned, determining that the larger the lesion, the greater the mass effect ($p<0.001$)[75]. Due to the descriptive objective of our study, and the small sample size of patients, this analysis was not carried out. Nevertheless, as previously described in the literature, the mass effect conditioned by these lesions, in principle; appears in a considerably smaller proportion than would be expected due to the size of the lesions, compared to other expansive SNC processes such as abscesses or tumors[50,72–74].

In conclusion, our results, regarding the characterization of pseudotumoral lesions in MRI studies; are broadly consistent with those of previous studies.

8.4.2. Non-pseudotumoral lesions or typical MS plaques research

The guidance of pseudotumoral lesions´ differential diagnosis towards an inflammatory demyelinating disease as MS, is supported by the concomitant evidence of typical MS plaques; which is a fairly common occurrence described by current literature[23,69,72]. Therefore, the presence of this finding also helps in the characterization of the pseudotumoral lesions in our patients because they were not present in just one patient (7.1%). Classically, in clinical trials, the number of these lesions is described by intervals. Our study revealed a tendency towards the existence of 10 to 50 MS typical plaques, implying a moderate lesion charge.

Typical MS plaques of periventricular and juxtacortical location were described in 76.9% of our patients, and subcortical lesions were described in 69.2%. On the other hand, infratentorial (46.2%), medullary (23.1%) and optic nerve (7.7%) lesions were found in smaller proportions. The locations described for these lesions in the patients included in our study are consistent with the regions described as preferential for the development of typical MS plaques[6,23,44,49].

In 42.6% of our patients, MS typical plaques that showed enhancement after intravenous contrast administration in T1-weighted sequences were detected at the same time as pseudotumoral lesions, and therefore; they can be considered as active lesions)[21,23,44,50]. Furthermore, consistent as well with the literature described, all of these lesions showed a nodular enhancement pattern[44,50,54].

Since the number of enhanced MS-typical plaques ranged from 2 to 18 lesions, with a median of 2, these data suggest that, in addition to detecting activity in pseudotumoral lesions, the concomitant appearance of active MS-typical lesions is not a rare discovery. This particular finding during the first clinical episode suggestive of MS in a patient debuting with a pseudotumoral lesion may have implications for subsequent prognosis, but further research is needed.

8.5. Analytical research

Data for different analytical parameters were collected in order to assess them. The following is a commentary on the most relevant findings.

The published literature to date has described low vitamin D levels as a risk factor for both the development and progression of the disease, therefore; deficiency of this vitamin is common among MS patients[12,13,16,95,96]. Our results are consistent with this, as a mean vitamin D level of 21.54 (±14.472) ng/mL was described, meaning it was at the low limit of the normal range; meanwhile, the median for vitamin D levels was 18 ng/mL, and therefore; already within what would be considered low vitamin D levels.

However, these data could be affected by the geographical location of the autonomous community of Cantabria, since another risk factor directly related to the prevalence and incidence of the MS disease is the north-south gradient, which also has been described within Spain. MS tends to be more prevalent as the distance from the equator (latitude) increases, which is directly related to a decrease in UBR exposure and, consequently, to a decrease in vitamin D levels in patients[13,16,97,98].

On the other hand, the consideration of MS as an inflammatory demyelinating disease could imply a slight increase in acute phase reactants during the relapses or disease progression, as had been suggested by previous studies[99,100].

Although CRP had been suggested as correlates well with the severity of clinical symptoms[99], as described in the systematic review by Olsson et al in 2020, after analysing the results for CRP levels in 14 subsequent studies, the inconsistency of the results implies insufficient evidence to support the use of CRP as a diagnostic or prognostic biomarker of MS due to its lack of specificity[101]. Our study would support the unspecificity of CRP levels as a biomarker in diagnosis, as the mean for our patients' levels (0.507 (±0.612) mg/dL) was within the normal range.

Regarding ESR, the cross-sectional study by Nazeri et al[99], which included 80 patients with a definitive diagnosis of multiple sclerosis, found an association between ESR levels and lesions showing MRI enhancement after intravenous contrast administration. Therefore, since the presence of this neuroradiological finding has been established as a reflection of multiple sclerosis activity[21,23,44,50], the study supported the hypothesis that ESR could have prognostic value and be useful to monitor disease activity and distinguish relapse from relapse[99]. In our patients the mean for ESR levels was 11.800(±17.306) mm/h; therefore, although the mean was within the normal range, the variability in the levels detected was evident.

Although this is not the aim of our research, the relationship between ESR levels and the disability experienced by our patients in their first episode suggestive of MS is discussed below.

No significant alterations were found in the rest of the analytical variables assessed.

8.6. Serological research

Concerning the serologies analysed, we emphasise above all the unanimous positivity for EBV in all patients in whom data could be obtained, which supports recently published studies that point to this virus as another risk factor for developing the disease[3,7,12–16].

In addition, other viruses were described in a significant proportion of patients, such as varicella-zoster virus (91.7%), cytomegalovirus (63.6%), and herpes (50%). Current literature has described many infectious agents as potential causative agents of the disease, including those described above, but none of them has been confirmed[7]. In addition, our study found a substantial proportion of positivity for sarampion (80%) and rubella (50%) serologies, which have not been assessed by previous studies as other viruses.

Our findings could serve as a basis for future research to further investigate the epidemiology and risk factors of this complex disease.

8.7. HLA-DRB1 research

As described in the background, genome-wide association studies have identified more than 200 genetic variants that increase the risk of the disease, of which the most significant remains the HLA DRB1*1501 haplotype (with an odds ratio of approximately 3)[3,5,12,13].

However, in contrast to these data, this haplotype was only identified in one of the patients for whom this immunological study was available. In our study, although the sample is small, and therefore this data could be, as a consequence, biased; the most identified haplotype was HLA-DRB1*04*15 (27.27%). Furthermore, it should be noted that, although this is the most reported haplotype, a large variability of them for this locus was observed in our patients.

Overall, our characterization of the HLA-DRB1 haplotype in patients presenting with pseudotumoral lesions during a first clinical episode could serve as a basis for further studies assessing the risk of developing a pseudotumoral lesion as a form of disease presentation; if a particular haplotype for the HLA-DRB1 locus is present.

8.8. CSF examination research

CSF analysis following lumbar puncture is one of the tools in the diagnostic arsenal for MS. As evidence of this, all our patients underwent this procedure.

The literature reviewed to date describes that an increase in the intrathecal synthesis of IgG occurs in almost 95% of patients with established MS. It is qualitatively measured by the presence of oligoclonal bands. Therefore, their presence strongly supports the diagnosis of the disease[22,55–58]. In our patients, at the time of the first clinical outbreak, oligoclonal bands were present in 50% of the patients.

The presence of BOC may aid the MS diagnostic process and, hence; its inclusion in the MS diagnostic criteria[22,25]. Nevertheless; although it is described to be present in a high number of MS patients, it is not universal; as we see in our results. As this is a crude test, it was not repeated to see if they developed in the course of the disease.

Other parameters analysed in the cerebrospinal fluid were protein levels and CSF cell counting. In the field of protein levels, the mean of 53.93 mg/dL (24.806) in our patients is consistent with the current literature, as it is described how the finding of very high CSF protein levels (>100 mg/dL) should suggest a diagnosis different from MS. The same is true for the median number of leukocytes/mm3 (3 leukocytes/mm3 in our patients), as the finding of pleocytosis with >50 cells/mm3 should also suggest a diagnosis other than MS[22,58].

8.9. Neurophysiological test research

The study of MEPs and ERG are other useful tools in the diagnosis and monitoring of MS[58,59]. Although its diagnostic and prognostic value in the detection of formed plaques and the recording of “silent changes of the sensory pathways” has been described, especially VEPs for manifesting lesions of the optical nerve; MacDonald criteria do not include them because of considering insufficient data about VEPs diagnostic sensitivity and specificity, to support their incorporation into the criteria at that time to demonstrate optic nerve lesions in patients without a clear history or clinical evidence of optic neuritis[22].

Consequently, neurophysiological studies are not included among the diagnostic tools included in the diagnostic process of routine practice, as opposed to the assessment of CSF. Our study supports these data, as although VEPs, which have been described as highly sensitive for the detection of optic nerve lesions[60], were performed in 64.3% (9 patients), ENG was performed in only 41.9% (6 patients), and SSPs in 28.6% (4 patients).

For all these diagnostic tests, the proportion of detected alterations was really low or practically null, as alterations were only detected in VEPs for 2 patients, and in SSPs for 1 patient, whereas no alterations were described with ENG. Even so, and although the sample of our patients is really small, it has been described in the literature that the neurophysiological studies that most often detect alterations are VEPs, as observed in our data.

Our study could provide data for future lines of research evaluating this type of studies as diagnostic tests in patients with pseudotumoral lesions since in the literature described to date, there are no data available on neurological studies performed in these patients.

Initially, the data from our study would imply a low proportion of alterations in neurophysiological studies in patients who debut with a pseudotumoral form of the disease. Still, due to the low sample size, these data should be interpreted cautiously.

8.10. Brain biopsy research

In our patients, brain biopsy to clarify the differential diagnosis of an intracerebral mass suggestive of a pseudotumoral lesion (detected by MRI) was only necessary for 21.4% of patients, which is in line with the previous studies[69,71,93]. In all cases, the results obtained served to confirm the suspected MS as the cause of the lesión due to the demonstration of characteristic features of inflammatory demyelinating disease.

Although the number of brain biopsies performed for the definitive diagnosis of a pseudotumoral lesion is low, providing a better characterization of both these lesions and the patients who develop them, will assist in future to further reducing the need for such invasive procedures, which are associated with a high morbidity rate[68].

8.11. Clinical evolution research

Throughout the retrospective evaluation of our patient's medical histories, it should be noted that the duration of this evaluation was very variable, as each patient had a different follow-up time, having been diagnosed at different times since 1996. Therefore, although the mean duration in months was 63.79 (±82.905), the median was 12 months.

Our study found relapses in 28.6% of patients, with a mean number of relapses of 1.5 (±0.577). However, it should be noted that the impossibility to perform a standardised annual rate, due to the different time length of the retrospective analysis, makes comparison with previous studies impossible.

As described by previous studies[73], there is a tendency toward developed clinically definite MS in these patients. This finding is consistent with our results, as all of the patients eventually met the diagnostic criteria for MS (78.6% for RRMS and 21.4% for CIS).

Independently of the recovery from the first clinical flare-up described above, the improvement in the EDSS scale score was assessed at the last available clinical review for each patient. Thus, although again, it is not a parameter evaluated at the same time for each of them, the median EDSS score was 1.5 points, showing an improvement compared to that observed in the first clinical episode (3 points). This reduction in EDSS score at the last clinical review for which data were available, has been described before by different studies[69,73], and therefore our results are in line.

As in previous studies, most of our patients (71.4%) started DMT as a chronic treatment of the disease. The different treatments administered coincide with those described as available by current literature[1,102], with fingolimod being the most frequently administered in our patients (30%); but also noted a wide variability in the different drugs selected for each one.

This tendency towards the onset of chronic DMT would be directly related to the decrease in the EDSS score in our patients. Therefore, these data suggest that, overall, presenting with a pseudotumoral form of MS at disease onset does not imply a worse prognostic significance, as many people experience a significant recovery of the deficits presented during the first clinical episode; and also the mean number of relapses found during the retrospective analysis of patient medical files is not higher than that of MS patients in general clinical practice. These are consistent with hypotheses by previous studies suggesting that patients presenting with a pseudotumoral lesion as a form of multiple sclerosis presentation, have a comparatively benign course compared to those presenting with another form of the disease[103,104].

8.12. RMN evolution research

Regarding the evolution of pseudotumoral lesions in MRI, although it should be noted that the evolution time from the first MRI performed to the last available follow-up MRI is different for each patient; all lesions presented by our patients showed a decrease in MRI volume, any of them showed enhancement after endovenous administration of contrast a and no new pseudotumoral lesions were detected in any of our patients; which is consistent with current literature[76,77].

8.13. Other analysis research

Although not the aim of our work, we assessed using Spearman's p coefficient whether the size of the pseudotumoral lesions correlated with demographic, clinical or radiological variables. In our study, a statistically significant correlation (r=0.78, p=0.0) was found between the longest diameter of the pseudotumoral lesion and the disability experienced by our patients, measured by the EDSS scale. This particular association suggests that the larger the size of the pseudotumoral lesions, the greater the disability experienced by patients during the first clinical episode, and therefore, the more severe the symptoms presented.

Similarly, in our study, a statistically significant correlation (r=0.69, p=0.0484) was found (p=0.0484) between the largest diameter of the pseudotumoral lesion and the levels of acute-phase reactants such as ESR observed in our patients. This association has been described previously in the cross-sectional study by Nazeri et al, which included 80 patients with a definitive diagnosis of multiple sclerosis, found an association between ESR levels and lesions showing MRI enhancement after intravenous contrast administration, as previously described.

8.14. Limitations

Our study included a relatively low number of patients (n=14) considering the overall prevalence of MS in Spain. Moreover, the data collected are extracted from the MS database of a single tertiary hospital centre; therefore, this may be a source of potential bias when it comes to identifying different trends among the characteristics of the patients included in our study. Even so, it is one of the longest series described in the literature, and the study of a wide range of demographic, clinical and radiological variables allows for a detailed characterisation of the sample.

Furthermore, regarding the retrospective individualised assessment of the patients, the duration of the retrospective study was different in each case, as the patients were diagnosed at different times since 1996. Consequently, there is a significant impact on disease monitoring and prognosis, as the therapeutic arsenal has multiplied over the last 20 years. It implies that the natural history of the disease is not fully comparable between different individuals.

The limited number of patients also complicates the performance of comparative studies across the variables studied. Although not being one of the objectives of the study, further research aimed at finding out the potential relationships between the data described would be desirable.

Finally, as this was a retrospective research study, there may be biases in the collection of information or in some of the characteristics analysed as a consequence of the fact that the diagnostic studies and follow-up of each patient were not carried out uniformly in each one of them. Therefore, it also leads to the absence of specific data in some of the variables studied.

As a result of the previously related, and although most of the demographic, clinical and radiological data coincide with the literature described to date, our results should be interpreted with caution, as we cannot confirm that these results are statistically significant when extrapolated to the general population of MS patients with this type of lesion. Future studies with larger samples and multicentre studies that confirm the results described would be desirable.

9. Conclusions

Multiple sclerosis is a chronic and incapacitating disease that particularly affects young patients and may lead to significant disability.

Regarding pseudotumoral lesions in particular, although infrequent, constitute one of the possible forms presenting in some patients during the first clinical episode suggestive of multiple sclerosis, so it is important to know their characteristics and prognostic significance.

Moreover, pseudotumoral lesions represent a diagnostic challenge due to their characteristics, especially if they occur early in the course of the disease. This implies that a detailed knowledge of both lesions characterization and the main processes that can mimic these lesions, is necessary.

Firstly, the most frequent forms of presentation of pseudotumoral lesions are motor or sensory deficits and the predominant location for them is periventricular. In addition, the radiological pattern of incomplete ring-like enhancement after intravenous contrast administration is the most prevalent form of appearance of these lesions in neuroimaging (MRI) studies.

On the other hand, the concomitant occurrence of typical MS lesions combined with pseudotumoral lesions supports the inflammatory demyelinating etiology of these lesions.

A high percentage of patients with pseudotumoral lesions require hospital admission, or even brain biopsy, to establish the diagnosis of the disease.

Brain biopsy enables us to confirm the demyelinating inflammatory origin of these lesions in whom it is performed.

In terms of treatment, intravenous methylprednisolone boluses are the preferred treatment in the acute phase. Furthermore, follow-up of most patients show a conversion to MS according to McDonald criteria, and consequently, disease-modifying treatment is initiated in the majority of them.

Focusing on the neuroradiological evolution, most of the lesions show a decrease in largest diameter, volume and inflammatory activity ceases, denoting the cessation of inflammatory activity in the lesions. Generally, no recurrences of similar lesions are described.

Finally, concerning clinical evolution; the prognosis, the number of relapses described and the significant recovery of the disability experienced, measured by the Kurtzke´s expanded disability scale score; support that the debut of the disease with a pseudotumoral lesion would suppose a benign course compared to other forms of the disease. Nevertheless, future studies with larger samples and multicentre studies that confirm our results described would be desirable.

10. Glossary

- **Ab:** Antibody
- **Ag:** Antigen
- **BMI:** Body Mass Index
- **CIS:** Clinically Isolated Syndrome
- **CNS:** Central Nervous System
- **CRP:** C-Reactive Protein
- **CSF:** Cerebrospinal Fluid
- **DIR:** Double inversion recovery
- **DIS:** Dissemination in space
- **DIT:** Dissemination in time
- **DMT:** Disease-modifying therapies
- **DMT**: Disease-modifying therapy
- **EBV:** Epstein-Barr virus
- **EDSS:** Kurtzke´s Expanded Disability Scale Score
- **ENG:** Electroneurography
- **ESR:** Erythrocyte Sedimentation Rate
- **Ig:** Immunoglobulin
- **IgG:** Immunoglobulin G
- **IQR:** Interquartile range
- **MEPs**: Multimodal evoked potentials
- **MRI:** Magnetic Resonance Imaging
- **MS:** Multiple Sclerosis
- **OCBs:** Oligoclonal bands.
- **PPMS:** Primary progressive MS
- **RIS:** Radiologically Isolated Syndrome
- **RRMS:** Relapsing-remitting MS
- **SD:** Standard Deviation
- **SPMS:** Secondary progressive MS
- **SSEPs:** Somatosensory Evoked Potentials
- **UVB:** Ultraviolet B Light
- **VEPs:** Visual Evoked Potentials

11. Appendix 1

<table>
<tr><th colspan="4">Disease-course definitions</th></tr>
<tr><td>CIS</td><td colspan="3">Referring to a first episode of inflammatory demyelination in CNS that shows characteristics of inflammatory demyelination that could be MS, but has yet to fulfill criteria of DIT. CIS, if subsequently clinically active and fulfilling current MS diagnostic criteria, becomes RRMS.</td></tr>
<tr><td rowspan="4">RRMS</td><td colspan="3">Episodes of acute worsening of neurologic functioning (new symptoms or the worsening of existing symptoms) with total or partial recovery and no apparent progression of disease. RRMS can be further characterized as:</td></tr>
<tr><td>Active: showing evidence of new relapses, new gadolinium enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time period.</td><td rowspan="3">AND</td><td>Worsening: defined as increased disability confirmed over a specified time period following a relapse.</td></tr>
<tr><td>OR</td><td>OR</td></tr>
<tr><td>Not active: showing no evidence of disease activity.</td><td>Stable: defined no evidence of increasing disability over a specified time period following a relapse</td></tr>
<tr><td rowspan="4">PPMS</td><td colspan="3">Steadily worsening neurologic function from the onset of symptoms without initial relapses or remissions. PPMS can be further characterized as:</td></tr>
<tr><td>Active: showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time period.</td><td rowspan="3">AND</td><td>With progression: evidence of disease worsening on an objective measure of change[a], confirmed over a specified period of time, with or without relapses.</td></tr>
<tr><td>OR</td><td>OR</td></tr>
<tr><td>Not active: showing no evidence of disease activity.</td><td>Without progression: no evidence of disease worsening on an objective measure of change[a] over a specified period of time.</td></tr>
<tr><td rowspan="4">SPMS</td><td colspan="3">Following an initial relapsing remitting course, the disease becomes more steadily progressive, with or without relapses. SPMS can be further characterized as:</td></tr>
<tr><td>Active: showing evidence of new relapses, new gadolinium-enhancing lesions and/or new or enlarging T2 lesions on MRI over a specified time period.</td><td rowspan="3">AND</td><td>With progression: evidence of disease worsening on an objective measure of change[a], confirmed over a specified period of time, with or without relapses.</td></tr>
<tr><td>OR</td><td>OR</td></tr>
<tr><td>Not active: showing no evidence of disease activity.</td><td>Without progression: no evidence of disease worsening on an objective measure of change[a], over a specified period of time</td></tr>
</table>

Table 13: Disease-course definitions according to Lublin et al., Neurology 2014[21]*. [a] For example, EDSS. Adapted from Klineova et al., Cold Spring Harbor Perspectives in Medicine 2018*[18]*.*

13. Appendix 2

Patient	Sex	Age at PL detection	Symptoms	EDSS onset	BOC	Biopsy	Acute treatment	Recovery	PL	Largest diameter (mm) and area (cm^2)	Location	Contrast enhancement pattern	MS typical plaques	Duration of retrospective study (months)	Relapses	Clinical Phenotype	DMT	EDSS last revision
1	F	23	Motor deficit Sensitive deficit Cerebellar symptoms	3	+	No	Methylprednosolone 1 gr I.V– 5 days	Partial	2	48 mm 6.3 cm2	Periventricular	Incomplete ring-like	10-50	8	1	RRMS	Ocrelizumab	2
2	F	43	Cerebellar symptoms	1,5	+	No	Methylprednosolone 1 gr I.V – 5 days	Complete	1	36 6.51 cm2	Subcortical	Incomplete ring-like	>50	15	0	RRMS	Fingolimod	1
3	M	29	Motor deficit Sensitive deficit Cerebellar symptoms Brain stem symptoms Ataxia	4,5	+	No	Methylprednosolone 1 gr I.V – 5 days	Partial	1	37,42 11 cm2	Juxtacortical	Complete ring-like	>50	12	0	RRMS	Natalizumab	4
4	F	40	Motor deficit Sensitive deficit Cerebellar symptoms Brain stem symptoms Ataxia	4,5	-	Yes	Methylprednosolone 1 gr I.V – 3 days	Partial	1	28,39 6.33 cm2	Periventricular	Incomplete ring-like	<10	51	0	RRMS	Teriflunomide	3
5	M	44	Cerebellar symptoms Brain stem symptoms Headaches	2,5	+	No	Methylprednosolone 1 gr I.V – 5 days	Partial	1	28,6 5.96 cm2	Periventricular	Incomplete ring-like	10-50	6	1	RRMS	Dimethyl-fumarate	1
6	M	24	Sensitive deficit Brain stem symptoms	2,5	+	No	Methylprednosolone 1 gr I.V – 5 days	Complete	1	28,73 6.3 cm2	Periventricular	Incomplete ring-like	10-50	13	0	RRMS	Dimethyl-fumarate	1
7	M	22	Motor deficit Headaches	2	-	No	Methylprednosolone 1 gr I.V – 7 days	Complete	1	28,73 6.48 cm2	Periventricular	Incomplete ring-like	0	40	0	CIS	No data	0
8	M	32	Sensitive deficit Cerebellar symptoms Brain stem symptoms	2	-	No	Methylprednosolone 1 gr I.V – 3 days	Complete	1	26,15 4.97 cm2	Infratentorial	Nodular	10-50	90	0	RRMS	No data	1,5

13. Appendix 2

Patient	Sex	Age at PL detection	Symptoms	EDSS onset	BOC	Biopsy	Acute treatment	Recovery	PL	Largest diameter (mm) and area (cm^2)	Location	Contrast enhancement pattern	MS typical plaques	Duration of retrospective study (months)	Relapses	Clinical Phenotype	DMT	EDSS last revision
9	F	40	Motor deficit Sensitive deficit Brain stem symptoms	4	+	No	Methylprednosolone 1 gr I.V – 3 days	Partial	1	26,59 5.44 cm2	Periventricular	Nodular	10-50	16	0	CIS	No data	3
10	M	28	Motor deficit Sensitive deficit	3,5	-	No	Methylprednosolone 1 gr I.V – 3 days	Partial	1	35 No data	Periventricular	Complete ring-like	No data	309	0	CIS	No data	1,5
11	M	48	Motor deficit Sensitive deficit Aphasia	2,5	-	Yes	Methylprednosolone 1 gr I.V – 5 days	Partial	1	34,14 9. 16 cm2	Periventricular	Complete ring-like	10-50	143	0	RRMS	Fingolimod	1
12	F	26	Motor deficit Sensitive deficit Headaches Visual deficit	6	+	No	Methylprednosolone 1 gr I.V – 5 days	Partial	1	42 6.4 cm2	Subcortical	Nodular	<10	120	2	RRMS	Natalizumab	0
13	M	47	Motor deficit Brain stem symptoms Ataxia	3	-	No	Methylprednosolone 1 gr I.V – 5 days	Complete	2	28 7.5 cm2	Brainstem	Nodular	10-50	48	0	RRMS	Fingolimod	2
14	F	25	Motor deficit Sensitive deficit Cerebellar symptoms Headaches	3	-	Yes	No administered	Partial	1	38 10 cm2	Periventricular	Complete ring-like	<10	22	2	RRMS	Ocrelizumab	4

Table 14: Main data recorded for the 14 patients belonging to MS database of the Neurology Department of the Marqués de Valdecilla University Hospital (Santander, Cantabria); who met the inclusion criteria for our study.

13. Bibliography

1. Reich DS, Lucchinetti CF, Calabresi PA. Multiple Sclerosis. *New England Journal of Medicine*. 2018;378(2):169-180. doi:10.1056/NEJMra1401483

2. Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*. 2017;390(10100):1211-1259. doi:10.1016/S0140-6736(17)32154-2

3. Ghasemi N, Razavi Sh, Nikzad E. Multiple sclerosis: pathogenesis, symptoms, diagnoses and cell-based therapy. *Cell J*. 2017;19:1-10.

4. Stys PK, Tsutsui S. Recent advances in understanding multiple sclerosis. *F1000Res*. 2019;8:2100. doi:10.12688/f1000research.20906.1

5. Tafti D, Ehsan M, Xixis KL. *Multiple Sclerosis*.; 2022.

6. Yousem MBA DM, Zimmerman RD, Grossman RI. Neuroradiology: The Requisites, 3rd ed. *Radiology*. 2011;261(1):68-68. doi:10.1148/radiol.11114024

7. Tarlinton RE, Martynova E, Rizvanov AA, Khaiboullina S, Verma S. Role of Viruses in the Pathogenesis of Multiple Sclerosis. *Viruses*. 2020;12(6):643. doi:10.3390/v12060643

8. Lassmann H. Multiple Sclerosis Pathology. *Cold Spring Harbor Perspectives in Medicine*. 2018;8(3):a028936. doi:10.1101/cshperspect.a028936

9. Lassmann H. Pathogenic Mechanisms Associated With Different Clinical Courses of Multiple Sclerosis. *Frontiers in Immunology*. 2019;9. doi:10.3389/fimmu.2018.03116

10. Huang WJ, Chen WW, Zhang X. Multiple sclerosis: Pathology, diagnosis and treatments. *Experimental and Therapeutic Medicine*. 2017;13(6):3163-3166. doi:10.3892/etm.2017.4410

11. Cree BAC, Gourraud P, Oksenberg JR, et al. Long-term evolution of multiple sclerosis disability in the treatment era. *Annals of Neurology*. 2016;80(4):499-510. doi:10.1002/ana.24747

12. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle and environmental risk factors for multiple sclerosis. *Nature Reviews Neurology*. 2017;13(1):25-36. doi:10.1038/nrneurol.2016.187

13. Adamczyk- Sowa M, Gębka- Kępińska B, Kępiński M. MULTIPLE SCLEROSIS – RISK FACTORS. *Wiadomości Lekarskie*. 2020;73(12):2677-2682. doi:10.36740/WLek202012122

14. Ascherio A. Environmental factors in multiple sclerosis. *Expert Review of Neurotherapeutics*. 2013;13(sup2):3-9. doi:10.1586/14737175.2013.865866

15. Houen G, Trier NH, Frederiksen JL. Epstein-Barr Virus and Multiple Sclerosis. *Frontiers in Immunology*. 2020;11. doi:10.3389/fimmu.2020.587078

16. Alfredsson L, Olsson T. Lifestyle and Environmental Factors in Multiple Sclerosis. *Cold Spring Harbor Perspectives in Medicine*. 2019;9(4):a028944. doi:10.1101/cshperspect.a028944

17. Simone IL, Carrara D, Tortorella C, Ceccarelli A, Livrea P. Early onset multiple sclerosis. *Neurological Sciences*. 2000;21(0):S861-S863. doi:10.1007/s100720070027

18. Klineova S, Lublin FD. Clinical Course of Multiple Sclerosis. *Cold Spring Harbor Perspectives in Medicine*. 2018;8(9):a028928. doi:10.1101/cshperspect.a028928

19. Karunesh Ganguly M. The Diagnosis of Multiple Sclerosis. *AMA Journal of Ethics*. 2006;8(2):93-96. doi:10.1001/virtualmentor.2006.8.2.cprl1-0602

20. de Sa JCC, Airas L, Bartholome E, et al. Symptomatic therapy in multiple sclerosis: a review for a multimodal approach in clinical practice. *Therapeutic Advances in Neurological Disorders*. 2011;4(3):139-168. doi:10.1177/1756285611403646

21. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: The 2013 revisions. *Neurology*. 2014;83(3):278-286. doi:10.1212/WNL.0000000000000560

22. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology*. 2018;17(2):162-173. doi:10.1016/S1474-4422(17)30470-2

23. *Núñez Moreno L, Corbalán Sevilla MT, Vara Cilla R, Vega Villar J, Sánchez Reyes JM, Cobos Alonso J. Manifestaciones Radiológicas de La Esclerosis Múltiple. Seram [Internet]. 22 de Noviembre de 2018 [Citado 05 de Mayo de 2022];. Disponible En: Https://Piper.Espacio-Seram.Com/Index.Php/Seram/Article/View/2503*.

24. Kremenchutzky M, Rice GPA, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of multiple sclerosis: a geographically based study 9: Observations on the progressive phase of the disease. *Brain*. 2006;129(3):584-594. doi:10.1093/brain/awh721

25. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 Revisions to the McDonald criteria. *Annals of Neurology*. 2011;69(2):292-302. doi:10.1002/ana.22366

26. National Multiple Sclerosis Society. Types of MS. Accessed May 5, 2022. https://www.nationalmssociety.org/What-is-MS/Types-of-MS

27. *Institute of Medicine (US) Committee on Multiple Sclerosis: Current Status and Strategies for the Future; Joy JE, Johnston RB Jr., Editors. Multiple Sclerosis: Current Status and Strategies for the Future. Washington (DC): National Academies Press (US); 2001. 2, Clinical and Biological Features.* doi:10.17226/10031

28. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1444. doi:10.1212/WNL.33.11.1444

29. Meyer-Moock S, Feng YS, Maeurer M, Dippel FW, Kohlmann T. Systematic literature review and validity evaluation of the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Functional Composite (MSFC) in patients with multiple sclerosis. *BMC Neurology*. 2014;14(1):58. doi:10.1186/1471-2377-14-58

30. Cree BAC, Arnold DL, Chataway J, et al. Secondary Progressive Multiple Sclerosis. *Neurology*. 2021;97(8):378-388. doi:10.1212/WNL.0000000000012323

31. Inojosa H, Proschmann U, Akgün K, Ziemssen T. A focus on secondary progressive multiple sclerosis (SPMS): challenges in diagnosis and definition. *Journal of Neurology*. 2021;268(4):1210-1221. doi:10.1007/s00415-019-09489-5

32. Coret F, Pérez-Miralles FC, Gascón F, et al. Onset of secondary progressive multiple sclerosis is not influenced by current relapsing multiple sclerosis therapies. *Mult Scler J Exp Transl Clin*. 2018;4(2):2055217318783347. doi:10.1177/2055217318783347

33. Romo-Sanchez M, Nelson F, Sangrador-Deitos MV. Resonancia Magnética en Esclerosis Múltiple: un repaso de los principios básicos de imagenología y guías prácticas de uso. *Archivos de Neurociencias*. 2021;25(4). doi:10.31157/archneurosciencesmex.v25i4.229

34. Saldívar-Uribe C, de La Portilla-Villanueva MA, Esau-Mendoza-García A. *Comparar La Actividad de Las Lesiones de Esclerosis Múltiple (EM) al Minuto y a Los 20 Minutos de La Aplicación de Gadolinio En La Resonancia Magnética (RM) de Cerebro*. Vol 153.; 2017. www.anmm.org.mx

35. Rovira À, Wattjes MP, Tintoré M, et al. MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—clinical implementation in the diagnostic process. *Nature Reviews Neurology*. 2015;11(8):471-482. doi:10.1038/nrneurol.2015.106

36. Wattjes Mike P, Rovira Àlex, Miller David, et al. MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis—establishing disease prognosis and monitoring patients. *Nature Reviews Neurology*. 2015;11(10):597-606. doi:10.1038/nrneurol.2015.157

37. Guarnizo Á, Bermúdez S, Torres Ó, Nassar A, Torres C. *DIAGNOSIS AND EVALUATION OF MULTIPLE SCLEROSIS: WHAT THE RADIOLOGIST SHOULD KNOW AND REPORT. CURRENT CONCEPTS*. Vol 27.; 2016.

38. Ge Y. Multiple sclerosis: the role of MR imaging. *AJNR Am J Neuroradiol*. 27(6):1165-1176.

39. Hemond CC, Bakshi R. Magnetic Resonance Imaging in Multiple Sclerosis. *Cold Spring Harbor Perspectives in Medicine*. 2018;8(5):a028969. doi:10.1101/cshperspect.a028969

40. Rovira A, Tintoré M, Álvarez-Cermeño JC, Izquierdo G, Prieto JM. Recomendaciones para la utilización e interpretación de los estudios de resonancia magnética en la esclerosis múltiple. *Neurología*. 2010;25(4):248-265. doi:10.1016/j.nrl.2010.03.001

41. Wattjes MP, Steenwijk MD, Stangel M. MRI in the Diagnosis and Monitoring of Multiple Sclerosis: An Update. *Clinical Neuroradiology*. 2015;25(S2):157-165. doi:10.1007/s00062-015-0430-y

42. Okuda DT, Siva A, Kantarci O, et al. Radiologically Isolated Syndrome: 5-Year Risk for an Initial Clinical Event. *PLoS ONE*. 2014;9(3):e90509. doi:10.1371/journal.pone.0090509

43. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: The radiologically isolated syndrome. *Neurology*. 2009;72(9):800-805. doi:10.1212/01.wnl.0000335764.14513.1a

44. Filippi M, Preziosa P, Banwell BL, et al. Assessment of lesions on magnetic resonance imaging in multiple sclerosis: practical guidelines. *Brain*. 2019;142(7):1858-1875. doi:10.1093/brain/awz144

45. Tillema JM, Pirko I. Neuroradiological evaluation of demyelinating disease. *Therapeutic Advances in Neurological Disorders*. 2013;6(4):249-268. doi:10.1177/1756285613478870

46. Tomassini V, Palace J. Multiple sclerosis lesions: insights from imaging techniques. *Expert Review of Neurotherapeutics*. 2009;9(9):1341-1359. doi:10.1586/ern.09.83

47. Aljure V de J, Pulido-Arias EA, Rodríguez-Monroy JA, Rodríguez-Mateus MN, Ramos-Hernández JA. Diagnóstico diferencial de lesiones cerebrales con realce en anillo en tomografía computarizada y resonancia magnética. *Duazary*. 2016;13(2):149. doi:10.21676/2389783X.1721

48. Medrano Martorell S, Cuadrado Blázquez M, García Figueredo D, González Ortiz S, Capellades Font J. [Hyperintense punctiform images in the white matter: a diagnostic approach]. *Radiologia (Panama)*. 2012;54(4):321-335. doi:10.1016/j.rx.2011.09.015

49. Bester M, Petracca M, Inglese M. Neuroimaging of Multiple Sclerosis, Acute Disseminated Encephalomyelitis, and Other Demyelinating Diseases. *Seminars in Roentgenology*. 2014;49(1):76-85. doi:10.1053/j.ro.2013.09.002

50. Miki Y. Magnetic resonance imaging diagnosis of demyelinating diseases: An update. *Clinical and Experimental Neuroimmunology*. 2019;10(S1):32-48. doi:10.1111/cen3.12501

51. Diogo MC, Glatter S, Binder J, Kiss H, Prayer D. The MRI spectrum of congenital cytomegalovirus infection. *Prenatal Diagnosis*. 2020;40(1):110-124. doi:10.1002/pd.5591

52. Wang MM. Chapter 47 - CADASIL. In: Geschwind DH, Paulson HL, Klein C, eds. *Neurogenetics, Part II*. Vol 148. Handbook of Clinical Neurology. Elsevier; 2018:733-743. doi:https://doi.org/10.1016/B978-0-444-64076-5.00047-8

53. Elkholy SF, Sabet MA, Mohammad ME, Asaad REI. Comparative study between double inversion recovery (DIR) and fluid-attenuated inversion recovery (FLAIR) MRI sequences for detection of cerebral lesions in multiple sclerosis. *Egyptian Journal of Radiology and Nuclear Medicine*. 2020;51(1):188. doi:10.1186/s43055-020-00298-9

54. Saade C, Bou-Fakhredin R, Yousem DM, Asmar K, Naffaa L, El-Merhi F. Gadolinium and Multiple Sclerosis: Vessels, Barriers of the Brain, and Glymphatics. *American Journal of Neuroradiology*. 2018;39(12):2168-2176. doi:10.3174/ajnr.A5773

55. Jarmi V, de Elías R, Kiener O, Villate S, Vrech C, Barzón S. Bandas oligoclonales: aporte e interpretación en pacientes con sospecha de esclerosis multiple. *Acta Bioquím Clín Latinoam*. 2015;49(2):257-265. Accessed May 5, 2022. http://www.scielo.org.ar/scielo.php?script=sci_arttext&pid=S0325-29572015000200009&lng=es.

56. Nieto A, Anguiano O, Ordoñez G. Bandas oligoclonales en líquido cefalorraquídeo de pacientes con esclerosis múltiple. *Arch Neurocien (Mex)*. 2013;18(4):194-200.

57. lo Sasso B, Agnello L, Bivona G, Bellia C, Ciaccio M. Cerebrospinal Fluid Analysis in Multiple Sclerosis Diagnosis: An Update. *Medicina (B Aires)*. 2019;55(6):245. doi:10.3390/medicina55060245

58. Ganguly K. The Diagnosis of Multiple Sclerosis. *AMA Journal of Ethics*. 2006;8(2):93-96. doi:10.1001/virtualmentor.2006.8.2.cprl1-0602

59. Djuric V, Djuric S, Jolic M, Stamenovic J. Diagnostic value of multimodal evoked potentials in patients with multiple sclerosis. *International Congress Series*. 2005;1278:160-162. doi:10.1016/j.ics.2004.12.015

60. Calugaru L, Calugaru GT, Calugaru OM. Evoked Potentials in Multiple Sclerosis Diagnosis and Management. *Current Health Sciences Journal*. 2016;42(4). doi:10.12865/CHSJ.42.04.08

61. Janáky M, Jánossy Á, Horváth G, Benedek G, Braunitzer G. VEP and PERG in patients with multiple sclerosis, with and without a history of optic neuritis. *Documenta Ophthalmologica*. 2017;134(3):185-193. doi:10.1007/s10633-017-9589-7

62. López-Dorado A, Pérez J, Rodrigo MJ, et al. Diagnosis of multiple sclerosis using multifocal ERG data feature fusion. *Information Fusion*. 2021;76:157-167. doi:10.1016/j.inffus.2021.05.006

63. Rodriguez-Mena D, Almarcegui C, Dolz I, et al. Electropysiologic Evaluation of the Visual Pathway in Patients With Multiple Sclerosis. *Journal of Clinical Neurophysiology*. 2013;30(4):376-381. doi:10.1097/WNP.0b013e31829d75f7

64. Noyes K, Weinstock-Guttman B. Impact of diagnosis and early treatment on the course of multiple sclerosis. *Am J Manag Care*. 2013;19(17 Suppl):s321-31.

65. Calabresi PA. Diagnosis and management of multiple sclerosis. *Am Fam Physician*. 2004;70(10):1935-1944.

66. Berger JR. Functional improvement and symptom management in multiple sclerosis: clinical efficacy of current therapies. *Am J Manag Care*. 2011;17 Suppl 5 Improving:S146-53.

67. Seewann A, Enzinger C, Filippi M, et al. MRI characteristics of atypical idiopathic inflammatory demyelinating lesions of the brain. *Journal of Neurology*. 2008;255(1):1-10. doi:10.1007/s00415-007-0754-x

68. Hardy TA. Pseudotumoral demyelinating lesions: diagnostic approach and long-term outcome. *Current Opinion in Neurology*. 2019;32(3):467-474. doi:10.1097/WCO.0000000000000683

69. Mauri-Fábrega L, Díaz-Sánchez M, Casado-Chocán JL, Uclés-Sánchez AJ. Pseudotumoral Forms of Multiple Sclerosis: Report of 14 Cases and Review of the Literature. *European Neurology*. 2014;72(1-2):72-78. doi:10.1159/000358385

70. Patriarca L, Torlone S, Ferrari F, et al. Is size an essential criterion to define tumefactive plaque? MR features and clinical correlation in multiple sclerosis. *The Neuroradiology Journal*. 2016;29(5):384-389. doi:10.1177/1971400916665385

71. Sánchez P, Meca-Lallana V, Barbosa A, Manzanares R, Palmí I, Vivancos J. Tumefactive demyelinating lesions of 15 patients: Clinico-radiological features, management and review of the literature. *Journal of the Neurological Sciences*. 2017;381:32-38. doi:10.1016/j.jns.2017.08.005

72. Comi G. Multiple sclerosis: pseudotumoral forms. *Neurological Sciences*. 2004;25(S4):s374-s379. doi:10.1007/s10072-004-0345-x

73. Lucchinetti CF, Gavrilova RH, Metz I, et al. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. *Brain*. 2008;131(7):1759-1775. doi:10.1093/brain/awn098

74. Xia L, Lin S, Wang Z cheng, et al. Tumefactive demyelinating lesions: nine cases and a review of the literature. *Neurosurgical Review*. 2009;32(2):171-179. doi:10.1007/s10143-009-0185-5

75. Altintas A, Petek B, Isik N, et al. Clinical and radiological characteristics of tumefactive demyelinating lesions: follow-up study. *Multiple Sclerosis Journal*. 2012;18(10):1448-1453. doi:10.1177/1352458512438237

76. Jeong IH, Kim SH, Hyun JW, Joung A, Cho HJ, Kim HJ. Tumefactive demyelinating lesions as a first clinical event: Clinical, imaging, and follow-up observations. *Journal of the Neurological Sciences*. 2015;358(1-2):118-124. doi:10.1016/j.jns.2015.08.034

77. Sarbu N, Shih RY, Jones R v., Horkayne-Szakaly I, Oleaga L, Smirniotopoulos JG. White Matter Diseases with Radiologic-Pathologic Correlation. *RadioGraphics*. 2016;36(5):1426-1447. doi:10.1148/rg.2016160031

78. Bastianello S, Pichiecchio A, Spadaro M, et al. Atypical multiple sclerosis: MRI findings and differential diagnosis. *Neurological Sciences*. 2004;25(S4):s356-s360. doi:10.1007/s10072-004-0340-2

79. Lin X, Li H. Obesity: Epidemiology, Pathophysiology, and Therapeutics. *Frontiers in Endocrinology*. 2021;12. doi:10.3389/fendo.2021.706978

80. Wingerchuk DM. Smoking: effects on multiple sclerosis susceptibility and disease progression. *Therapeutic Advances in Neurological Disorders*. 2012;5(1):13-22. doi:10.1177/1756285611425694

81. Baena Díez JM, del Val García JL, Tomàs Pelegrina J, et al. Epidemiología de las enfermedades cardiovasculares y factores de riesgo en atención primaria. *Revista Española de Cardiología*. 2005;58(4):367-373. doi:10.1157/13073893

82. Hedstrom AK, Baarnhielm M, Olsson T, Alfredsson L. Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis. *Neurology*. 2009;73(9):696-701. doi:10.1212/WNL.0b013e3181b59c40

83. Marrie RA, Horwitz RI. Emerging effects of comorbidities on multiple sclerosis. *The Lancet Neurology*. 2010;9(8):820-828. doi:10.1016/S1474-4422(10)70135-6

84. Marrie RA. Autoimmune disease and multiple sclerosis: Methods, methods, methods. *Lancet Neurology*. 2007;6(7):575-576.

85. Magyari M, Koch-Henriksen N, Pfleger CC, Sørensen PS. Gender and autoimmune comorbidity in multiple sclerosis. *Multiple Sclerosis Journal*. 2014;20(9):1244-1251. doi:10.1177/1352458514521515

86. Matías-Guiu J, Porta-Etessam J, Mateos V, Díaz-Insa S, Lopez-Gil A, Fernández C. One-year prevalence of migraine in Spain: A nationwide population-based survey. *Cephalalgia*. 2011;31(4):463-470. doi:10.1177/0333102410382794

87. *Garrido Cumbrera M, Gálves Ruiz D, Braçe O, Nieblas Rosado MI, Delgado Domínguez CJ, Colomina I, et al. Impacto y Situación de La Migraña En España: Atlas 2018. (Universidad de Sevilla, Ed.). AEMICE; 2018. Available at. Https://Editorial.Us.Es/Es/Detalle-Libro/720013/Impacto-y-Situacion-de-La-Migrana-En-Espana-Atlas-2018*. AEMICE.

88. Ruiz M, León C, Castillo J, Martínez M, Sánchez S, Quintela E. Distribución por diagnósticos de las cefaleas que acuden a los servicios de urgencias de atención primaria. *SEMERGEN - Medicina de Familia*. 2010;36(1):10-15. doi:10.1016/j.semerg.2009.10.002

89. Kister I, Caminero AB, Herbert J, Lipton RB. Tension-type Headache and Migraine in Multiple Sclerosis. *Current Pain and Headache Reports*. 2010;14(6):441-448. doi:10.1007/s11916-010-0143-5

90. Gelfand AA, Gelfand JM, Goadsby PJ. Migraine and multiple sclerosis: Epidemiology and approach to treatment. *Multiple Sclerosis and Related Disorders*. 2013;2(2):73-79. doi:10.1016/j.msard.2012.10.003

91. Kister I, Caminero AB, Monteith TS, et al. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. *The Journal of Headache and Pain*. 2010;11(5):417-425. doi:10.1007/s10194-010-0237-9

92. Villani V, Prosperini L, Pozzilli C, Salvetti M, Ciuffoli A, Sette G. The use of ID migraine™ questionnaire in patients with multiple sclerosis. *Neurological Sciences*. 2011;32(2):269-273. doi:10.1007/s10072-010-0443-x

93. Kiriyama T, Kataoka H, Taoka T, et al. Characteristic Neuroimaging in Patients with Tumefactive Demyelinating Lesions Exceeding 30 mm. *Journal of Neuroimaging*. 2011;21(2):e69-e77. doi:10.1111/j.1552-6569.2010.00502.x

94. Inojosa H, Schriefer D, Ziemssen T. Clinical outcome measures in multiple sclerosis: A review. *Autoimmunity Reviews*. 2020;19(5):102512. doi:10.1016/j.autrev.2020.102512

95. Saini V, Nadeem M, Kolb C, et al. Vitamin D: Role in Pathogenesis of Multiple Sclerosis. In: *Multiple Sclerosis*. Elsevier; 2016:127-152. doi:10.1016/B978-0-12-800763-1.00007-5

96. Runia TF, Hop WCJ, de Rijke YB, Buljevac D, Hintzen RQ. Lower serum vitamin D levels are associated with a higher relapse risk in multiple sclerosis. *Neurology*. 2012;79(3):261-266. doi:10.1212/WNL.0b013e31825fdec7

97. Lucas RM, Byrne SN, Correale J, Ilschner S, Hart PH. Ultraviolet radiation, vitamin D and multiple sclerosis. *Neurodegenerative Disease Management*. 2015;5(5):413-424. doi:10.2217/nmt.15.33

98. Simpson S, Blizzard L, Otahal P, van der Mei I, Taylor B. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *Journal of Neurology, Neurosurgery & Psychiatry*. 2011;82(10):1132-1141. doi:10.1136/jnnp.2011.240432

99. Nazeri M, Bazrafshan H, Abolhasani Foroughi A. Serum inflammatory markers in patients with multiple sclerosis and their association with clinical manifestations and MRI findings. *Acta Neurologica Belgica*. Published online April 9, 2021. doi:10.1007/s13760-021-01647-9

100. Aksungar FB, Topkaya AE, Yildiz Z, Sahin S, Turk U. Coagulation status and biochemical and inflammatory markers in multiple sclerosis. *Journal of Clinical Neuroscience*. 2008;15(4):393-397. doi:10.1016/j.jocn.2007.02.090

101. Olsson A, Gustavsen S, Gisselø Lauridsen K, et al. Neutrophil-to-lymphocyte ratio and CRP as biomarkers in multiple sclerosis: A systematic review. *Acta Neurologica Scandinavica*. 2021;143(6):577-586. doi:10.1111/ane.13401

102. McGinley MP, Goldschmidt CH, Rae-Grant AD. Diagnosis and Treatment of Multiple Sclerosis. *JAMA*. 2021;325(8):765. doi:10.1001/jama.2020.26858

103. Kepes JJ. Large focal tumor-like demyelinating lesions of the brain: Intermediate entity between multiple sclerosis and acute disseminated encephalomyelitis? A study of 31 patients. *Annals of Neurology*. 1993;33(1):18-27. doi:10.1002/ana.410330105

104. Hayashi T, Kumabe T, Jokura H, et al. Inflammatory demyelinating disease mimicking malignant glioma. *J Nucl Med*. 2003;44(4):565-569.

14. Acknowledgements

En primer lugar, gracias a todas las personas que fueron incluidas en este análisis y, que sin ellas, nada de esto hubiese sido posible. A todas y cada una de las personas que un día han sido diagnosticados de esclerosis múltiple, cambiando desde entonces sus vidas. En especial a ti, mi ángel, que sin ti todo esto no habría tenido ningún sentido. Mi mayor deseo es que este estudio pueda aportar algo al progreso de la medicina en este ámbito, pudiendo mejorar, aunque sea un poquito, el pronóstico de personas, que desgraciadamente, serán diagnosticadas en el futuro de la misma enfermedad que me cambió la vida, y marcó un antes y un después en el camino de mi futuro profesional.

Por otro lado, gracias a mi familia, mi sustento, los que me han levantado del suelo cuando he caído y los que me han alzado celebrando mis victorias como propias. Sin vosotros no sería la persona que soy ahora. Gracias por enseñarme a luchar cada día, a no rendirme y a perseguir mis sueños. Sois el mayor apoyo que la vida me podría haber regalado, mi casa, mi refugio. En especial, gracias a ti mi niño, por sentir como tuyos mis llantos, por sufrir cuando sentía que no llegaba, por alentarme hasta el último segundo y estar conmigo tantas veces hasta altas horas de la madrugada.

A mis amigas, las de toda la vida y las que aparecieron algo después pero como si lo fuesen, gracias por confiar siempre en mi, por recorrer el mundo conmigo, por estar ahí aunque la distancia nos haya separado estos 6 años, por las horas al teléfono o las videollamadas que me hacían sentiros tan cerca, por las visitas al Norte que me regalasteis... Compartir la vida con vosotras es algo que no se puede describir con palabras, algo por lo que me siento realmente afortunada.

A mis amigos de la carrera, que han convertido esta bonita etapa en algo inolvidable que se quedara en nuestros corazones para siempre. Por todos los momentos vividos, las ilusiones, los llantos, las risas, gracias. Sin vosotros todo esto habría sido imposible. Gracias por todos esos instantes en los que me he sentido pequeñita por estar lejos de casa y habéis conseguido que sienta Santander como otro hogar. Dicen que la amistad no se mide en tiempo, y vosotros sois el claro ejemplo de ello. Aunque sean pocos los años que llevamos juntos, espero seguir con vosotros el resto de mi vida.

Por último, y no por ello menor importante, gracias al Doctor González-Quintanilla y al Doctor Infante, por acompañarme y apoyarme durante la realización de este trabajo que supone el final de una etapa tan importante en mi vida. Vicente, Jon; gracias por confiar en mí, y ayudarme día a día para poder lograr mis objetivos.