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Leonor Manuela Gomes Sousa Marques

White matter lesions in young adults: a diagnostic review

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White matter lesions in young adults: a diagnostic review

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Dra. Joana Cruz Guimarães Ferreira Almeida

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White matter lesions in young adults: a diagnostic review

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Abstract

Multiple sclerosis (MS), an idiopathic inflammatory demyelinating disease (IIDD), is a major cause of neurological disability in young adults. Since early treatment leads to better prognosis, an accurate diagnosis at symptoms onset is needed. This retrospective analysis, conducted in Centro Hospitalar de São João – EPE, included patients with a focal symptom/signal suggestive of an inflammatory/demyelinating process or, alternatively, patients with an asymptomatic inflammatory/demyelinating lesion found on magnetic resonance imaging (MRI). Of the 82 included individuals, clinical definite MS was observed in 25 (30.5%) and clinical isolated syndromes in 27 (32.9%). Other diagnosis (36.6%) comprised non-MS IIDDs, systemic inflammatory diseases with central nervous system (CNS) involvement, CNS vasculitis, chronic relapsing inflammatory optic neuropathy and metabolic disorders. From descriptive analysis, monosymptomatic onset predominated for all and, while non-MS group showed a higher mood disorders and systemic symptoms prevalence, MS group presented higher fatigue and previous neurological events prevalence. Brain MRI findings included T1-hypointense lesions as a major MS feature; absent infratentorial lesions and negative enhancement were more frequent in non-MS group. On spinal MRI, single lesion, extra-cervical and longitudinally extensive lesions were a major finding in non-MS group. On cerebrospinal fluid (CSF) analysis, positive oligoclonal bands (OCB) support a MS diagnosis. Statistical analysis revealed a significant relation between MS and cranial MRI abnormal findings, T1-hypointensity, enhancement and multiple lesions; while, for spinal MRI findings a significant relation was noted for MS and T1-hypointensity and no longitudinally extensive lesions. Finally, the strongest relation was found for the presence of CSF-OCB in MS patients.

White matter lesions, young adults, differential diagnosis, multiple sclerosis, idiopathic inflammatory demyelinating disease, secondary inflammatory disease of central nervous system

Introduction

An acute neurologic deficit in young adults poses a diagnostic challenge for clinicians and often non-multiple sclerosis (non-MS) demyelinating diseases are initially miss-diagnosed. This tendency may result from the findings that an acute neurologic deficit is the first observed symptom in approximately 85% of young adults diagnosed with MS [1]. Notwithstanding, a significant number of patients with clinical and imaging evidence of demyelinating lesion(s) – generally termed clinical isolated syndrome (CIS) – are initially (miss)ascribed a MS "label." This represents a problem because the ability to make an accurate diagnosis as early as possible is important for patient management, counseling and optimal therapy. Here, we have retrospectively analyzed a cohort of patients, from the Centro Hospitalar de São João - EPE (Porto, Portugal), with a first experienced neurological sign or symptom consistent with a central nervous system (CNS) inflammatory demyelinating disease or, alternately, patients with an asymptomatic CNS white matter lesion(s), incidentally found on a neuroaxis magnetic resonance imaging (MRI). Epidemiological, clinical and paraclinical findings were reviewed in order to identify and characterize distinct subsets of patients in the setting of clinical/MRI suspected MS. The work followed other studies that have reviewed clinical and MRI presentations of patients with suspected MS in order to identify distinguishing features that may suggest an alternative diagnosis ("red flags") [2, 3, 4].

Multiple sclerosis is a common chronic disorder of the CNS that is pathologically characterized by areas of inflammatory demyelination, which, over time, spread throughout the CNS. It is the most common non-traumatic cause of neurologic disability in Caucasian young adults, affecting predominantly women between 20 and 45 years of age [5]. In 85% of patients the disease onset is an acute or subacute neurological attack that can be adequately explained by a single white matter lesion [1]. In the last decades, different MS diagnostic schemes have emerged indicating that clinically definite MS (CDMS) diagnosis requires (i) clinical and/or paraclinical evidence displaying involvement of at least two separate areas of the CNS ("dissemination in space" - DIS) and (ii) the occurrence of two different lesions more than one month apart ("dissemination in time" - DIT) [6-9]. Regardless of the applied criteria, MS diagnosis should still remain clinical evaluation-based and, when facing a possible CIS case, the initial step must be the exclusion of a "better explanation" for the clinical syndrome. In fact, all revised criteria on MS has emphasized that MS should only be considered once alternative explanations for the clinical presentation have been ruled out. On this, it´s important to consider that a wide range of demyelinating and non-demyelinating pathologies may mimic MS in presentation, namely: other, non-MS, idiopathic inflammatory demyelinating disease (non-MS IIDD); CNS primary vasculitis; systemic inflammatory diseases with secondary CNS involvement (as neurolupus, neuro-Beçhet disease, neurossarcoidosis, SUSAC syndrome, Sjogren syndrome); metabolic abnormalities (vitamin B12

deficiency, leukodystrophy with axonal spheroids); and, infectious, neoplastic and congenital diseases [2, 10, 11]. Within these possibilities, epidemiological, clinical and paraclinical consensual “red flags” must be pursued in the context of clinically suspected inflammatory demyelinating diseases so to alert for a likely non-MS diagnostic [2]. The diagnostic work up is particularly important in patients with (i) an atypical neurological presentation, (ii) a relapse-remitting clinical profile or (iii) lack of response to the regular MS treatment [12], as well as in those with (iv) associated systemic manifestations, (v) prominent family history and (vi) normal results in MRI, cerebrospinal fluid (CSF) and evoked potential studies [13]. In order to exclude a spectrum of diseases that might be considered in the differential diagnosis of MS, the most useful tools are clinical history and physical examination, MRI scanning, CSF analysis (for total leucocyte count and cell type, total protein and albumin, glucose, serologic testing for infectious agents, culture and CSF immunoelectophoresis) and serum analysis.

In this study the aims are to describe clinical, laboratory and radiological characteristics of young adult patients presenting with a CIS as the first clinical event or with an asymptomatic white matter lesion incidentally found on a MRI ordered by other, non-inflammatory, syndromes. The association between these characteristics and the final diagnosis was explored and, finally, the prevalence and epidemiological characteristics of diagnosed diseases in the studied population were revised.

Methods

Ethics statement

The study was conducted in accordance with the principles expressed in the Declaration of Helsinki and approved by the local ethical committee (Comissão de Ética do Centro Hospitalar de São João – EPE). All medical and/or research professionals involved in the study were asked to sign a responsibility document, as specified by the national ethical committee.

Population sample

The present retrospective study was carried out in Neurology Service of the Centro Hospitalar de São João – EPE, a central hospital that functions as a secondary and tertiary referral center. The population sample under study was composed of young adults between the ages of 18 to 45 years, living in the North of Portugal, which attended the Centro Hospitalar anywhere from January of 2007 until September of 2011 and were hospitalized following a neurological evaluation in a medical office or emergency setting. All patients were diagnosed with a neurological signal or symptom consistent with site specific inflammatory CNS demyelination or, alternatively, with a white matter lesion on MRI study. Initial neurological symptoms were clinically categorized as monofocal or multifocal; further categorization of monofocal symptoms was performed in accordance to Miller DH et al. [2] CIS features as (i) optic nerve, (ii) brain stem/cerebellum, (iii) spinal cord and (iv) cerebral hemispheres symptoms (Suplemmentary Table 1). Clinical isolated syndrome likelihood of signaling an MS diagnosis was not evaluated. Symptoms onset were categorized as acute or progressive. An “acute onset” is here defined as a neurological syndrome that evolves over a 48h period, whereas a “progressive onset” as one that evolves over a 48h to 3-week period. A minimum 24h duration of symptoms was needed for study inclusion. Following these initial inclusion criteria, the medical records and MRI scans of 119 patients from the Neurology Service were reviewed. A total of 37 patients were further excluded due to fulfilling one or more exclusion criteria: (i) MRI scans without white matter lesions, (ii) CNS demyelinating disease with an already established diagnosis, (iii) cerebrovascular disease and (iv) other neurological diseases, as epilepsy and intracranial idiopathic hypertension, all of which could justify the lesions found on neuroaxis MRI scans.

Study variables

Demographic and clinical data for all patients were entered into a database. The following details were recorded based on (and in) accordance to a standardized hospital discharge note

performed by the assistant clinician: (i) basic demographic data [sex, ethnicity, date of birth and age at current (demyelinating) clinical event]; (ii) presenting demyelinating symptoms/signs and associated systemic symptoms; (iii) symptoms onset; (iv) personal history of previous attacks, recent infection (last three months) or vaccination (last six months), past symptoms suggestive of autoimmunity/systemic disease; (v) current medication and (vi) family history of CNS demyelinating diseases, neurodegenerative disorders, brain neoplasms, cerebrovascular diseases in young adults and autoimmunity. A neurological examination was performed for all subjects at the time of hospitalization and at the time of discharge. Paraclinical data was also gathered from clinical records, including (i) brain and/or spinal cord MRI findings, (ii) electrophysiological findings [visual evoked potentials (VEP), brain auditory evoked potentials (BAEP), somatosensory evoked potentials (SSEP)], (iii) laboratory tests, CSF, blood and sera analysis included and (iv) chest x-ray (CXR) or other performed studies according to their clinical relevance. The final diagnosis was established and registered by the expert opinion of the assistant clinician, according to the established criteria at the time of hospitalization (Supplementary Table 2).

MRI scanning

Neuroaxis MRI scans were performed in all patients, in the hospital setting or in ambulatory. Conventional MRI protocols were used: T1 with and without gadolinium enhancement, T2, fluid attenuated inversion recovery (FLAIR) in brain MRI; T1 with and without gadolinium enhancement and T2 in spinal cord MRI. All MRI scans were analyzed by an experienced neuroradiologist and for the present study the report was reviewed for specific details as to the (i) number, (ii) shape, (iii) location, (iv) size, (v) signal characteristics of the lesions and (vi) lesions' enhancement after gadolinium. Whenever applicable, these details were entered into the database.

Blood and cerebrospinal fluid assessments

Serum and CSF samples were analyzed for the presence of oligoclonal bands (OCBs) and IgG index to identify systemic or neurologic inflammatory disease. Samples were classified according to whether the patients had evidence of intrathecal IgG synthesis, evidence of a systemic oligoclonal response with matched bands in the serum and CSF or no evidence of an intrathecal neither systemic oligoclonal IgG response. Additional measurements regarding standard CSF and blood analysis were also performed, namely: (i) glucose, proteins and lactate CSF content; (ii) microbiological CSF and blood analysis; (iii) immunological studies, including antinuclear antibodies (ANAs: anti DNSds included), anti-neutrophil cytoplasmic antibodies (ANCAs: ANCA PR3 and ANCA MPO included), anti-phospholipid antibodies [aPL: anti-β2 glicoprotein I (anti-β2GPI) IgM and IgG, anticardiolipin antibodies (aCL) IgM and IgG included], anti-extractable

nuclear antigens (ENAs: anti-Jo 1, anti-RNP, anti-SCL70, anti-Sm, anti-SSa and anti-SSb included) and serum reumatoid factor (RF); (iv) hematocrit and biochemistry blood analysis; (v) folic acid (vitamin B9) and cobalamin (vitamin B12) assays and (vi) other measurements performed according to individual-specific clinical relevance.

Statistical analysis

Descriptive analysis and chi-square test (based on crosstabs and used to test interdependency of variables) were performed in SPSS.

Results

Sample characterization

The study included a total of 119 patients, of whom 37 were excluded as they fulfilled one or more of the exclusion criteria. Of the excluded patients, 26 (70.3%) were female and 11 (29.7%) were male, with an average age of 28.9±7.1 (18-41) and 33.1±7.5 (21-42) years old, respectively. The most frequent diagnoses of this group were inflammatory diseases without white matter lesions [including idiopathic and systemic disease-associated optic neuritis (Sjogren's syndrome, Behçet disease and Cogan's syndrome)] and patients with previous MS diagnosis (41%). These were followed in frequency by vascular (cerebrovascular disease, ischemic neuropathy and vasculo-neurobehçet) (19%), ophthalmological (16%), infectious [Epstein-Barr Virus (EBV), *Treponema pallidum* and *Brucella* infections included] (8%), other neurological (epilepsy and idiopathic intracranial hypertension included) (8%), toxic/metabolic (5%) and degenerative (pseudoxantoma elasticum) (3%) disorders, all of which without inflammatory/demyelinating lesions described on neuroaxis MRI report.

Apart of the excluded patients, the study included a total of 82 individuals, 53 (64.6%) females and 29 (35.4%) males, with an average age of 30.5±7.1 (19-42) and 31.3±6.1 (21-44) years, respectively. The majority of the patients sought first medical care within the first seven days of symptom development, with a progressive onset described in 57.3% of patients, acute in 39.0% and non-determined in 3.7%. Monofocal presentation was observed in 85.3% of the patients, with spinal cord and optic nerve syndromes being the most frequent (28.0% and 24.4%, respectively), followed by cerebral hemispheres and brain stem/cerebellum (22.0% and 11.0%, respectively); multifocal symptoms were observed in 9.8%. A minor subset of patients (4.9%) presented a non-inflammatory clinical syndrome, although the MRIs from these patients showed lesions that might have an inflammatory/demyelinating etiology [this is known by radiological isolated syndromes (RIS)] (Table 1).

From total patient records, 81 underwent brain MRI, with white matter lesions being described in 76 (93.8%) individuals, and 58 patients had spinal cord MRI, with 40 (69.0%) reporting white matter lesions. From patients with an abnormal brain MRI, 73 (96.1%) presented multiple and 3 (3.9%) a single lesion. From the 40 patients with spinal cord demyelination 19 (47.5%) had multiple lesions, 20 (50.0%) a single lesion and no available data was available for one (2.5%). Longitudinally extensive lesions (LELs, extending along three or more contiguous vertebral segments) were described in 6 of the scans (15.0%). Oligoclonal bands in CSF and serum were available for 76 patients: positive CSF-OCBs were described in 56 (60.5%) with only one patient displaying simultaneous serum-OCBs. IgG index was also available for 59 individuals and, for this cohort, average value was 0.92 ± 0.50 (0.2-2.9). Of the 82 patients, VEP were studied in 63, BAEP

in 4 and SSEP in 30 patients. Abnormal results were detected in 27 (42.9%), 2 (50.0%) and 6 (20.0%) patients, respectively.

Final diagnosis

When the cohort was analyzed attending to the final diagnosis, an IIDD was established for 71 patients (71/82; 86.6%), 45 females (63.4%) and 26 males (36.6%) (female to male ratio of 1.73:1), with an average age of 31.1±6.7 (19-44) years old. From this major group, 52 patients were diagnosed with MS IIDD, namely CDMS (25/82; 30.5%) and CIS (27/82; 32.9%); the remaining 19 were diagnosed with non-MS IIDD, including RIS (4/82; 4.9%), acute disseminated encephalomyelitis (ADEM; 3/82; 3.7%) and other IIDDs (12/82; 14.6%). Radiological isolated syndromes encompassed 4 patients who had evidence of CNS inflammatory demyelinating lesions on brain MRI scans performed by clinical conditions not typically neuro-inflammatory in nature (migraine, Todd´s paresis, somatization disorder and inflammatory orbital symptoms). Other IIDDs included 6 acute myelitis (3 idiopathic and 3 parainfectious), 4 idiopathic optic neuritis and 2 IIDDs cases in whom a definite diagnose was not performed (NA IIDD) (Fig. 1).

From the remaining 11 individuals, 4 (4/82; 4.9%) were discharged with a CNS inflammatory disease, but an etiological diagnose was not performed (NA). A miscellaneous group of disorders comprised the remaining 7 patients (7/82; 8.5%) who were assigned a non-IIDD: 3 diagnosis of systemic inflammatory disease with CNS involvement (neurossarcoidosis, neurolupus and neurobeçhet diseases)(3/82; 3.7%), one of primary CNS vasculitis (1/82; 1.2%), one of probable chronic relapsing inflammatory optic neuropathy (CRION; 1/82; 1.2%), and 2 (male) patients with a metabolic disorder (one leukodystrophy with axonal spheroids and one subacute combined degeneration of spinal cord)(2/82; 2.4%) (Fig. 1).

"Non-MS" Group Characterization

The "non-MS" group [patients with non-MS IIDD, non-IIDD and cases without a definite diagnose (NA)] was comprised of 30 patients, with an average age of 30.8±7.0 years old (20-44) (Supplementary Table 3). The most frequent clinical presentation included optic nerve (33.3%) or spinal cord (30.0%) symptoms, with one (3.3%) patient presenting a clinical multifocal presentation. Symptoms onset was progressive in 16 (53.3%) individuals (Table 1). Clinical records showed, as other presenting symptoms, 2 (6.7%) patients with fatigue (Fig. 2a), 8 (26.7%) with past or present history of mood disorders (Fig. 2b), 9 (30.0%) with previous systemic symptoms (infectious symptoms in last three months, reumathological disease, oral and/or genital ulcers and rash included) (Fig. 2c), and 8 (26.7%) patients with previous neurological events. A positive family history of vascular, neurological and/or reumathological disease was

reported by 9 (30.0%) patients (Fig. 2d). Imaging evidence of brain lesions was detected in 24 (82.8%) of the 29 patients that performed a brain MRI. Specifically, in these, a single T2 hyperintensity was detected in 3 (12.5%) patients, while 21 (87.5%) had multiple lesions. Isolated supratentorial lesions were the most frequent finding (15/24; 62.5%), followed by supratentorial and infratentorial lesions (7/24; 29.2%), and by isolated optic nerve lesions (2/24; 8.3%) (Fig. 3a). In respect to the T1 signal, lesions were T1 hypointense in 6 (25.0%) patients and enhanced after gadolinium in the same frequency (Fig. 3b and 3c). For spinal cord MRI, abnormal results were described in 12 (66.7%) out of the 18 screened patients. Findings included a single T2 hyperintense lesion in 9 (75.0%) patients, with the remaining 3 (25.0%) having multiple lesions with same signal characteristics (Fig. 4b). Cervical levels were the most affected (5/12; 41.7%), followed by dorsal (3/12; 25.0%) and cervical plus dorsal levels (2/12; 16.7%) (Fig. 4a). Longitudinally extensive lesions were found in 5/12 (41.7%) individuals (Fig. 4c), cord swelling in 2/12 (16.7%) and positive enhancement in 6/12 (50.0%). Visual evoked potentials (VEP) were abnormal in 7/19 (36.8%) of patients who performed this electrophysiological exam; 9 patients performed somatosensory (SSEP) and 2 auditory (AEP) evoked potentials, with normal results in both. Available laboratory tests (CSF and serum), showed positive CSF-OCBs in 6 out of 26 patients (23.1%) and an IgG index greater than 0.6 was observed in 7 out of 21 patients (0.62±0.27, 0.30-1.40). None of these individuals had matched OCBs in serum. Average CSF-count of cells was 21.9±51.7 (0-230µL) and average CSF-protein content was 0.52±0.18 (0.10-1.04g/L). Microbiological assays were positive in 6/26 (23.1%) patients, with positive CSF results for cytomegalovirus (CMV; one patient by PCR), EBV (one patient by PCR), enterovirus (2 patients by PCR), human herpes virus 6 (HHV6; one patient by PCR) and *Mycoplasma pneumonia* (one patient by PCR). Five out of 30 patients (16.7%) had a positive immunological study: ANAs in 3, anti-β2GPI in one, anti-PR3 and anti-β2GPI in another one patient.

"MS" Group Characterization

The group comprised 52 subjects of which 27 CIS and 25 CDMS, with an average age of 30.8±6.6 (19-41) year old (Supplementary Table 4). The most frequent presenting symptoms were monofocal and clinically restricted to the spinal cord (14/52; 26.9%), followed by cerebral hemispheres (13/52; 25.0%), optic nerve (10/52; 19.2%) and brain stem/cerebellum (8/52; 15.4%) symptoms. A multifocal presentation was recorded in 7 (13.5%) of the patients and a progressive presentation was the most frequent onset (31/52; 59.6%) (Table 1). Clinical interview records included, as other presenting symptoms or past medical history, 8 (15.4%) patients with fatigue (Fig. 2a), 7 (13.5%) with history of mood disorders (Fig. 2b), 11 (21.2%) with systemic symptoms (mostly of these having a previous infection in the last 3 months, but also some experiencing past or present reumathological symptoms, oral and/or genital ulcers, SICCA symptoms and rash) (Fig. 2c), and 23 (44.2%) individuals with previous neurological events. A

positive family history of vascular, neurological and/or reumathological disease was reported by 7 patients (13.5%) (Fig. 2d). Imaging evidence of demyelinating disease was detected in the brain MRI scans of all patients, with dissemination in space being verified in all. The most frequent neuroradiological findings were T2/FLAIR hyperintense and T1 hypointense (33/52; 63.5%) multifocal lesions, with localization in both supratentorial and infratentorial areas in 71.2% (37/52) of patients (Fig. 3a), with positive enhancement after gadolinium being described in 28/52 (53.8%) (Fig. 3c). Other lesion locations included supratentorial only (12/52; 23.1%) and simultaneous supratentorial, infratentorial and optic nerve (3/52; 5.8%) (Fig. 3a). A spinal cord MRI was obtained in 40 patients, with abnormal results recorded in 28 (70%). Findings included T2 hyperintense and T1 hypointense signal lesions in 8 (28.6%). Multiple lesions were verified in 16/28 (57.1%) of the scans (Fig. 4b), with cervical levels being the most affected (15/28; 53.6%), followed in frequency by cervical and dorsal (8/28; 28.6%) and dorsal (3/28; 10.7%) levels (Fig. 4a); longitudinally extensive lesion was described in one (3.6%) patient (Fig. 4c), cord swelling in 6 (21.4%) and positive enhancement in 13 of available results (13/28; 46.4%). VEP was abnormal in 20/44 (45.5%) of patients; SSEP anomalous in 6/21 (28.6%) and PEA in 2/2 (100.0%). The laboratory tests performed in these patients and accessible for data analysis, displayed positive CSF-OCBs in 40 out of 50 patients (80.0%) and an IgG index greater than 0.6 in 31 out of 38 patients (1.09±0.52, 0.20-2.90). One of these patients had matched OCBs in serum, however electrophoresis analysis showed a lower number of bands. Within this group, OCBs were also analysed by gender and by age: positive CSF bands were detected in 84.4% of female MS patients *versus* 72.2% of male MS patients and in 81.1% of MS patients less than 30 years of age *versus* 78.6% of patients with 30 or more years. Average CSF-count of cells was 9.6±14.6 (0-90µL) and average CSF-protein content was 0.57±0.34 (0.10-2.47g/L). A positive microbiological assay was positive in 2/51 (3.9%) patients, with positive CSF results for enterovirus (one patient by PCR) and *Mycoplasma pneumonia* (one patient by PCR). Seven out of 52 patients (13.5%) had a positive immunological study: ANAs and anti- SSa in one, anti-β2GPI in 5, β2GPI and aCL in another one patient.

From the descriptive analysis the more relevant parameters were analyzed by chi-square tests. These included: i) clinical parameters (fatigue, mood disorders, systemic symptoms and familiar history); ii) biochemical parameters (CSF-OCBs and auto- antibodies); and iii) MRI findings [cranial (parameters: normal or abnormal, number of lesions, signal characteristics of the lesions and enhancement) and spinal cord (parameters: normal or abnormal, number of lesions, longitudinally extensive lesions, signal characteristics of the lesions and enhancement)]. No significant relation between the clinical parameters and clinical diagnosis (MS or non-MS) was noted. For the biochemical parameters, a significant relation was found between MS and CSF-OCBs ($p<0.001$). Regarding the MRI findings, for the cranial parameters the following significant relations were identified for the MS group with: abnormal findings ($p=0.005$), T1 hypointense

lesion (p=0.003), and positive lesion enhancement (p=0.026). For the same parameter, regarding the non-MS group a relation was found for single lesion (p=0.029), meaning that multiple lesions were related with the MS group. Finally, for the spinal MRI observations, a relation was found for the MS group with T1 hypointense lesions (p=0.039) and no longitudinally extensive lesions (p=0.009).

Discussion

The aim of this retrospective study was to systematically describe and analyze clinical, imaging, CSF and blood findings of a cohort of patients who entered the Neurology Department with a focal symptom/signal suggestive of an inflammatory demyelinating process or, alternately, patients with an asymptomatic inflammatory demyelinating lesion incidentally found on a MRI scan performed for other neurological symptoms, atypical for a CNS demyelinating process. Regarding final diagnosis, the present data analysis demonstrated that 52/82 (63.4%) patients had MS diagnosis. This incidence is relatively high when comparing with other published retrospective/prospective studies, namely by Kelly et al. (2011) and Carmosimo et al. (2005), which showed a cohort incidence of MS/CIS of 119/244 (49.0%) and 94/281 (33%), respectively [3, 4]. However, both studies included a larger number of adult patients of all ages.

Clinical onset

An abrupt clinical onset is considered by the European MAGNIMS group as a minor "red flag", meaning that, while facing a CIS case with such onset, the clinician should seek also for other, non-MS causes that might be possible explanations for that symptoms. However, of note, our study design initially excluded patients with focal symptoms of a definitive vascular origin, the major differential diagnosis in this hypothetical setting. Even though our MS cohort is in accordance to this, as a small group of patients (38.5%) presented an acute onset.

Here, clinical symptoms were categorized according to their anatomical correlation (and not by their likelihood of signaling an MS diagnosis) and mono/multifocal categorization was based solely on patients' reported symptoms. The MS population here studied presented mostly with a monofocal picture: spinal cord symptoms were the most frequent finding (14/52; 26.9%) (e.g. numbness, (a)symmetrical progressive spastic paraplegia, segmental loss of sensation, progressive sensory ataxia, urinary symptoms) followed, similarly in frequency, by cerebral hemispheres (hemiparesis, quadrantanopsia, cognitive function), optic nerve (unilateral optic neuritis, pain on eye movement, visual blurring, no light perception) and brain stem/cerebellum (internuclear ophthalmoplegia, cranial nerves palsies) symptoms. These findings are in accordance with reports that describe an isolated optic nerve symptoms incidence of 20.1% and 18.8% and of an isolated brainstem dysfunction of 14.7% and 25.0% [14, 15]. In fact, altogether, only a small percentage of MS patients showed a multifocal symptoms onset (7/52; 13.5%); this finding is also similar to other studies which report a 14.2% and 29.4% (based on symptoms and signs) prevalences [15, 14]. A multisymptomatic/multifocal presentation was a rare condition in our cohort, but this should be taken with some caution: as expected by the diagnostic criteria (which includes DIS), and by the well known course of the disease, the MS patients suffer from

progressive neurological deficits. So, as it is recognized by the MAGNIMS group, persistently monofocal manifestations should be regarded as a major clinical “red flag” finding suggestive of an alternative diagnosis. This study, because it is a transversal analysis, was not able to account for such possible findings.

Other presenting systemic symptoms, past medical history and family history

When analyzing the MS patients, non-focal and systemic symptoms are also of clinical relevance and, for that reason, patients were inquired about fatigue, mood disorders, recent infection (previous 3 months), recent vaccination (previous 6 months), genital/oral ulcers, reumathologic symptoms (arthritis, polyarthalgias, myalgias included), SICCA symptoms and skin rash, some of which constitute clinical “red flags”. In our cohort, the MS group presented a higher prevalence in fatigue and previous neurological events, while the non-MS group showed a higher prevalence in mood disorders and systemic symptoms (Fig. 3). Considering fatigue and mood disorders, these are well recognized symptoms in MS and it´s not uncommon to evaluate these symptoms at the same time [16, 17]. In the MS group, the prevalence of these 2 symptoms was similar which could suggest an association between them, however, only one patient within this group actually presented both symptoms simultaneously. Also important is the prevalence of fatigue in the MS population, which is reported to have an incidence of 10% to 20% at MS disease onset [18]. Previous/concurrent infection is also important in the patients’ diagnosis as it can suggest an ethiological process (e. g. parainfectious). Besides, a transient emergence or worsening of neurological symptoms, chronologically related to a change in body temperature as a febrile illness for instance, is highly suggestive of a demyelinating disorder (Uhthoff’s phenomenon) [5]. Here, a higher prevalence of previous infection was found in the non-MS patients with ADEM (3 out of 3 diagnosed patients), acute myelitis (one out of 6) and optic neuritis (one out of 4). This agrees with the well described abrupt onset of neurological symptoms and signs within days to weeks after a viral infection or immunization that occurs in ADEM and parainfectious monossimptomatic IIDDs [19]. A positive family history of CNS demyelinating diseases, neurodegenerative disorders, brain neoplasms, cerebrovascular disease in young adults and/or autoimmunity was also more frequent in the non-MS compared to the MS group. The neurolupus case should be here emphasized, as a patient’s sister was also diagnosed with systemic lupus erythematous (SLE), whereas only one patient from the MS group presented a family case of MS.

Brain and spinal cord MRI findings

Magnetic resonance imaging is without a doubt an important tool in the diagnostic pathway for symptoms consistent with inflammatory demyelinating disease. It allows, for instance, the initial exclusion of some non-demyelinating causes that might mimic those symptoms and, once demyelination is confirmed, for the characterization of the process, further leading to a specific/definitive diagnostic [20]. Some paradigmatic cases were present in our cohort (leukodystrophy, subacute combined degeneration of spinal cord, primary CNS vasculitis) and, in this context, an imaging characterization of the studied population was performed.

Adding to the value of abnormal imaging findings in MS diagnosis, only 30% of studied MS population presented no spinal cord lesions, with a similar incidence in the non-MS group. The latter, also presented some cases without brain MRI detected lesions (17.2%). Not only a normal brain MRI precludes a MS diagnosis, but also the absence of spinal cord lesions makes this an improbable diagnosis.

Perhaps, more relevant than the presence or absence of lesions is their characteristics, which are more useful while trying to rule in or out a diagnosis. In accordance to this: T1 hypointense brain MRI lesions were the most frequent finding in the MS group, while in the non-MS only 25.0% patients' lesions had these signal characteristics; the absence of infratentorial lesions and negative enhancement in brain MRI were more frequent in non-MS group, which can suggest/reinforce that these parameters should be also considered in the diagnosis process. Concerning the spinal cord MRI, single lesion detection was a major finding in the non-MS group, with a 75% reported frequency, in face of the 39.3% of MS patients. Also, medullary cone location and longitudinally extensive lesions suggested a non-MS diagnosis as none MS patient had lesions on that location and only one patient having LELs. Some of these parameters are already considered as MRI "red flags" and, therefore, their presence should alert the clinician to seek an alternative diagnosis [2].

Cerebrospinal fluid findings

The last revised McDonald criteria recognizes the value of CSF findings in MS diagnosis, namely elevated IgG index or 2 or more OCBs. Positive findings support the inflammatory demyelinating nature of the underlying conditions and can be important in alternative diagnosis evaluation and CDMS prediction [9]. However, with the recent simplification of DIS and DIT criteria, CSF positivity for OCBs is no longer a validated tool in MS diagnosis since DIS criteria rely only on MRI. Our records emphasize the supportive role of OCBs in MS diagnosis as, even in such a small cohort, there is a great discrepancy between prevalence values of OCBs positivity between groups, which makes this an important clinical practice tool. Prevalence of OCBs positivity in this cohort was

only slighter lower than other reported incidences (CSF-restricted OCBs were found in 89% of 411 patients with MS in Franciotta D et al (2008) [21]), with 70% of negative results attributable to CIS diagnosis. However, these findings are highly variable between reports, as different laboratory methods are used. Records from serum OCBs showed positive results in only one (MS) patient; of note, these were in lesser number than in CSF matched sample. An analysis attending the CSF-OCBs in MS group by age (patients with less than 30 years old *versus* patients with 30 or more years old) and gender (female *versus* male) was also performed: positive results were only marginally higher in the younger than 30 years old sub-group (81.3% vs 78.6%) and in female MS patients (84.4% vs 72.2%). Finally, other parameters analyzed that may constitute clinical clues for diagnostic decision between the two compared groups are (i) the lower average content of CSF cells in the MS group, (ii) the slighter higher protein content and (iii) the higher average IgG index in this biologic fluid in the MS group.

Imunological studies

A number of neurologic syndromes may be evoked by involvement of the CNS due to systemic diseases such as SLE, sarcoidosis, Beçhet disease and Sjorgren´s syndrome and may be confounded with another chronic inflammatory diseases restricted to CNS, as MS or other non-MS IIDD. Exclusion of such MS mimics is important as immunomodulatory treatment of MS may potentially induce (drug-induced SLE) or aggravate lupus disease activity [12, 22]. Blood tests and autoantibodies assays in a CIS setting may be helpful as they can provide diagnostic clues for systemic inflammatory diseases. Although, a normal immunological status in a patient gives no guarantee for the absence of collagenoses or vasculitidis and, in some cases, further investigations have to be considered if there is uncertainty about the diagnosis. Still, an abnormal immunological status doesn´t preclude a MS diagnosis: the presence of non-organ-specific autoantibodies in sera of MS patients has been described (among others, ANAs and anti- β2GPI IgM) [23]. Our study is consistent with this variability in the described phenotypes: 16.7% of non-MS and 13.5% of MS patients had a positive immunological study. In the latter group, only one patient showed ANA (and SSa) positivity, while the 6 remaining patients were aPL (β2GPI) positive. However, according to Szmyrka-Kaczmarek, ANAs are related with a shorter disease duration and a lower disability score, while anti-β2GPI antibodies were more frequent in patients with secondary progressive MS form, with a longer disease duration [23]. Because auto-antibodies positivity may precede clinical disease presentation and because a neurological presentation is well-known, this subgroup would require further follow-up.

Conclusion

An acute/subacute isolated neurological syndrome is a diagnostic challenge: it is the most common presentation in MS, but it can also be the first clinical manifestation of other, CNS restricted or systemic, diseases. Also, the conversion rate from a CIS to CDMS exhibits a great variation. Because of different treatment strategies and because early MS treatment leads to a better prognosis, it is important to distinguish between the different "MS mimics". In our cohort, a careful clinical history on actual/previous neurological/systemic events, as well as on family history of neurological, vascular and systemic inflammatory diseases, provided some diagnostic clues, although not statistically significant. Normal brain MRI or isolated optic nerve T2 hyperintensity were here considerable "red flags" and, once an abnormal brain MRI was detected, non-enhancing lesions restricted to the supratentorial area were also "red flags", which was confirmed by statistical analysis (significant relation between MS and lesion enhancement was noted). Spinal cord MRI also provided information on final diagnosis: abnormal scans with a single lesion, extra-cervical lesions and longitudinally extensive lesions were less suggestive of a MS diagnosis (the latter confirmed by statistical analysis). On the other hand, short segment T1 hypointense lesions with a cervical or cervical plus dorsal location pointed to a MS. Finally, laboratory findings in MS group, as expected, showed a higher prevalence of positive OCBs restricted to CSF (which revealed to be the most statistically significant finding establishing a relation/strong association between MS and CSF-OCB presence) and higher IgG index average, with lower average value of CSF-cells. In our cohort, a positive autoantibody assay didn't preclude a MS diagnosis, especially if the positive autoantibody were aPL. Neither clinical symptoms nor additional analyses such as serological findings or CSF analyses are able to differentiate between these diseases with certainty. Nevertheless, taking all findings together, an early and accurate diagnosis may be possible. Once the diagnosis of MS is made, a careful follow-up must be provided, with regular re-evaluations in face of unexpected or atypical clinical/paraclinical findings.

Conflict of interest

The authors declare that they have no conflict of interest.

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Tables

Table 1 Demographic and clinical features at onset of total population, non-MS and MS groups

Characteristic	*Non-MS group*	*MS group*	*Total population*
Number of patients	30 (36.6%)	52 (63.4%)	82 (100.0%)
Sex			
Female	20/30 (66.7%)	33/52 (63.5%)	53/82 (64.6%)
Male	10/30 (33.3%)	19/52 (36.5%)	29/82 (35.4%)
Female/male ratio	2/1	1.7/1	1.8/1
Age at onset (average ± SD), years	30.8 ± 7.0	30.8 ± 6.6	30.8 ± 6.7
Presenting symptoms			
Multifocal symptoms	1/30 (3.3%)	7/52 (13.5%)	8/82 (9.8%)
Monofocal symptoms			
Cerebral hemispheres	5/30 (16.7%)	13/52 (25.0%)	18/82 (22.0%)
Brain stem/cerebellum	1/30 (3.3%)	8/52 (15.4%)	9/82 (11.0%)
Optic nerve	10/30 (33.3%)	10/52 (19.2%)	20/82 (24.4%)
Spinal cord	9/30 (30.0%)	14/52 (26.9%)	23/82 (28.0%)
Other symptoms	4/30 (13.3%)	-	4/82 (4.9%)
Symptoms onset			
Acute	12/30 (40.0%)	20/52 (38.5%)	32/82 (39.0%)
Progressive	16/30 (53.3%)	31/52 (59.6%)	47/82 (57.3%)
NA	2/30 (6.7%)	1/52 (1.92%)	3/82 (3.7%)

Figure Captions

Fig. 1 Final diagnosis in eighty-two patients admitted into Centro Hospitalar de S. João – EPE with white matter lesions on MRI scans and/or with neuro-inflammatory syndromes, expressed by percentage of patients. IIDD, idiopathic inflammatory demyelinating disease; NA, diagnose not performed; CRION, chronic relapsing inflammatory optic neuropathy; ADEM, acute disseminated encephalomyelitis; RIS, radiological isolated syndrome; CIS, clinical isolated syndrome; CDMS, clinically definite multiple sclerosis

Fig. 2 Clinical characteristics at onset of MS and non-MS patients, expressed by percentage of patients a. Fatigue in MS diagnosis b. Mood disorders in MS diagnosis c. Systemic symptoms in MS diagnosis d. Family history in MS diagnosis

Fig. 3 Brain MRI characteristics at onset of MS and non-MS patients, expressed by percentage of patients a. Location of lesions in MS diagnosis b. T1 hypointense lesions in MS diagnosis c. Lesions enhacement in MS diagnosis. Statistical significance is shown, *P < 0.01, Fisher's exact test

Fig. 4 Spinal cord MRI characteristics at onset of MS and non-MS patients, expressed by percentage of patients a. Location of lesions in MS lesions b. Number of lesions in MS diagnosis c. Longitudinally extensive lesions (LELs) in MS diagnosis. NA, data not available for this analysis. Statistical significance is shown, *P < 0.01, Fisher's exact test

Figures

Fig. 1

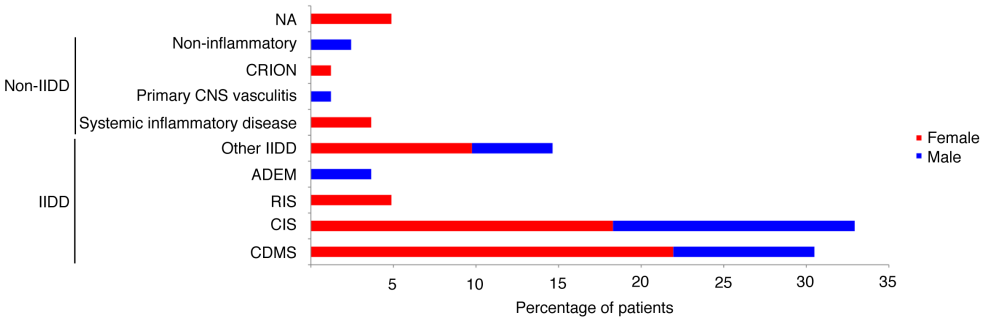


Fig. 2

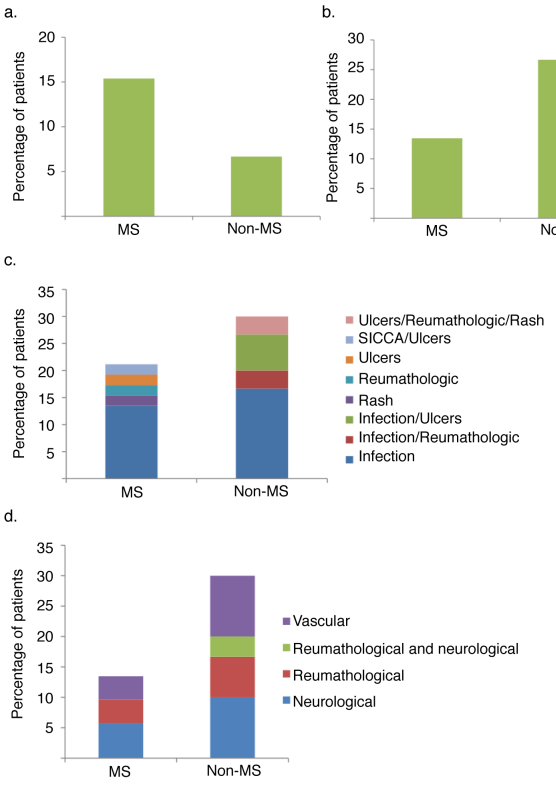


Fig. 3

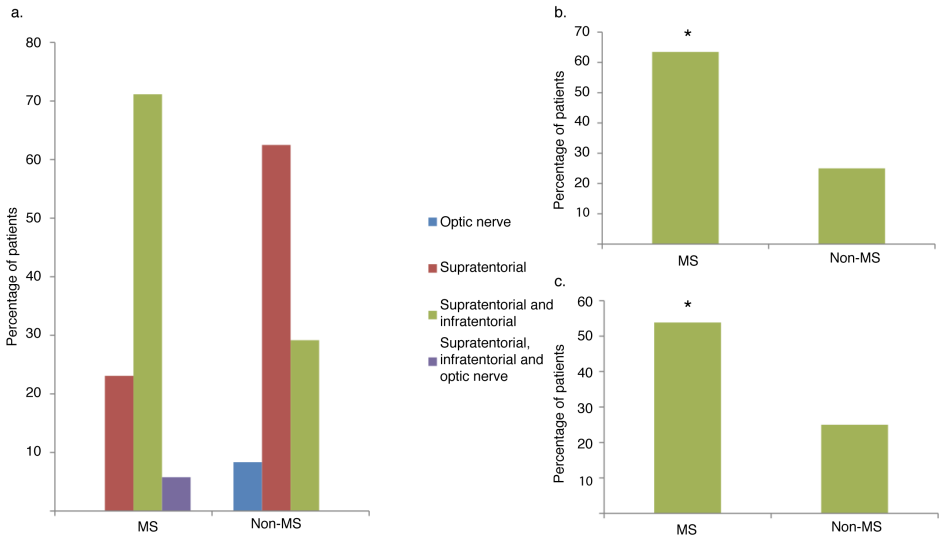
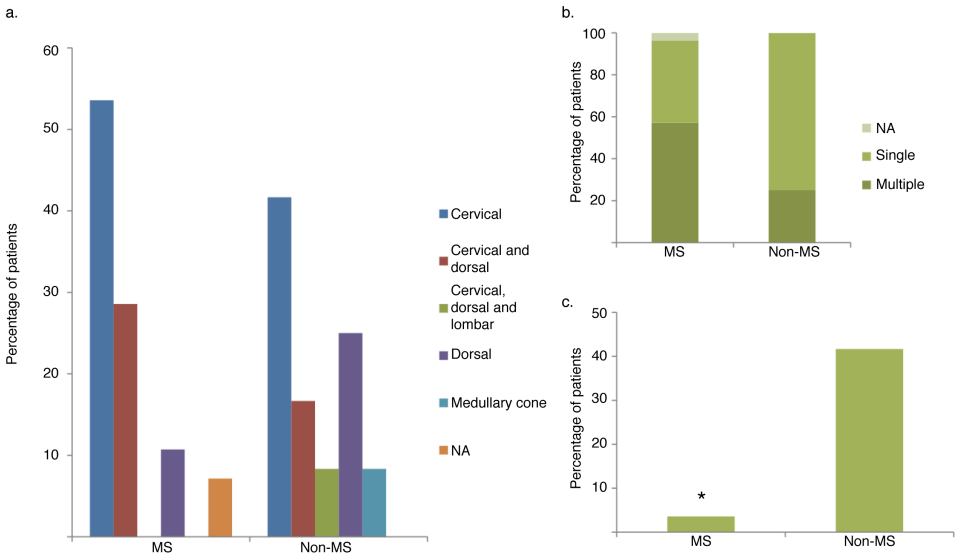

a.
Percentage of patients
80
70
60
50
40
30
20
10
MS
Non-MS
Optic nerve
Supratentorial
Supratentorial and infratentorial
Supratentorial, infratentorial and optic nerve
b.
Percentage of patients
70
60
50
40
30
20
10
*
MS
Non-MS
c.
Percentage of patients
60
50
40
30
20
10
*
MS
Non-MS

Fig. 4


a.
Percentage of patients
60
50
40
30
20
10
MS
Non-MS
Cervical
Cervical and dorsal
Cervical, dorsal and lombar
Dorsal
Medullary cone
NA
b.
Percentage of patients
100
80
60
40
20
MS
Non-MS
NA
Single
Multiple
c.
Percentage of patients
50
40
30
20
10
*
MS
Non-MS

White matter lesions in young adults: a diagnostic review

Journal of Neurology

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Supplementary Material

Supplementary Table 1 CIS clinical features and likelihood of signaling an MS diagnosis [2]

CIS typically seen in MS	*Less common CIS features which may be seen in MS*	*Atypical CIS features not expected in MS*
	Optic nerve	
Unilateral optic neuritis	Bilateral simultaneous optic neuritis	Progressive, optic neuropathy
Pain on eye movement	No pain	Severe, continuous orbital pain
Partial and mainly central visual blurring	No light perception	Persistent complete loss of vision
Normal disk or mild disk swelling	Moderate to severe disc swelling with no hemorrhages	Neuroretinitis (optic disk swelling with macular star)
	Uveitis (mild, posterior)	Uveitis (severe, anterior)
	Brain stem/Cerebellum	
Bilateral internuclear ophthalmoplegia	Unilateral internuclear ophthalmoplegia, facial palsy, facial myokymia	Complete external ophthalmoplegia; vertical gaze palsies
Ataxia and multidirectional nystagmus	Deafness	Vascular territory syndrome, e.g., lateral medullary
Sixth nerve palsy	One-and-a-half syndrome	Third nerve palsy
Facial numbness	Trigeminal neuralgia	Progressive trigeminal sensory neuropathy
	Paroxysmal tonic spasms	Focal dystonia, torticollis
	Spinal cord	
Partial myelopathy	Complete transverse myelitis	Anterior spinal artery territory lesion (sparing posterior columns only)
Lhermitte´s symptom	Radiculopathy, areflexia	Cauda equine syndrome
Deafferented hand	Segmental loss of pain and temperature sensation	Sharp sensory level to all modalities and localized spinal pain
Numbness	Partial Brown-Sequard syndrome (sparing posterior columns)	Complete Brown-Sequard syndrome
Urinary urgency, incontinence, erectile dysfunction	Faecal incontinence	Acute urinary retention
Progressive spastic paraplegia (asymmetrical)	Progressive spastic paraplegia (symmetrical)	Progressive sensory ataxia (posterior columns)
	Cerebral hemispheres	
Mild subcortical cognitive impairment	Epilepsy	Encephalopathy (obtundation, confusion, drowsiness)
Hemiparesis	Hemianopia	Cortical blindness

Supplementary Table 2 Differential diagnosis for the central nervous system lesions disseminated in space and time [10]

Type	***Disease***
Inflammatory	MS, NMO, ADEM, ITM, SLE, Sjogren syndrome, Behçet´s disease, neurosarcoidosis, Wegener´s granulomatosis, CNS vasculitis, Susac´s syndrome
Infectious	HIV, HTLV, neurosyphilis, PML, neuroborreliosis, Whipple´s disease
Metabolic	Vitamin B12 deficiency, porphyria
Degenerative	Mitochondrial encephalomyopathy, hereditary spastic para-paresis, Fabry´s disease, leukodystrophies
Vascular	CADASIL, anti-phospholipid antibody syndrome, multiple emboli, small vessel disease, migrane
Neoplastic	Metastases, lymphoma

Supplementary Table 3 Synopsis of demographic, clinical and paraclinical features of non-MS group, thirty patients included

Age/Sex	*Clinical presentation*	*Other presenting/past symptoms*	*CSF findings*	*Blood analysis/other diagnostic procedures*	*Final diagnosis*
24/M	Optic nerve	-	Cells	ESR	Optic neuritis, idiopathic
40/F	Other	Recent infection	Proteins	-	RIS
35/M	Cerebral hemispheres	Recent infection	HHV6 (+)	Anemia; Neutrophilia; ESR; CPR	ADEM
22/F	Optic nerve	-	IgG Index	-	Optic neuritis, idiopathic
36/M	Brain stem	Recent infection; Ulcers	Proteins; Neutrophils	Neutrophilia; CPR	ADEM
21/M	Optic nerve	Recent infection; Reumathologic symptoms	Proteins; Cells; OCBs (+)	-	Optic neuritis, idiopathic
25/F	Spinal cord	-	OCBs (+)	Anemia	NA IIDD
20/F	Multifocal symptoms	-	Proteins	ESR	CRION
36/F	Other	-	IgG Index	ESR	RIS
24/F	Optic nerve	-	Proteins	Leukocitosis	Optic neuritis, idiopathic
33/M	Cerebral hemispheres	-	-	Trombocytopenia	Leukodystrophy with axonal spheroids
38/F	Spinal cord	Recent infection	-	-	Acute myelitis, parainfectious
29/F	Other	-	-	β2GPI (+)	RIS
27/F	Optic nerve	Recent infection	Lymphocytes; IgG Index; OCBs (+)	ANA (+)	Inflammatory disease
26/F	Cerebral hemispheres	-	EBV (+)	ANA (+)	Inflammatory disease
42/F	Spinal cord	-	-	-	Acute myelitis, idiopathic
30/F	Spinal cord	-	Proteins; Lymphocytes; IgG Index; OCBs (+)	-	Acute myelitis, idiopathic
34/F	Optic nerve	-	Proteins; Mononuclear cells; *M. pneumoniae* (+)	Anemia; ESR; CPR; abnormal CXR; abnormal adenopathy biopsy	Type 1 pulmonary sarcoidosis; Neurossarcoidosis
24/F	Cerebral hemispheres	Fatigue; Ulcers; Reumathological symptoms; Rash	Proteins; Lymphocytes; OCBs (+)	Low vit B12; anti-PR3 (+); β2GPI (+)	Neurolupus
36/M	Spinal cord	-	-	Macrocytosis; low vit B12	Subacute combined degeneration of spinal cord
23/F	Optic nerve	-	-	-	Inflammatory disease
33/M	Spinal cord	Recent infection	Proteins; Mononuclear cells	Anemia; trombocytopenia; ESR	ADEM
36/M	Cerebral hemispheres	Fatigue	Proteins	CPR; ANA (+)	Primary CNS vasculitis
26/F	Other	-	Proteins	Trombocytosis; ESR	RIS
44/M	Spinal cord	-	Proteins; Lymphocytes; CMV (+)	-	Acute myelitis, parainfectious
31/M	Spinal cord	-	IgG Index; Enterovirus (+)	Neutrophilia; CPR	Acute myelitis, parainfectious
20/F	Optic nerve	Recent infection; Ulcers	Proteins; IgG Index; Enterovirus (+)	HLAB51 (-); pathergy test (+); abnormal oral ulcer biopsy	Neurobeçhet
40/F	Optic nerve	-	Proteins	-	NA IIDD
35/F	Spinal cord	-	IgG Index; OCBs (+)	-	Acute myelitis, idiopathic
35/F	Optic nerve	-	Proteins	ESR	Inflammatory disease

Recent infection, systemic inflammatory symptoms/signs in previous 3 months; reumathologic symptoms, arthritis, polyarthalgias, myalgias included; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; β2GPI, anti-β2 glicoprotein I antibodies; CXR, chest X-ray; OCB (+), oligoclonal bands in cerebrospinal fluid; IIDD, idiopathic inflammatory demyelinating disease; NA IIDD, diagnose not performed on an IIDD; CRION, chronic relapsing inflammatory optic neuropathy; ADEM, acute disseminated encephalomyelitis; RIS, radiological isolated syndrome

Supplementary Table 4 Synopsis of demographic, clinical and paraclinical features of MS group, fifty-two patients included

Age/Sex	*Clinical presentation*	*Other presenting/past symptoms*	*CSF findings*	*Blood analysis/other diagnostic procedures*	*Final diagnosis*
32/F	Multifocal symptoms	Fatigue	IgG Index; OCBs (+)	-	MS, relapse remitting
41/F	Spinal cord	Fatigue	Protein; IgG Index; OCBs (+)	β2GPI (+)	MS, relapse remitting
19/F	Cerebral hemispheres	-	Cells	-	CIS
38/F	Spinal cord	Fatigue; SICCA/Ulcers	IgG Index; OCBs (+)	ESR	MS, relapse remitting
21/M	Spinal cord	-	Protein; OCBs (+)	β2GPI (+)	CIS
40/F	Spinal cord	-	OCBs (+)	-	MS, primary progressive
30/F	Optic nerve	-	OCBs (+)	-	MS, relapse remitting
28/M	Brain stem	-	Cells; IgG Index; OCBs (+)	-	CIS
34/M	Optic nerve	-	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting
23/M	Spinal cord	-	-	ANA (+);anti- SSa (+)	CIS
36/F	Spinal cord	-	OCBs (+)	-	CIS
22/F	Cerebral hemispheres	-	IgG Index; OCBs (+)	Neutropenia; ESR	CIS
32/M	Brain stem	-	-	-	CIS
24/F	Cerebral hemispheres	-	IgG Index; OCBs (+)	-	MS, relapse remitting
23/F	Multifocal symptoms	-	Protein; IgG Index; OCBs (+)	ESR and CRP	MS, relapse remitting
27/M	Brain stem	Fatigue	IgG Index; OCBs (+); Enterovirus (+)	-	CIS
29/M	Spinal cord	-	Protein; Cells; IgG Index; OCBs (+)	-	CIS
28/F	Cerebral hemispheres	-	Protein; IgG Index	-	CIS
23/F	Optic nerve	-	OCBs (+)	-	CIS
38/F	Optic nerve	Fatigue	OCBs (+)	-	MS, relapse remitting
24/M	Spinal cord	-	IgG Index; OCBs (+)	-	MS, relapse remitting
40/M	Cerebral hemispheres	Recent infection	Protein	-	MS
19/F	Multifocal symptoms	-	Protein; IgG Index; OCBs (+)	-	CIS
35/M	Cerebral hemispheres	-	OCBs (+)	-	MS, relapse remitting
37/F	Optic nerve	-	IgG Index; OCBs (+)	-	CIS
40/F	Multifocal symptoms	-	Cells; IgG Index; OCBs (+)	-	MS, relapse remitting
33/F	Brain stem	Recent infection	OCBs (+)	-	CIS
30/F	Multifocal symptoms	-	Protein; IgG Index; OCBs (+)	-	MS, pseudotumoral
40/F	Brain stem	-	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting
27/F	Cerebral hemispheres	-	IgG Index; OCBs (+)	-	MS, relapse remitting
22/F	Multifocal symptoms	Recent infection	IgG Index	ESR	MS, relapse remitting
27/F	Optic nerve	-	Protein	-	CIS
31/M	Spinal cord	-	Protein; IgG Index;	ESR	CIS
23/M	Optic nerve	-	Protein; Cells; OCBs (+)	-	CIS
27/M	Multifocal symptoms	-	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting
30/M	Cerebral hemispheres	Recent infection	Protein; IgG Index;	Anemia; ESR	CIS
36/F	Brain stem	Fatigue; Reumathologic symptoms	-	-	CIS
26/F	Cerebral hemispheres	Recent infection	Protein; IgG Index; OCBs (+)	-	CIS
36/F	Brain stem	-	Protein; Cells	ESR; β2GPI (+)	MS, relapse remitting
37/M	Optic nerve	-	Protein	β2GPI (+)	CIS
19/F	Cerebral hemispheres	Recent infection	Protein; IgG Index; OCBs (+); *M. pneumoniae* (+)	Low vit B9	CIS
27/F	Cerebral hemispheres	Rash	Protein; Cells; IgG Index; OCBs (+)	CRP	MS, relapse remitting
38/F	Cerebral hemispheres	-	Protein; OCBs (+)	-	MS, relapse remitting
27/M	Spinal cord	-	Protein; Cells; IgG Index; OCBs (+)	-	CIS
40/M	Optic nerve	-	Protein; Cells; OCBs (+)	-	CIS
32/M	Spinal cord	-	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting
37/F	Spinal cord	Fatigue	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting
31/F	Brain stem	Ulcers	Protein; IgG Index; OCBs (+)	aCL (+); β2GPI (+)	CIS
36/F	Cerebral hemispheres	Fatigue	IgG Index; OCBs (+)	-	MS, relapse remitting
27/F	Optic nerve	Recent infection	Protein; OCBs (+)	CRP	CIS
40/F	Spinal cord	-	OCBs (+)	β2GPI (+)	CIS
38/M	Spinal cord	-	Protein; IgG Index; OCBs (+)	-	MS, relapse remitting

Recent infection, systemic inflammatory symptoms/signs in previous 3 months; reumathologic symptoms, arthritis, polyarthalgias, myalgias included; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; ANA, antinuclear antibody; β2GPI, anti-β2 glicoprotein I antibodies; aCL, anticardiolipin antibodies; OCB (+), oligoclonal bands in cerebrospinal fluid; CIS, clinical isolated syndrome; MS, multiple sclerosis

Author: Leonor Marques

Title: "White matter lesions in young adults: a diagnostic review"

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Author: Leonor Marques

Title: "White matter lesions in young adults: a diagnostic review"

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Anexo I

Journal of Neurology - Instructions for Authors

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Journal no. 415

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Instructions for Authors

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- Book chapter

  Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

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  Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. http://physicsweb.org/articles/news/11/6/16/1. Accessed 26 June 2007

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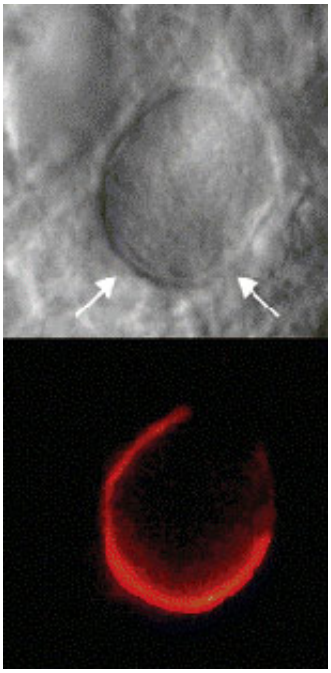

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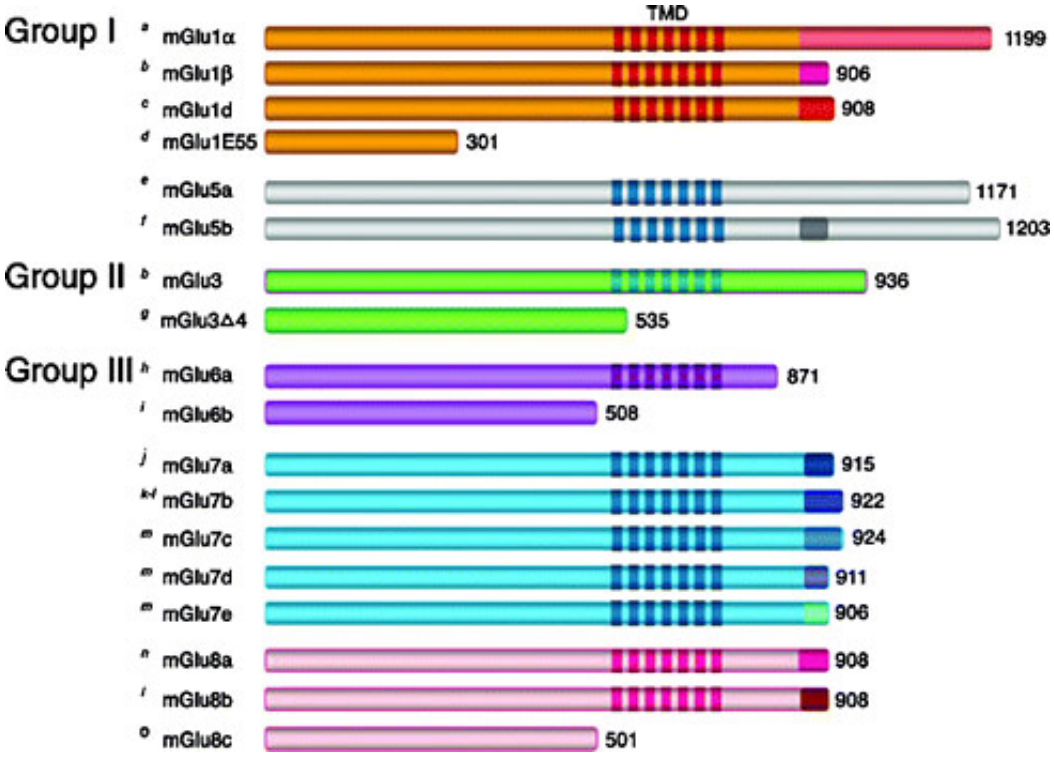
Combination Art



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