The diagnosis of Multiple Sclerosis: pinpointing the concept of "no better explanation"

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The RIREMS group (Rising Italian Researchers in Multiple Sclerosis')

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Background

The differentiation of MS from other conditions that can mimic it can be difficult.
MS diagnostic criteria have evolved over time with the increasing use of paraclinical markers, especially MRI, allowing for a definite diagnosis earlier in the disease course than a strict reliance on clinical features would allow. Despite the technological advancements, current criteria still rely on the key principles of MS diagnosis articulated in the middle of 20th century: 1) demonstration of dissemination in space and in time and 2) the exclusion of alternative etiologies
Unfortunately, data on the frequency of alternative diseases that can mimic the MS in "real life situations" are poor. This makes it complicated to judge the pertinence of the examinations usually required, in the diagnostic workup, to confirm that "no better explanation" for those symptoms exists.

Objectives

The aims of our study were: 1) To perform an epidemiological evaluation of the main diseases that mimic MS clinical onset 2) To analyse the main clinical, haematological, CSF and instrumental characteristics of these diseases 3)To evaluate the best diagnostic workup to exclude other possible explanations of the clinical symptoms suggesting MS.

Methods

The first step of the study was to identify the minimum set of exams required to exclude alternative diagnosis in patients presenting with clinical symptoms suggestive of demyelinating diseases of the CNS. A restricted sub-group of RIREMS revised the literature on differential diagnosis of MS and produce a list of possible "alternative" diseases and the related blood, CSF and instrumental examinations needed to identify these alternative diseases.
Clinicians from a large number of Italian MS centers took part at the second phase of the process aimed at obtaining consensus statements among the participants.
During the meeting of the RIREMS group, held in Milan on November 3, 2013, the panel suggested the minimum set of examinations required to exclude the main alternative diseases. The list below, therefore is the results of the consensus among the entire RIREMS group. Of course, this list should be updated/revised at the end of the study based on the actual frequency of alternative diagnosis.

Study Population. Here we included data of all patients which have been evaluated from March 1st through september 30, 2014 in our outpatient clinics for signs or symptoms suggestive of a demyelinating disease of the CNS, irrespective of the examinations already done, and also for whom in depth evaluation (including MRI, CSF analysis or other neurological exams) was required since diagnostic criteria were not met.

Table 1. Minimum set of exams required to exclude alternative diagnosis in patients presenting with clinical symptoms suggestive of demyelinating diseases of the CNS

Clinical Evaluation	Hematological Exams
Neurological examination with EDSS	Complete blood count
CSF Exams	AST, ALT, gGT
IgGOB	Kidney profile
IgG Index	ANA, ENA
Total proteins	anticardiolipin
Cell count	Lupus anti coagulant
CSF/serum albumin ratio	B12 vitamin and folate
Instrumental Exams	Antiphospholipid
VEP	VES and PCR
MRI	Unine examination

Results

Diagnosis	n	Age (mean ± SD)		Disease Duration (mean ± SD)		EDSS (mean ± SD)	
Acute disseminated encephalomyelitis	1	48,0		1,0		3,5	
atypical facial pain	1	43,0		3,0		0,0	
birth related enceaphalopathy	1	29,0		2,0		2,0	
Glaucoma	1	45,0		1,0		2,0	
Methabolic Leucoencephalopathy	1	69,0		2,0		1,5	
Polyneuritis cranialis	1	40,0		1,0		2,0	
Psychiatric disease	1	42,0		1,0		0,0	
Recurrent Myelitis	1	42,0		9,0		1,5	
Reumatic disease	1	45,0		1,0		0,0	
SCA	1	35,0		11,0		4,5	
Steinert myotonic dystrophy syndrome	1	47,0		11,0		2,0	
Susac syndrome	1	30,0		2,0		1,5	
Syringomyelia	1	17,0		3,0		1,5	
vascular malformation	1	33,0		3,0		1,0	
antiphospholipid syndrome	2	28,5	3,5	2,0	0,0	1,0	1,4
CIDP	2	38,0	19,8	14,0	1,4	3,3	0,4
lupus erythematosus sistemicus	2	48,0	4,2	2,0	0,0	3,0	1,4
Myelopathy	2	30,0	9,9	1,0	0,0	0,8	1,1
Optic Neuritis	2	27,5	12,0	1,5	0,7	1,0	1,4
Bechet disease	4	33,5	12,9	5,0	3,2	4,6	1,8
SJOGREN' syndrome	4	43,8	15,4	7,5	6,0	2,5	1,7
Recurrent optic neuritis	5	38,6	20,9	4,2	2,7	2,2	1,6
Myelitis	7	41,4	9,1	1,4	0,5	1,9	1,2
Neuromyelitis optica	10	44,0	12,3	1,7	0,9	3,6	2,7
Migraine	20	37,6	9,2	4,2	4,2	0,3	0,6
Vascular Encephalopathy	23	50,0	9,3	4,7	5,2	0,9	0,9
Multiple Sclerosis	**271**	**36,6**	**11,9**	**4,0**	**4,9**	**2,2**	**1,5**
Under Investigation	**283**	**38,3**	**12,2**	**3,1**	**4,3**	**1,6**	**1,4**
Other diseases (all togeter)	**97**	**41,6**	**12,2**	**3,9**	**4,2**	**1,6**	**1,7**

652 patients were included in the study, as they required in-depth analysis following the onset of symptoms suggesting MS: 448 females and 204 males. Following the clinical and paraclinical examinations: 271 were diagnosed with MS; in 97 a different disease was recognized, and 284 are still under investigation.

Vascular Encephalopathy, Migraine and Devic's syndrome were the most common alternative diagnosis observed. (Table 2)

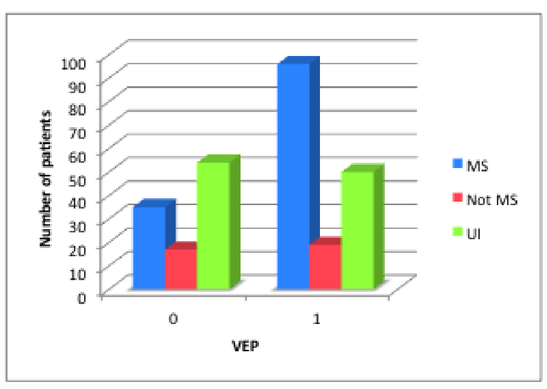
Among the examinations performed, VEP, MRI and CSF analysis resulted in significant differences between the MS and non MS group (Table 3).

Table 3. Demographic, clinical and paraclinical characteristics of the groups of patients

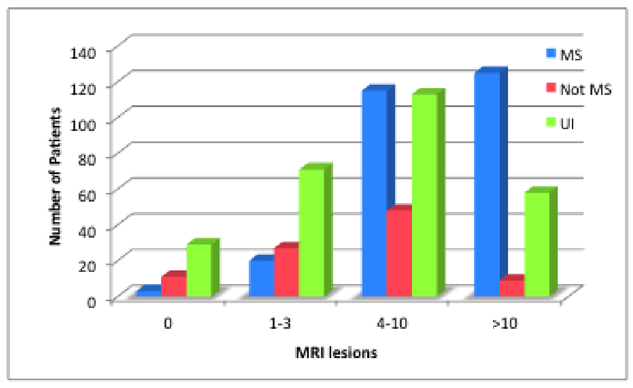
		Mean	Std Dev	Std Error	Min	Max	p value
Age	Under Investigation	38,3	12,2	1,1	15,0	76,0	0.084
	MS	36,6	11,9	1,3	13,0	67,0	
	Not MS	41.6	12.6	2,3	16,0	62,0	
Disease duration	Under Investigation	3.1	4,3	0,5	0,0	31,0	0.999
	MS	4.0	6,2	0,6	0,0	30,0	
	Not MS	3.9	4,5	0,8	0,0	14,0	
EDSS	Under Investigation	1,4	1,2	0,1	0,0	5,5	0.774
	MS	1.5	1,6	0,2	0,0	7,0	
	Not MS	1,7	1,8	0,5	0,0	7,5	

VEP		**Normal Lat**		**Abnormal Lat**		**p value**	**(Chi Square)**
	MS	35		96		0.018	
	Not MS	17		19			
		Normal Mor		**Abnormal Mor**		**p value**	**(Chi Square)**
VEP						0.257	
	MS	**68**		**9**			
	Not MS	**19**		**5**			
IgG OB		**Absent**		**Present**		**p value**	**(Chi Square)**
	MS	27		201		<0.00001	
	Not MS	59		11			
MRI		**0-3 lesions**		**>3 lesions**			
		0	**1-3**	**4-10**	**>10**	**p value**	**(Chi Square)**
	MS	3	20	115	125	<0.00001	
	Not MS	11	27	48	9		

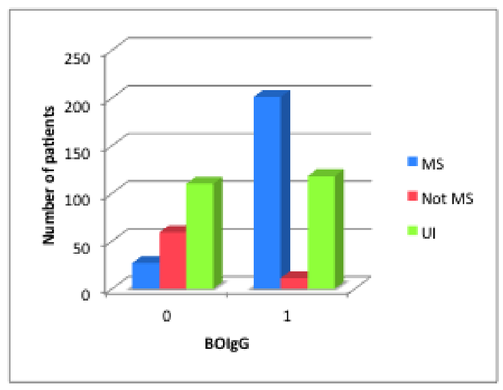
For MRI lesions, beyond their location and shape, it is remarkable the relevance of their number since the large majority of the patients having more than 10 MRI lesions, had the diagnosis of MS.



VEP



MRI lesions



Oligoclonal Bands

Discussion & conclusions

Multiple Sclerosis is by far the most frequent diagnosis in the case of symptoms suggestive of CNS demyelinating disease. However, after clinical and paraclinical examination, only 368 (56.4%) of the 652 patients have so far reached the definitive diagnosis; among these, 97 patients had an alternative diagnosis.

Large consensus was obtained for statements grouped under the following main MS themes: identification of the most useful blood, CSF and instrumental examinations. Among these, MRI and CSF analysis have been shown to be the most important exams for diagnosis, thus far being the only exams showing significant differences in patients with definitive diagnosis. Further analysis of clinical data and blood tests are ongoing as well as the clinical follow up of several patients.

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