



## Alternative diagnoses in patients referred to specialized centers for suspected MS



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### ABSTRACT

**Objectives:** The aim of this study is to explore the frequency, type, and predictors of alternative diagnoses among patients referred with a recent diagnosis of multiple sclerosis (MS) to two specialized MS centers in the Middle East.

**Methods:** This is a retrospective review of a prospectively followed cohort of MS patients at 2 University specialized MS centers. All patients referred for MS were included. The final diagnosis was recorded and demographic, clinical, laboratory, electrophysiological and radiological variables were collected.

**Results:** A total of 554 patients were included in this study of which 431 were referred for diagnostic confirmation. The final diagnosis of MS was confirmed in 300 (70%), while 114 (26%) turned out to have an alternative diagnosis and 15 (3.5%) fulfilled criteria for radiologically isolated syndrome (RIS). The most common alternative diagnoses were psychogenic (16.3%), non-specific MRI white matter lesions (14.7%), NMO (9.5%), migraine (8.6%) and systemic autoimmune disorders (8.6%). The strongest predictors of a final diagnosis of MS were: younger age, presence of oligoclonal bands in the CSF, periventricular, corpus callosum, spinal ( $P < 0.0001$ ), or enhancing lesions ( $P < 0.005$ ) on MRI.

**Conclusions:** Our study shows that 30% of patients referred for a suspicion of MS end up with a different diagnosis. The most common alternative diagnoses of MS in the Middle East are not different from what has been described in Western countries. Age, MRI and CSF findings can help with the differential diagnosis.

### 1. Introduction

The diagnosis of multiple sclerosis (MS) requires the demonstration of disease dissemination in space (DIS) and time (DIT) as documented by clinical and paraclinical criteria. Unfortunately, initial misdiagnosis of MS is still common resulting in serious consequences for patients (Solomon and Weinschenker, 2013). Although the most recent revised McDonald criteria report a diagnostic specificity around 85% (Schaffler et al., 2011), all criteria from Poser (Poser et al., 1983) to McDonald's (Polman et al., 2011) stressed the need to rule out any "other better explanation" of the presenting symptoms before a definite diagnosis of MS is made. An international consensus paper summarized the potential mimickers that need to be considered in the differential diagnosis of MS upon initial presentation, and listed 36 major red flags for

misdiagnosis (Miller et al., 2008). Extensive testing to rule out all possibilities might not be cost-effective and even MRI, with its high sensitivity might not be specific enough to differentiate MS from certain mimickers.

Defining the frequency of early misdiagnosis, and determining the most common alternative diagnoses and their predictors among patients with a recent diagnosis of MS will improve diagnostic accuracy and allow for a better allocation of resources. The aim of this study was to explore the frequency, type, and predictors of non-MS diagnoses among patients referred with suspected MS to two specialized MS centers in the Middle East.

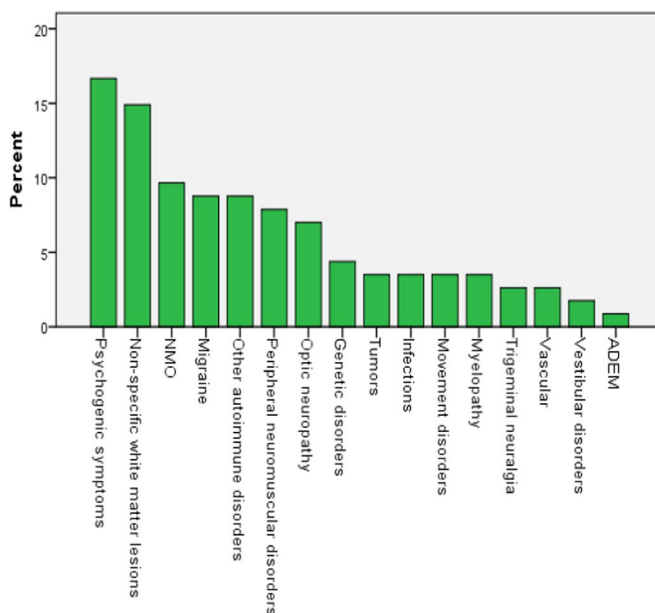
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**Table 1**  
Alternative diagnoses in patients referred for suspected MS<sup>a</sup>.

Final Diagnosis	Frequency	Percent
Psychogenic	19	14.7
Non-specific ischemic white matter lesions	16	12.4
RIS	15	11.6
NMO	11	8.5
Migraine	9	7.0
Isolated Optic neuritis without MS	4	3.1
Peripheral Neuropathy	4	3.1
Trigeminal neuralgia	3	2.3
Behcet Disease	2	1.6
Leber Optic Neuropathy	2	1.6
Leukodystrophy	2	1.6
SCA	2	1.6
SLE	2	1.6
Stroke	2	1.6
Uveitis	2	1.6
ADEM	1	0.8
ALS	1	0.8
Antiphospholipid Syndrome	1	0.8
BPPV	1	0.8
CADASIL	1	0.8
Dural AV fistula	1	0.8
Encephalitis	1	0.8
Essential tremor	1	0.8
Fascioscapulothoracic muscular dystrophy	1	0.8
Friederich ataxia	1	0.8
Gliomatosis Cerebri	1	0.8
Granulomatous meningoencephalitis	1	0.8
Guillain Barre Syndrome	1	0.8
HSP with neuropathy	1	0.8
Invasive pituitary macroadenoma	1	0.8
Ischemic optic neuropathy	1	0.8
Limb Girdle Myopathy	1	0.8
Lymphoma versus sarcoidosis	1	0.8
Myopathy	1	0.8
Neurobrucellosis	1	0.8
Non-specific ischemic white matter lesions + peripheral Neuropathy	1	0.8
Optic nerve meningioma	1	0.8
Recurrent Optic neuritis	1	0.8
Restless leg syndrome	1	0.8
Retinal migraine	1	0.8
Rheumatologic	1	0.8
Sciatica	1	0.8
Syringohydromyelia/untethered cord	1	0.8
Tethered cord syndrome	1	0.8
Tolosa-Hunt Syndrome	1	0.8
Toxocara Myelitis	1	0.8
Transverse Myelitis	1	0.8
vasculitis	1	0.8
Vestibular neuritis	1	0.8
Total	129	100.0

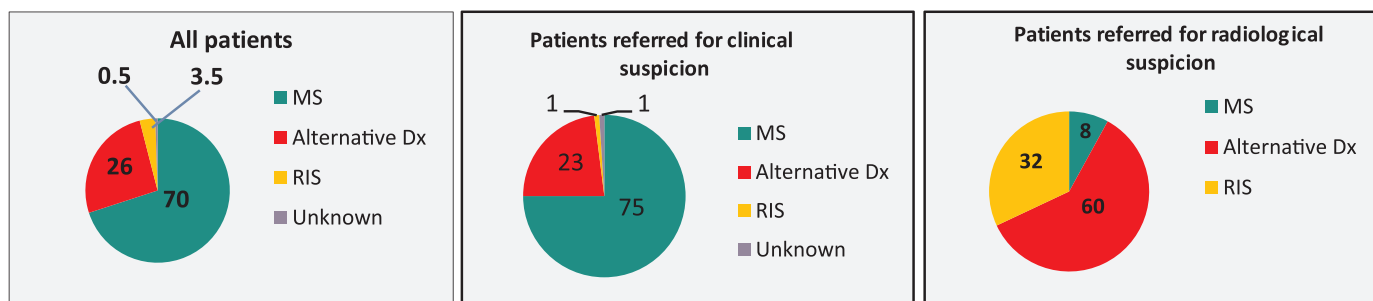
<sup>a</sup> RIS cases were included.



**Fig. 2.** The most common diagnostic categories among 114 patients with a final alternative diagnosis.

**2. Methods**

A retrospective review of medical records of all patients referred with a suspected diagnosis of MS to the American University of Beirut MS Center between October 2011 and March 2015 and to the Amiri Hospital MS center in Kuwait between January 2015 and March 2016 was carried out. Both centers are tertiary referral facilities for their respective countries and the Middle East region. All patients were seen by another physician prior to referral, either a primary care doctor or a neurologist, and almost all had at least a brain and/or spine MRI before referral. Around 50% of patients were assessed by neurologists prior to referral. Patients referred for suspicion of non-MS entities, and patients with inadequate follow up information to confirm the diagnosis were excluded. The final diagnosis reached after further laboratory work-up and clinical follow-up was recorded. The diagnosis of MS and radiologically isolated syndrome (RIS) were based on the 2010 McDonald (Polman et al., 2011) and Okuda (Okuda et al., 2009) criteria, respectively. Patients with clinically isolated syndrome (CIS) highly suggestive of MS (n = 19) were lumped with MS patients for the purpose of this analysis. Patients` data were collected and analyzed to determine the frequency and diagnostic predictors of a final non-MS diagnosis. The variables analyzed included: age, sex, disease duration, family history, past medical history, presenting symptoms, neurological exam abnormalities, MRI findings (presence of enhancing lesions and lesion localization), evoked potentials including visual (VEP), brainstem auditory (BAER), and somatosensory (SSEP), CSF findings, and serological testing.



**Fig. 1.** Final diagnosis in patients referred for suspected MS diagnosis based on reason for referral.

**Table 2**  
Univariate analysis of all clinical and paraclinical predictors of MS vs. alternative diagnosis in all referred patients\*.

Variable		MS N = 422	Alternative Diagnosis N = 115	p-value
Age	Mean ( ± SD)	30.38 ± 10.75	38.81 ± 14.32	< 0.0001
Gender	Woman	285 (67.5)	68 (59.1)	0.09
	Man	137 (32.5)	47 (40.9)	
Disease duration (months)	Mean ( ± SD)	27.00 ± 48.84	39.92 ± 70.03	0.07
Brainstem presentation	Yes	88 (21.0)	12 (10.5)	0.01
Visual presentation	Yes	158 (37.6)	40 (35.1)	0.62
Motor presentation	Yes	218 (51.9)	40 (35.1)	0.001
Sensory presentation	Yes	218 (52.0)	44 (38.6)	0.01
Systemic symptoms	Yes	4 (1.0)	12 (10.5)	< 0.0001
Family History	None	305 (72.4)	74 (64.9)	0.19
	Positive for MS	45 (10.7)	12 (10.5)	
	Positive for systemic autoimmune diseases	6 (1.4)	4 (3.5)	
	Positive for other systemic diseases	65 (15.4)	24 (21.1)	
Medical History	None	320 (75.8)	58 (50.4)	< 0.0001
	Positive for systemic autoimmune diseases	15 (3.6)	8 (7.0)	
	Positive for other systemic diseases	87 (20.6)	49 (42.6)	
Enhancing lesions	Yes	159 (38.3)	8 (8.1)	< 0.0001
Abnormal spine MRI	Yes	216 (58.5)	19 (22.6)	< 0.0001
Infratentorial lesions	Yes	230 (55.7)	19 (19.2)	< 0.0001
Juxtacortical lesions	Yes	342 (83.0)	32 (32.7)	< 0.0001
Callosal lesions	Yes	284 (68.9)	15 (15.3)	< 0.0001
Periventricular lesions	Yes	392 (95.1)	48 (49.0)	< 0.0001
OCB present	Yes	251 (87.5)	13 (26.0)	< 0.0001
IgG Index	Normal	55 (48.2)	35 (89.7)	< 0.0001
	Increased	59 (51.8)	4 (10.3)	
Serology	Yes	27 (21.4)	13 (28.9)	0.31
VEP- abnormality (if done)	Normal	117 (42.1)	32 (61.5)	0.002
	Unilaterally abnormal	36 (12.9)	10 (19.2)	
	Bilaterally abnormal	125 (45.0)	10 (19.2)	
SSEPs – abnormality (if done)	Normal	169 (65.8)	31 (67.4)	0.21
	Unilaterally abnormal	17 (6.6)	6 (13.0)	
	Bilaterally abnormal	71 (27.6)	9 (19.6)	
BAERs – abnormality (if done)	Normal	205 (79.2)	31 (81.6)	0.07
	Unilaterally abnormal	14 (5.4)	5 (13.2)	
	Bilaterally abnormal	40 (15.4)	2 (5.3)	
Any Neurological exam abnormality	Yes	371 (88.1)	70 (62.5)	< 0.0001
Protein	Mean ( ± SD)	0.36 ± 0.15	0.42 ± 0.29	0.14
Glucose	Mean ( ± SD)	69.32 ± 18.95	71.48 ± 15.68	0.48
Cell count	Mean ( ± SD)	6.66 ± 10.71	5.23 ± 10.68	0.42

\* Patients with RIS or unknown diagnosis were excluded.

**Table 3**  
Multivariate analysis for the predictors of an alternative diagnosis vs. MS in patients with available brain and spine MRI (n=357).

Variables	OR ( 95% CI)	P-value
Age*	1.72 (1.24 – 2.39)	0.001
Systemic symptoms	15.73 (2.21 – 111.95)	0.01
Enhancing lesions	0.20 (0.07 – 0.60)	0.004
Infratentorial lesions	0.41 (0.17 – 0.95)	0.03
Corpus callosum lesions	0.17 (0.07 – 0.39)	< 0.0001
Periventricular lesions	0.08 (0.03 – 0.23)	< 0.0001
Abnormal spine MRI	0.18 (0.08 – 0.44)	< 0.0001

\* For every increment of 10 years.

**Table 4**  
Multivariate analysis for the predictors of an alternative diagnosis vs. MS in patients with available brain MRI, spine MRI and CSF studies (n=245).

Variables	OR ( 95% CI)	P-value
Age*	1.84 (1.12 – 3.04)	0.02
Presenting sensory symptoms	0.41 (0.13 – 1.26)	0.12
Systemic symptoms	17.82 (1.97 – 161.03)	0.01
Family history of MS	2.98 (0.67 – 13.27)	0.15
Family history of systemic disorders	0.12 (0.02 – 0.88)	0.04
Enhancing lesions	0.10 (0.02 – 0.50)	0.005
Periventricular lesions	0.04 (0.01 – 0.23)	< 0.0001
OCB present	0.04 (0.01 – 0.14)	< 0.0001

\* For every increment of 10 years.

### 2.1. Statistical analyses

All variables were summarized using frequency distributions, and their differences were examined using the chi-squared test or Fisher's exact test, as appropriate. Continuous variables were compared using the student's *t*-test. The incidence of the different alternative diagnoses was reported as proportions. Logistic regression analyses were carried out with “alternative diagnoses” as the outcome variable, and different clinical and paraclinical variables as covariates. The final models included only variables that would either show statistical significance or possible confounding effect. Two logistic regression models were constructed; one for patients with available spine MRI but not CSF studies and the other for patients who had both spine MRI and CSF studies. Both crude and adjusted odds ratios (OR), their corresponding 95% confidence intervals (CI) and two-sided P-values were reported. Log-likelihood ratio was used to assess the goodness of fit of the model. Significance was set at the 5% level and all statistical analyses were performed using the Statistical Package for Social Sciences (IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The institutional ethical boards approved the study in both MS centers.

### 3. Results

Of the 554 patients presenting for a first visit, 123 (22%) were referred for an opinion regarding therapy. Of the remaining 431 patients included in this study, 394 (92%) were referred for clinical and 37 (8%)

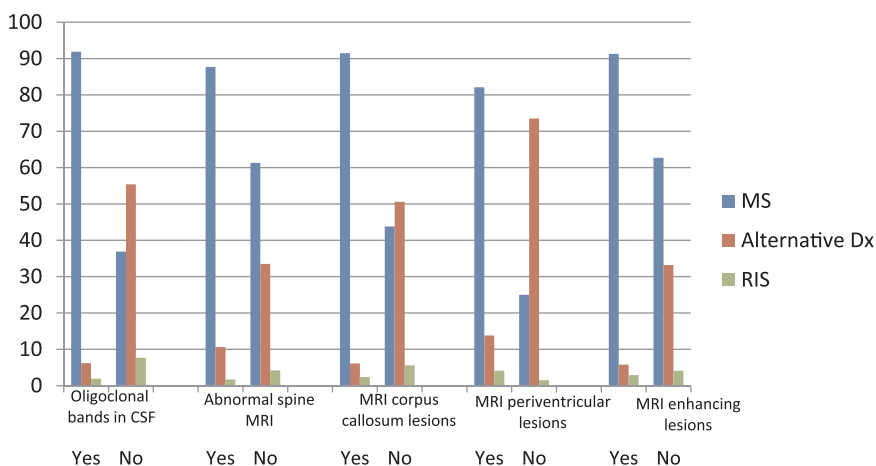


Fig. 3. Probability (%) of having MS based on presence or absence of different variables.

for radiological suspicion of MS. The diagnosis of MS was confirmed in 300 (70%) patients, while an alternative diagnosis was established in 114 (26%) (Table 1), RIS in 15 (3.5%), and an unknown diagnosis in 2 (0.5%) patients. Of 394 patients referred for clinical suspicion, 75% turned out to have MS as opposed to only 8% of 37 patients referred for radiological suspicion (Fig. 1). Among the 114 patients who ended up with a non-MS diagnosis, the most common alternative diagnostic categories were psychogenic (16.3%), non-specific MRI white matter lesions (14.7%), neuromyelitis optica (NMO) (9.5%), migraine (8.6%) and systemic autoimmune disorders (8.6%) (Fig. 2).

The results of univariate analysis of all clinical and paraclinical predictors of MS vs. alternative diagnosis is summarized in Table 2. Patients with RIS or unknown final diagnosis were excluded from this analysis. Clinically, younger age, motor presentation, absence of systemic symptoms, negative medical history and abnormal neurological examination were the strongest predictors of a final MS diagnosis. Radiologically, periventricular, callosal, infratentorial, juxtacortical, spinal and enhancing lesions were significantly associated with a final MS diagnosis. With respect to laboratory investigations, presence of CSF oligoclonal bands, elevated CSF IgG index, and bilaterally abnormal VEP were associated with a final MS diagnosis. On the other hand, gender, disease duration, family history, abnormal serology, abnormal SSEP or BAER and abnormal CSF cell count, glucose or protein were not predictive of the final diagnosis. Two multivariate analyses were carried out. The first was on patients who had both brain and spine MRI available, and the second on patients with brain and spine MRI in addition to CSF studies. The strongest predictors of a final MS diagnosis were presence of oligoclonal bands in the CSF, and periventricular, corpus callosum, spinal ( $P < 0.0001$ ) or enhancing ( $P = 0.005$ ) lesions on MRI (Tables 3, 4). The predictive value of each of those parameters is shown in Fig. 3. The probability of a final MS diagnosis in patients with periventricular, corpus callosum or enhancing lesions on MRI was 82%, 92% and 91%, respectively, and 92% for patients with CSF oligoclonal bands. However, the absence of those parameters was not helpful in differentiating between MS and other alternative diagnoses.

#### 4. Discussion

This is the largest published series addressing the initial misdiagnosis of MS, and the first regional study to comprehensively assess clinical, radiological and laboratory predictors of a non-MS diagnosis among patients referred to specialized MS centers for suspected MS. Among patients referred for a suspicion of MS, 30% turned out to have a different diagnosis, a proportion similar to that reported by Poser: of 366 patients referred to his clinic with a diagnosis of MS, 35% ended up with an alternative diagnosis (Poser et al., 1983). Similarly, Nielsen et al. could confirm the diagnosis of definite or probable MS in 67% of 377 patients referred with a suspected diagnosis of MS (Nielsen et al.,

2005). Carmosino et al. however, reported that only 33% of 281 patients referred with a question regarding diagnosis of MS were confirmed to have MS or possible MS, but a longer follow-up would have probably increased that percentage (Carmosino et al., 2005). It is of interest that autopsy studies of patients with a definite diagnosis of MS before the advent of MRI, showed that the diagnosis was incorrect in only 6%. In the pre-MRI era, the proportion of patients with MS misdiagnosis was also estimated to be around 5–10% (Davis, 1990; Engell, 1988). The significantly higher percentage of misdiagnosis in the modern era is partly due to the overuse and probable misinterpretation of MRI studies. In our study, the proportion of patients with a final MS diagnosis among those referred solely for MRI suspicion was only 8% as opposed to 75% of patients referred based on clinical symptoms or physical findings. It should be noted that MRI criteria for MS diagnosis were not developed to differentiate MS from other mimickers but rather to identify patients with symptoms typical of inflammatory demyelination who are at high risk for converting to MS. In real world practice however, such as in our study, this is frequently not the case since patients with atypical or psychogenic symptoms such as paresthesias, dizziness, blurred vision or migrainous auras are frequently referred for brain MRI. Since nonspecific white matter abnormalities are not uncommon in the general population especially in migraineurs, this combination of clinical and radiological features might lead to misdiagnosis of MS. In fact, the most common MS misdiagnoses reported in a survey of American and Canadian MS specialists were nonspecific white matter abnormalities and small vessel ischemic disease (Solomon et al., 2012). It is of note that initial misdiagnosis led to inappropriate initiation of disease modifying therapies in > 26% of those patients. Our study reflects real world practice whereby patients are referred to our MS centers with a diagnosis of MS and sometimes already started on treatment based on nonspecific symptomatology and radiological features. In the study by Solomon et al., the combination of nonspecific symptoms and MRI abnormalities accounted for more than half of the misdiagnosed patients. The type and frequency of alternative diagnoses in our Middle Eastern population was not significantly different from what has been reported in Western populations (Carmosino et al., 2005; Solomon et al., 2012). The most common non-MS diagnoses in our series were psychogenic disorders, nonspecific MRI lesions, NMO and migraine, similar to the most common MS misdiagnoses recently reported by Solomon et al. (2016) namely migraine, fibromyalgia, abnormal MRI with nonspecific symptoms, psychogenic disorders and NMO.

When a multivariate logistic regression analysis was carried out for patients with available brain and spine MRI, or additional CSF studies, the strongest predictors of a final MS diagnosis were presence of oligoclonal bands in the CSF, and periventricular, corpus callosum, spinal or enhancing lesions on MRI. But once CSF studies were included in the analysis, the presence of oligoclonal bands became the strongest

predictor of a final MS diagnosis. In all the published McDonald criteria, the panelists have stressed that such criteria should only be applied in patients presenting with typical CIS suggestive of MS or symptoms consistent with CNS inflammatory demyelinating disease. In clinical practice however, as our cohorts have shown, this is not always the case. In spite of that, the most significant predictors of a final MS diagnosis in our patients were similar to the McDonald criteria for dissemination in space and time, namely presence of periventricular, spinal and enhancing lesions, with the addition of CSF oligoclonal bands. Many experts have recommended adding the latter to the diagnostic criteria to improve their specificity.

The main limitation of this study is the retrospective nature of data collection. However, all patients were prospectively followed as part of local MS registries in both centers. Although MRIs protocols were not standardized as expected in a real world setting, all MRI images were reviewed by neurologists with MS expertise.

In conclusion, misdiagnosis of MS is still frequent in clinical practice despite the advances in neuroimaging, which is partly due to the indiscriminate use of this new technology. The type and frequency of alternative diagnoses are similar in the Middle East and North America. We identified certain clinical, radiological and laboratory predictors of a final MS diagnosis which would help practicing neurologists avoid diagnostic pitfalls.

#### Appendix A. Supporting information

Supplementary data associated with this article can be found in the

online version at <http://dx.doi.org/10.1016/j.msard.2017.09.016>.

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