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A Meta-Analysis on the Performance of the gMS-Classifier Dx Blood Test for Differentiating RRMS Patients from Other Neurological Disease Patients

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INTRODUCTION

A diagnosis of multiple sclerosis (MS) can be elusive, because of variability and vagueness of symptoms that may mimic other neurological diseases (OND). After initial diagnostic work-up, and careful consideration of MS diagnostic criteria;[1-4] for some patients a diagnosis of MS or a diagnosis of an alternative neurological disease may be concluded by the neurologist. However, many patients leave the MS center not receiving a diagnosis or timely and appropriate treatment. These patients look forward to repeated imaging and laboratory tests over a period of observation before reaching a conclusive diagnosis.[5]

OBJECTIVE

Summarize the overall diagnostic performance of the gMS-Classifier Dx blood test for differentiating relapsing remitting multiple sclerosis (RRMS) from other neurological disease (OND) patients. Including patients with potential typical, atypical and MS-like symptoms.

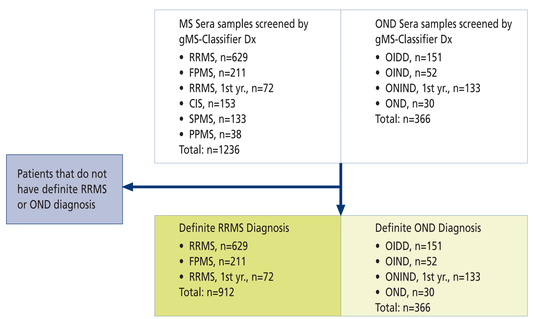
METHODS

Design Meta-analysis based on five gMS®Dx cohort studies published before October 2010.[6-9]

Serum Biomarker IgM antibodies to α-glucose antigen GAGA4 normalized by total IgM (gMS-Classifier Dx).

Selection Criteria In order to reduce heterogeneity only definite RRMS patients and other neurological disease patients were selected (**Figure 1**). Patient description is in **Table 1 and Table 2.**

Figure 1: Patient Selection Flow Chart



RRMS=Relapsing Remitting Multiple Sclerosis, FPMS= First Presentation Relapsing Remitting Multiple Sclerosis, CIS=Clinically Isolated Syndrome, SPMS=Secondary Progressive Multiple Sclerosis, PPMS=Primary Progressive Multiple Sclerosis, OIDD=Other Inflammatory Demyelinating Disease, OIND=Other Inflammatory Neurological Disease, ONIND=Other Non-Inflammatory Neurological Disease OND=Other Neurological Disease.

Statistical Analysis Diagnostic performance was tested by fixed and random effects analyses, calculating diagnostic-odds ratio (dOR) and 95% confidence intervals (CI). Specificity, Sensitivity and likelihood ratios (LR) and χ^2 are also reported. Heterogeneity among studies was measured by the Q statistic.

RESULTS

Q-Test for Heterogeneity

There was no variation in study outcome between the five cohort studies (p=0.17).

Diagnostic Accuracy

A higher proportion of RRMS patients (297/912), were positive for the gMS-Classifier Dx test compared to OND patients (33/366). Results, correspond to:

Specificity 91%, Sensitivity 33%, LR+ 3.61, LR- 0.74 (χ^2, p<0.0001). Other neurological disease patients details are listed (**Table 2 and Table 3**).

Diagnostic Odds Ratio (dOR)

The overall, dOR of the gMS-Classifier Dx test according to fixed-effects model was 5.7, 95% CI, 3.7 to 8.7, p-value<0.05 (**Table 3 and Figure 2**). When central nervous system (CNS) OIDD patients were not included the dOR was 7.2, 95% CI 4.1 to 12.5 (**Figure 3**).

Table 1: Details of Other Neurological Disease Patients Screened by gMS-Classifier Dx

Type of Disease	Disease
	(n Positive for gMS-Classifier Dx/n Total)
OIDD (16/151)	Optic Neuritis (9/87), Transverse Myelitis (4/23), Acute Disseminated Encephalomyelitis (2/16), Guillain–Barré Syndrome (0/13), Neuromyelitis Optica (1/7), Chronic Inflammatory Demyelinating Polyneuropathy (0/5)
OIND (6/52)	Meningitis (4/22), Borreliosis (0/6), Vascular (1/5), HIV (0/4), Myasthenia Gravis (0/1), Sarcoidosis (1/2), Labyrinthitis (0/2), Encephalitis (0/1), Graves disease (0/1), Sinusitis (0/1), Epidural Abscess (0/1), Brachial Plexitis (0/1), Brachial Plexopathy (0/1), Neurosyphilis (0/1), Cerebral Malaria (0/1), Systemic Lupus Erythematosus (0/1), Sjögren Encephalopathy (0/1)
ONIND (11/133)	Amyotrophic Lateral Sclerosis (2/18), Headache (1/12), Stroke (0/10), Migraine (3/12), Dementia (0/8), Ophthalmologic Disorder (0/7), Parkinson's (1/4), Fibromyalgia (0/4), Facial Hemiatrophy (0/4), Motor Disorder (0/5) , Dystonia (0/3), Huntington's (0/3), Anxiety (0/3), Vertigo (2/3), Intracranial Hypertension (0/1), Cancer (0/3), Diabetic Retinopathy/Amyotrophy (0/3), Degenerative Disc Disease (0/2), Cerebrovascular (1/2), Meniere's (0/2), Facialis (0/2), Facial Myokymia (1/2), Psychiatric Disorder (0/2), Nerve Palsy (0/2), Tumor (0/3), Valproate-Induced Encephalopathy (0/1), Brain Stem Ischemia (0/1), Numbness (0/1), Occipital Neuralgia and Ataxia (0/1), Chronic Insomnia (0/1), Tingling NYD (0/1), Neurogenic Bladder (0/1), Myelopathy (0/1), Neuralgia (0/1), Quadriplegia (0/1), Meningismus (0/1), Adrenomyelopathy (0/1), Normal Pressure Hydrocephalus (0/1)
OND (0/30)	Ganglioside (0/7), Myelin Associated Glycoprotein (0/5), Amphiphysin (0/5), Yo (0/5), HU (0/4), Ri (0/3), Ribosomal-P for Suspected Lupus (0/1)

Table 2: Details of OND Type According to Cohort

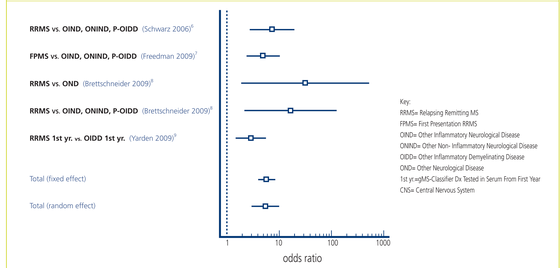
Cohort	RRMS	ONIND	OIND	OND	Peripheral OIDD	CNS OIDD	Total
Schwarz 2006 (n)	49	39	7		2		97
Freedman 2009 (n)	211	74	39		5	11	340
Brettsneider-I 2009 (n)	497			30			527
Brettsneider-II 2009 (n)	83	20	6		9		118
Yarden 2009 (n)	72				2	122	196
Total (n)	912	134	51	30	18	133	1278

Table 3: Meta Analysis Odds Ratio Results

Study Cohort	CNS OIDD	RRMS Positive gMS Dx/ Total RRMS	OND Positive gMS Dx/ Total OND	Diagnostic Odds Ratio (95%CI)
RRMS vs. OIND, ONIND, OIDD (Schwarz 2006)	With	27/49	7/48	7.2 (2.7 to 19.1)
	Without	27/49	7/48	7.2 (2.7 to 19.1)
RRMS vs. OIND, ONIND, OIDD (Freedman et al., 2009)	With	56/211	9/129	4.8 (2.3 to 10.1)
	Without	56/211	9/118	4.4 (2.1 to 9.2)
RRMS vs. OND (Brettsneider 2009)	With	166/497	0/30	30.6 (1.9 to 504.2)
	Without	166/497	0/30	30.6 (1.9 to 504.2)
RRMS vs. OIND, ONIND, OIDD (Brettsneider 2009)	With	27/83	1/35	16.4 (2.1 to 126.2)
	Without	27/83	1/35	16.4 (2.1 to 126.2)
RRMS vs. OIDD (Yarden 2009)	With	21/72	16/124	2.8 (1.3 to 5.8)
	Without	Cohort not included, since 122/124 OND were excluded		
Total (Fixed Effects)	With	297/912	33/366	
	Without	276/840	17/231	
Total (Diagnostic Accuracy)	With	Specificity 91%, Sensitivity 33%, LR+ 3.61, LR- 0.74		
	Without	Specificity 93%, Sensitivity 33%, LR+ 4.46, LR- 0.73		

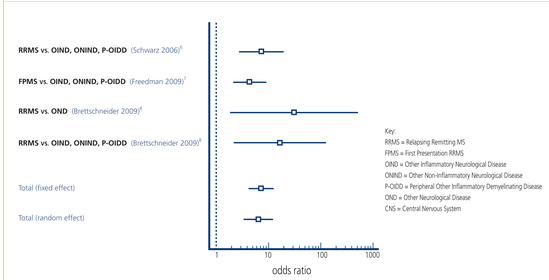
Number of patients positive for gMS-Classifier Dx is shown over total number of patients. Diagnostic odds ratio is shown for the separate cohort studies. The Q-Test for heterogeneity was negative, thus the weighted summary odds ratio is according to the fixed effects model calculated by the Mantel-Haenszel method. The Meta-Analysis was performed with and without CNS OIDD. Abbreviations are detailed in figure below.

Figure 2. Meta-Analysis with CNS OIDD



Forest Plot of the five cohort studies[6-9] included in the gMS-Classifier DX Meta-Analysis, with 95% CI and the overall effect with 95%CI. The odds ratio with 95% CI is drawn in logarithmic scale. Emphasis is put on fixed effects model, since there was no heterogeneity between the outcomes of the studies.

Figure 3. Meta-Analysis without CNS OIDD



Forest Plot extracted from Figure 2, excluding CNS OIDD patients. The odds ratios with 95% CI are drawn in logarithmic scale. Emphasis is put on fixed effects model, since there was no heterogeneity between the outcomes of the studies.

CONCLUSIONS

gMS-Classifier Dx is a highly specific "rule in" blood test for the diagnosis of RRMS, being highly informative when positive. Such "rule-in" tests are usefully applied when confirming a diagnosis suggested by other data, or when treatment has severe side effects.[10]

The diagnostic OR improved when patients having typical MS symptoms (CNS OIDD patients) were excluded from the Meta-analysis. This is most likely due to their high risk of eventually being diagnosed with MS compared to patients with atypical MS or MS-like symptoms.[5]

MS diagnostic tests put much emphasis on magnetic resonance imaging (MRI), which is highly sensitive but lacking in specificity.[11] Thus, gMS-Classifier Dx can be used in conjunction with MRI tests allowing for much needed earlier diagnosis of inconclusive cases.

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DISCLOSURES

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