

Anti-GAGA4 IgM Antibodies (gMS[Dx Test) Differentiate Newly Diagnosed Relapsing Remitting Multiple Sclerosis Patients from Other Inflammatory Demyelinating Disease Patients within One Year from Diagnosis

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Objective: To assess the ability of the gMSDx test, which is based on anti-GAGA4 IgM antibody detection, and additional anti-alpha-glucose IgM antibodies to differentiate newly diagnosed relapsing remitting multiple sclerosis (RRMS) patients from patients with other inflammatory demyelinating diseases (OIDD) within one year from diagnosis.

Background: Previous studies found that the anti-Glc(-1,4)Glc() (anti-GAGA4) IgM serum biomarker can differentiate RRMS/CIS patients from other neurological disease (OND) patients. **Design/Methods:** Cross-sectional retrospective analysis of frozen sera with masked identity and clinical data that were collected throughout the first year after diagnosis, in five centers (n=205): USA (n=98), Denmark (n=73), Italy (n=10) and two German centers (n=24). Sixty-eight RRMS patients (35.58.1yrs, 72.1%F) and 137 OIDD patients (optic neuritis, n=77; transverse myelitis, n=40; acute demyelinating encephalomyelitis, n=12; neuromyelitis optica, n=8; 36.48.4yrs, 65.7%F) entered the study. Samples were tested for anti-GAGA4 IgM(EU)/TIgM(g/L)0.5 (gMSDx), and other five anti-alpha-glucose IgM antibodies (Glycominds, Lod, Israel).

Results: The gMSDx test distinguished newly diagnosed RRMS patients from newly diagnosed OIDD patients [p=0.005, Mann-Whitney; specificity, 85%; sensitivity, 31%; likelihood ratio (LR)₊, 2.12; LR₋, 0.82]. Furthermore, significant differences were observed in RRMS vs. OIDD patients for other anti-alpha-glucose antibodies (anti-GAGA2, p=0.003; anti-GAGA3, p=0.004; anti-GAGA6, p=0.006; anti-a-GlcNAc, p=0.02; anti-P63, p=0.03; Mann-Whitney). An algorithm combining several glycans, anti-GAGA4, anti-GAGA3 and anti-P63 showed that if one or more antibodies were positive, test performance remained similar to anti-GAGA4 alone (specificity, 89%; sensitivity, 31%; LR₊, 2.82; LR₋, 0.78), whereas if two or more antibodies were positive, the LR₊ increased dramatically, but sensitivity decreased (specificity, 96%; sensitivity, 22%; LR₊, 6.04; LR₋, 0.81).

Conclusion/Relevance: The gMSDx test based on anti-GAGA4 IgM(EU)/TIgM(g/L)0.5 immunoassay can differentiate RRMS patients from OIDD patients at the early diagnostic work-up. Other anti-glucose IgM antibodies can also significantly differentiate RRMS patients from OIDD patients, but further studies are required to assess their potential contribution to the anti-GAGA4 antibodies.