

Validation of anti-GAGA4 IgM antibodies for predicting the development of relapsing remitting MS after the first neurological event

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Background: There is an unmet need to develop specific serum based biomarkers for the diagnosis and prognosis of relapsing-remitting MS (RRMS). We have reported that elevated levels of serum anti Glc(alpha,4)Glc(alpha) (GAGA4) IgM antibodies (Ab) exist in RRMS (n=44) patients in comparison to patients with other neurological diseases (OND, n=44) enabling to discern which post-CIS patients convert to RRMS vs. OND. To validate our findings we have further investigated an additional and larger cohort of patients. Objectives: To validate the predictive value of IgM Ab against GAGA4, to identify patients with CIS that will evolve to RRMS in a larger cohort.

Methods: Retrospective analysis of 167 frozen sera taken from patients presenting for diagnostic work-up after a first acute neurological event consistent with demyelination (CIS) and were followed for a minimum of 4 years to confirm RRMS diagnosis. The "other neurological disease" (OND) control group comprised of 85 patients, 32 with other inflammatory disorders (OIND), and 53 with non-inflammatory neurological disease (ONIND). Sera were diluted 1:1200 and levels of anti GAGA4 IgM Ab measured by immunoassay normalized by dividing to square root of IgM levels (mg IgM/ml serum).

Results: Significantly higher levels of anti-GAGA4 IgM/Total IgM ($p=0.029$, T test) Ab were observed in CIS patients who converted to RRMS compared to the OND group. Using a cut-off of 42 (anti GAGA4 IgM EU/square root (mg IgM/ml serum)), we have found that 46/167 (28%) converting CIS patients were positive, whereas 77/85 (91%) OND patients were negative, corresponding to a sensitivity of 28% (CI 95%: 22.8-34.6%), a specificity of 91% (CI 95%: 82.3-95.8%), PPV of 86.5%, and NPV of 36.4%.

Conclusions: A higher level of anti-GAGA4 IgM Ab was further validated as a predictor for the development of RRMS in CIS patients.