

## **Intrathecal immunoglobulin M synthesis is associated with higher disease activity and severity in multiple sclerosis**

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## Abstract

### Introduction:

Biomarkers predicting acute inflammatory activity and chronic worsening of multiple sclerosis (MS) are in need for individually adapted therapy (precision medicine). We aimed to determine how in relapsing MS (RMS) intrathecal immunoglobulin M (IgM) synthesis, in addition to presence of IgG synthesis, is associated with 1.) time to first relapse, 2.) degree of neuronal damage, 3.) MRI disease activity, 4.) clinical disability and 5.) choice of therapy.

### Methods:

Cerebrospinal fluid measurements, clinical, MRI data as well as Serum neurofilament light chain (sNfL) concentrations from 530 patients with RMS in the observational longitudinal Swiss MS Cohort Study were included. Patients were either untreated (197 individuals) or under disease modifying therapies (DMTs) according to national treatment algorithms.

Patients were categorized by presence or absence of oligoclonal IgG bands (OCGB), and intrathecal IgG and IgM fraction (IgG<sub>Intrathecal Fraction</sub> (IF), IgM<sub>IF</sub>). Time to first relapse and associations with sNfL concentrations, total and new/enlarging T2w lesions, MS Severity Score (MSSS), and first initiation of a high efficacy therapy were analyzed in uni- and multivariable (adjusted for age at first symptoms, sex and DMT category) statistical models.

### Results:

By *categorical* analysis, the median time to first relapse in patients with IgM<sub>IF</sub> was 28 months shorter (HR 1.944 [CI 1.237; 3.054],  $p < 0.01$ ) and they had on average a 1.11 steps higher MS Severity Score ([CI 0.382, 1.843],  $p < 0.01$ ) compared to patients without any immunoglobulin synthesis. Moreover, they had more yearly new/enlarging T2w lesions with an incidence ratio of 3.13 ([CI 1.29; 7.58],  $p = 0.01$ ), higher sNfL-Z-scores and higher total T2w lesion counts (IR 2.53 [CI 1.63, 3.93],  $p < 0.01$ ). Eventually, those patients with additional IgM<sub>IF</sub><sup>+</sup> also had a shorter interval from disease onset to a first relapse (HR 1.944 [CI 1.237; 3.054],  $p < 0.01$ ). These associations were absent, or smaller by a similar level degree, in patients only positive for OCGB or OCGB/IgG<sub>IF</sub>.

Furthermore, *quantitative* analyses revealed that in patients with IgM<sub>IF</sub><sub>≥median</sub>, time to a first relapse and to escalation to high efficacy therapy was 32 (HR 1.851 [CI 1.172, 2.922],  $p < 0.01$ ) and 203 (HR 2.347 [CI 1.325, 4.156],  $p < 0.01$ ) months earlier, respectively, versus those with IgM<sub>IF</sub><sub><median</sub>; similar dose-dependent associations were found for MRI disease activity and sNfL-Z-scores. Again, no corresponding correlations of these measures with IgG<sub>IF</sub> levels were observed.

### Conclusion:

Intrathecal Immunoglobulin M synthesis is a biomarker associated with higher clinical (relapse, progression) and paraclinical (MRI lesional load, neuronal loss) disease activity and severity, and earlier escalation to high efficacy DMTs and may support its use for therapeutic decision making in early MS.