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Diagnostic, Prognostic, and Disease Activity Biomarkers in Multiple Sclerosis

Akademisk avhandling

Som för avläggande av Igal Rosenstein doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Sahlgrens Aula, Blå stråket 5, den 2023-03-31, klockan 09:00.

av Igal Rosenstein

Fakultetsopponent:

Manuel Comabella

Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, CEM-Cat. Barcelona, Spain.

Avhandlingen baseras på följande delarbeten

I. Rosenstein I, Axelsson M, Novakova L, Blennow K, Zetterberg H, Lycke J. Exploring CSF neurofilament light as a biomarker for MS in clinical practice; a retrospective registry-based study. *Mult Scler.* 2021:13524585211039104.

II. Rosenstein I, Rasch S, Axelsson M, Novakova L, Blennow K, Zetterberg H, Lycke J. . Kappa free light chain index as a diagnostic biomarker in multiple sclerosis: A real-world investigation. *Journal of neurochemistry.* 2021.

III. Rosenstein I, Rasch S, Axelsson M, Novakova L, Blennow K, Zetterberg H, Lycke J. Increased intrathecal neurofilament light and immunoglobulin M predict severe disability in relapsing-remitting multiple sclerosis. *Frontiers in immunology.* 2022;13:967953.

IV. Rosenstein I, Axelsson M, Novakova L, Rasch S, Blennow K, Zetterberg H, Lycke J. High levels of kappa free light chain synthesis predict cognitive decline in relapsing-remitting multiple sclerosis. *Frontiers in immunology.* DOI: 10.3389/fimmu.2023.1106028.

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Diagnostic, Prognostic, and Disease Activity Biomarkers in Multiple Sclerosis

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Abstract

Multiple sclerosis (MS) is the most common immune-mediated disease of the central nervous system. While benign cases exist, if left untreated, MS results in the compounding accumulation of disability. In the last two decades, various highly effective disease-modifying therapies (DMTs) have evolved, precipitating significant improvements in prognosis. The prompt diagnosis of MS and initiation of DMT are therefore essential to reduce the risk of disability. The gold standard for diagnosing and monitoring MS is currently magnetic resonance imaging (MRI), but since MS pathophysiology is multifaceted, there is a growing necessity for the use of various biomarkers. Research concerning fluid biomarkers in MS has rapidly evolved in recent decades. Biomarkers are now used to increase diagnostic precision, to make prognostic predictions that may influence treatment decisions, and to monitor treatment response. In this thesis, we have evaluated the clinical utility of cerebrospinal fluid (CSF) neurofilament light (NfL), intrathecal kappa free light chain (KFLC) index, and immunoglobulin (Ig) M synthesis (ITMS) in retrospective real-world cohorts. In study **I**, we included 757 individuals with relapsing-remitting MS (RRMS) with determination of CSF NfL (cNfL) between 2001 and 2018. We demonstrated that cNfL reflects both clinical and radiological signs of inflammatory disease activity, as well as treatment response. The sensitivity and specificity of cNfL to detect disease activity were 75% and 98.5%, respectively. High cNfL at the onset of MS predicted the progression to meaningful disability milestones, such as secondary progressive MS (hazard ratio [HR] 2.5, 95% confidence interval [CI] 1.4–4.2, p=0.001). In study **II**, KFLC index had a higher diagnostic sensitivity than IgG oligoclonal bands to distinguish MS (n=223) from controls (n=104) and had comparable diagnostic specificity. DMT did not influence the level of KFLC index, and it was not affected by demographic factors or associated with other degenerative or inflammatory CSF biomarkers. In study **III**, we demonstrated the ability of ITMS as a disease severity biomarker to predict early disease activity and disability worsening in RRMS. The intrathecal fraction of IgM exhibited a moderate association with evidence of disease activity within 24 months of diagnosis (adjusted HR [aHR] 3.7, 95%CI 2.7-5, p<0.001). For the first time, we showed that combining ITMS with cNfL substantially increased the magnitude of the predicted risk of severe MS disease course (for expanded disability status scale ≥6 & $cNfL^{+}$/IgM-$index^{+}$: aHR 8.2, 95% CI 2.3-30, p<0.001). In study **IV**, high KFLC index (>100) at MS onset was predictive of cognitive impairment, as determined by serial single-digit modalities tests (SDMT; aHR 10.5, 95% CI 2.2-50.8, p=0.003; median time to SDMT reduction 7 years). In summary, we showed that CSF biomarker data retrieved from real-world RRMS cohorts had diagnostic and prognostic utility. Our data support the inclusion of cNfL, KFLC-index, and ITMS in the routine diagnostics and evaluation of suspected RRMS.

Keywords: multiple sclerosis, fluid biomarkers, cerebrospinal fluid, diagnosis, prognosis
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