Investigation of the pathophysiology of progression in multiple sclerosis

Studies on cerebrospinal fluid biomarkers

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av

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Avhandlingen baseras på följande delarbeten:

I   M. Axelsson, C. Malmeström, S. Nilsson, S. Haghighi, L. Rosengren, J. Lycke. *Glial fibrillary acidic protein: a potential biomarker for progression in multiple sclerosis. J Neurol 2011*; 258: 882-888

II   N Mattsson, M Axelsson, S Haghighi, C Malmeström, G Wu, R Anckarsäter, S Sankaranarayanan, U Andreasson, S Fredrikson, A Gundersen, L Johnsen, T Fladby, A Tarkowski, E Trysberg, A Wallin, H Anckarsäter, J. Lycke, O Andersen, AJ. Simon, K Blennow, H Zetterberg *Reduced cerebrospinal fluid BACE1 activity in multiple sclerosis Mult Scler* 2009 ; 15: 448-454

III   K. Augutis[®], M. Axelsson[®], E. Portelius, G. Brinkmalm, U. Andreasson, M. K. Gustavsson, C. Malmeström, J. Lycke, K. Blennow, H. Zetterberg and N. Mattsson. [®]contributed equally *Cerebrospinal fluid biomarkers of ß-amyloid metabolism in multiple sclerosis* *Mult Scler* published online 15 October 2012

IV   M. Axelsson, C. Malmeström, M. Gunnarsson, H. Zetterberg, P. Sundström, J. Lycke[®], A. Svenningsson[®]. [®]contributed equally *Immunosuppressive therapy reduces axonal damage in progressive multiple sclerosis* *Manuscript-Submitted*

V   M. Axelsson, N. Mattsson, C. Malmeström, H. Zetterberg, J. Lycke *The influence from disease duration, clinical course, and immunosuppressive therapy on the synthesis of intrathecal oligoclonal IgG bands in MS Manuscript-Submitted*

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Abstract

Multiple Sclerosis (MS) is considered an autoimmune disease of the central nervous system (CNS). It usually starts with a relapsing remitting (RR) course that eventually transforms into progressive (P)MS, showing neurodegenerative features. The pathogenesis behind the transition from RRMS to PMS is essentially unknown. The aim of this thesis was to investigate if biomarkers in the cerebrospinal fluid (CSF) of MS patients could provide new insights into the pathophysiology of MS progression, and if biomarker levels could reflect disease activity, disability progression, or therapeutic efficacy.

Three study designs were established. The first was cross sectional and comprised MS patients, healthy controls (HC) and control subjects with another inflammatory disease. The second used a long-term follow-up setting in which RRMS, PMS and HC were assessed twice 8-10 years apart. The third used immunomodulatory or immunosuppressive intervention (natalizumab, mitoxantrone or rituximab) and assessed MS patients pre- and 12-24 months post-treatment. CSF biomarkers were analyzed for i) axonal damage (neurofilament light, NFL), ii) astrogliosis (glial fibrillary acidic protein, GFAP), iii) amyloid precursor protein metabolism (BACE1 activity, and sAPP/$A\beta$ metabolites) iv) B-cell regulation (CXCL13) and v) intrathecal IgG synthesis (IgG index, oligoclonal IgG bands (OCB)).

Increased mean GFAP levels were found in all courses of MS with the highest levels in PMS, whereas the mean NFL level of this MS population was not different from that of HC (Paper I). At long-term follow-up GFAP levels correlated with disability and had prognostic value. In contrast, increased NFL levels were found in another MS population compared to HC (Paper IV). This discrepancy might be explained by differences in disease activities between the investigated populations and due to improved sensitivity of the NFL immunoassay. We found signs of downregulation of BACE1 activity (Paper II) and sAPP/$A\beta$ metabolism (Paper III) in MS. The levels of sAPP/$A\beta$ in MS were generally decreased compared to HC suggestive of impaired neuronal function in MS. Mass spectrometry studies indicated that the sAPP/$A\beta$ metabolism was changed in PMS compared to HC by formation of other decomposition products.

We demonstrated, in opposite to the general view, changed number and pattern of OCB in CSF over time, which correlated to CXCL13 levels (Paper V). Natalizumab treatment increased sAPP/$A\beta$ metabolites towards HC levels. Immunosuppressive treatment (mitoxantrone, rituximab) reduced NFL and CXCL13 in PMS. Interestingly, significantly lower NFL levels were found prior to immunosuppression in PMS patients previously treated with interferon beta or glatiramer acetate, suggesting an impact on axonal damage also with first line MS therapies. Immunosuppressive treatment did not influence the number or pattern of OCB (Paper V).

In conclusion, our studies present evidence that increased immune activity plays a critical role in PMS for axonal damage and seemed to influence sAPP/$A\beta$ metabolism. In PMS, the reduced NFL level following immunosuppressive treatment clearly supports a relationship between CNS inflammation and neurodegeneration. Biomarkers in CSF provide unique information about the pathophysiology in PMS, and may serve as complement to clinical and MRI measures for assessment of disease activity, progression, severity and therapeutic efficacy.

Key words: multiple sclerosis, cerebrospinal fluid, biomarker, disease progression, NFL, GFAP, CXCL13, BACE1, sAPP/$A\beta$, IgG, oligoclonal IgG bands, IgG index