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Investigations into the role of Epstein-Barr virus in the pathogenesis of multiple sclerosis

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg. Fredagen den 30 september 2022, klockan 9.00

av Daniel Jons

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Avhandlingen baseras på följande delarbeten

I. **Jons D**, Kneider M, Fogelstrand L, Jeppsson A, Jacobsson S, Andersen O. *Early hematopoiesis in multiple sclerosis patients.* J Neuroimmunol. 2016;299:158-63.

II. **Jons D**, Zetterberg H, Malmeström C, Bergström T, Axelsson M, Blennow K, Thulin M, Sundström P, Andersen O. *Intrathecal immunoreactivity in people with or without previous infectious mononucleosis.* Acta Neurol Scand. 2020;142(2):161-8.

III. **Jons D**, Persson Berg L, Sundström P, Haghighi S, Axelsson M, Thulin M, Bergström T, Andersen O. *Follow-up after infectious mononucleosis in search of serological similarities with presymptomatic multiple sclerosis.* Mult Scler Relat Disord. 2021;56:103288.

IV. **Jons D**, Zetterberg H, Biström M, Alonso-Magdalena L, Gunnarsson M, Vrethem M, Blennow K, Nilsson S, Sundström P, Andersen O. *Axonal injury in asymptomatic individuals preceding onset of multiple sclerosis.* Ann Clin Transl Neurol. 2022;9(6):882-7.

V. **Jons D**, Bergström T, Zetterberg H, Biström M, Alonso-Magdalena L, Gunnarsson M, Vrethem M, Brenner N, Butt J, Blennow K, Nilsson S, Huang J, Kockum I, Olsson T, Waterboer T, Sundström P, Andersen O. *Increase in Epstein-Barr virus sero-reactivity precedes neuroaxonal damage in pre-symptomatic multiple sclerosis*. Manuscript .

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

GÖTEBORGS UNIVERSITET

Investigations into the role of Epstein-Barr virus in the pathogenesis of multiple sclerosis

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Abstract

Epstein-Barr virus (EBV) infection may be a prerequisite for the development of MS. Virtually all MS patients have antibodies to Epstein Barr virus nuclear antigen 1 (EBNA1), compared to 90-95% of healthy individuals. This antibody response is increased both in pre-symptomatic and manifest MS. Infectious mononucleosis (IM) the symptomatic variant of primary EBV infection of adolescence, doubles the risk of future MS. This thesis investigates the EBV-MS connection both by studying individuals with the risk factor for MS of previous IM and by investigating samples acquired prior to MS onset. It aims at determining the temporal relationship between neuroaxonal damage and EBV antibody response before MS onset and searches for an immunological residual state after IM. The first paper examined B cell populations in bone marrow from MS patients. Two papers were follow-up studies that investigated individuals for persistent immunological activity a decade after IM. We assayed seven selected cytokines and chemokines in the CSF (study II), and antibody reactivity to EBV, Measles and Varicella zoster in sera and CSF (study III). Two nested case–control studies (IV and V), of 669 pre-symptomatically acquired blood samples from individuals who later developed MS, investigated the marker of neuroaxonal damage, serum neurofilament light (sNfL), and several anti-EBV antibodies.

No deviations in early B cell lineages were found in MS bone marrow. SNfL concentrations were increased in pre-MS compared to matched controls ($p < 0.0001$). The increase started approximately 10 years before MS onset, significant from 5-10 years before onset ($p = 0.02$), with increasing difference over time. Anti-EBNA1 reactivity showed an increase in pre-MS compared to controls from 10–15 years before onset ($p = 0.001$) and did not increase over time. In the pre-MS group, the percentage of samples with an increased sNfL were concentrated to the EBV positive group compared to the EBV negative group ($p = 0.038$). EBVgp350 antibodies were elevated 10 years after IM ($p = 0.007$), while no significant increase in CSF cytokines was detectable with low power after IM.

In conclusion, neuroaxonal damage is detectable 10 years before MS onset but still preceded by an EBV serological response. We observed less neuroaxonal damage in the small group of EBV negative samples acquired before MS. This strengthens the connection between a previous EBV infection and the start of neuroaxonal damage in pre-symptomatic MS.

Keywords: Multiple sclerosis, Epstein-Barr virus, Serology, Neurofilament light.

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