Respiratory burst and severity of demyelinating diseases

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Based on the following papers

I. **Mossberg N**, Andersen O, Nilsson S, Dahlgren C, Hellstrand K, Lindh M, Svedhem Å, Bergström T, Movitz C. Oxygen radical production and severity of the Guillain-Barré syndrome. *Journal of Neuroimmunology*. 2007; 192(1-2):186-91.

II. **Mossberg N**, Movitz C, Hellstrand K, Bergström T, Nilsson S, Andersen O. Oxygen radical production in leukocytes and disease severity in multiple sclerosis. *Journal of Neuroimmunology*. 2009; 213(1-2):131-4.

III. **Mossberg N**, Nordin M, Movitz C, Nilsson S, Svedhem Å, Hellstrand K, Bergström T, Andersson B, and Andersen O. The Recurrent Guillain-Barré syndrome. Submitted.

IV. **Mossberg N**, Andersen O, Nordin M, Nilsson S, Svedhem Å, Bergström T, Hellstrand K, and Movitz C. Leukocyte oxygen radical production determines disease severity in the recurrent Guillain-Barré syndrome. *Journal of Inflammation.* 2010 Aug 8;7(1):40.

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Respiratory burst and severity of demyelinating diseases

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Multiple sclerosis (MS) and the Guillain-Barré syndrome (GBS) are tissue-specific inflammatory diseases of the central and the peripheral nervous system, respectively. A contemporary analysis infers that these are complex autoimmune disorders. Issues remaining to be solved are the factors determining susceptibility and the extreme variability in severity displayed by these diseases. The present study examines whether this variability is related to a basal function of the innate immune defence, regulating the intensity of inflammation.

The severity of MS and GBS were evaluated by standard scoring systems, the Multiple Sclerosis Severity Score and the Medical Research Council Score. In addition, hard endpoints such as the need for intensive care unit treatment and the time to independent walking were used in the GBS, which was also evaluated for its proneness to recur.

A possible relationship between these clinical parameters and the function of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase was examined. Phagocytes are endowed with this oxygen radical-forming enzyme, which reduces molecular oxygen to form several reactive oxygen species such as superoxide anion. This process, the "respiratory burst", is a pivotal part of the innate defence against invading micro-organisms. The NADPH oxidase also has a regulatory influence upon the adaptive immune system. A lack of this enzyme elicits a human disease (Chronic Granulomatous Disease) characterized by extensive spontaneous inflammation, while recent studies in animal models imply that a deficiency of NADPH oxidase activity is related to the severity of organ-specific autoimmunity.

The respiratory burst was assayed in the stationary (attack-free) phase of relapsing or slowly progressive multiple sclerosis (N = 60), in the monophasic GBS (N = 23), and in the recurrent GBS (RGBS) (N = 10), each with one age-matched healthy control analyzed simultaneously. The assay was performed by stimulating peripheral leukocytes by peptides, and measuring the amount of superoxide anion produced.

The respiratory burst was markedly weaker in the group of GBS patients with a severe course ($p = 0.0004 - 0.04$). The same relationship was found in RGBS where the severity was expressed as degree of remission ($p = 0.001 - 0.004$) and individual recurrence proneness (interval between relapses and the time from onset to the second episode, $p = 0.006 - 0.03$). An analogous relationship was also demonstrated between a weaker respiratory burst and a severe course of multiple sclerosis ($p = 0.0035 - 0.04$).

In conclusion, the present study demonstrates that the intensity of the respiratory burst markedly contributes to the extreme variability in the severity of these demyelinating disorders. The innate immune system regulates the intensity rather than the susceptibility to these diseases. While loss of this system results in spontaneous autoinflammatory disease, we found that a low function predisposes for a more severe autoimmune disease. The mechanism may be a less effective control of infection and/or of the adaptive immune system.

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