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Review articles

Influences of sex hormones and pregnancy in multiple sclerosis

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Multiple sclerosis (MS) is a chronic, immune-mediated neurodegenerative disabling disease of young adults, and the unpredictable effects last for the rest of their lives. Sex hormones have major effects on brain and spinal neurons. The theory of hormones influencing inflammation and neuronal and glial function has been slowly unraveled. There is increasing evidence that estrogen, progesterone, and testosterone contain immune responses and influence damage repair in the nervous system and play an important role in neuroprotection following brain injury both *in vivo* and *in vitro*. Hormones such as prolactin and vitamin D may be used to modulate the immune response and may also influence the course of MS. The influence of pregnancy in MS has been a matter of controversy for a long time. There is a concept of possible beneficial effect of pregnancy on disease progression. The pursuit of personalized medicine requires development of biomarkers to predict disease course, monitor disease evolution and response to therapies.

Key words: sex hormones, multiple sclerosis, pregnancy

Multiple sclerosis is a common neurological disease in young adults between the ages of 15-40 with an unpredictable course that may be associated with significant disability and diminishing the patient's quality of life. MS affects approximately one of every 1000 people in North America, northern Europe and Australasia. Relapsing-remitting (RRMS) accounts for approximately 80-85 % of all MS cases. MS is characterized by intermittent or chronic damage to the myelin sheaths, focal inflammation and axonal degeneration. Myelination, the process in which oligodendrocytes coat central nervous system (CNS) axons with a myelin sheath, represents an important but poorly understood form of neural plasticity that may be sexually dimorphic in the adult CNS [2,3].

MS is considered to be multifactorial with an autoimmune component. There is growing evidence suggesting that hormones, including sex hormones, can affect and

be affected by the immune system. Higher levels of testosterone in men may partially account for the fact that women with MS outnumber men by 2-3 to 1.

The present pharmacological treatment of MS is limited to the administration of immunomodulatory and anti-inflammatory drugs, which are only palliative and do not significantly slow down the disease progression. Agents that target different cell types in the CNS, protect axonal networks and stimulate the endogenous capacity of myelin repair are of specific need. Estrogens and progestins may be the basis for such a new therapeutic approach and could help protect against myelin loss. Both types of hormones have been shown to promote the viability of neurons and the formation of myelin [1].

Sex hormones have major effects on brain and spinal neurons. The theory of hormones influencing inflammation and neuronal and glial function has been slowly unraveled. There is increasing evidence that estrogen, progesterone, and testosterone contain immune responses and influence damage repair in the nervous system. Hormones such as prolactin and vitamin D, and more recently identifiedones, such as leptin and gherlin, may be used to modulate the immune response and may also influence the course of MS [10]. The effect of female sex hormones is associated with hormonal alteration on the disease process. Sex steroids (particularly estrogen, androgen, and progesterone) also play an important role in neuroprotection following brain injury both *in vivo* and *in vitro* [7]. The role of male steroids in neuroprotection is less clear.

Prolactin (PRL) is a neuroendocrine peptide with potent immunomodulatory properties. Hyperprolactinemia enhances several autoimmune disorders and may play a role in the pathogenesis of MS [4]. Significantly higher prolactin levels in serum and cerebrospinal fluid (CSF) were found in female relapsing-remitting MS (RRMS) patients, but not in males. The elevated PRL levels could be the result of an increased predisposition of females to synthesize and release PRL [8].

The effect of sex hormones function on MS disease course and their relationship in pregnant women with MS is still unclear. It is known that the levels of two important female sex hormones (estrogen and progesterone) are very high during pregnancy and that may suppress immune activity to some degree. Lately the importance to detect the hormonal changes in pregnant women with MS has grown. It is known that hormonal changes during pregnancy promote increased oligodendrocyte production in the maternal CNS. Remission of MS during this process led to hypothesize that remyelination is enhanced in the brain [2,3]. The researchers demonstrated that pregnant mice (animal model of MS) have an enhanced ability to remyelinate white matter lesions. The hormone prolactin regulates oligodendrocyte precursor proliferation and mimics the regenerative effects of pregnancy. What's unique about prolactin is that it promotes the formation of new oligodendrocytes – cells that produce myelin. Gregg et al. [2,3] suggest that prolactin may be used as a potential therapeutic agent for MS. PRL produced during pregnancy could reverse some of the neurological damage associated with MS. This finding could help explain why women with MS suffer fewer symptoms during pregnancy. The authors suspected that rising levels of the hormone prolactin which promotes breast development and milk production might cause protective effect and might be used to treat people with early stages of MS [6]. By promoting repair, which is the goal of prolactin therapy, Gregg et al. [2,3] have hope of actually improving symptoms in people with MS. Paavilainen et al. [9] also report that the relapse frequency of MS decreases during pregnancy.

However, during late pregnancy Voskuhl and Palaszynski [11] demonstrated that there is an improvement in disease activity in animal model for MS, experimental autoimmune encephalomyelitis (EAE) in female SJL mice. The gender differences in EAE susceptibility is due primarily to a protective effect of testosterone in male mice.

Voskuhl (2002) report about the protective role of testosterone in young men and the protective role of the pregnancy hormone estriol in pregnant women [12].

The roles of progesterone (Pg), an immunomodulatory sex steroid, are poorly understood. Pg's immunomodulatory effects differ from those of estrogens and androgens. At pregnancy levels, Pg may suppress disease activity in MS [5].

In conclusion, the findings about the influence of sex hormones on the course of MS and the effect of the hormone treatment would allow to treat patients with MS according to their pathogenetic subtype and disease status.

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