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Sex hormones, brain damage and clinical course of Multiple Sclerosis

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ABSTRACT

There is evidence that gender influences the clinical course of Multiple Sclerosis (MS). Symptom prevalence as well as characteristics differs between the sexes. These differences can be, at least partly, explained by gender differences in the characteristics of tissue damage and disease progression measured by Magnetic Resonance Imaging (MRI). The interaction between sex hormones and MS damage, supported by both MRI and clinical evidence, seems to play an important role in the clinical and sub-clinical gender bias in MS. Experimental data testing directly the effects of sex hormones on brain damage and their clinical relevance show that sex hormones have the potential of exerting anti-inflammatory and protective effects on brain tissue. Both data in experimental models and patient studies discussed in this review encourages a gender-based approach to MS.

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1. Introduction

There is evidence that gender influences the susceptibility as well as the clinical course of Multiple Sclerosis (MS) [1]. A gender difference has been described in MS, as well as in other autoimmune diseases, with a higher prevalence of disease in women than in men (F/M=2/1). Gender can also affect the disease course and severity of MS. Women develop a benign course more frequently than men, typically in a 4:1 ratio [2], while men tend to experience a primary progressive course more frequently than women [3]. Male sex has also been associated with a poor prognosis. Men with MS tend to develop a more severe MS, defined as a shorter time to reach severe disability, than women [4–6].

Gender differences can be observed not only *across types*, but also *within type* of disease. Symptoms may be influenced in their prevalence and characteristics by gender. It has been reported that motor symptoms, especially at the MS onset, are associated with male gender and late disease onset [2]. Cognitive impairment is also more frequent in men than in women [7]. Sensory symptoms, for example those in the range of pain, are more frequent in women than in men [8] and, within sensory symptoms, men suffer more frequently from spasticity-related pain, while women are more frequently affected by central pain, trigeminal neuralgia or peripheral neuropathic pain [8].

To support the hypothesis of a biological basis for gender differences in clinical characteristics, there is also evidence from magnetic resonance imaging (MRI) studies in MS. Indeed, gender differences in brain damage characteristics have been observed in a large cohort ($n=413$) of MS patients [9]. Results from this study show that men are prone to develop less inflammatory, but more destructive brain lesions than women, suggesting a modulation of MS pathological changes by gender.

Not only white matter pathological changes show gender-related differences. Intra-cortical lesions are indeed more frequent in men than in women (79% of men vs. 51% of women) both in the early and in the late stages of the disease [10]. The mean number of intra-cortical lesions is also higher in men (3.4 vs. 2.2, $p<0.001$) and male gender is associated with higher risk of developing cortical lesions than women (OR 3.6). Consistently with these findings, men with MS have also reported to experience cognitive impairment more frequently than women [7]. Cognitive impairment in MS has been related to neocortical volume changes measured by MRI [11]. The higher prevalence of cognitive disturbances in men with MS, where intra-cortical damage seems to be also more frequent, provides an example of the clinical relevance of gender-differences in brain damage characteristics.

If there is evidence for a gender difference in brain damage characteristics in MS [9,10], sex-related differences in the structure of the normal brain should also be taken into account when explaining gender differences in clinical manifestations of MS. The normal brain structure indeed differs between the sexes [12]. Diffusion imaging shows that anisotropy, a measure of the directional dependence of water molecule diffusion along white matter tracts, which is an

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indirect index of microstructural integrity of white matter fibres [13], is higher in men when compared with women in the corpus callosum [14]. This difference could reflect thicker myelinated fibres in men than in women or it can be explained by decreased inter-fibre space in men when compared with women. Gender differences can be also observed in the structure of normal grey matter. Maps of differences between the sexes in cortical thickness reveal a gender difference in the temporal lobes, where cortical grey matter is thicker in women than in men, and dorsal prefrontal cortex, where thickness is higher in men than in women [15]. Interestingly, grey matter regions showing gender differences in the normal brain (temporal and prefrontal cortices) are also more susceptible to gender effect in the development of brain atrophy [16]. Indeed, a regional influence of gender on atrophy of white matter tracts has been reported [16]. Atrophy rate in white matter tracts of cingulate and the inferior longitudinal fasciculus is specifically influenced by gender, suggesting that gender differences in regional brain structure may affect the development of brain atrophy in MS.

The evidence reported so far suggests a link between hormonal factors, on one hand, and gender-related susceptibility to as well as clinical characteristics of MS, on the other hand. It also supports the hypothesis that this relationship is mediated by the interaction between sex hormones and the brain tissue. The following section will discuss the evidence supporting the hypothesis that sex hormones may be responsible for gender differences in the brain damage and clinical characteristics of MS.

2. Relationships between sex hormones and clinical/sub-clinical characteristics in MS

The relationship between sex hormone levels and tissue damage has been explored in MS [17,18]. Progesterone to oestradiol (PEL) ratio levels during the luteal phase of a menstrual cycle showed a positive correlation with both the number and the volume of brain enhancing lesions in women with relapsing-remitting (RR) disease [18].

The relationship between PEL fluctuations and MRI disease activity seems to reflect the association between changes in progesterone and oestrogen levels and changes in clinical MS activity. The premenstrual period, for example, can trigger relapses as well as worsen symptoms in a subgroup of women with MS [19,20]. Symptoms and signs typically getting worsened during the premenstrual period include fatigue, myalgia, depression, spasticity, weakness, incoordination, somatosensory and visual disturbances. Changes in temperature through the menstrual cycle, as well as withdrawal of hormones affecting axonal conduction through damaged areas may explain fluctuation of symptoms with menstrual cycle [21,22]. Among those patients who do not report influence of the premenstrual periods on MS symptoms a significantly high proportion uses oral contraceptives [19].

Pregnancy provides another example of changes in hormonal patterns paralleling changes in clinical as well as subclinical disease activity. The rate of relapses declines during pregnancy, especially in the third trimester [23], when changes in progesterone and oestrogens become more significant. This decrease in disease activity during pregnancy is also supported by a reduced MRI activity in the second and third trimester of pregnancy [24]. Changes in the immune tolerance physiologically occurring during pregnancy may explain the favourable influence of pregnancy on MS disease activity [25,26].

The evidence provided so far supports the hypothesis that sex hormones modulate mechanisms of tissue damage and possibly repair in MS with clinically relevant consequences. Their complex effects on brain tissue, as well as on the endocrine and immune systems [27], may contribute to clarify their influence on damage and repair in MS.

3. Effects of sex hormones on brain pathology

Sex hormones [e.g. oestrogens (oestrone, oestradiol, oestriol), progestins (progesterone), androgens (testosterone, dehydroepiandrosterone)] are secreted by many tissues in addition to the gonads. They have physiological complex effects on the brain tissue as well as on the immune system.

3.1. Evidence from experimental models

Sex hormones may modulate immune responses [27]. There is evidence for a role of sex hormones in animal models of MS such as Theiler's murine encephalomyelitis and experimental autoimmune encephalomyelitis (EAE) [28], where they show concentration-related effects with opposite actions at low and high levels. Oestrogens may facilitate immune response at low concentration and suppress responses at high concentrations [29].

There is evidence for *oestrogens* exerting inhibitory effects on EAE [30]. Oestrogens, especially oestradiol, mediate inhibition of encephalitogenic T cells [31], inhibition of cell migration into CNS tissue [32], up-regulation of Treg cells [30,33,34], and neuroprotective effects that promote axon and myelin survival [35–37]. Oestrogens promote growth and differentiation of neurons. Oestrogens and neurotrophins (i.e., NGF, BDNF, NT 3, 4–5) may influence each other's actions by cross-coupling of their signaling pathways that lead to induction of the same set of genes involved in neurite growth and differentiation [38]. In the developing brain, neurotrophins up-regulate oestrogen receptors, thus inducing neural growth. A loss of neurotrophin neurite-promoting effects physiologically occurs during the adulthood. In the damaged brain, a switch back to the developmental pattern (i.e., regulation of oestrogen receptor by neurotrophins) can be observed, which results in the re-expression of growth-promoting properties of oestrogen receptors [38]. This switch is mediated by enhanced neurotrophin-sensitivity of brain tissue during damage.

Oestrogen actions are mediated by oestrogen receptors, which are distributed widely in the CNS with two types of receptors, alpha and beta [39]. Oestrogens have transcriptional effects through direct and indirect genomic mechanisms [39]. Transcriptional effects on enzyme production mediate oestrogen actions on neurotransmitter systems such as cholinergic, serotonergic, glutamaergic systems [40]. There is also increasing evidence for transcription-independent actions of oestrogens. Oestradiol can induce a rapid increase in the intracellular free Ca^2 concentration resulting from influx of external Ca^2 or release of Ca^2 from intracellular stores. These actions seem to be mediated by plasma membrane-associated, G protein-coupled oestrogen receptors [41]. At high concentrations, oestrogens also exert antioxidant effects through non-genomic mechanisms [40].

Oestrogen modulatory effects on the experimental model of MS result in a suppression of disease activity [33]. Treatment with oestrogen receptor (ER)-alpha ligand reduces the clinical severity of EAE [42]. Lower clinical impairment can be observed in mice receiving ER-alpha ligand before EAE induction. This effect can be mediated by decreased WM demyelination and inflammation as well as increased preservation of neuronal cells. In MS, orally administered oestradiol can reduce disease activity on MRI scans in patients with MS [43], suggesting protecting, anti-inflammatory effects of oestrogens in the human disease.

Progesterone has been demonstrated to have both neuroprotective and pro-myelinating effects on CNS. It preserves neurons, following brain traumatic or vascular injury [44–46]. In the spinal cord, progesterone increases motoneuron survival after injury, protects cultured neurons against glutamate toxicity and normalizes functional impairment of injured neurons [47–49]. Progesterone also influences myelin synthesis both in the Peripheral and Central Nervous System [50–52]. It increases the proliferation and differentiation of oligodendrocyte precursor cells that play an important role in remyelination after toxin-induced lesions and aging [52,53]. In addition to neuronal and myelinating effects, progesterone may modulate the immune system, shifting a Th1 pro-inflammatory response to a Th2 anti-

inflammatory response [54–56]. Progesterone has shown variable effects in EAE, ranging from inactivity, increased vulnerability of neurons, to disease improvement when given with oestradiol [57]. Because of its increased levels during pregnancy, when a reduction in disease activity can be observed [23], it has been suggested that progesterone may have protective effects on MS. Indeed, progesterone administered in a single dose of either 20 mg or 100 mg before EAE induction produces a delay of disease onset and reduction of clinical severity [58]. Reduced demyelination processes, recovery of myelin proteins and preservation of neuronal integrity accompany clinical effects of progesterone. Because of its effects on proliferation/differentiation of oligodendrocyte precursors, remyelinating and neuroprotective effects of progesterone in MS deserve further investigations.

Testosterone has been also implicated in modulation of brain damage in MS. It has shown protective effects in EAE [59,60]. It has been observed that male SJL mice develop a monophasic EAE disease course after immunization with PLP 139–151, in contrast to the relapsing disease pattern observed in females [61], suggesting that testosterone produced by the gonads in male animals has a regulatory effect on the immune response and inhibits relapses. The effect of endogenous testosterone has been studied in male SJL mice [59], where clinical EAE relapses occurred only in male SJL mice castrated prior to immunization. Widespread *vs.* sparse demyelination was observed in castrated *vs.* control mice sacrificed at the same time post immunization. These neuropathological findings support the observed clinical differences. Exogenous testosterone administered to female mice before EAE induction also reduces the clinical severity of EAE. This effect seems to be mediated by an enhanced production of interleukin 10 [60]. Androgen precursors also appear to suppress EAE [62]. Androgen treatment leads indirectly to increase thymocyte (T-cell) apoptosis, which could provide another means by which testosterone could be beneficial in EAE [63].

If, on one hand, sex hormones seem to play a protective role on brain tissue, on the other hand, they have been associated with *excitotoxic and apoptotic mechanisms*. Testorestone amplies excitotoxic damage of cultured oligodendrocytes [64]. This mechanism could contribute to explain the worse prognosis of MS in men, accounting, at least partially, for the greater risk for a progressive course. Progesterone seems to increase the vulnerability of neurons to apoptotic injury in EAE [57]. It has been also associated with enhancement of EAE [65]. When mice are castrated and then treated with progesterone alone disease is worsened [57]. Although several neuroprotective and anti-inflammatory effects have been proven for oestrogens [39], following moderate traumatic brain injury, oestrogens as well as progesterone show deleterious effects in females, but protective effects in males [66,67], suggesting a gender-by-damage interaction in the effects of sex hormones on the brain tissue damage and repair.

3.2. Evidence from MS

There is evidence that sex hormones play a complex role in modulation of brain damage in MS [68]. In men with MS, higher tissue damage measured as T2-hyperintensities and T1-hypointensities ("black holes") on brain MRI scans is associated with higher levels of oestradiol. In women with MS, higher levels of testosterone are associated with higher level of T1-hypointensities. There is a trend in the correlation between T2-hyperintense lesion volume and levels of testosterone in women. No correlation has been found between oestradiol levels and brain damage in women, as well as no relationship has been found between levels of testosterone and tissue damage in men with MS. Several reasons may account for these relationships. *First*, in men, levels of testosterone are quite stable and in a narrow range of values. Testing for correlation between a wide range of values quantifying tissue damage may make the correlation with testosterone levels in men hard to prove. *Second*, there is a close physiological relationship between levels of testosterone and levels of oestradiol, as testosterone is converted peripherally to oestrogens both in women and in men. *Third*, in women, female sex hormones tend to play a combined physiological role with the implication that level of oestradiol alone may not explain the role of female sex hormones in women with MS. Indeed, studies testing the relationships between sex hormones and tissue damage in women with MS have shown combined effects of progesterone and oestradiol on brain damage [18]. *Fourth*, gender differences in the receptor binding capacity [69] may expose the tissue to different types of sex hormone effects.

Overall, this evidence suggests that both oestradiol and testosterone play an important modulatory role in MS damage, possibly with differential effects in women and men. This modulatory role is supported further by differences in hormonal levels between patients and matched controls [68]. Indeed, although the general pattern of sex hormones and their physiological fluctuations are preserved in controls as well as in patients, women with MS show lower levels of testosterone than normal controls in the follicular as well as luteal phases of the menstrual cycle. It is worth noting that MS women with low testosterone levels (two standard deviations below the control mean) had higher number of enhancing lesions than MS women with normal testosterone levels, suggesting that testosterone does interfere with inflammatory mechanisms, as supported by experimental data [59,60]. No significant difference has been observed between male patients and normal controls in the levels of sex hormones.

4. Implications of the relationship between sex hormones and brain damage in MS

Interaction between gender and brain damage may influence the management of MS at different levels. Gender differences in symptom prevalence and characteristics [2,7,8] may affect the clinical detection of the disease, with the implication on the time to diagnosis. Although some studies suggest that pregnancy is associated with a more favourable long-term prognosis [3,70,71] this is still a matter of controversy [72,73].

Interaction between gender and brain damage may also influence the clinical responses to disease modifying treatment such Interferon beta (IFN beta) [74]. As expected, greater tissue damage at the beginning of IFN beta treatment is associated with higher risk of developing disability during the follow-up in 68 RRMS patients. One year after the beginning of therapy, however, only male gender is associated with higher risk of developing disability during the subsequent five years, suggesting that gender may reflect brain damage characteristics (i.e., inflammation and/or degeneration) on which therapy can or cannot be effective. Alternatively, gender as well as sex hormones may influence the clinical response to therapy beyond its effects on brain pathology by influencing plastic mechanisms of functional or structural recovery after injury [75].

Because of their effects on brain tissue as well as on the immune system, sex hormones have been tested as potential treatment option in MS [43,76]. Ten clinically definite RRMS men (18–65 years old, EDSS $\leq$ 5.0) have been followed-up before and after the beginning of *testosterone* treatment [76]. Patients were followed-up both clinically and sub-clinically with brain MRI. Sustained attention as measured by PASAT score gradually increased during the last six months of testosterone treatment. Clinical cognitive changes paralleled a 67% reduction in the rate of brain atrophy, suggesting a significant pharmacological modulation of cognitive performance by sex hormones.

Because of the dramatic reduction of relapse rate during pregnancy, *oestriol* has been explored as a therapeutic option to treat women with MS [43]. Ten MS women have been treated with oestriol (8 mg/day) in a cross-over study testing cognitive performance and subclinical disease activity assessed by using immunological as well as imaging measure. PASAT scores improved in RRMS women after

6 months of oestriol treatment. As compared with pretreatment baseline, patients treated with oral oestriol demonstrated significant decreases in delayed type hypersensitivity responses to tetanus, interferon-gamma levels in peripheral blood mononuclear cells, and MRI enhancing lesion number and volume. Cessation of treatment induced a relative increase in the MRI disease activity, which was subsequently significantly reduced by reintroduction of oestriol. Overall, this evidence supports a clinically relevant effect of hormonal treatment on clinical manifestations of MS, as well as on the underlying pathological substrates. It also supports previous results on a protective effect of sex hormones on risk of developing cognitive impairment [77–79].

The preventive effect of progesterone combined with oestradiol on post-partum relapses is currently being tested in a large randomized, placebo-controlled European trial (POPART'MUS study).

5. Conclusions

There is increasing evidence from studies combining imaging and clinical markers of disease burden supporting the hypothesis that gender does affect clinical manifestations as well as characteristics of brain damage in MS. Sex hormones may be responsible for gender differences in clinical and MRI brain injury characteristics by modulating mechanisms of damage and tissue repair both directly and indirectly. The relevance of the interaction between gender (or sex hormones) and brain damage is suggested by data showing that gender is indeed an independent predictor of clinical evolution during disease modifying treatment therapy. The inter-relationship between gender (or sex hormones) and brain damage characteristics prompts towards a gender-based approach to therapy choice in MS.

Sex hormone therapy has already proven to have the potential of modulating brain damage directly and/or indirectly with clinically relevant effects. The effects of a hormone-based therapy alone or in combination with current disease modifying options are currently under evaluation and promise to reveal a strategy to preventing damage as well as enhancing plastic changes in the damaged brain.

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