Sex Hormone Treatments for Multiple Sclerosis

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Abstract *Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system with a pathophysiology resembling that of an autoimmune disease. The use of estriol for MS stems from the observation that women with this disease typically enter into a state of remission when they become pregnant. Promising results from human trials using estriol in non-pregnant women have been reported. Estriol induces an immunological shift from a TH1 to a TH2 dominant state, which can bring about a state of remission. Preliminary evidence from human trials evaluating testosterone treatment for male patients with MS has been positive. This review discusses how the interplay of sex hormones and the immune system improves the symptoms of MS, and highlights areas of future research.*

Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system. Although the exact aetiology has yet to be elucidated, its pathophysiology resembles that of an autoimmune disease. MS affects females more often than males, with the ratio being approximately 3:1 in North America.[1] There are various patterns of disease progression, with relapsing remitting MS (RRMS) being the most common, and which as the name implies follows a course of relapse and remission. The second most common type of MS is secondary progressive (SPMS), which is often the sequelae of long-standing RRMS, and is characterized not by relapses and remissions, but by a steady progression and worsening of symptoms. The symptoms of MS typically subside, and enter into a state of remission during pregnancy, especially during the third trimester. Further, relapse rates return to normal, sometimes after a temporary increase beyond pre-pregnancy rates, within the first three months post-partum.[2] There are numerous physiological changes that occur during pregnancy that might explain this phenomenon, but of particular interest is estriol due to its dramatic increase in serum levels (i.e., relative to the other estrogens – estrone and estradiol) during the third trimester, and its sharp fall post-partum; events that coincide with the aforementioned changes in relapse rates. These observations have sparked great interest in determining whether estriol could successfully be used as a novel treatment for this debilitating disease.

Immunologically, MS is classified as being a TH1 dominant condition, and is associated with inflammatory cytokines, such as IL-2, IL-12, IFN-γ and TNF-α. During pregnancy, the immune system shifts to a state of TH2 dominance, and is associated with anti-inflammatory cytokines, such as IL-4, IL-5, IL-6 and IL-10. This shift to a TH2 dominant state is advantageous as it plays a role in the mother not rejecting the developing foetus. Effective treatment strategies in MS, therefore, should be aimed at inducing the shift from a TH1 to a TH2 dominant immunological state. In addition to the inflammatory nature of the disease,

MS is characterized by neurodegeneration of the gray matter.[3] Most pharmaceutical treatments for MS are aimed at inhibiting inflammation, but they do not prevent the progression of the disease, as seen in SPMS. Neuroprotective mechanisms would involve substances that cross the blood brain barrier and directly promote the health of neurons and oligodendrocytes.[4]

Many studies have been conducted to date using mouse models of experimental autoimmune encephalitis (EAE), and these studies have shown estrogens, both estradiol and estriol, to have a beneficial effect on cytokine profiles. However, in humans, researchers have had to carefully consider whether the use of estradiol has a safe risk-benefit profile. Estradiol preferentially binds estrogen receptor alpha (ERα), and this receptor is found predominantly in the bones, testes, epididymis, prostate, uterus, ovary, liver, mammary gland, heart, vascular system and brain.[5] Stimulation of ERα by estradiol for the purposes of hormone replacement therapy can significantly increase the risk of developing endometrial cancer if unopposed by oral progesterone or progestin. However, estriol preferentially binds estrogen receptor beta (ERß), which is found predominantly in the bladder, prostate, ovary, colon, immune system, heart, lung and brain.[5] Estriol, therefore, is most likely the safest form of estrogen to supplement as it has not been associated with endometrial or ovarian cancer.[5]

Testosterone, a predominant male hormone, might be an important intervention for males with MS. It possesses anti-inflammatory and neuroprotective properties, and several mechanisms are posited, including its ability to increase the production of IL-5 and IL-10, as well as decrease the production of IFN-γ and TNF-α.[6] Testosterone may also increase brain derived neurotrophic factor (BDNF), a protein that supports the survival and growth of nerve cells.[7]

Estrogen Treatment and MS

The first major study to examine the effects of pregnancy on MS was the "Pregnancy in Multiple Sclerosis Study" (PRIMS),[2] which examined 254 women between 4 and 36 weeks gestation. Women were examined by a neurologist at 20 and 28 weeks gestation, depending on the time of enrolment, and at 36 weeks. Postpartum, they were examined at 3, 6 and 12 months. The results showed that during the last trimester, relapse rates were substantially lower, and in the first three months postpartum, relapses were higher compared to the pre-pregnancy stage. In the remaining follow up periods, disease status was similar to that prior to pregnancy. The risk of a relapse was not related to the use of epidurals, and was also lower in women who breast fed. The overall rate of progression of the disease did not change, but the decrease in the relapse rate during pregnancy was more marked than any other intervention previously reported.

Following this observational study, clinical trials were conducted to determine whether supplementing with estriol could induce the same effect in non-pregnant females with MS. In one study, women between the ages of 28 and 50 were included, 6 with SPMS and 4 with RRMS.[8] There were 4 phases to the trial; a 6 month pre-treatment phase where women received monthly magnetic resonance imaging (MRI) studies to establish a baseline; a 6 month treatment phase where women were supplemented with 8 mg/day of oral estriol; a 6 month post-treatment observation period; and finally a 4 month re-treatment phase with estriol supplementation once again. Blood tests were taken during the treatment phases and showed that estriol levels in the blood were similar to those of six month pregnant females. For safety concerns, gynaecological exams and mammograms were performed at the beginning and end of the study, with no evidence of hyperplasia. Results showed that estriol was well tolerated with only a few women having menstrual cycle irregularities. Additionally, the size and number of neurological lesions shown on MRI decreased in all 10 patients during the treatment and re-treatment phases, but only reached significance in the RRMS patients.Lesions returned to the original size and number

during the six month observation period. Additionally, all participants were given the same cognitive function test. The cognitive function scores improved in the RRMS group, but not in the SPMS group.

This preliminary evidence is promising. Since remissions result from a TH1 dominant state shifting to a TH2 dominant state, it would be interesting to ascertain whether estriol affects changes in cytokine production related to these immunological changes. A study evaluated RRMS patients given 8 mg/day of estriol in combination with 100 mg/day of progesterone (i.e., to protect against endometrial hyperplasia).[9] Monthly MRIs and blood draws were taken and peripheral blood mononuclear cells were isolated and analyzed to detect cytokine secretion. During the treatment and re-treatment phases, IL-5 and IL-10, and both TH2 associated cytokines were significantly increased, while TNF-α and IFN-γ, and TH1 associated cytokines were significantly decreased. There was no effect on IL-2 and IL-4. Like the previous study, lesions on MRI decreased in size and number in the RRMS group only. Therefore, it appears that there is a relationship between estriol supplementation and its ability to support a shift from TH1 to TH2 dominance, which is associated with decreased lesions as evidenced by MRI findings. However, this effect seems to only be beneficial in women with RRMS compared to women with SPMS. RRMS is characterized by inflammation, whereas SPMS is characterized by neuronal cell loss and degeneration with little inflammation. Treatments that moderate cytokine production and reduce inflammation are therefore more efficacious among patients with RRMS.

Subsequent studies have continued to further examine the effects of estriol supplementation on symptoms of MS. Ten women with MS (6 with RRMS and 4 with SPMS) were supplemented with 8 mg/day of oral estriol for 6 months, followed by a 6 month observation period and 4 month re-treatment period.[4] In the RRMS group, MRIs showed fewer lesions during the treatment period, which returned to baseline during the post-treatment period, only to again decrease during the re-treatment period. Improvements in cognitive function were also observed. No significant clinical benefits were shown in the SPMS group.

Epidemiological evidence has reviewed the use of oral contraceptives (OCs) and the risk of developing MS.[10] Data was obtained from 106 women younger than 50 years old with a definitive diagnosis of MS. Women were included if they were either past users or current users of OCs. The types of OCs used in the analysis included synthetic estrogens and progestins. The results showed that users of OCs had a 40% decreased incidence of MS than women who had never used them. While previous research has been extremely mixed on this subject, a recent review suggested that the use of OCs might delay the onset of disease, as opposed to preventing its development.[11]

Testosterone Treatment and MS

In a pilot study by Sicotte et al, 10 males with MS were treated with 10 g of transdermal testosterone (delivering 100 mg/day) for 12 months.[7] Results showed that IL-2 decreased, BDNF levels increased, natural killer (NK) cells increased, and scores on cognitive function tests improved. MRIs showed a slowing of brain atrophy; however, there was no effect on the size and number of brain lesions. A similar pilot study by Gold et al was conducted to confirm these preliminary results.[12] Ten male MS patients were treated with the same daily dose of testosterone in a cross-over design (i.e., 6 month observation period followed by 12 months of treatment). Levels of IL-2 decreased, NK cell populations increased, and BDNF levels increased. These studies suggest that testosterone treatment induces favourable immunomodulatory effects and possibly neuroprotective effects in male patients with MS.

Discussion

While there are numerous studies that have started to elucidate the mechanism of actions of estriol and testosterone with respect to how they modulate the immune sys-

tem and impact MS, the data is only preliminary and larger clinical trials are required. An obvious limitation to the clinical trials reviewed was their small sample sizes and lack of adequate control groups. The designs of the studies were crossover, which relied on the participants serving as their own controls instead of properly matched control groups.

Other studies have evaluated the putative therapeutic properties of sex hormones in MS. One study assessed the impact of exclusive breast feeding on post-partum relapses in MS.[13] Thirty-two pregnant women with MS completed questionnaires during their last trimester, as well as at 2, 4, 6, 9 and 12 months post-partum with respect to changes in neurological status, breast feeding, supplemental feeding behaviour, menstrual history and medication use. Only 69% of the women breast fed at all, and of these, 30% began to supplement with formula within the first two months. The women who did not breast feed at all and those who supplemented had a significantly higher risk of post-partum relapses during the year following delivery than women who breast fed exclusively ($p=0.003$). The relapse rates in mothers who breast fed some, but not exclusively, were statistically similar to not breast feeding at all. However, the physiological state in a post-partum woman who breast feeds exclusively is one of very low estrogen and high prolactin, which contradicts previous research. One hypothesis that has been advanced is that a state of anovulation (common to a high estrogen state and lactational amenorrhoea) is what might protect against relapses in MS, but clearly further research is warranted.

Another novel treatment for MS is the use of tamoxifen, which is a commonly prescribed anti-estrogenic treatment for breast cancer in post-menopausal women.[14] Studies have shown that peripheral lymphocyte counts were significantly reduced in women treated with tamoxifen, which has implications for the treatment of conditions that require immunosuppression.[14] Other studies using the EAE mouse model of MS showed that tamoxifen induced a TH2 bias, reduced demyelination, suppressed T cell production stimulated by myelin, and impaired the stimulation of myelin specific T cells by dendritic cells.[14] The purported mechanism of action involves the inhibition of P-glycoprotein, which is an active transporter required for T cell activation and the maturation of antigen presenting cells. Regardless of the immunological mechanism of action, tamoxifen also interacts with estrogen receptors via an inhibitory process, and overall its beneficial effects for the treatment of MS seem counterintuitive.

While the use of estriol or testosterone as monotherapy is promising, it is likely that the therapeutic effects of sex hormones are due to their interactions with the immune system. Progestin is also beginning to interest researchers, and there is currently a large scale study underway to determine whether a synthetic progesterone derivative administered post-partum can help to prevent post-partum relapses when combined with low dose estradiol.[15] Preliminary evidence from this study has indeed shown that progestin is capable of supporting a TH2 biased immune response, as well as having an effect on remyelination. Despite such promising preliminary evidence, it might be preferable to use progesterone instead of its synthetic derivatives. Progesterone plays a crucial role in stimulating new oligodendrocytes and might facilitate myelin repair. For a more elaborate understanding of the neurostimulatory mechanisms of progesterone, please review the work of Schumacher et al.[16]

Application to Patient Care

The most commonly used pharmaceutical for the treatment of MS is glatiramer acetate, whose mechanism of action is by immunomodulation in that it induces a shift from TH1 to TH2 dominance. The drug also structurally resembles myelin basic protein, and therefore it may also act as an immunological decoy.[17] Like all other pharmaceuticals for the treatment of MS, glatiramer acetate is delivered via injection, and a common side effect is a lump at the injection site, and local destruction of fat tissue may

develop resulting in a visible indentation in the skin. Other side effects include flu-like symptoms, flushing, shortness of breath and rapid heart rate. Monoclonal antibody therapy is also approved for MS, such as Natalizumab and Rituximab (although Rituximab is only approved off-label), but the side effects are numerous, including progressive multifocal leukoencephalopathy, which is a rare and untreatable brain infection that results in death.[17] Given this data, the interest and need for complementary and orthomolecular treatments is immense.

Further, as orthomolecular clinicians, we should be prepared to answer the questions of female MS patients who are contemplating having children, as they may be fearful about what impact their disease will have on their children. Women may wonder whether they can pass on the disease genetically, but no evidence supports this to date. Women may also be hesitant about discontinuing their medications during pregnancy for fear of symptom exacerbation. We can assure these patients that they will most likely experience a natural remission during their third trimester, and should they choose to breast feed, they should do so exclusively without supplementing formula to further support the remission period. The topic of labour and birth may come up, and should be discussed that there is some evidence of a prolonged second stage of labour, most likely due to exhaustion in an already exhausted woman.[18] In terms of the use of analgesia during labour, epidurals are not contraindicated, but should be considered cautiously because of the potential risk of demyelinated neurons being exposed to neurotoxic drugs.[18] Finally, women may wonder if pregnancy will make their condition worse. We can inform them that pregnancy may actually have a protective effect on the progression of the disease. One long term study showed that in patients with at least one pregnancy after the onset of MS, it took 12.5 years for women without children to become wheelchair bound compared to 18.6 years for women having had at least one pregnancy.[19]

No discussion about sex hormone treatment would be complete without mention of phytoestrogens. Phytoestrogens, while not orthomolecules, are structurally similar to endogenous estrogens and act as weak agonists of estrogen receptors. It would therefore be interesting to look at whether phytoestrogens would be therapeutic as a treatment for MS. A recent study looked at whether the effects of genistein, an isoflavone found in soy, showed benefit in the EAE mouse model.[20] One group of mice received 200 mg/kg body weight for 7 days, while the control group received no treatment. Signs of EAE in mice include weight loss, tail paralysis and hind limb weakness. Brain tissue was also analyzed for cytokine production. Results showed that genistein treated mice recovered their initial weight, and there was a decrease in IL-10, IFN-γ, and TNF-α. One of the more interesting findings was that genistein diminished the ability of leukocytes to adhere to vascular endothelium. This has important implications since one of the pathological hallmarks of MS is the infiltration of leukocytes across the endothelium of the blood-brain-barrier. Future research should continue to address this topic.

Conclusion

In limited clinical trials, estriol induced a remissive state via its ability to provoke an immunological shift from a TH1 pro-inflammatory state to a TH2 anti-inflammatory state, and is of therapeutic benefit in women with RRMS, but not SPMS. Additionally, there is emerging evidence that supports the use of testosterone as a therapeutic agent in men with MS. While testosterone has not been shown to induce remission in male patients, it does appear to play a role in both the inflammatory and neurodegenerative processes of MS. Progesterone might also mitigate the neurodegenerative process, in that it stimulates remyelination. Future research should be aimed at further understanding the pathogenesis of the disease, and fully understanding the mechanisms of action of sex hormones as well as their relationships with each other and with immunological processes.

Competing Interests

The author declares that she has no competing interests.

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