# Multiple sclerosis (ms): pathophysiology and management

Multiple sclerosis (MS) is an autoimmune inflammatory disease, in which multiple lesions or plaques are formed within the brain and spinal cord. It can be characterised as a demyelinative disease of the central nervous system that is associated with relative loss of the myelin sheath and axon. The hallmark feature of the disease is the loss of this myelin sheath which leads to scarring and various other symptoms including muscle weakness and visual disturbances. The myelin sheath is a vital component of the axon as it provides protection and insulation (figure 1). Demyelinization of the sheath exposes the underlying axon and can lead to defects in synaptic transmission. In healthy individuals, myelin repair is spontaneous however in patients with MS this repair process occurs slowly or not at all. The integrity and functioning of the nervous system relies on myelinated neurons which allow fast and efficient transfer of electrical impulses and when this function is impaired it can contribute to complete or partial loss of central nervous system (CNS) functions. MS can be a potentially debilitating disease with unpredictable results and sadly there is no cure, however there are some treatments available that assist in the management of the disease. There has been noted beneficial effects with either immunosuppressive or immunomodulatory therapies, though these effects are somewhat reserved as patients responses to treatment are variable (lassmann, 2002). There have been many investigations into the use of novel immunomodulatory therapies, in particular, those using sex hormones such as oestrogen and testosterone. It is thought by many (Voskuhl 2002, Eikelenboom et al 2009, Nicot 2009) that gender is a contributing factor to the initiation and course of MS and that underlying mechanisms of the disease can be linked to sex

hormones. The contribution of sex hormones and their actions in the management of the disease will be further discussed.

## The immune system plays fundamental role in Multiple Sclerosis

The immune system can be linked to the gender differences in MS, as sex hormones are thought to affect the immune systems cytokine response (Eikelenboom 2009). It has been perceived that cytokines play an important, however complex, role in the pathogenesis of multiple sclerosis, as well as many other inflammatory diseases (Imitola et al, 2005). The disease is thought to be initiated by the release of Th1 cells which have a pro-inflammatory affect (Figure 2). Subsequent to this is an anti-inflammatory response that is mediated by the Th2 cytokines. MS is thought to occur in genetically susceptible individuals in whom Th1 autoimmunity is activated, thus multiple sclerosis is seen primarily as a Th1- mediated auto-immune disese (Gold et al, 2009). One of the more recent theories on MS pathology is that the establishment of the disease is thought to be triggered by an imbalance between Th1 and Th2 cytokine responses (Van den Broek et al 2005). It has been known for some time that gender and gonadal hormones can influence and modulate the immune cytokine response (Schuurs et al 1990, Van den Broek et al 2005). The differences between males and females are first seen during teenage years when testosterone levels in males and oestrogen levels in females start to increase. Furthermore, multiple sclerosis is more common in those who have reached sexual maturity and the disease can be influenced by other changes in hormone levels such as menopause and menstruation (Smith et al 1992). Thus, factors

such as gender, that contribute to sex hormone levels, and cytokine regulation and secretion are fundamental in understanding MS pathogenesis.

## Gender issues in Multiple Sclerosis

There have been several studies that have linked gender to the clinical course of MS (Voskuhl 2002 , Reipert 2004). Females have been found to be most frequently affected by MS and this is the case in many other auto-immune diseases (McCarthy 2000). Also, there is higher disease prevalence and better prognosis amongst women with the disease (Whitacre et al 1999). The severity of the disease may often be greater in men, as both sexes follow a different course of the disease. The onset of MS in males is linked with the beginning of the decline in bioavailability of testosterone in healthy men (Reipert 2004). Therefore, susceptibility and severity of the disease between men and women are frequently contrasting. The causes of gender specificity remain unclear; however current interpretations may push towards identifying factors that lead to female bias in MS. Due to the fact that females are dominated by the the disease, it can be proposed that differences in sex hormones may offer protection to males against the disease.

## The influence of sex hormones in Multiple Sclerosis

It has already been established that gender plays a role in MS susceptibility. These differences can be explained by differences in sex hormones and their affect on the brain i. e. roles in damage and repair. Female to male ratios are seen to be approximately 2: 1. MS susceptibility has been tested in EAE mice models (Figure 3) and the outcome has been that female mice are most susceptible when compared to male mice (Voskuhl et al, 2001). Sex

hormones, oestrogen and testosterone may offer neuroprotection. For many years, it has been known that the prevalence of multiple sclerosis is higher in females than it is in males. This is often the case in many auto-immune diseases. Therefore, it is fair to say that sex hormones play specific roles in the immune responses of these auto-immune diseases such as Multiple sclerosis and Rheumatoid Arthritis (Cutolo 1997). Research into the roles of sex hormones in the immune system has been of topic sincethe 1950's and 60s (Kappas et al 1963). It is differences in production and secretion patterns of cytokines that seems to vary between males and females with MS and each sex hormone is associated with different clinical manifestations of multiple Sclerosis. Therefore, the concentrations of sex hormones within the body during a certain period can influence the production of cytokines, which in turn affects disease severity and recovery.

## Oestrogens

Oestrogen can been described as an immunomodulator and its concentrations can vary within the body and can rise or fall, for example pregnancy, menstruation and menopause. The effects of oestrogen on the immune response have been studied in both In vivo and In vitro environments. In particular its effects on cytokine production have been noted. Also, it is thought that oestrogens have two effects on the immune system; one involving the suppression T cell development and the other stimulation of antibody production (Van den Broek). Oestrogen is one of the most researched sex hormones, which is thought to have a protective and favourable affects against the progression and clinical course of MS (Eikelenboom et al 2009). This effect is shown in pregnancy, particularly

during the third trimester, where the levels of Oestrogen (and progesterone) are high (Figure 4) . The urine of nonpregant and pregnant women was tested for levels of oestrogen. In non pregnant women, the ratio of estriol to estron plus estradiol was approximately 1: 1 compared to 10: 1 in pregnant women (DraÄ‹a et al 2006). These increased levels of oestrogens are thought to delay MS progression, which is beneficial. It was found that MS patients experienced clinical improvement during pregnancy (VOSKUHL , 2007) and decreased relapse rates. However, these effects are not permanent and subside post-partum. There may be periods of disease exacerbation post partum, where there is an increase in relapses (Sandyk 1996). Although pregnancy offers favourable disease conditions, these effects have not been conclusively shown to have long term effects. This theory has been supported in EAE, where a reduction in EAE was most prominent during late pregnancy. In addition, Van den Broek has shown that castrated female mice experience a delay in the onset of the disease, when supplemented with oestrogens. This may be indicative of disease modification by hormones. Furthermore, oral contraceptives, containing oestrogen may have similar effects in altering the course of the disease (Jama and archives journals 2005), however long term effects have not been extensively confirmed. Thus, the beneficial effects must outweigh the side effects of long term use for sufficient justification.

As previously mentioned Th1 and Th2 cells are involved in the mediation of the disease. Using the EAE animal model, it has been demonstrated that oestrogens promote a Th2 phenotype, which is considered to have anti-inflammatory affects (offner et al 2006). These protective effects seen in

EAE, propose the use of oestrogen as a possible therapy for multiple sclerosis. During periods of high oestrogen levels, there is seen to be a decrease in pro-inflammatory cytokines such as TNF-α and an increase in suppressor cytokines such as IL-10, which are known to be beneficial on the clinical manifestations of Multiple Sclerosis. Furthermore, oestrogens have been shown to inhibit the production of nitric oxide and TNF-α, which are both toxic to myelin producing oligodendrocytes (Bruce-keller et al 2000). Past findings suggest that oestrogens used as hormonal supplementation may be beneficial in menopausal and post menopausal MS patients (Sandyk 1996). It was found that the risks hormonal replacement therapy outweighed the benefits in healthy menopausal women; however the risk/benefit ratio was thought to be more tolerable in women with autoimmune disease (Soldan et al 2003).

## Testosterone

Testosterone has many functions; however one of the less recognized is its role in nervous system development. Testosterone, as well as oestrogen, is seen as an immunomodulator, however each sex hormone has differing roles in MS. It has been suggested by clinical studies that testosterone could offer neuroprotection that could be useful in the management of MS (Gold et al 2008). Testosterone can offer direct or indirect neuroprotection. Free testosterone may pass the blood brain barrier to directly modulate neuronal cells or it may be converted into oestrogen in the brain, acting indirectly (Bialek et al 2004). The possible protective effects of testosterone have mainly been investigated by studying the effects of castration of male animals. It has been demonstrated that testosterone can decrease the

production of inflammatory cytokines that appear to contribute to the pathogenesis of MS (D'Agostino et al 1999). Moreover, a shift towards Th2 immunity has been noted in testosterone treated EAE mice, suggesting the potential use of testosterone in treatment of auto- immune diseases such as multiple sclerosis. Gold et al explored the immune-modulatory effects of testosterone on a group of males, clinically defined for MS. An anti-inflammatory effect was seen due to a decrease in IL-2 and DTH (delayed type hypersensitivity) responses and an increase in TGFβ-1. Also, testosterone was shown to increase the production of BDNF (brain derived neurotrophic factor) and has a suggestive neuroprotective effect in MS. BDNFs were the first neurotrophin to be detected in inflammatory lesions (Hohlfeld 2008). BDNFs may have a role in limiting the damage caused by inflammation. Furthermore, there has been a link between MS severity and production of BDNFs (Bialek et al 2004). More damage to the white matter was associated with decreased levels of BDNF.

# Oestrogen and testosterone in the management of MS

## Oestrogens

The current observation that oestrogens produced during pregnancy subdue clinical manifestations of MS and other auto-immune diseases, has lead to the use of oestrogen therapy in patients whom are not pregnant and suffer severely from MS . There has been suggestion that this type of therapy will be able to mimic the Th1 to Th2 shift that is seen during pregnancy and is correlated with improved clinical symptoms. Oestrogen treatments such as oestriol and oestradiol may offer protection against the clinical severity of MS, as its effects have been shown in EAE (Gold et al 2009). The mechanism

of protection that is offered by oestrogens is thought to exert anti-inflammatory processes, by affecting the cytokine response. Treatment with oestrogen has been shown to protect oligodendrocytes from cytotoxic attack (Sur et al 2003). This can be seen as beneficial as oligodendrocytes are responsible for producing myelin proteins that are need for nerve insulation and conductivity. The loss of myelin integrity and function can leave the individual vulnerable to MS. Many clinical studies have been carried out that have aimed to determine the effects of oestrogens for the management of MS. One particular study performed by Soldan et al involved the treatment with oral oestriol. The study intended to showcase the immunological effects of oestriol and the results showed significant decreases in CD4+ and CD8+ T cells. As well as these results, significant increases in anti-inflammatory cytokines, IL-5 and IL-10 and decreases in pro-inflammatory cytokines, TNFα were observed. The alterations in cytokine secretions were linked to reductions in lesions seen in monthly MRIs. Overall, it can be suggested that oestriols can influence the course of MS.

Oestrogens can regulate gene transcription, acting via oestrogen receptors, ER α and ER β. It has further been assessed whether or not oestrogen treatment was gender specific (Palaszynski et al 2004). It was found that the expression of ER α and ER β were equal in both genders and the disease severity was found to decrease in both males and females with oestriol treatment. Moreover, a decrease in proinflammatory cytokines resulted after oestriol treatment in both males and females. This reveals that therapies need not be gender specific and also a potential use of oestrogen treatment for men, as well as women.

### Testosterones

Recent studies and clinical trials have been able to highlight the roles of testosterone in the management of multiple sclerosis. It is well known that testosterone offers protection to males which may be why they are less susceptible to MS and other auto-immune diseases, compared to females. One recent pilot study conducted by Sicotte et al treated 10 male MS patients with gel testosterone. The results concluded an improvement in spatial and working memory performance; however no changes in inflammatory immune responses were noted in MRI. Overall, the study indicated that testosterone was a safe potential treatment and it was well tolerated. Although the treatments have shown success, more investigations are required to further evaluate the neuroprotective roles of testosterone in the management of MS. Overall, it can be said that testosterone can be protective in MS. The cytokine responses vary between males and females which may explain why men are less affected by MS. These cytokine differences could be due to testosterone (Liva at al 2004).

## Conclusion

From the numerous studies that have been undertaken to further understand and explore the roles of Oestrogens and testosterones in disease initiation and progression, it can be concluded that sex hormones may have powerful anti-inflammatory and neuroprotective functions. In spite of there being no specific treatments that are able to offer improvements to the long term prognosis of the disease, there has been increasing evidence to suggest that gender and hormonal profile can affect therapy and that these factors should be taken into account (Nicot 2009). Using a gender based approach in the

management of Multiple Sclerosis may be beneficial as many studies have pointed towards the importance of sex hormones in the pathogenesis of the disease. It has been acknowledged that sex hormones have roles in MS pathology therefore can be utilised in potential therapeutic measures for the treatment of the disease. It is known that immune mechanisms that promote the release of pro-inflammatory cytokines lead to a more severe and progressive disease and the mechanisms that promote the release of anti-inflammatory cytokines have shown to be protective (Palaszynski 2003). Sex hormones such as oestrogen and testosterone have been shown to encourage a shift towards an anti-inflammatory immune response which is favoured in multiple sclerosis. Therefore, oestrogen and testosterone are promising candidates for the treatment and management of multiple sclerosis as they posses anti-inflammatory and neuroprotective traits.