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The prognostic value of age, gender, pregnancy and endocrine factors in multiple sclerosis

Abstract The evolution of multiple sclerosis at the time of diagnosis remains unpredictable since a reliable prognostic marker is not yet available. Nevertheless, a series of useful prognostic indicators have been singled out from epidemiological studies. Young age at onset, female gender, relapsing/remitting course, and sensitive or visual disturbances as initial symptoms are considered favourable prognostic factors. Conversely, late age at onset, male gender, progressive course, and pyramidal or cerebellar symptoms at the first episode predict an unfavourable evolution. Another prognostic indicator has been recognized in pregnancy: although the overall effect of pregnancy on short-term MS course is neutral, in the long-term it seems to protect from disease progression. Most prognostic indicators seem to act through the neuro-endocrine-immune network, modulating the immune response in the context of the Th1/Th2 paradigm.

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Introduction

Relevant progress has been made in understanding multiple sclerosis (MS) pathogenesis but, once the disease is diagnosed, its outcome remains substantially unpredictable since a reliable prognostic marker is still not available. Presently, lesion load as determined by magnetic resonance imaging seems to be the most accurate prognostic measure available at the time of diagnosis. Significant information, however, has also been obtained from epidemiological investigations.

MS, similarly to other autoimmune diseases, shows significant bias in gender, age and geographical distribution. It occurs more frequently at high latitudes, in females and in early adulthood, although differences are detectable among clinical subtypes, suggesting that environmental, hormonal and other age- and gender-related factors play a role in triggering the disease onset. In addition, certain endocrine factors may influence disease evolution. The main aspects of these issues will be reviewed here in the light of their possible prognostic implications.

Age and gender

The majority of retrospective studies, cited in [1], agree that a young age at onset (less than 40 years) is linked with a more favourable evolution of the disease. In addition to a younger age, certain clinical features of the first episode of the disease correlate with a better prognosis. Namely, a fully remittent outcome of the onset episode and sensitive or visual symptoms at onset are significantly predictive of a more prolonged relapsing-remitting course, i.e. a more delayed conversion to a chronic-progressive evolution [2, 3].

Recently, a linkage between age at onset and certain immunogenetic markers has been reported. Carriers of the B1 allele of the interleukin 4 (IL-4) gene show a delayed age

at onset [4], while patients carrying the DR15 (formerly DR2) allele of HLA genes are prone to develop MS at an earlier age; however none of the HLA-DRB1 alleles seem to influence disease course or outcome [5]. A more aggressive disease course is associated with the A1 allele of the IL-1 receptor antagonist (IL-1Ra) gene, possibly reflecting a reduced ability of mononuclear cells to produce IL-1Ra [6].

In contrast to patients with a relapsing-remitting course, chronic-progressive MS patients show an older age at onset, especially those with primarily progressive or progressive-relapsing evolution [7]. A large cohort of chronic-progressive patients has recently been studied by Cottrel and coworkers [8]: their findings indicate that patients with a primarily progressive course reach complete disability more rapidly and have an earlier age at onset among males. As a whole, their data demonstrate a relatively worse prognostic role of male gender and late age at onset.

Although MS is rare in childhood, interesting data can also be drawn from investigations on sufficiently large series of subjects. Analyzing the characteristics of 149 MS patients with an age at onset less than 15 years, we found that MS affects males relatively more frequently before age 10 years while the proportion of females diagnosed with MS increases rapidly after age 12 years [9]. This indicates that hormonal changes related to puberty may play an important role in the pathogenesis of MS, as yet suggested by other investigators.

Sexual hormones

The gender-biased distribution of autoimmune disease can be explained in terms of Th1/Th2 polarization. According to the most recent knowledge, these two fundamental types of immune response are induced by two different sets of cytokines. The hormonal condition of males, characterized by high testosterone, low prolactin and pulsatile levels of growth hormone, favours the production of Th2 cytokines in experimental models. In contrast, females, characterized by high estrogens, high prolactin, basal levels of growth hormone and low concentrations of testosterone, are more inclined to produce Th1 cytokines [10]. Consequently, females are more likely to generate immune responses of the Th1-type, resulting in an increased susceptibility to certain autoimmune diseases, including MS.

There are also some clinical observations suggesting that the menstrual cycle, menopause and the use of oral contraceptives can influence MS course. Smith and Studd [11], in a questionnaire-based study, found that 82% of women with MS reported a pre-menstrual worsening of symptoms and 54% suffered a worsening of the disease in the post-menopausal period. The same authors reported that 75% of women who tried hormonal replacement therapy experienced an improvement of their neurological conditions. On the other hand, it is generally assumed that oral contraceptives do not modify the risk of having MS [12]. Another study confirmed that 43% of relapsing-remitting patients report worsening prior to menstruation, while primary progressive MS patients do not show any influence of the menstrual cycle on neurological symptoms [13]

Pregnancy

The question if pregnancy can modify the course of multiple sclerosis has long been debated in the past. Several retrospective studies and anecdotal reports have been published which gave conflicting results. For this reason, a widely diffused, although unjustified, opinion took shape that pregnancy could negatively modify the course of the disease, inducing several neurologists even to recommend therapeutic abortion. This prejudice persisted until recently, despite the fact that more than one prospective survey convincingly documented a lower risk of relapse during pregnancy, concluding that women with MS must not be advised against pregnancy. This issue was definitely resolved by the PRIMS study [14]: as many as 269 pregnancies in 254 MS women were prospectively followed for two years post-delivery in a cooperative, international multicentric study. The results indicated that the relapse rate declines progressively during pregnancy, then it rebounds in the first three months post-delivery before going down gradually to baseline values. This trend was also confirmed by monitoring MRI activity in pregnant women. Actually, the overall effect of pregnancy on the short-term MS course is neutral: whether the increased risk of relapse in the puerperium deserves a preventive treatment, as suggested by some authors, is still a matter of discussion.

The long-term effects of pregnancy on MS are more difficult to study because of the obvious bias introduced by the disease on the conceptive behaviour of the patients, since women with a more aggressive disease course tend to avoid pregnancy. A reliable cohort study investigated this issue and found that the risk of MS onset is higher in nulliparous with respect

Table 1 Natural immunosuppression in pregnancy

Reduced lymphocyte proliferative response to mitogens and MLR
Weak anticorpal response
Increased viral infections during the second and third trimesters
Plasma and amniotic liquid reduce T and B lymphocyte responses
Immunosuppressive effect of placental lactogen, alpha-fetoprotein and pregnancy-associated alpha-2-glycoprotein
Beta-HCG reduces T lymphocytes, NK cells and MLR
Synthesis of anti-HLA antibodies

MLR, mixed lymphocyte reaction; *HCG*, human chorionic gonadotropin

to parous women and the risk ratio tends to increase with time [15]. In addition, there was a significantly decreased risk of a progressive course in women who were pregnant after multiple sclerosis onset: for each year of observation, the risk of entering a progressive course was 3.2-times higher in the non-pregnant state compared with that after pregnancy.

In synthesis, the whole body of these data is consistent with the conclusion that the course of MS does not worsen during pregnancy at all and, conversely, maternity may play a "protective" role against disease progression.

Pregnancy is considered by many investigators to be a unique condition for better understanding the immune mechanisms underlying MS. In fact, in addition to the previously described hormonal factors, several observations suggest that a sort of "natural immunosuppression" occurs during the state of pregnancy (Table 1). It is believed that this condition prevents the rejection of foetus (which must be considered like a true allograft) from the maternal organism. It is well known that this immune state is sustained by the so-called foetal-placental unit and is characterized by the synthesis of Th2-type cytokines, particularly IL-10 [16]. As a result, there is a deviation of the maternal immune system toward responses of the Th2-type. This condition is considered to protect against the onset and the evolution of MS. For this reason, there is a great interest concerning pregnancy-specific immune factors and their potential application in the treatment of MS.

Other endocrine factors

One of the most striking features of MS is its increasing prevalence with increasing latitude. This observation suggested that an environmental variable like exposure to sunlight might be an important risk factor for MS. The effects of daylight on human body are manifold: those mediated by vitamin D3 and melatonin received particular attention in MS research.

Ultraviolet irradiation of the skin is the major source of activated vitamin D3, calcitriol, which is particularly relevant for calcium metabolism. When the exposure to sunlight is inadequate, as occurs at high latitudes during winter months, the synthesis of active vitamin D may be ineffective. It has been reported that as much as 46% of subjects with MS have vitamin D insufficiency and 23% have vitamin D deficiency [17].

On the other hand, prolonged darkness causes a sustained, non-cyclic synthesis of melatonin in the pineal gland. This peptide is an effective inhibiting factor for the hypothalamus to release the corticotrophin-releasing factor, which induces ACTH and, in turn, cortisol synthesis. As a consequence of high levels of melatonin, plasma concentration of cortisol decreases.

It has recently been established that the circadian variations of these hormone-like molecules play an important role in the more complex neuro-immuno-endocrine network [18]. The identification of receptors for these molecules on T cells increased the interest for these substances as regulators of the immune system. Vitamin D3, for example, effectively prevents and blocks progression of EAE. In humans, as well as in experimental models, vitamin D3 increases IL-4 and TGF-β and decreases IL-12 levels, both in vitro and in vivo. For its properties, vitamin D3 downregulates immune responses of the Th1-type [19].

Melatonin, on the other hand, can activate corticosteroid hormone receptors on T cells. It has also been found to induce IFN-gamma and IL-12 synthesis in vitro and in vivo, thus enhancing Th1-type immune responses [18]. According to these findings, melatonin antagonists were found to protect mice from EAE.

In conclusion, an insufficient exposure to sunlight, as occurs at high latitudes during wintertime, induces a prolonged release of melatonin and an inadequate synthesis of vitamin D3. This neuro-endocrine state is favourable to the onset and the maintenance of autoimmune diseases like MS, once more through a deviation of the immune system toward Th1-type responses.

Conclusions

Although a reliable prognostic marker of MS evolution is still missing, a series of effective prognostic indicators have been singled out from epidemiological observations. In synthesis, young age at onset, female gender, relapsing/remitting course, and sensitive or visual disturbances as initial symptoms are considered favourable prognostic factors. Conversely, late age at onset, male gender, progressive course *ab initio*, and pyramidal or cerebellar symptoms at the first episode predict an unfavourable evolution. The actual value of each factor is not quantifiable but, obviously, the simultaneous presence of the whole set of favourable or unfavourable predictors strengthens the prognostic reliability. In clinical practice, this concept is translated into a wide spectrum of prognostic assessments, in a continuum ranging from a benign to a malignant form of MS. Besides these constitutive prognostic indicators, other transitory ones have been recognized, mostly associated with hormonal changes, such as puberty, pregnancy and menopause.

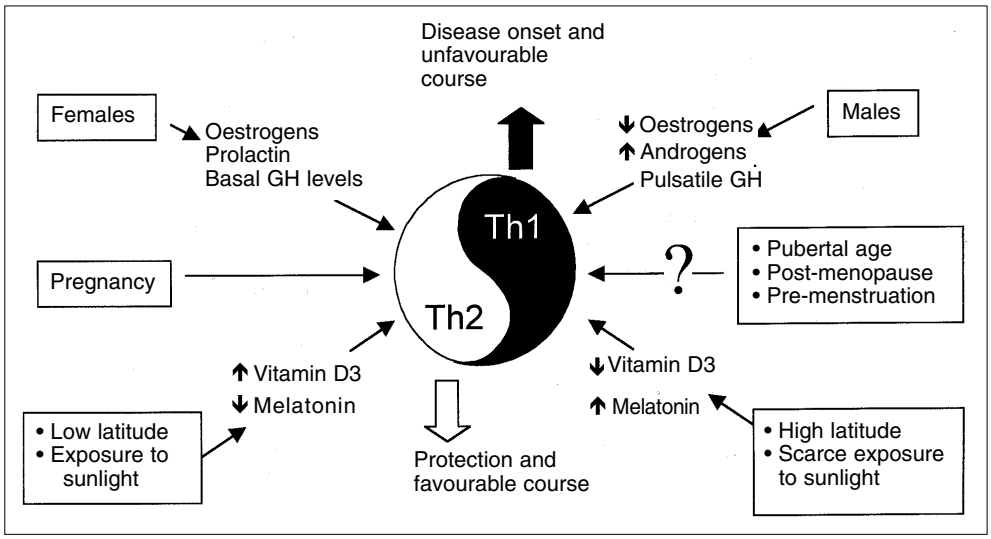

Fig. 1 Condition that modify the prognosis of MS inducing a shift toward Th1- or Th2-polarized immune responses through a modulation of the neuro-endocrine-immune network; *GH*, growth hormone

The mechanisms of action of all these prognostic factors have not been completely elucidated, but most of them lead to a modulation of the immune response in a direction that fosters MS onset and maintenance of its pathogenic process, in the context of the complex neuro-endocrine-immune network (Fig. 1).

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