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Potential Enviromental Risk Factor of MS

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Multiple sclerosis is **(MS)** is a chronic complex disease of the central nervous system **(CNS)** with autoimmune inflammation base resulting in demyelinating plaque within white matter [1,2]. It seems that the origin of MS plaques is the activation of autoreactive T cells directed against myelin antigens of CNS. The etiology of this activation and then MS is unknown. Researches mentioned many factors for this disease, however none of them are the sole responsible for MS.

It seems this disease occurs due to variable genetic traits and environmental triggers.

There is a strong evidence showing the importance of environmental triggers in the pathogenesis of multiple sclerosis. Many studies demonstrated that about 80% of MS patients do not have affected relatives, and that about 75% of twins with an affected identical twin do not develop multiple sclerosis [3-5].

Several of the probable environmental exposures that have been investigated are latitude, hours of daylight, viruses, immunization, smoking, nutritional habit, pets, and toxic chemicals [6,7].

MS is the most costly chronic disease with high psychosocial and economic burden on individuals, their families and society [8,9]. So investigation on environmental trigger to decrease the incident is necessary.

The aim of this chapter was to review the probable environmental exposure in MS.

CIGARETTE SMOKING

There is some evidence that smoking has an association with the risk of MS severity and progressive form [10,11]. It seems some mechanisms are involved in these results. Smokers (and ex-smokers) demonstrate a dysregulation of lymphocytes homeostasis and have inflammatory factors (e.g. C-reactive protein, fibrinogen IL-6) in serum [12]. Furthermore, cigarettes contain nitric oxide **(NO)** [13] and Carbon monoxide **(CO)** [14]. NO-gas causes damages to oligodendrocyte necrosis, axonal degeneration and mitochondrial [15]. Also, CO causes demyelination and blocks tissue oxygenation [16].

Smoking surely has adverse effects on the immune system. It increases the level of C-reactive protein, fibrinogen and inflammatory factors **(IL-6)**. Also it may lead to dysregulation of B-cell and T-cell homeostasis [12]. Mitochondrial damage is seemingly attributed to the NO in cigarettes, which may result in axonal degeneration and oligodendrocyte necrosis [13]. During MS relapses and disease progression, NO levels raised in cerebrospinal fluid [14]. The main culprit for blocking tissue oxygenation and demyelination is the carbon monoxide in the cigarettes [15]. Although nicotine, acting on α7-cholinergic receptors present on immune cells, may have an immunosuppressive effect [16,17], cigarette smoking may lead to oxidative damage in smokers. All in all, not only smokers have a high risk of developing MS, but also it advances to higher levels of disability much faster [18].

SUNLIGHT RADIATION AND VITAMIN D

Recent studies have showed an inverse association between MS risk and sunlight radiation [17]. Sunlight radiation decreases MS risk by producing vitamin D. Vitamin D decreases this risk by the effect of IL-10, TNF-α and Treg cells, all of which can ultimately have anti-inflammatory effects [18].

Vitamin D

Vitamin D shows itself as ergocalciferol and cholecalciferol in nature. 7-dehydrocholesterol in skin will change to cholecalciferol when exposed to sunlight. A hepatic hydroxylation phase mediated by several P450 cytochromes leads to the production of 25-OH-cholecalciferol. Afterwards, a renal hydroxylation step starts leading to the formation of 1α, 25-dihydroxyvitamin D3 **(1α,25-(OH)2D3)**, the active metabolite [19]. Vitamin D, playing a role in gene expression, binds to the intracellular vitamin D receptor **(VDR)**, binding to the retinoid X receptor to create a heterodimer identifying specific base sequences in DNA, known as vitamin D response elements **(VDREs)**.Vitamin D has effects on protein transcription, calcium and phosphate metabolism, lithocolic acid **(LCA)** inactivation [20], keratinocyte differentiation and innate and adaptive immunity regulation. This is done by binding to the intracellular vitamin D receptor **(VDR)**, which in turn binds to the retinoid X receptor creating a heterodimer that recognizes specific base sequences in DNA. Most of vitamin D is produced in the skin via exposure to the sunlight [21].

VDREs are usually in several immune cells, e.g., macrophages, lymphocytes and dendritic cells. Vitamin D causes apoptosis in B cells [22], subdues the T-cell response by inducing naive T-cells to mature into regulatory T cells **(Tregs)** having an anti-inflammatory effect [23], inducing interleukin **(IL)**-10 synthesis [24] and suppressing IFN-γ [25] and IL-2 [26]. Vitamin D have more powerful effects in females due to a synergistic action of 17β-estradiol and 1α,25-(OH)2D3 [27]. VDRs and 1α-hydroxylase are in the pancreas, muscle, ovary breast and brain. They can also be found in neurons and glia, mainly in the hypothalamus and substantia nigra [28].

30-40 ng/mL of 1α,25-(OH)2D3 is enough for bone health and preventing fractures according to the scientific community [29]. Moreover, this community states that a level > 24 ng/mL improves muscle performance and decrease the risk of falls [30]. Levels < 20 ng/mL are widely considered as deficiency, while levels of 21-29 ng/mL are assumed as *insufficiency* [31]. Levels < 15 ng/mL may lead to a higher risk of cardiovascular diseases [29]. As intake of 2.5 μg is required to enhance vitamin D blood levels by 1 ng/mL, 75 μg/day is minimum requirement for meeting the safety threshold of 30 ng/mL [32]. A small portion of vitamin D supply is provided by our dietary intake. For instance, it is 2.5-5 μg/day in North America and Europe, while the European recommendations advocate offer 20 μg/day [33]; Skin contains most of our vitamin D since it is the most exposed part to the sunlight [21]. Therefore, those who have less exposure to the sunlight have the higher risk of vitamin D deficiency [34,35]. Adipocytes consumes the vitamin D in skin and therefore reduces its serum concentration leading to a higher risk of vitamin D deficiency.

Many studies demonstrated the relation between vitamin D level and the possibility of developing MS. For instance, a negative association between high levels of 1α, 25-(OH)2D3 and risk of MS have been found in a study on US military personnel [36]. Moreover, it has been suggested that low serum vitamin D may lead to a higher risk of developing clinically definite MS in an Italian study [37]. Long-term MS activity and its progression may have an association with vitamin D incompetency [38].

Sunlight Exposure

Recent researches show that exposure to UV radiation lessens the risk of MS [39]. It is done by producing vitamin D and maybe by creating IL-10, TNF-α and Treg cells [40]. In contrast, in some Italian regions with a high level of UV radiation exposure, an increased number of MS have been reported. This may be assigned to a high frequency of HLA-DRB1. On the other hand, low number of MS have been reported in Scandinavia with low level of sunlight exposure. This can be explained by their daily vitamin D intake [41]. This supports the assumption that MS has a multifactorial pathogenesis.

VACCINATION

Vaccines perform similar to the infection mechanism in increasing the risk of CNS ADS. This is done by increasing autoimmunity by expanding the auto reactive T-cell clones or increasing the antigen presentation [26]. These associations are so intricate and depend on many different factors such as the timing of exposure, antigen type, genetic background, and coadministration of adjuvants. Therefore, on specific occasions, both of them can help to improve level of tolerance and autoimmunity [27,28]. That's why they say "less exposure to infections enhances the risk of autoimmunity" [26,29].

But theresult of studies is contraverted. Several studies demonstrated no association between vaccination and MS risk in the short time or long term (41 years) [19,20,22-25]. A nested case-control study demonstrated an association between HB vaccination and risk of MS within 3 years of vaccinationin adults [26]. IT seems that these findings do not warrant any change in vaccine policy.

TYPE OF DELIVERY, BREAST FEEDING

Several studies showed a parent-of-origin (maternal) effect on MS [28,30]. Prematurity has an association with developmental and neurologicdisability [31,32].

The effect of type of delivery on MS risk is controversy. Some studies found no significant association between Cesarean section (C-section) and the risk of MS [33]. On the other hand, some studies have another opinion. They suggested that C-section could increase the risk of immune base disease [21].

One of the important contributors to stimulating the progress of the immune system is gut microbiota [42]. This factor composition depend on many situations, for instance it is different for those born by Caesarean section than those born vaginal section [8-11]. This may be explained by the fact that they are first exposed to bacteria originating from hospital environment, not to maternal bacteria [11]. That's may be the reason that the hygiene hypothesis proposes that these kinds of children enhance the risk of autoimmunity since they have decreased or delayed exposure to infection [43]. That's why those born by Caesarean section enhances their autoimmune risk.

Some studies demonstrated that breastfeeding shows an independent association with a lower risk of MS [34]. These results confirm the previous ones that breastfeeding have defensive effects. Moreover, it has been reported that this also leads to enhancing the immunologic tolerance and reducing risk of autoimmune disorder.

PHYSICAL AND EMOTIONAL STRESS DURING LIFE TIME

Evidence suggests that early life stress can influence CNS development. The mechanisms underlying of this association by hypothalamic-pituitary-adrenal axis activity and immune-related mechanisms such as maternal immune activation enhanced levels of pro-inflammatory

cytokine and may also act independently or together with GCs to influence CNS development and function [35]. Furthermore, some studies demonstrated that stress during lactation may lead to behavior and hormonal profile change and growth in offspring [37,38,44].

Our result showed a strong relation between Stress and MS risk. Nielsen et al in cohort study showed a relation between major stressful life events and MS risk [38].

INFECTION

History of Measles and Mumps infection are more frequent in MS group in our study. Up to now, some studies confirm the high prevalence of virus anti body such as Measles and Mumps. Studies demonstrated the high prevalence of Measles anti body in serum [39] and cerebral spinal fluid [39,40], in compare to control groups. Furthermore, Cloning of IgG in brain plaque sites and CSF of MS patients have demonstrated over-represented heavy-chain sequences [41].

Evaluation the IgG heavy-chain sequences in MS and subacute sclerosingpanencephalitis demonstrated features of an antigen-driven response in these diseases. Since the antigen in subacute sclerosingpanencephalitis is known to be measles virus, the parallel results in MS propound an antigen-driven immune response [45] instead a non-conventional mechanism of B-cell activation. Moreover, the antigen-driven clonal B-lymphocyte and plasma-cell response is discovered after a single clinically isolated syndrome [46,47] which propounds that finding of the disease-relevant antigens in early CNS demyelination may bear on the inciting antigens in MS. Further analysis of the specificity of IgG in brain and CSF has the potential to identify an infectious agent in MS. These results are confirmed by data from the fast reduction in MS disease activity achieved by anti-CD 20 monoclonal antibody therapy [42,48,49], which results in B cell depletion in the peripheral blood. However, the mechanism seems to not be associated with decreased autoreactive antibody synthesis as the IgG levels are only slightly affected [42,48,49].

CONSERVED FOOD, MICROWAVE

Studies showed that Perinatal bisphenol A **(BPA)** exposure (the chemical agent used in Can) is relatedto increased cytokine and antibody production, and decreased number of regulatory T cells in mice [43,50]. Furthermore, BPA resulted in a decreased viral antibodies level, accelerated the Theiler's-virus induced demyelination symptoms onset, enhanced inflammation in the spinal cord [51].

CALCIUM SUPPLEMENTATION AND DAIRY CONSUMPTION

Our result demonstrated that calcium supplementation and dairy consumption can be protective to MS risk factor. Up to now, the role of calcium metabolism in the interaction between vitamin D and MS is unclear. In experimental autoimmune encephalomyelitis **(EAE)**, calcium supplementation and the subsequent elevation of serum calcium concentration were critical factors in the clinical and immunological effects of 1,25(OH)2D therapy [52]. Calcitonin, a protein released during hypercalcaemia, increased the clinical effectiveness of 1,25(OH)2D in EAE [53],

but was not mandatory [54]. Soilu-Hanninen et al. demonstrated that MS groups had lower total calcium and higher intact PTH in serum during spring and winter compared to healthy controls, despite similar 25(OH)D levels [55]. Contrastingly, Smolders J et al. showed that serum calcium, PTH, and 1,25(OH)2D are not critically involved in the interaction between vitamin D status and T cell regulation in MS patients [56]. It seems that more studies are required to determine this interaction.

PET EXPOSURE, TOXIN EXPOSURE AND HEAVY METAL EXPOSURE

Ghadirian et al showed that contact with cats was inversely related with MS risk, especially in men, whereas contact with caged birds was significantly related with MS risk, particularly in women [57]. Also Napier et al demonstrated that mercury and lead exposure was more frequent in MS group [58]. And statistically significant potential gene-environment interactions were recognized on the multiplicative scale with SNPs (Single Nucleotide Polymorphism) in five of the genes examined (TNF-α, TNF-β, VDR, MBP, and APOE) [58]. Several studies demonstrated the relation to environment-gene interactions in MS and inconsistency in results may be due to this factor.

HEAD TRAUMA

Similar to our study, meta-analysis of 36 case-control studies demonstrated a significant relation between childhood and premorbid head trauma, other trauma premorbid, and spinal trauma premorbid and risk of MS [59]. On the other hand, meta-analysis of cohort studies did not support a statistical relation between head trauma and risk of MS [59]. It seems that head trauma may cause a disturbance in the blood-brain barrier [60], that could lead to passing the autoreactive immune cells into the central nervous system and finally cause a MS lesions or plaques [60].

However, one should consider that there is a high frequency of blood-brain barrier disturbance in MS patients without experiencing a trauma and in contrast, many with trauma experience has not developed MS [61]. So more studies are needed to find whether a purely coincidental exists or it's just a causal association.

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