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Missing links in multiple sclerosis etiology. A working connecting hypothesis

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ABSTRACT

The etiology of multiple sclerosis is still elusive despite an extended patchwork of mechanistic events has been accumulated. In this article, are tentatively identified from scattered literature sources new factors that may link well known characteristic of MS such as the central alteration of BBR selectivity, its association with EBV status and its biased distribution of the globe more comprehensively. The hypothesis proposes that the concomitant important rise in some heterophilic antibodies (anti Neu5Gc) which activate BBB endothelial cells and in the frequency of anti EBV committed T cells and of memory B infected cells with EBV contemporary to EBV infection play a major role in MS etiology. In addition, the hypothesis proposes new possible explanations for the elevated risk of MS in specific geographical area.

Forewords

A new hypothesis cannot explain every aspect of a disease but must provide sounder explanations than those that already exist. To stand as such, a hypothesis must pave the way for future avenues in research and yet it clearly faces commonplace statements such as, "The greatest obstacle to discovery is not ignorance, it is the illusion of knowledge" (Daniel Boorstin), which is worth keeping in mind. However, new speculations that may, ironically and at least momentarily, escape other dangers, ("for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias", John Ioannidis [1] are potentially important tools in the discovery process.

Missing links in the hypothesis of MS etiology

There is compelling evidence that overt MS contains a major immune component (see [2,3] for reviews). Recently, the demonstration of significant clinical effectiveness of compounds such as anti-a4 integrins [4], 2), anti-CD20 [5] and inhibitors of sphingolipid receptor [6], targeting well documented elements of the immune response, has brought further information to light about the mechanisms of the immune component of the disease. Examples include the limitation of entry of immune effectors into the Central Nervous System (CNS) by anti-a4 integrins and the reduced autoantigen presentation and possible EBV carry-over into the CNS [7] for depleting anti-B lymphocyte agents. However, contrasting with the abundance of documentation regarding the immune response in the CNS of patients suffering from MS, the disease's etiology remains elusive. Not only is the nature of the initial immune dysfunction leading to an overt MS disease speculative in the "outside in" side of the model, there remains the plausible possibility of an intrinsic non-immune-mediated dysfunction of CNS tissue (see [8] for review). Such dysfunction would generate secondary autoimmune processes leading to "immunological convolution". This could then benefit from the recent observations of secondary inflammation and eventually autoimmune processes occurring in diseases such as Parkinson's or Alzheimer's or Leber–Harding disease and juvenile adrenoleukodystrophy. The hypothesis developed below, which primarily tackles the initial step of the "outside in" autoimmune model of MS etiology, does not exclude the possibility of a degenerative trigger [8,9]. Despite there being no animal model representing the entire spectrum of MS, rodent EAE has nevertheless proved its usefulness for deciphering the immune component of MS and has pointed to relevant treatment strategies such as anti-a4 integrins [10], and anti-IL7R [11]. Primate EAE models, particularly those using marmosets, which display an expanded pool of memory cells [12,13], and to some extend "spontaneous" EAE in rodent which circumvent active induction and transfer, are the most representative of the human form of the disease. However, a new understanding of MS etiology must be fostered based on (and complying with) observations made in humans.

GWAS have identified an ever increasing series of genes that are likely to be involved in the physiopathology of MS [14,15]. Moreover, GWAS have demonstrated a possible increased susceptibility of specific T cells to react to epitopes through MHC restriction, or to mount deleterious immune responses by increasing effector activity or decreasing regulation through the alteration of cytokine

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signaling pathways (IL2 [16] or IL7 [15,17]). Interestingly, these studies have also emphasized certain molecular risk similarities with other diseases that also have a strong autoimmune component, such as Type 1 diabetes. However, most patients do not exhibit genotypes that grossly affect their immune response, suggesting that these traits affect the level of the response in some individuals only, rather than providing a global comprehensive model of disease etiology. Moreover, although certain diseases nosologically related to MS have been associated with precise genetic defects [18,19], GAWS have provided no evidence that the etiology of MS may lie in a yet unidentified primary neurodegenerative process that would secondarily initiate an autoimmune response. This has led to much frustration given such a major collaborative endeavor. Finally, studies in twins [2,20] as well as those reporting on the striking increase in MS incidence since the mid 19th century [21], have emphasized the major role of environmental factors – most spectacular in Japan over the last decades-in the occurrence of the disease.

Studies of peripheral immune responses and central lesions during MS, especially in the rodent EAE models [13], have provided us with a working model of the immune physiopathology of overt MS. In the latter model, committed activated blood mononuclear cells (generated by T cell transfer or using transgenic animals) enter the CNS tissues across an inflamed blood brain barrier (BBB). According to imaging studies using anti-Mog or Ovalbumin clones, only clones committed to brain antigens initially penetrate brain tissues [22,23]. In addition, the model proposes that activated T cell clones committed (or cross-reactive) to brain autoantigens themselves are instrumental in altering BBB permeability [23]. After entering the brain, these cells are believed to initiate an *in situ* immune conflict, leading to demyelination and axonal loss, ultimately resulting in overt disease symptoms. The physiopathological representations of the immunological events derived from these models form an evolving dendrogram. Although primates, such as marmosets, still require immunization against myelin antigenic peptides and ICF in order to develop EAE [12], they may be more relevant to the human disease as they are similarly characterized by an expanded pool of memory cells, which is absent in laboratory rodents. In addition, anti-Mog TCR-transgenic mice seldom develop overt disease spontaneously, but the incidence of the clinical symptoms is notably increased if the animals are provided a bacterial adjuvant [24,25]. These models, which emphasize a possible role of a preexisting expanded pool of peripheral antigen-experienced T cells [12,13], and are obtained either by immunization, transgenesis or cell transfer, all suggest a missing factor necessary to trigger the full EAE disease phenotype.

Furthermore, in humans, the model also fails to explain or does not fit with several observations. Firstly, there is no clear evidence of a pre-existing or *de novo* high frequency of autoreactive T cells in a sizable proportion of MS patients with overt disease as compared to age and gender-matched controls [26] and, in contrast to EAE models, there are as yet no identified autoantigens in MS, rather multiple determinants are recognized by T cells or antibodies [27], MOG may be an auto antigen in childwood, aquaporin in NMO. Secondly, there is a beneficial effect of anti-a4 integrin and anti-CD20, suggesting that the potential effectors of CNS lesions are continuously replenished from the periphery, rather than being "autonomous" – at least in the remitting/relapsing phase of the disease-indicating a role for sustained altered BBB regulation. Third, the nature of the BBB endothelial cell inflammatory trigger that may facilitate activated T and B cell entry to the CNS is unknown. The possibility itself of a non T cell-driven process of BBB permeability changes and its potential part in the spreading of such changes to apparently normal white and grey matters is also unknown. Finally, there are major epidemiologic trends, including the tight links between certain viral diseases, such as EBV, and risk of MS, the influence of pregnancies on disease activity, the gender imbalance, the possible dietary influence and the specific geographic distribution of the disease i.e., all of the parameters that are characteristic of MS but are not satisfactorily explained by the current etiological hypotheses.

Outline of the working connecting hypothesis

For the sake of clarity, let us start by outlining the major elements of the hypothesis, which will be developed in more detail hereafter. As alluded to in the title itself, the hypothesis described in this paper primarily aims at bridging missing links in our current understanding of MS etiology. The hypothesis also relies on observations specific to MS, not to EAE, and focuses more on disease etiology than on the immune component of the overt disease.

I propose that the major event of the disease relates to a primary deregulation of BBB permeability concomitant to an increase in the frequency of circulating activated T and B cells- which then acts as a positive amplifying loop-, rather than to a specific breakdown of tolerance with subsequent autoimmune responses to CNS determinants that will decide who will make the disease. The proposed hypothesis suggests that this chronic deregulation of immunocyte entry into the CNS is modulated by an *in situ* BBB antibody–antigen interaction ccurring within a "physiological system", namely the presence of natural and elicited "heterophilic" antibodies recognizing antigenic determinants expressed by BBB endothelial cells (EC). The levels of such antigens and antibodies are also regulated by clinical events or epidemiologic trends associated with disease risk factor, such as EBV infection and diet (likely linked to the geographical distribution bias – see below). The framework of the proposal is based on the co-existence of (i) natural and elicited anti-Neu5Gc antibodies, which coexist in normal individuals due to an accumulation of Neu5Gc determinants [28] in various tissues, especially in brain endothelial cells [29,30], and (ii) the clinical condition of a simultaneous explosive elevation of the frequency of activated/memory circulating T and B cells. Most human beings develop various levels of anti-Neu5Gc antibodies which, in some individuals, can make up a substantial proportion of total circulating Ig molecules [28]. These antibodies are elicited by a lack of functional CMAH, a gene encoding a hydrolase that converts the Acetyl form of neuraminidic acid into the Glucyl form [31]. As the deletion of the functional CMAH gene occurred ~3.5 M years ago, the effect of antibodies against such "xeno–auto" antigens cannot be explored in species other than human beings. However, importantly, despite an inefficient CMAH gene, exogenous Neu5Gc can enter the neuraminidic pathway [32] and deposit in brain endothelial cells where, upon interaction with anti-Neu5Gc and complement, they create a condition of acute or chronic local inflammation and an impaired regulation of immunocyte entry into the CNS. Anti-Neu5Gc antibodies that bind these "xeno–auto" antigens activate EC and, in the presence of complement, increase leukocyte binding to EC [29]. This atypical situation of "physiological" immune complex formation has been suggested to induce inflammation of the large vessel walls and even to lead to oncogenesis [29].

EBV primo infection (infectious mononucleosis,IMN) occurs simultaneously to a significant increase in "heterophilic" antibodies that are highly enriched in anti-Neu5Gc antibodies (Paul–Bunnell/Davidsohn reaction, [33]), the titers of which also remain higher than prior to the IMN in the long term. This is accompanied by a striking increase in circulating EBV-committed T cells [34,35]. Furthermore, as a large proportion of activated and memory B cells are infected by EBV following primo infection [36], a concomitant increase in anti-Neu5Gc subsequent to inflammation of BBB EC, promoting B cell migration into the CNS, gives credit to the possibility of B cells acting as EBV antigen carriers in MS, with