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From the "little brain" gastrointestinal infection to the "big brain" neuroinflammation: A proposed fast axonal transport pathway involved in multiple sclerosis

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SUMMARY

The human central nervous system (CNS) is targeted by different pathogens which, apart from pathogens' intranasal inoculation or trafficking into the brain through infected blood cells, may use a distinct pathway to bypass the blood–brain barrier by using the gastrointestinal tract (GIT) retrograde axonal transport through sensory or motor fibres. The recent findings regarding the enteric nervous system (often called the "little brain") similarities with CNS and GIT axonal transport of infections resulting in CNS neuroinflammation are mainly reviewed in this article. We herein propose that the GIT is the vulnerable area through which pathogens (such as *Helicobacter pylori*) may influence the brain and induce multiple sclerosis pathologies, mainly via the fast axonal transport by the afferent neurones connecting the GIT to brain.

Infections and multiple sclerosis

A common characteristic of many neurodegenerative disorders of the central nervous system (CNS) is neuroinflammation, marked by augmented numbers of activated and primed microglia, increased steady-state levels of inflammatory cytokines and decreases in anti-inflammatory molecules. These conditions sensitise the brain to produce an exaggerated response to the presence of an immune stimulus in the periphery or following exposure to a stressor [1,2]; neurodegenerative brain disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis involve neuroinflammatory reactions [3–5].

Specifically, MS is a chronic, unpredictable inflammatory demyelinating disease in the CNS; it affects more than two million people worldwide and has been recognised as the leading cause of neurological disability causing chronic paralysis and immersing socio-economic problems among young adults [6]. The aetiology of MS is an elusive field due to the lack of the standard cause–effect relationship model to explain a disease. Despite the enormous hard works made in MS research, the pathogenic mechanisms involved in the inflammatory and degenerative process of MS are still unclear. In fact, current data suggest that MS is a multi-factorial disease, where an infective agent on a genetically permissive host can result in neuroinflammation, demyelination, and ultimately in neurological damage with dire consequences for the patients. While genetic susceptibility explains the familial clustering of MS and the sharp decline in risk with increasing genetic distance, it cannot completely explain the geographical variations in the MS frequency and the changes in risk that occur with migration, which support the action of strong environmental factors. Among these, infections are emerging as the most consistent predictors of MS risk [7]; genes and infections by pathogens might act synergistically to trigger the disease [8]. In this respect, the possibility that microorganisms can cause MS has recently been addressed: Epstein-Barr virus, human herpes virus 6, *Chlamydia pneumoniae* (*C.* pneumoniae), and possibly *Helicobacter pylori* (*Hp*) by eliciting inflammation may cause the neurological damage that results in MS [5,8–12]. It has been suggested that the communicable factor is acquired in early adolescence [13]. Although the early events underlying MS remain uncertain, active inflammation may determine the initial phase of the disease. The infectious agents may exist at the origin of MS and other autoimmune diseases [14,15]; infection-induced molecular mimicry can induce autoimmune disorders including an early onset of the demyelinating disease associated with activation of CD4+ T cells [14].

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While demyelination might be a secondary phenomenon in the acute lesions of MS and the first visible event appears to be the apoptotic death of oligodendrocytes [16], active plaques occur early during the disease and are characterised by the presence of mononuclear cells, including T- and B-lymphocytes and macrophages in brain perivascular spaces. Despite the fact that no single causal agent or event has yet been identified, a long-favoured hypothesis in MS pathology is largely attributed to autoreactive effector T cells generated in the periphery that penetrate the blood–brain barrier (BBB) and become activated within the CNS [17,18]. Importantly, as autoreactive T cells are present in the blood of MS patients, other regulatory mechanisms exist to prevent autoreactive T cells from causing immune disorders. In this respect, the function of T regulatory (Treg) cells which play a key role in the control of self-antigen-reactive T cells and the induction of peripheral tolerance may be diminished in MS and may be correlated with impaired inhibitory activity [18]. As a result, autoreactive CD4+ and CD8+ T cells have been found to invade and clonally expand in inflammatory CNS plaques in MS [19]. Of note, CD4+ effector T cells are categorised into three subsets: T-helper type 1 (Th1), Th2, and Th17 cells; the latter have also been involved in the pathophysiology of MD [20]. Specifically, the interaction of activated CD4+ T cells with microglia led to a pro-inflammatory Th1 response with a Th1-type cytokine expression profile involved in the pathogenesis of apoptotic neuronal cell death in MS; secretion of substantial levels of pro-inflammatory Th1-type cytokine tumour necrosis factor (TNF)-α leads to TNF-α-related apoptotic neuronal cell death in MS [21]. Notably, apoptotic rather than necrotic microglia-associated nerve cell death appears as likely to underlie a number of common neurological conditions including MS, AD, PD, and glaucoma ('ocular' AD) [3,22]. MS is crucially dependent on activation of pro-inflammatory Th1 T cells by antigen-presenting cells, resistance of T cells to Fas-mediated apoptosis is involved in its exacerbation, and auto-aggressive Th1 cells can be adoptively transferred to non-diseased recipient mice that subsequently develop disease [23].

The activated encephalitogenic immune effectors (CD4+, CD8+ T cells, B cells, and macrophages) express surface molecules that allow them to penetrate the BBB and enter the CNS [24]. However, the explanation of the initial process of breakdown of normally tight BBB and the association of cellular infiltration into the CNS remains unanswered. In this regard, a series of factors have been implicated in inducing BBB disruption, including inflammatory mediators [e.g., cytokines and chemokines induced by *Hp* infection (*Hp*-I)] and oxidative stress [25,26]. *Hp* could indirectly affect the brain and other target organs, e.g., the heart, through the release of numerous cytokines such as TNF-α acting at distance; TNF-α is involved in BBB disruption through a mechanism involving matrix metalloproteinases upregulation [27]. In addition, *Hp*-induced cytotoxin VacA exhibits chemotactic activities to the bone marrow-derived mast cells (BMD-MCs) and induces BMD-MCs to produce pro-inflammatory cytokines including TNF-α [28]; BMD-MCs reside adjacent to blood and lymphatic channels, mainly under epithelial surfaces including the BBB and gastrointestinal tract (GIT) [29]. MCs can be stimulated by corticotropin-releasing hormone, secreted under stress, to release mediators including histamine, interleukin (IL)-8, tryptase, and vascular endothelial growth factor, which disrupt the BBB [30]. Therefore, regarding the pathogens' access the CNS, apart from pathogens' intranasal inoculation, the influx of activated monocytes infected with pathogens such as *C. pneumoniae* through the disrupted BBB in the brain could lead to the development of degenerative diseases [31].

In this study we propose that the GIT is the vulnerable area through which pathogens (such as *Hp*) influence the brain and induce CNS neuroinflammation, via another rational pathway; inflammatory GIT reactions may access the brain and induce degenerative pathologies, mainly via axonal transport by the afferent neurones connecting the GIT to the brain.

From the periphery to brain

Gastrointestinal tract

Inflammation in the brain might initiate from the periphery and relative data suggest that peripheral conditions powerfully influence processes in the brain relevant to MS. Indeed, systemic infections influence CNS function, and microbial invasion and traversal of the BBB is a prerequisite for CNS infections. Pathogens can cross the BBB transcellularly, paracellularly, and/or in infected phagocytes (the so-called Trojan-horse mechanism). Subsequently, pathogens can induce BBB dysfunction, including increased permeability, pleocytosis, and brain pathologies [32,33]. Notably, sickness behaviour appears to be the expression of the adaptive reorganisation of the host priorities during an infectious episode. This process is triggered by pro-inflammatory cytokines (i.e., IL-1β, IL-6, IL-8, and TNF) produced by peripheral phagocytic cells in contact with invading microorganisms. The peripheral immune message is relayed to the brain through a fast neural pathway and a slower humoral pathway, leading to the expression of pro-inflammatory cytokines in macrophage-like cells and microglia in the brain [32].

An alternative route of entry for pathogens into the CNS is through the nasal olfactory pathways [31]. Because, *C. pneumoniae,* being a causal factor of MS [34], readily infects epithelial cells and has direct access to the olfactory neuroepithelium of the nasal olfactory system, this pathway of infection would seem likely, given that *C. pneumoniae* is a respiratory pathogen. Subsequently, infection, inflammation, and/or damage of the olfactory bulbs could result in brain damage [31].

The nasal olfactory pathway is connected directly and the blood pathway is connected indirectly with GIT, a susceptible area by which pathogens invade the brain. In the human body, the GIT mucosal surfaces are the largest and one of the most complex parts of the immune system. The GIT microflora plays an essential role in host health owing to its involvement in nutritional, immunological, and physiological functions [35]. Discrimination between beneficial commensal bacteria, harmless antigens, and pathogenic microorganisms is a fundamental issue in the role that GIT immune cells play in maintaining the balance between immune response and tolerance [36]. Microbial imbalances have been associated with enhanced risk of specific diseases [35]. Under the conditions of disturbed microflora homeostasis, impaired mucosal permeability, and immunocompromisation, microbial translocation is pathologically increased, and then causes systemic inflammatory responses which play an important role in the eventual outcome towards multiple-organ involvement including the brain [37,38].

Peripheral (GIT) infection associated with MS

The microorganism itself can initiate an immune response in GIT. Molecular mimicry has been proposed as an explanation for autoimmune side effects/disorders of microorganism infections including MS [39]. In this respect, current *Hp*-I induces humoral and cellular immune responses that, owing to the sharing of homologous epitopes (molecular mimicry), cross-react with components of nerves, thereby contributing and possibly perpetuating neural tissue damage in neurodegenerative disorders including MS [3,5,40,41]. Infectious stimuli may also participate in the development of autoimmunity by inducing an increased expression of heat shock proteins, chaperones, and transplantation antigens, which results in abnormal processing and presentation of self antigens; superantigens appear to be one of the most effective bacterial