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Chronic viral infections of the central nervous system:
Aspects specific to multiple sclerosis

Infections virales chroniques du système nerveux central :
aspect spécifique à la sclérose en plaques

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Abstract
The involvement of a viral infection in the physiopathology of multiple sclerosis has been said to cause certain viruses to target the central nervous system and induce neuroinflammation leading to cell dysfunction, as seen, for example, by demyelination or neuronal death. The most recent results of the literature have focused on the Herpes family viruses (HHV-6 and HHV-4/Epstein-Barr virus) and their possible role in the development of multiple sclerosis. Even if no virus has been identified so far as the multiple sclerosis etiological agent, our aim here is to show that some viruses may be responsible for triggering or sustaining neurological diseases. This is particularly the case for Paramyxoviruses, in the late appearance of functional alterations, Picornaviruses, in inducing a breakdown of immune tolerance, epitope spreading and demyelination, and Herpes viruses in inducing T and B lymphocyte activation, T lymphocytes dysregulation and autoimmunity after their reactivation. Therefore, “common” viruses can play a role as potential modulators of the immune and nervous systems which, in the specific context of dysimmunity and genetic susceptibility, stimulate a favorable background to the development of multiple sclerosis. Tracing and studying viruses in multiple sclerosis patients may improve our understanding of their actual involvement in multiple sclerosis physiopathology.

Résumé
L’implication d’une infection virale dans la physiopathologie de la sclérose en plaques a été proposée depuis plusieurs décennies, sans doute en raison de la capacité de certains virus à cibler le système nerveux central et induire une neuro-inflammation propice aux dysfonctions cellulaires, révélées notamment par une démyélinisation ou une mort neuro nale. Les données récentes de la littérature suscitent un regain d’intérêt pour des virus de la famille Herpès (HHV-6, HHV-4/virus d’Epstein-Barr) et leur implication potentielle dans le développement de la sclérose en plaques. L’identification et l’étude des virus dans les patients atteints de sclérose en plaques peuvent améliorer notre compréhension de leur implication réelle dans la physiopathologie de la sclérose en plaques.
More than 140 years have elapsed since multiple sclerosis (MS) was first diagnosed by JM Charcot. Whereas the clinical and histological characteristics of this chronic neuroinflammatory and degenerative disease of the central nervous system (CNS) are now clearly defined, its etiology still remains uncertain. Recent biological data give renewed support to a possible viral implication, as already suggested for several decades. After a short review of virus–CNS relationships and the various changes associated with viral infection, we will focus on the viruses recently associated with the physiopathology of MS, notably human herpesvirus-6 (HHV-6) and Epstein-Barr virus (EBV).

1. **Viruses and the central nervous system**

Viruses have always been hosted by human beings, influencing their dynamics and human activities. One group of viruses, the neurotropic viruses, are especially associated with the nervous system. Indeed, they can penetrate it (neuroinvasion) through vascular and ependymal interfaces and peripheral nerves. In addition, infected immune cells can act as “Trojan horses” by crossing blood-brain barriers. Thereafter, infection of neurons and glial cells by viruses (neurotropism) rests in part on their individual permissiveness. This involves not only the expression of specific receptors, allowing the viral particle to penetrate the nerve cell, but also the ability to replicate the virus. Several scenarios are thus possible. For example, polioviruses (Picornavirus) cause an acute viral infection of motor neurons, producing virions and cellular lysis, leading to major functional changes in neurons and glial cells. The clinical consequence is delayed-onset clinical episodes (Garg, 2008). In contrast, neuronal infection by certain Paramyxoviruses causes a rapidly persistent infection, producing antigens but not virions, which leads to major functional changes in neurons and glial cells. The clinical consequence is a persisting or recurrent inflammatory response (Grubor-Bauk et al., 2008). Neurological consequences of a viral infection (neurovirulence) are therefore determined both by the nature of the targeted cell or nervous structure, as well as the mode of infection per se. Thus, a virus may be the cause of brain damage even if no infection has been suspected first. Moreover, the activity of neurotropic viruses is not restricted to nerve cells: some of them can target cells in the immune system and disturb the immune response (McCoy et al., 2006). Such viruses therefore are harmful to the CNS through various mechanisms, either inducing a destructive antiviral response by cytolysis of infected nerve cells, triggering an autoimmune response due to structural homology of some viral antigens with constitutive proteins of the CNS, inhibiting the control of “naturally” autoimmune T and B lymphocytes, or promoting the penetration of immune cells into the CNS. In short, viruses are able to induce and maintain inflammation and neurodegeneration in many ways.

The hypothesis of a viral infection as a MS co-factor emerged in the 1970s (Cathala and Brown, 1972), in parallel with the concept of “slow viral diseases” of the CNS (Fuccillo et al., 1978). CNS infections, like subacute sclerosing panencephalitis (SSPE), progressive multifocal leucoencephalopathy (PML) or Kuru, share an infection by conventional or unconventional agents, sometimes a long incubation period, leading to a pathology limited to a single organ with a slow but relentless progression (Gajdusek and Zigas, 1957; Zurhein and Chou, 1965; Payne et al., 1969). A study of these attacks has led to the general acceptance that viruses can persist in the CNS, sometimes at undetectable levels, and progressively provoke functional changes in the host cell (de la Torre and Oldstone, 1996; Fujinami et al., 2006).

2. **Heterogeneity of multiple sclerosis attacks: multi-factorial etiology involving several viruses?**

MS is an autoimmune disease related to the penetration and the proliferation of autoreactive cells in the CNS (Merrill et al., 1984; Kornek and Lassmann, 1999; Lucchinetti et al., 2000; Prineas et al., 2001). It is characterized by the multifocal presence of demyelinated plaques and axonal and tissue destruction. An infiltrate, composed of macrophages, B and CD4/CD8 T lymphocytes, plays a major role in acute, then chronic inflammation. Astrocyte and microglial stimulation maintains and amplifies the chronic inflammation (Hafler and Weiner, 1987; Link et al., 1989; Bruck et al., 1996). Recent analyses of tissue lesions, of the clinical regression and genetic susceptibility of patients have emphasized the heterogeneous development of the malady. Bien qu’aucun virus n’ait, à ce jour, été identifié comme l’agent étiologique de la sclérose en plaques, cet article vise à montrer le potentiel de certains d’entre eux à promouvoir des processus nécessaires à l’établissement ou au maintien de la maladie. Nous rappelons notamment le rôle des infections virales persistantes du système nerveux central par : les Paramyxovirus dans l’apparition tardive d’altérations fonctionnelles ; les Picornavirus dans l’induction d’une rupture de la tolérance immune, d’une extension épitopique et d’une démyélinisation ; les virus Herpes dans l’induction d’une activation lymphocytaire T et B, d’une défécience des lymphocytes T régulateurs et d’une auto-immunité après leur réactivation. Ainsi, ne pourrait-on pas considérer les virus « communs » comme autant de modulateurs potentiels des systèmes immuns et nerveux qui, dans le contexte particulier de dysimmunité ou de susceptibilité génétique, stimulent un environnement favorable à la sclérose en plaques. C’est en cherchant et en étudiant les virus chez ces patients que l’on pourra comprendre leur véritable rôle dans la physiopathologie.
nature of MS (Roxburgh et al., 2005; Confavreux and Vukusic, 2006a, Confavreux and Vukusic, 2006b). Thus, anatomopathology distinguishes four groups of patients, whose lesions are characterized either by:

- infiltrated macrophages and Th1 lymphocytes secreting pro-inflammatory cytokines;
- autoimmune antibodies and molecules of the complement system;
- primary degeneration of the myelinating cell, the oligodendrocyte or;
- oligodendrocyte apoptosis resulting from progressive cell change (Lucchini et al., 2000).

The fact that these changes have also been observed in viral infections of the CNS suggests a viral involvement in the pathophysiology of MS.

To refine this hypothesis, traces of a viral infection linked to MS have been actively investigated during the past 30 years. Viral genome detection in the central nervous tissue and cerebrospinal fluid of patients (Nordal et al., 1978), as well as the preferential expression of antibodies against viral antigens, has led to believe that several viruses, from different families, may cause or contribute to MS (Pette, 1968; Cook, 2004; Sotelo et al., 2007; Krone et al., 2008; Lincoln et al., 2008). Some of them are listed in Table 1 (Adams and Imagawa, 1962; Fuccillo et al., 1978; Appel et al., 1981; Martin, 1981; Salmi et al., 1982; Bray et al., 1983; Haahr et al., 1983; Liedtke et al., 1995; Yao et al., 2008; Zivadinov et al., 2006; Brudek et al., 2007; Pender et al., 2009; Shindler et al., 2008; Sotelo et al., 2008; Tucker and Andrew Paskauskas, 2008; Iacobaeus et al., 2009). Presumably, in the next few years, many emergent neurotropic viruses will be added to this list (Johnson, 2003). One question is still unanswered however. Do these viruses cause the disease? Alternately, are they only re-expressed as a consequence of the immune alterations? Their potential involvement in disrupting brain function, establishing neuroinflammation and dysregulating the immune response supports the hypothesis that they are, at least, partly responsible for triggering and maintaining the disease, even though none of them appears to be the unique MS etiological agent. Their study in humans, or animal models as well, has contributed greatly to deciphering the mechanisms at the background of MS. Human infections by the Paramyxovirus MV and by Herpes virus HHV-6 and EBV, as well as the murine demyelination model using the Thieier virus have been chosen to illustrate this proposal.

3. Persistent viral infection of the central nervous system by Paramyxovirus: late-onset virus-induced functional alterations

Measles virus (MV) was one of the first viruses suspected in the etiology of MS due to the significant high levels of anti-MV antibodies in the serum and cerebrospinal fluid (CSF) of patients (Adams and Imagawa, 1962) and the presence of virus in the brain of MS patients (Geeraedts et al., 2004). This Paramyxovirus (Morbillivirus), both neurotropic and immune-suppressive (Schneider-Schaulies and Schneider-Schaulies, 2008), is sometimes responsible for SSPE, a fatal demyelinating disease, which develops late (8 years on average) after a primary benign infection (Tucker and Andrew Paskauskas, 2008; #21). The virus infects neurons and oligodendrocytes, in which it accumulates mutations, leading to functional changes in the viral proteins (Cattaneo et al., 1988; Patterson et al., 2001). This is notably the case for the M protein, essential to viral budding. Protected from a cytotoxic immune response, inactivated by the virus itself and without the possibility of budding progeny virions, the viral infection becomes progressively persistent. Although “silent”, the virus nevertheless alters so-called luxury cell functions (as opposed to vital ones) and leads to dysfunctions in brain homeostasis. It ends with neurons and oligodendrocytes dying, the appearance of demyelinated areas and a cortical atrophy (Morgan and Rapp, 1977; Kato et al., 2002).

A murine model of infection by the Paramyxovirus CDV (Bernard et al., 1983) has allowed us to clarify the different steps leading to these changes. In mice susceptible to the virus, the selective infection of monoaminergic brain structures, the cortex, the hippocampus and the hypothalamus leads to progressive and persistent inflammation, even though the virus is no longer detectable (Bencsik et al., 1996). The inflammation is characterized by an infiltration of CD4 and CD8 T lymphocytes, and macrophages and by the production of cytokines and metalloproteases by glial cells and neurons (Khuth et al., 2001). The alterations in the synthesis of neuromediators and neuropeptides leads to neuronal death (Bencsik et al., 1997; Griffon et al., 2004), showing the major role played by virus-induced inflammation in neurodegeneration. Infection of the CNS by Paramyxoviruses illustrates the “hit-and-run” concept typical of persistent viral infections of the CNS suggested by Oldstone: an acute, then persistent viral infection of the CNS could be responsible for progressive cell damage expressed clinically when the virus is not detectable or quiescent (Oldstone, 1998). This scenario is pertinent to MS.
4. Brain infection by Theiler’s murine encephalomyelitis virus: a model of breakdown of tolerance and epitope spreading

Brain infection by the Theiler’s murine encephalomyelitis virus (TMEV, Picornavirus) was undoubtedly one of the first indicators linking viruses with MS. Right from 1937, Max Theiler demonstrated the demyelinating role of TMEV. In genetically susceptible mice, infection by this virus leads to progressively chronic demyelination of the spinal cord and encephalon associated with an infiltration of immune cells (Lipton, 1975). The recent identification of human viruses related to TMEV has renewed interest in this virus family (Chiu et al., 2008). In mice, demyelination results from the infection of oligodendrocytes and an autoimmune response directed against myelin proteins. Epitope spreading takes place at the same time as clinical signs appear (Yu et al., 1996). Thus, a CD4 T-cell-type immune response directed against a viral epitope to control the acute phase of the infection (aa74–86 of antigen VP2) first recognizes a single epitope and thereafter several epitopes of the myelin proteolipid protein (PLP) (PLP aa139-151; aa178-191; and aa56-70) and includes, progressively, myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) (Miller et al., 1997). This leads to an expansion in the T-cell repertoire associated with a breakdown of immune tolerance towards the subject’s own proteins, although no structural homology between TMEV and the myelin proteins has been detected. Viruses other than TMEV (the human viruses MV, hepatitis B, influenza, Papillomavirus) are also able to provoke an anti-myelin autoimmune response with epitope spreading due, in these cases, to a sequence homology between their epitopes and those of MBP (molecular mimicry) (Fujinami et al., 1983). Theiler’s demyelination model therefore covers several aspects of MS, especially autoimmunity, since anti-MOG, anti-PLP and anti-MBP T lymphocytes accumulate in the CNS of patients. This model of virus-induced demyelination has also demonstrated the major role of CD8 lymphocytes in tissue damage other than demyelination, and that of dendritic cells in individual susceptibility to the establishment of a persistent viral infection, and thus to the development of demyelination (Murray et al., 1998; Hou et al., 2007).

5. Brain reactivation of HHV-6 in multiple sclerosis, CD46 activation and T regulator deficiencies

Viruses of the Herpes family (HHV-1–8) have been suspected in MS for long because of their ability to target neurons and remain quiescent while modifying their genome (Danaher et al., 2008). Of the two HHV-6 variants described, HHV-6A is the neurotropic variant. This virus can establish a latent infection in nerve cells, which is reactivated in an immunosuppressive context (viral infection by MV, HIV, transplant [de Pagter et al., 2008]). HHV-6 also infects immune cells (Blumberg et al., 2000). A possible connection between HHV-6 infection in nerve cells, which is reactivated in an immune-suppressive context, and that of dendritic cells in individual susceptibility to the establishment of a persistent viral infection, and thus to the development of demyelination (Murray et al., 1998; Hou et al., 2007).

New data have confirmed this association. Compared to other neurological patients, all MS patients have anti-HHV-6 serum antibodies (Virtanen et al., 2007). The presence of antibodies in the CSF, which indicates a primary brain infection, is more frequent in clinically probable MS patients (CPMS) than in clinically definite MS patients (CDMS). The preferential presence of the HHV-6 genome in the serum of patients in a clinically active phase is suggestive of a virus-producing viral replication and, therefore, of a correlation between viron production and MS exacerbation (Berti et al., 2002). Furthermore, the detection of viral DNA in the CNS of patients, at high levels in demyelinated plaques (Cermelli et al., 2003), is also favouring the concept of a HHV-6 brain infection/reactivation during the course of the MS. It should be noted, however, that this virus is also detected, though at lower levels, in subjects not suffering from MS (Theodore et al., 2008). There are many potential mechanisms of brain damage related to HHV-6 infections involving both immune and neural cells. One of the key pathways is the ubiquitous transmembranous molecule CD46, a regulator of complement action, also known as a “pathogen magnet” due to its ability to bind viruses, such as HHV-6 (Cattaneo, 2004). CD46 activation causes T lymphocytes to proliferate by acting as a co-stimulator of the T-cell receptor (TcR). Thus, after reactivation of the virus in nerve cells, ligation of HHV6 to CD46 is likely to stimulate the proliferation of T lymphocytes infiltrated into the CNS of patients. CD46 also participates in the induction of the type 1 regulatory T lymphocyte phenotype (Treg1) (Astier, 2008). These lymphocytes are interleukin-10 (IL-10) producers and Th1 lymphocyte regulators. A reduction in Treg1 function and IL-10 secretion after CD46 activation has been observed in relapsing-remitting MS patients (RR-MS) and suggests an important role of this membrane protein in MS physiopathology (Astier and Hafler, 2007). Therefore, HHV-6 might control the function of T lymphocytes after its reactivation in neural cells, thus contributing to neuroinflammation. In addition, excessive activation of the complement system after HHV-6 binding to CD46 is suspected. Although the HHV-6 virus is a serious candidate in MS physiopathology, the conditions required for its reactivation in patients still need to be elucidated.

6. B lymphocyte infection by the Epstein-Barr virus and autoimmunity

New attention is brought on B lymphocytes as being pathophysiological actors in MS. Follicular aggregates of B lymphocytes (ectopic B-cell follicles) have been detected in the cerebral meninges of patients (Serafini et al., 2004). The benefits of a therapeutic trial targeted against B lymphocytes (rituximab) have confirmed their involvement in the development of the disease (Hauser et al., 2008). The detection in these B lymphocytes of a virus known to induce their proliferation, the EBV (EBV/HHV-4), interest in this virus (Franciotta et al., 2008). Belonging to the Herpes family, EBV targets and establishes a latent infection in memory B lymphocytes. This infection provides lymphocytes with protection against apoptosis and maintains their survival by mimicking both intracellular signals downstream from the B receptor and T lymphocyte helper...
action (Babcock et al., 2000). The virus persists throughout life, yet most of the infected subjects (90% of the population) remain asymptomatic due to an effective immune response, which limits virus production. Several wide-scale sero-epidemiological studies support the argument that EBV infection is involved in the development of MS (De Lorenze et al., 2006; Lunemann et al., 2007). Increased levels of anti-EBV antibody titers detected long before the first clinical signs appear (20 years) show that the anti-EBV immune response is an early indicator of MS rather than a consequence of the disease. An association between antibody titers directed at EBNA and EBV proteins and a risk of developing MS has been reported (Ascherio et al., 2001). Although the immune response seems effective at controlling EBV infection, it is however disturbed: patients do indeed present with greater numbers of anti-EBV CD4 T lymphocyte clones in the blood and cerebrospinal fluid, whereas their viral charge, which is expected to be high, is similar to that of healthy donors. In addition, the immune T response is characterized by epitope spreading, reflecting perhaps a T-B-cell interaction. In MS, the immune T response is modified by the viral infection (Lunemann et al., 2008). Probably as a result of these disturbances, a considerable number of B lymphocytes and plasmocytes infected by EBV have been observed in the brain of MS patients (Franciotta et al., 2008). The role of these cells in MS physiopathology is the subject of a key study. Several hypotheses are under investigation (Haahr and Hollisberg, 2006). A sequence homology between epitopes of myelin proteins, notably of MBP, and viral epitopes recognized by anti-EBV T lymphocytes, suggests myelin and oligodendrocyte destruction via an anti-viral immune response. Persistent EBV infection implies molecular signals favorable to B lymphocytes survival. EBV could thus control the pool of natural autoreactive B lymphocytes or those reactivated by another viral infection (MV, TMEV), even in the absence of autoimmune T lymphocytes (Thorley-Lawson, 2001). Finally, several Herpes viruses, including EBV, have the ability to transactivate the expression of endogenous retroviruses (HERV). The presence of HERV in brain lesions and their ability to induce a toxic lytic infection of oligodendrocytes suggests that this deleterious viral cooperation is possible in MS patients (Tai et al., 2008).

To conclude, all these data show that a single virus is unable to cause MS. However, from their ability to trigger T- and B-cell autoimmune responses against myelin and oligodendrocytes and to maintain a chronic inflammation potentially deleterious to neurons, persistent or reactivated viruses within neural tissue seem to be potential co-factors in the appearance and development of MS. This new overview should help modify our conceptual approach to the physiopathology and treatment of this disease.

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