

Mini review

Herpesviruses—a rationale for antiviral treatment in multiple sclerosis

Tomas Bergström *

Department of Clinical Virology, Göteborg University, Guldhedsgatan 10b, S-413 46 Göteborg, Sweden

Received 22 October 1998; accepted 14 December 1998

Abstract

In multiple sclerosis (MS), the extensive and long lasting search for viruses or other pathogens has hitherto failed to identify a common etiological agent. However, the beneficial effects by interferon- β treatment in MS, although suggested to depend mainly on immunomodulation, might lend support to a viral involvement in the pathogenesis. The human herpesviruses have attracted interest since their recurrent modes of infection share some similarity with the relapsing-remitting course of MS, most members are readily detected within the brain, and several of these viruses may induce demyelination within the central nervous system in human hosts as well as in animal models. Accumulated diagnostic and epidemiological data are compatible with a role for the herpesviruses as possible cofactors rather than etiological agents, and recent studies showing early neuronal damage in MS patients focus attention on the neurotropic α -herpesviruses. Antiviral treatment trials with safe and effective drugs such as valaciclovir offer a possibility of testing the hypotheses concerning herpesviral involvement in MS. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Multiple sclerosis; Herpesviruses; Demyelination; Antiviral treatment; Valaciclovir

1. Introduction

The increasing number of safe and effective antiviral substances available for clinical use has

offered new therapeutic possibilities as regards chronic diseases of suspected viral origin. Shortly after the definition of multiple sclerosis (MS) as a clinical entity in form of a chronic, multifocal, demyelinating disease of the central nervous system (CNS), an infectious etiology was suggested (Marie, 1884). During the century that has followed since, and despite considerable diagnostic

* Tel.: +46-31-3424735; fax: +46-31-827032.

E-mail address: tomas.bergstrom@microbio.gu.se (T. Bergström)

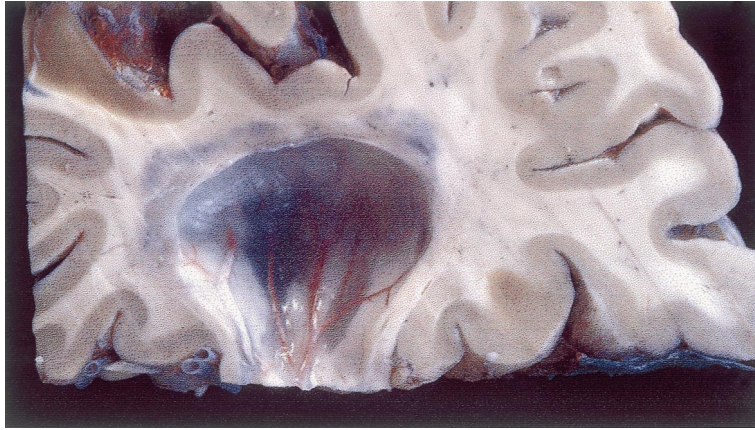


Fig. 1. An increased permeability over the blood–brain barrier is a pathological hallmark in multiple sclerosis. Supravital dye test of plaques in the anterior horn and subependymal zone of lesion with an increased vascular permeability. Illustration from: Broman (1949) The permeability of the cerebrospinal vessels in normal and pathological conditions. Munksgaard, Copenhagen, Plate III, Figure 1.

efforts (Johnson, 1994; Gilden et al., 1996), no etiological agent or causal treatment for MS has hitherto been identified. Among viruses, candidates from almost all virus families have been suggested as contributors to the pathogenesis of MS, often stimulated by the discovery of new viral members or findings concerning known viruses obtained after improved diagnostic means.

Yet, after some years of presentations of contradictory data most viral candidates have disappeared into oblivion, replaced by new candidates, without their involvement being decisively refuted or strengthened. Advancements in the field of antiviral treatment provide new opportunities of testing hypotheses concerning viral involvement in MS. The aim of the current review is rather not to cover the immense and often contradictory literature on the association of viruses with this disease, but to provide a rationale for clinical trials with antivirals on patients with MS, focusing on the possible contributing pathogenic role of the presently known herpesviruses.

2. Pathological hallmarks

The progression of neurological deficits in MS often follows a relapsing–remitting course, where exacerbations are associated with expanding or

new areas of demyelination in the CNS, and recovery with remyelination (Prineas et al., 1993). The typical demyelinated lesions (plaques) found in the brains of MS patients show histological signs of active inflammation, and have a typical perivenular and often symmetrical localization (Fog, 1965). Central to the pathology of the plaque is a local breakdown of the blood–brain barrier early during development of a lesion, as can be visualized by supravital dye test of the brain at autopsy as illustrated in Fig. 1, or by magnetic resonance imaging (MRI) (Fig. 2).

Laboratory diagnostic criteria (Poser et al., 1983) include presence of a pathological IgG index as well as oligoclonal bands in the gamma region after isoelectric focusing of the CSF proteins, indicative of a clonal expansion of B-cells and intrathecal antibody production. A mild mononuclear pleocytosis is often found in the CSF, including clones of activated T-cells targeting myelin-related autoantigens such as myelin basic protein (MBP), possibly due to molecular mimicry with pathogens such as herpesviruses (Hafler and Weiner, 1987; Ota et al., 1990; Wucherpfennig and Strominger, 1995). Hence, MS has been regarded as a T-cell mediated autoimmune disease due to aberrant immune regulation (Waksman and Reynolds, 1984). Support for this hypothesis has been obtained from animal

models reproducing the symptoms and signs of demyelination after injection of myelin or activated T-cells reactive with this substance (Wekerle et al., 1994). According to this theory, the extensive and reiterated autoinflammatory demyelination ultimately leads to a chronic phase of the disease in which neuronal destruction and axonal damage occur. The rationale for treatment with immunomodulatory drugs such as steroids and

interferons is derived from this hypothesis (Bashir and Whitaker, 1998).

As an expansion of and partly in conflict with this concept, recent investigations employing new techniques indicate that the onset of axonal lesions may be an early rather than late event in MS. Using antibodies against amyloid precursor protein as a marker of axonal destruction, expression of this protein was documented in areas of acute inflammation and demyelination as well as at the border zone of active chronic lesions in brains from MS patients (Ferguson et al., 1997). In another autopsy study, an abundance of axonal transections was documented in active lesions (Trapp et al., 1998). Furthermore, a soluble marker for neuronal damage, neurofilament protein, was detected in the CSF during the early, relapsing-remitting phase of the disease, with the highest concentrations of this protein found at onset of exacerbations (Lycke et al., 1998). In addition, magnetic resonance spectroscopic imaging using the neuronal marker *N*-acetylaspartate suggested a wide-spread axonal damage also in areas outside visible plaques (Narayanan et al., 1997).

Earlier reported clinical data regarding the succession of neurological symptoms during relapsing-remitting MS have indicated a restricted dissemination of symptoms to axonally connected areas of the brain (Andersen, 1980). Taken together, these findings suggest that axonal damage occurs already at the initial phase of neurological deterioration, maybe even preceding and/or extending beyond the inflammatory lesions, and that it may be a driving force of the pathogenesis of the disease. As a consequence, an early therapeutic intervention aimed at neuronal protection has been advocated (Ferguson et al., 1997; Trapp et al., 1998).

3. Pathogenesis: genetic susceptibility to neurotropic infectious agents?

Epidemiological data are compatible with an involvement of infections or other environmental factors in the pathogenesis of MS. The geographically uneven distribution of the disease in form of

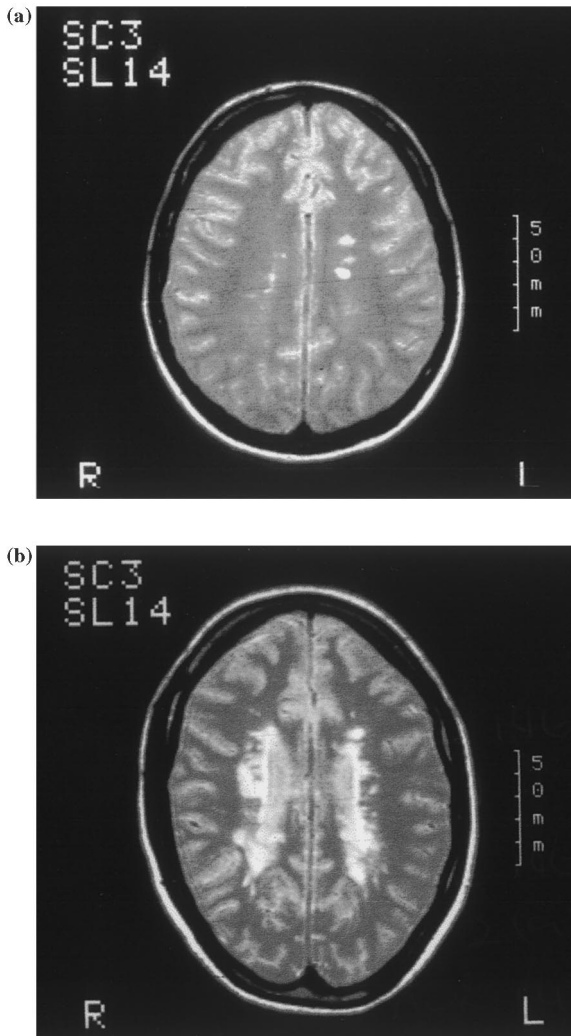


Fig. 2. Magnetic resonance imaging scans of brains of two patients with multiple sclerosis showing the characteristic periventricular localizations of plaques during (a) early and (b) late phase of relapsing-remitting disease (By courtesy of Dr Jan Lycke).

a sometimes debated north-south gradient of declining incidence, and the opposite observation reported from the southern hemisphere, together with migration data, suggest that environmental exposure to some unidentified risk factor before adolescence is of decisive importance (Detels et al., 1978; Kurtzke, 1993). That this factor might be a transmissible agent is supported by long-term epidemiological studies from the Faroe islands, suggesting the existence of four successive declining waves of MS incidence from the 1950s onwards which could be explained by an infectious agent introduced into the population during the second world war and now slowly vanishing (Kurtzke, 1993). In addition, several reports of non-familial clustering of MS cases have been published. These data argue for the existence of a specific, MS-related, pathogen, and for the adolescence being a vulnerable period (Pryse-Phillips, 1996).

There are, however, no epidemiological or diagnostic evidence that the postulated agent should be a virus. Although the CSF abnormalities found in MS patients in the form of persistent intrathecal IgG production as determined by elevated IgG-index and presence of oligoclonal bands are prominent in chronic viral infections such as HIV (Andersson et al., 1988) or following acute herpes simplex encephalitis (Vandvik et al., 1985), similar changes may also be evoked during chronic bacterial CNS infections such as neuroborreliosis (Kaiser, 1994). Attempts have been made to identify the putative MS-agent by antigen overlay of the oligoclonal bands but the intrathecal response in MS seems to have a broad specificity, as was also found to be the case for chronic neuroborreliosis (Kaiser, 1994). Furthermore, numerous studies have shown elevated IgG CSF titers to a plethora of viruses including morbilli and herpesviruses (Adams and Imagawa, 1962; Norrby, 1978; Salmi et al., 1983) and these findings have been proposed to represent an immunological reactivity termed the 'MS-trait' (Poser, 1993).

The importance of genetic factors, which could be deduced from the high incidence of MS in some ethnic groups, was further emphasized by the concordance rates for the disease in monozygotic (26%) and dizygotic twins (2.3%),

and the 30–40-fold increased risk of developing disease found in siblings of MS patients (Ebers et al., 1986, 1995). Extensive efforts have been made to identify responsible genes but with inconclusive results. Although candidate genes related to immune functions (Hillert, 1994) or myelin (Tienari et al., 1998) have been identified, recent studies have failed to define a single strong locus (Sawcer et al., 1996). To date, the overrepresentation of HLA class II molecules of the DR2 haplotype in MS patients remains the most important genetic basis for the susceptibility to the disease (Haines et al., 1998). Since no specific genetic alterations have been found, the normal DR2 haplotype might contribute to the MS trait (Hillert, 1994). The search continues by studies on possible genetic linkage between multiple loci (Sawcer et al., 1996; Hogancamp et al., 1997) or by detailed analyses of repeated sequences in the promoter region of the MBP gene in the Finnish population (Tienari et al., 1998). In conclusion, the genetic data collected hitherto is compatible with an MS trait which might confer genetic susceptibility to unique or common infectious agents, maybe by an altered immune response including antigen presentation and/or by affecting target tissues such as myelin.

4. Viral infections can trigger MS relapses

The role of environmental factors as triggers of MS relapses is best exemplified by epidemiological studies of upper respiratory tract infections (URTI). Four different groups have independently documented a 1.3–3.4-fold risk of clinical exacerbations during the weeks following the onset of the infection (Sibley et al., 1985; Andersen et al., 1993; Panitch, 1994; Edwards et al., 1998). A possible mechanism mediating the increased disease activity might be a virus-induced secretion of interferon- γ , a cytokine stimulated by several URTI-associated viruses and shown to induce rather than prevent MS attacks during a clinical trial (Panitch et al., 1987). In one study, when URTI epidemiology was evaluated during interferon- β treatment, the URTI-related attack rate was lowered despite the fact that the URTI's were

not prevented (Panitch, 1994). The author suggested that interferon- β might have modulated the immune response to the viral infections (Panitch, 1994), but another possibility could be that the treatment restricted the viral dissemination to the CNS. However, despite suggestion of adenovirus involvement by serological findings in one study (Andersen et al., 1993), and by several different viruses in another trial (Edwards et al., 1998), further studies including PCR-based diagnosis are necessary to define which viruses that may be responsible for the URTI-related bouts.

5. Possible role of herpesvirus infections in MS

If common URTI are involved in some (roughly estimated to 1/3 from the above cited studies) of the relapses in MS, what are the remaining attacks induced by? Among several attractive candidate agents, human herpesviruses show the following characteristic features which are of special interest in the context of MS pathogenicity: (1) after primary infection during childhood or adolescence, the lifelong infections may follow a latent-recurrent course similar to the relapsing-remitting character of MS; (2) most herpesviruses cause persistent infections of the CNS, at least in the form of DNA (Baringer and Pisani, 1994; Sanders et al., 1996); (3) some herpesviruses (such as α -herpesviruses) are axonally transported within the neurons (Kristensson et al., 1982a; Lycke et al., 1984; Wroblewska et al., 1993); (4) several herpesviruses can induce demyelinating disease in the CNS (Vahlne et al., 1985; Bray et al., 1992; Carrigan et al., 1996; Kleinschmidt-DeMasters et al., 1996).

In spite of the resemblance between these conditions, diagnostic data are currently not sufficiently strong to validate the argument that herpesviruses are more likely to be involved in the pathogenesis of MS than are other suggested viruses such as para- or orthomyxoviruses, papovaviruses or coronaviruses (Weiner et al., 1973; McDermott et al., 1974; Burks et al., 1980). In addition to being easily identified by modern diagnostic procedures, the herpesviruses have one clear advantage for the clinical MS researcher:

their contribution to disease activity might be tested by long-term antiviral suppression (Lycke et al., 1996). Below, results are reviewed from some of the previous and recent studies presenting evidence for or against involvement of the different herpesviruses in MS. Eight human herpesviruses have until now been identified, of which three are classified as α -herpesviruses: herpes simplex virus (HSV) types 1 and 2 and varicella-zostervirus (VZV); three as β -herpesviruses: cytomegalovirus (CMV) and human herpesvirus 6 (HHV-6) and 7 (HHV-7); and two as γ -herpesviruses: Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8), also descriptively known as Kaposi's sarcoma-associated herpesvirus. In Table 1, the clinical spectrum of CNS disease, association with demyelination and antiviral treatment possibilities are shown for the eight human herpesviruses.

6. α -Herpesviruses

In 1964 a case report was published regarding an Icelandic woman who died of pneumonia after suffering from MS for nearly three decades. From her midbrain HSV was isolated at autopsy and the strain, which was designated as the 'MS strain', was later serologically typed as HSV-2 (Gudnadottir et al., 1964). The MS strain has been widely used in experimental systems of demyelination (Martin and Nathanson, 1979; Henken et al., 1993). Comparative virulence studies to other HSV-2 strains are scarce, but it was recently noted that this isolate, in contrast to other HSV-2 strains, was unable to suppress delayed type hypersensitivity after eye infection (Akiba et al., 1996). No genotypic correlation to this phenotypic property has been presented.

A quarter of a century later, we isolated a HSV-1 strain (designated 'HSV-1 BAN') from the CSF of a previously healthy woman who showed symptoms of double vision, dizziness and sensory defects (Bergström et al., 1989). During the following years, she developed a clinically definite relapsing-remitting MS according to the criteria of Poser et al. (1983), and we judged that the HSV-1 BAN strain had been retrieved during her

Table 1
Human herpesviruses as possible targets for antiviral treatment in demyelinating diseases of the central nervous system (CNS)

	Virus	Viral detection reported from CSF/CNS	Spectrum of clinical manifestations from the nervous system	Association with demyelinating disease in humans	Animal models of demyelination	Registered antivirals for systemic use	Registered antivirals with proven effect on CNS infection
α	Herpes simplex virus type 1	+	Encephalitis, meningitis, cranial nerve affections	+	+	Aciclovir, valaciclovir, famciclovir, foscarnet	Aciclovir
α	Herpes simplex virus type 2	+	Meningitis, neonatal encephalitis, myelitis	+	+	Aciclovir, valaciclovir, famciclovir, foscarnet	(–) ^a
α	Varicella-zoster virus	+	Cerebellitis, meningitis, encephalitis, cranial nerve affections	+	–	Aciclovir, valaciclovir, famciclovir	–
β	Cytomegalovirus	+	Encephalitis, polyradiculomyelitis peripheral neuropathies Congenital encephalopathy	+	–	Ganciclovir, foscarnet, cidofovir	(–) ^b
β	Human herpesvirus 6	+	Febrile seizures, encephalitis	+	–	–	–
β	Human herpesvirus 7	+	Febrile seizures	–	–	–	–
γ	Epstein-Barr virus	+	Encephalitis, myelitis	+	–	–	–
γ	Human herpesvirus 8	+	Encephalitis	–	–	–	–

^a Aciclovir has effect in neonatal herpes, including cases of HSV-2 encephalitis.

^b Ganciclovir, foscarnet and cidofovir have proven efficacy in CMV retinitis.

first clinical attack of MS. Later attempts of virus isolation from the same patient were repeatedly negative and she has now entered a secondary progressive phase. The HSV-1 BAN strain differed from other clinical isolates as being lowly neurovirulent in an *in vivo* model (Bergström et al., 1990a), and the strain replicated to lower titers in cell culture. Genotypic characterization of this strain is ongoing. Intrathecal antibodies to HSV, a finding described in other MS patients (Roström et al., 1981; Sandberg-Wollheim et al., 1987) were detected in the CSF during the first and third but not the second attack in this patient. Motivated by the finding of this isolate, we have performed an extensive search by PCR for DNA from HSV and other herpesviruses in CSF and serum samples from MS patients. However, although the study included many samples drawn during acute attacks, the results were negative (Martin et al., 1997).

In a mouse model, HSV-1-induced demyelination was shown to exhibit some interesting features resembling MS (Vahlne et al., 1985). In a study of trigeminal ganglionic infection in mice, the myelin sheath of the trigeminal nerve root entry zone belonging to the CNS was severely injured by the virus, while the myelin of the PNS remained intact (Kristensson et al., 1979, 1982b). The demyelination, which was most pronounced after 3 weeks, appeared to involve a cytotoxic effect of oligodendrocyte infection of HSV-1 (Kristensson et al., 1979, 1982b). Furthermore, the demyelinating process might have followed a relapsing-remitting course since areas in the brain stem showed acute focal demyelination, as well as remyelination, also during the latent phase (Kristensson et al., 1979). A mouse strain-dependent susceptibility to HSV-1-induced multifocal demyelination was demonstrated by Kastrukoff et al. (1987). This group later reported that immunosuppression increased viral spread in the brain but prevented the development of demyelination in the mouse model (Kastrukoff et al., 1993).

VZV is one of few ubiquitous human viruses which, in parallel with MS, is more common in temperate zones. An exception is the North American Hutterite population, whose people live relatively isolated from the rest of the society and

have less clinical varicella as well as zoster. In this population, MS is less common than in surrounding populations (Ross, 1998). Although the finding could be merely an indicator of a population protected from several infectious agents, the combined epidemiological picture inspired an uncontrolled trial with VZV vaccination of 50 MS patients (Ross et al., 1997).

Support for a possible role for VZV in MS pathogenesis might be drawn from the presence of intrathecal antibodies to VZV in MS (Sindic et al., 1994), and the increase of these antibodies in the chronic progressive form of the disease (Schadlich et al., 1987). In addition, white-matter lesions indicative of myelin damage is a prominent finding in VZV encephalitis (Kleinschmidt-DeMasters et al., 1996), and focal demyelination in the brainstem was described after a trigeminal zoster in an AIDS patient (Rosenblum, 1989). In an animal model of virus distribution, an axonal as well as hematogenous mode of spread of VZV was suggested (Wroblewska et al., 1993).

The human α -herpesviruses, of which at least HSV-1 and VZV are reported to be present in the brains of MS patients as well as of control subjects (Baringer and Pisani, 1994; Sanders et al., 1996), share the capacity to induce demyelination that may be relapsing both in man and in animal models (Kristensson et al., 1982b; Martin and Nathanson, 1979; Vahlne et al., 1985; Kleinschmidt-DeMasters et al., 1996). Furthermore, these viruses can reactivate in the CNS without affecting the periphery (Mayo and Booss, 1989; Bergström et al., 1990b; Gilden et al., 1992; Echevarria et al., 1994; Bergström, 1996). In addition, the CSF findings show some similarities between MS and human α -herpesvirus CNS infection besides the specific antibody response (Vandvik et al., 1985; Sandberg-Wollheim et al., 1987) and possible presence of HSV-antigen (Coyle, 1985; Kamei et al., 1994). In both MS and α -herpesvirus CNS infections, a predominant Th1 response is suggested by cytokine profiles, including rises of IFN- γ , IL-2 and soluble receptor for IL-2 (Aurelius et al., 1994; Sivieri et al., 1998).

In facial palsy, a condition which routinely affects functions related to the neighbouring cranial nerves, elevated levels of MBP as well as

increased antibody titers to this protein are regularly detected in the CSF. Therefore, this disease might be regarded as a model disease of focal demyelination of the brainstem (Vahlne et al., 1985). An old suggestion of HSV etiology of facial palsy (McGormick, 1972) was recently supported by the report that endoneural fluid drawn from the facial nerve contained HSV-1 DNA in patients with Bell's palsy and VZV DNA in Ramsay-Hunt cases (Murakami et al., 1996). In another study of patients with Bell's palsy of serologically confirmed herpesvirus etiology, CSF samples were PCR-negative for herpesvirus DNA, exemplifying the diagnostic difficulties in limited CNS affections caused by these viruses (Larsson et al., 1998). In the same study elevated levels of TNF- α were found, a cytokine associated with demyelination and earlier shown to occur in raised CSF levels in MS patients (Selmaj and Raine, 1988; Sharief and Hentges, 1991). As a challenge of a hypothesis of HSV involvement, a treatment trial combining aciclovir and steroids in Bell's palsy suggested that this medication might prevent long-term sequelae in a subset of the patients (Adour et al., 1996). The extensive neurological involvement of other cranial nerves documented in the same study indicated a brainstem involvement rather than a limited affection of merely one peripheral nerve (Adour et al., 1996).

As mentioned above, relapses in MS might be induced by different trigger agents, among which could be α -herpesviruses in addition to URTI-related viruses and other microbial agents. This suggestion is supported by the fact that the intrathecal IgG response is directed against different viral antigens during separate relapses (Sandberg-Wollheim et al., 1987). The hypothesis that α -herpesviruses might cause relapses in MS could be challenged by antiviral trials. It may be reasoned that even if only some of the relapses in MS are related to recurrences of α -herpesviruses, antiviral treatment suppressing these viruses might reduce the number of attacks. Although famciclovir was reported to be superior to valaciclovir in reducing the amount of latent HSV-1 in CNS in a mice model (Thackray and Field, 1998), the antiviral drug with the hitherto best documented effect in human α -herpesvirus infections of the CNS is

aciclovir (Table 1). In herpes simplex encephalitis, two separate studies have shown that iv infusion of this drug is beneficial for outcome with little toxicity, and superior to vidarabine which earlier was shown to be effective also in neonatal encephalitis (Sköldenberg et al., 1984; Whitley et al., 1986; Whitley, 1993). Provided that adequate CSF concentrations are reached, involvement of α -herpesviruses in MS could therefore be tested in a trial using aciclovir (see below).

7. β -Herpesviruses

Of the β -herpesviruses, the relatively newly discovered T-lymphotropic virus HHV-6 has attracted considerable interest in the context of MS pathogenesis. In addition to causing exanthema subitum, HHV-6 was found to have a CNS tropism as demonstrated by associations with febrile seizures and meningoencephalitis (Asano et al., 1992; Kondo et al., 1993; Suga et al., 1993) and occasionally, acute demyelination (Kamei et al., 1997). HHV-6 may also induce an MS-like multifocal demyelinating encephalomyelitis with white matter lesions (Carrigan et al., 1996; Novoa et al., 1997), and was reported as causative agent in a case of encephalopathy in an MS-patient (Merelli et al., 1996).

During a search for unknown pathogens by representational differential analysis of DNA, DNA derived from a brain of an MS-patient differed from control DNA in that it contained extra viral sequences that were shown to belong to the HHV-6 genome (Challoner et al., 1995). Further studies showed that most control brains also contained HHV-6 DNA and even expressed antigen, but a difference was found in the form of a virus-related staining of the nuclei of the oligodendrocytes that was exclusively observed in the MS patients (Challoner et al., 1995).

Other groups have found increased IgM and IgG responses to HHV-6 in MS patients, and PCR-positivity for HHV-6 DNA in CSF or serum samples was also reported (Sola et al., 1993; Liedtke et al., 1995; Soldan et al., 1997). However, work from our laboratory and others have failed to detect HHV-6 DNA in any significant

number of serum or CSF samples from MS patients, and, in addition, HHV-6 antibody titers have been found to be similar to those in healthy controls (Martin et al., 1997; Nielsen et al., 1997; Fillet et al., 1998). Furthermore, in a recent study lymphocyte stimulation indices comparable to those in healthy individuals were found after stimulation with antigens from both HHV-6 type A and B in MS patients during the relapsing-remitting phase (M Enbom, personal communication). Further studies including animal models are needed to clarify the role of HHV-6 in MS, but the mere existence of a herpesvirus combining the properties of neurotropism with a T-cell lymphotropic infectious phase is intriguing.

Little is known regarding the neuropathogenicity of the closely related HHV-7, but the virus has recently been detected by PCR in the CSF of a child with epileptic syndrome (Portolani et al., 1998). No associations with demyelinating diseases including MS have been presented. There are no data regarding occurrence and importance of primary CMV infection or reactivation in MS patients, although this virus may be present in the normal brain (Sanders et al., 1996) and frequently is suggested as one of the agents inducing demyelination of the peripheral nervous system in form of Guillain-Barré syndrome (Schmitz and Enders, 1977; Liedtke et al., 1994). Cases of CMV-associated CNS demyelination include transverse myelitis (Baig and Khan, 1995) and cerebral white matter lesions (Moskowitz et al., 1984; Monno et al., 1998) which however rarely occurs in the non-immunocompromised host.

Regarding therapeutic interventions for CNS infections induced by β -herpesviruses, a combination of ganciclovir and foscarnet has been attempted both against CMV and HHV-6 due to low efficacy of single drug treatment (Cinque et al., 1998; Rieux et al., 1998). In an earlier study, IC_{50} values for several clinical isolates of HHV-6 were determined by replication in human peripheral blood monocytes for aciclovir (range 12–32 μ M), ganciclovir (range 1–2.5 μ M) and foscarnet (range 3–6.5 μ g/ml), indicating a therapeutic potential of the two latter antivirals for systemic infections with this virus (Agut et al., 1991). However, with the exception of CMV retinitis, in

which ganciclovir, foscarnet and cidofovir all have a beneficial effect (Whitley et al., 1998), no controlled trials have hitherto been reported for β -herpesvirus-induced CNS infections (Table 1), or even for any form of infection with HHV-6 and HHV-7.

8. γ -Herpesviruses

Several findings have justified an attention on the role of EBV infection in demyelinating disease. In MS patients, a history of mononucleosis is more common than in controls (Operskalski et al., 1989), and in a cohort of mononucleosis patients, MS cases were over-represented (Lindberg et al., 1991). In another study, a history of mononucleosis at younger age was especially associated with a higher risk of developing MS (Marty et al., 1993). Whether these findings could be directly related to the EBV infection and the related immune response, or merely indicated that MS cases in general were relatively shielded from viral infections during their early years (Bachmann and Kesselring, 1998), remains undecided. Still, if neurological complications occur during primary EBV infection, relapsing or progressive deficits linked to demyelination might develop (Bray et al., 1992). Whether this process is possible to influence by antiviral treatment is unknown since no controlled antiviral trials of EBV-induced CNS disease have been performed.

In a search of herpesviral DNA in MS brains, EBV was a relatively uncommon finding (Sanders et al., 1996), and EBV RNA as an indicator of active infection was not detected in plaques (Hilton et al., 1994). On the other hand, serological studies have repeatedly shown higher prevalence and higher titers of antibodies to EBV in MS patients as compared with controls (Larsen et al., 1985; Sumaya et al., 1985; Myhr et al., 1998). The possibilities of further addressing questions regarding EBV and demyelination by the development of animal models have not yet been exploited.

Concerning HHV-8, the latest discovered member of the human γ -herpesviruses and strongly linked to Kaposi's sarcoma and body cavity

lymphoma, data on seroprevalences are conflicting but is evidently lower than the other herpesviruses, suggesting a restricted infection in the general population (Regamey et al., 1998). Although HHV-8 has been associated with cases of encephalitis with characteristic swelling of endothelial cells (Said et al., 1997), demyelination associated with this virus has hitherto not been reported. In an unconfirmed report, HHV-8 DNA sequences were detected in a few brains of MS patients as well as in brains of controls (Merelli et al., 1997).

9. Avian herpesviruses

Animal viruses could constitute a geographically confined environmental factor and have therefore repeatedly been associated with the etiology of MS. The herpesvirus family is no exception, and an avian γ -like herpesvirus, Marek's disease virus (MDV), is of interest from a virological point of view since it, although being a lymphotropic herpesvirus, shares neurotropic properties with the α -herpesviruses and can cause outbreaks in poultry of a transient paralysis, showing similarities to Guillain-Barré-syndrome (Pepose et al., 1981; Parker and Schierman, 1983). Furthermore, the transient paralysis is a recessive genetical trait, possibly induced by the antibody response (Parker and Schierman, 1983). In this context it is notable that human IgG antibodies to EBV are crossreactive to MDV antigen (MacGregor and Latiwonk, 1993).

As a possible contributing factor to an unusual southerly cluster of MS in Key West, Florida, this population has been suggested to be highly exposed to MDV and other viruses by migrating wild seabirds (McStreet et al., 1992). Diagnostic epidemiology has not been utilized to address the question of avian herpesvirus in the MS-population of Southern Florida, but a large study of samples from MS patients living in Northern Germany failed to detect MDV DNA by quantitative PCR in peripheral leukocytes (Hennig et al., 1998). This line of research investigates the possibility of humans being susceptible to ancestral herpesviruses. Since several epidemiological stud-

ies suggest that MS patients have been more exposed to birds and other pets than matched controls (Operskalski et al., 1989; Cook et al., 1995), the role of avian and other animal herpesviruses in this disease warrants further investigation.

10. A retroviral connection

The family of retroviruses and particularly HTLV-I-like oncoviruses have since long been implicated in the pathogenesis of MS (Koprowski et al., 1985). Later, the suggestion was put forward that dual infection of EBV and a human retrovirus might be an event of importance to MS (Haahr et al., 1992). After establishing B-lymphoblastoid cell lines from an MS patient, simultaneous expression of EBV and retrovirus-like particles were found (Munch et al., 1995). The finding could be repeated in other patients, but was however not unique to MS. In another approach, PCR amplification on peripheral blood mononuclear cells was used for a longitudinal study of presence of herpesviral and retroviral sequences during acute attacks of relapsing-remitting MS. EBV-DNA was an early finding during attacks, often followed by amplification of HTLV-like sequences (Ferrante et al., 1997). Whether this finding of possible transactivation was occurring also in the CNS is unknown, since CSF samples were not included in the study.

The hitherto best characterized retrovirus associated with MS was derived from EBV-infected B-cells as well as from choroid plexus cells of MS patients (Perron et al., 1997). The virus, designated as multiple sclerosis associated retrovirus (MSRV), is closely related to but genetically distinct from known viruses of the oncovirus genus. It forms extracellular virus particles in cultured B-cells and specific RNA has been amplified from CSF and peripheral blood cells in MS patients but not in controls including cases of encephalitis and myelitis. Recently, an expression of a cytotoxic factor specific for glial cells including oligodendrocytes has been detected in supernatants of MSRV-containing peripheral blood cells, as well as in CSF drawn from MS patients (Menard et al., 1998).

It remains to be decided if the findings of activated retrovirus during acute relapses of MS have bearing on the etiology of the disease, or if they represent an interesting epiphenomenon related to the intrathecal immune activation which is an obligate constituent of the condition (Perron et al., 1997). The progress in the characterization of these agents may provide tools to be used in diagnostic and epidemiological studies in MS, and may shed light on processes related to immune activation within the CNS. Furthermore, the relationship between MS-related retroviruses and herpesviruses needs further clarification, for example whether they may transactivate each other *in vivo* as was shown *in vitro* for HSV-1 and MSRV (Perron et al., 1993), or if their simultaneous detection is merely coincidental. The recent discovery of retroviral inserts in a natural strain of an avian herpesvirus suggests that the cooperation between the two virus families might be intimate (Endoh et al., 1998).

11. The enigma of MS pathogenesis—is a piece of the puzzle still missing?

Great efforts have been made over the years to clarify the pathogenesis in MS. The work has profoundly increased our understanding of the intrathecal immune response including autoimmune attacks on myelin-related proteins, genes involved in susceptibility to demyelinating processes as well as of CNS and immune cell infection by a plethora of viruses as part of their natural life-cycle. In consideration of the incongruity of the current comprehension of MS pathogenesis despite the multitude of data accumulated it may be speculated that, in addition to a genetic trait and known pathogens possibly acting as cofactors, a key environmental factor, probably transmissible, remains to be identified. The search for such an agent should not be limited even to viruses. Most likely, if such a pathogen exists, the combined efforts of the research community utilizing the powerful tools of molecular biology will eventually find the missing piece. Awaiting such a discovery, therapeutic progress in MS is continuing.

12. Immunomodulatory treatment of MS

In the numerous clinical trials of immunopharmacological therapy which have been performed in MS patients, two substances have shown a clear beneficial effect, Interferon- β (IFN- β) and glatiramer acetate (Bashir and Whitaker, 1998). Recombinant IFN- β is produced in two forms, the glycosylated IFN- β -1a containing the natural a.a. sequence and the non-glycosylated IFN- β -1b carrying one a.a. deletion and an additional point mutation. Both show clinical effect in the form of reduced relapse rate and reduction of MR lesions (IFNB multiple sclerosis study group, 1993; Paty et al., 1993; Rudick et al., 1997). The former variant, which is more effective in *in vitro* antiviral assays (Runkel et al., 1998), has been reported to slow the progression of neurological disability (Rudick et al., 1997). Although the mechanism of action is not clarified, a recent report on the effects on cytokine expression in patients treated with IFN- β -1a lends support to an immunomodulatory effect in the direction from Th1 towards Th2 response, i.e. upregulation of interleukins 4 and 10 and downregulation of IFN- γ (Rudick et al., 1998).

In this context, the possibility of a direct antiviral effect contributing to the beneficial outcome of IFN treatment in MS patients is seldom referred to but deserves to be mentioned. In animal experimental systems, IFNs show broad antiviral effects against several RNA and DNA viruses including HSV (Pinto et al., 1990). In cell cultures, a direct antiviral effect against HSV, especially at low multiplicities of infection, has been shown for IFN- α , β , as well as γ (Taylor et al., 1998). A synergistic anti-HSV effect of IFNs and nucleoside analogues such as aciclovir has been reported in cell culture systems including human neural cell lines of varying origin (Hanada et al., 1989; Naito et al., 1990). However, controlled trials in humans of IFNs as single treatment or in combination with nucleoside analogues have hitherto not been performed in herpesvirus-induced CNS infections, and it is unknown if the doses of IFN- β used during the MS trials resulted in concentrations able to inhibit replication or prevent reactivation of herpesviruses.

Apart from interferon- β , the only substance with an established benefit in relapsing-remitting MS is glatiramer acetate, a copolymer of the four amino acids alanine, lysine, glutamic acid and tyrosine prepared to resemble MBP (Teitelbaum et al., 1971; Johnson, 1996; Bashir and Whitaker, 1998). The patients experienced 1/3 fewer relapses as compared with the controls, and a higher number of patients showed neurological improvement in the treatment group (Johnson, 1996). In addition, a small study evaluated by serial magnetic resonance imaging has shown a reduction of new lesions by more than 50% as compared with the pretreatment period (Mancardi et al., 1998). Although the mechanism of action has not been clarified, cytokine secretion in mouse T-cell lines after stimulation with glatiramer acetate suggested that a preferential Th2 response was induced, which was crossreactive to MBP and suppressed experimental allergic encephalitis (Aharoni et al., 1997). If this observation is valid also in MS-patients treated with the substance is currently not known.

13. Antiviral treatment with aciclovir

In addition to a possible direct antiviral mechanism contributing to the beneficial effect of interferon- β , the only antiviral compound hitherto investigated in a controlled trial of MS patients is aciclovir (Lycke et al., 1996). The aim of the study was to test an hypothesis of HSV involvement in MS, and the rationale for the choice of aciclovir was the documented effect on CNS infection caused by this virus (Table 1) and lack of toxicity. During a 2-year study period, 30 patients with relapsing remitting disease were orally treated with 800 mg of aciclovir t.i.d. and 30 received placebo in a double-blinded fashion. A total of 62 exacerbations were encountered in the aciclovir group versus 94 in the placebo group, (34% fewer relapses in the aciclovir recipients, $P = 0.083$). In a subgroup analysis of 20 placebo and 19 aciclovir recipients who were followed for 2 years before the initiation of treatment, the aciclovir recipients experienced a decrement of 0.44 annual exacerbations, while an increase of 0.37 annual exacerbations

($P = 0.024$) were recorded in the placebo group (Lycke et al., 1996). No convincing signs of reduced neurological deterioration in the aciclovir group were noted.

In a pharmacokinetic study of serum/CSF concentrations of aciclovir reached at steady state at this dosage in a subpopulation of the MS patients, mean serum peak and trough levels were 4.08 and 2.47 μM , respectively. In the CSF, the mean aciclovir concentration was 0.83 μM , and the values were only slightly affected by the fluctuations assayed in serum samples (Lycke et al., 1989). Thus, the mean penetration rate to the CSF was 31%. Aiming at α -herpesvirus replicating in the CNS, and assuming a roughly equal distribution between CSF and CNS tissue (Biron et al., 1982), a comparison of IC_{50} values of aciclovir for different herpesviruses (Elion, 1983; Fletcher and Bean, 1985) with the CSF concentrations reached suggests that a suppression of HSV-1 and HSV-2 but not of any other herpesviruses might have been achieved by the dosage used in the trial. In addition, the serum concentrations were judged adequate to inhibit also VZV replication (Lycke et al., 1989). The relative insensitivity of β - and γ -herpesviruses in vitro would not exclude a possible effect in vivo, but when titers of serum IgG antibodies to different herpesviruses were determined pre- and posttreatment, a significant reduction of HSV-1 and HSV-2 titers were found in the aciclovir recipients, but not in the placebo group, while titers to VZV, CMV and EBV remained constant (Lycke et al., 1996). As a further indication of achieved suppression of HSV, nine of the placebo recipients experienced oral lesions during the 2-year study period as compared to only one aciclovir recipient (Lycke et al., 1996).

14. The valaciclovir trial

Given the opportunity to improve the distribution of aciclovir into the CNS by the increased plasma levels reached by the prodrug valaciclovir (Beutner, 1995), a new investigation using this substance has been initiated. In an ongoing placebo-controlled bicenter trial of 70 evaluable patients (Aarhus, Denmark and Göteborg, Swe-

den), the effect of continuous valaciclovir treatment during 6 months is evaluated by serial MRI investigations. The oral dose selected is 1 g t.i.d., and preliminary results of a pharmacokinetic study in subjects given the identical dose indicates that the steady-state CSF concentration of aciclovir is approximately three times higher than the level reached during the aciclovir trial (Lycke et al., 1989; Lycke, personal communication). In addition to a suppression of HSV-1 and HSV-2, a possible effect on the replication of VZV also within the CNS might be achieved in the present study. Regarding the possible toxicity of the chosen dosage of 3 g/day, 1 g b.i.d. of valaciclovir was found to be safe in a trial of short-term treatment for recurrent genital herpes while long-term treatment with 8 g/day aimed at CMV suppression in severely ill HIV patients was toxic to some patients (Tyring et al., 1998; Feinberg et al., 1998). Although the chosen dosage in the current trial in MS is not expected to be harmful to the patients, the toxicity might create an upper limit in attempts to utilize valaciclovir for suppression of β - and γ -herpesviruses within the CNS during the course of MS. The possible problem of antiviral resistance after long-term treatment has been addressed by a surveillance of aciclovir sensitivity if any HSV and VZV strains are isolated during and after the study.

15. Concluding remarks and future outlooks

Despite considerable diagnostic efforts, no viral agent responsible for the etiology of MS has hitherto been identified. Circumstantial evidence from several lines of investigation suggest a role for herpesviruses as cofactors in this disease. Investigations of a possible association between MS attacks and reactivation of α -herpesviruses are motivated by the recent findings of early neuronal involvement in MS pathogenesis, results from animal models of HSV-induced demyelination, a recently confirmed etiological connection between HSV and another demyelinating condition of the CNS, i.e. facial palsy, and the diagnostic data in the form of previously reported CNS-derived HSV isolates and HSV specific immune responses found in MS patients.

Diagnostic shortcomings related to the inaccessibility of the MS lesions and the normal presence of herpesviruses in the brain prompted a challenge of this hypothesis by antiviral treatment with oral aciclovir. A possible beneficial effect shown as a reduction of number of attacks during a 2-year pilot study has motivated an ongoing trial using valaciclovir in order to achieve enhanced penetration of aciclovir into the CNS allowing suppression of at least the α -herpesviruses in this compartment. Following development of antivirals with improved safety and better CNS penetration than those currently available, future studies might target also β - and γ -herpesviruses such as HHV-6 and EBV. For the hematogenously spread herpesviruses, achieved suppression of viral replication might be monitored by quantitative PCR on white blood cells in addition to serology. A third possible target for antiviral treatment in MS patients could be viruses causing URTI such as rhinoviruses. Finally, in consideration of the recently reported beneficial outcome on disease progression by IFN- β treatment, a combination of effective and safe antiviral therapy with immunomodulatory/antiviral regimens with proven efficacy might be suggested for future treatment trials in MS patients.

Acknowledgements

The author is grateful to Oluf Andersen, Jan Lycke, Bo Svennerholm and Anders Vahlne for fruitful cooperation and discussions, and to Örjan Strannegård for careful reading of the manuscript. Financial support has been received from the Swedish Medical Research Council and the Göteborg LUA foundation.

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