INTERPRETIVE SYNTHESIS REVIEW

Acute disseminated encephalomyelitis progressing to multiple sclerosis: Are infectious triggers involved?

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Abstract Acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) are demyelinating disorders affecting the central nervous system. An autoimmune aetiology has been proposed for both. ADEM principally affects adolescents following acute infection by a variety of pathogens and has also been reported to occur following vaccination. ADEM typically resolves following medical treatment, whereas MS follows a more relapsing and remitting course. The pathogenesis of MS remains unclear, but it is thought that a combination of infectious and non-infectious environmental factors and host genetics act synergistically to cause disease. A variety of viruses, including Epstein Barr virus, cytomegalovirus, herpes simplex virus and varicella zoster virus, have been implicated as possible infectious triggers. The similar clinical and pathological presentation of ADEM and MS presents a diagnostic challenge for distinguishing ADEM from a first episode of MS. Some cases of ADEM progress to MS for reasons that are not currently clear. This review examines the evidence for infectious agents as triggers for ADEM progressing to MS and suggests potential methods that may facilitate identification of infectious agents that may be responsible for the pathogenesis of ADEM to MS.

Abbreviations

ADEM	Acute disseminated encephalomyelitis
CIS	Clinically isolated syndrome
CMV	Cytomegalovirus
CSF	Cerebrospinal fluid
EBV	Epstein–Barr virus
HHV6	Human herpes virus 6
HSV	Herpes simplex virus
MOG	Myelin oligodendrocyte glycoprotein
MS	Multiple sclerosis
URTI	Upper respiratory tract infection
VZV	Varicella zoster virus

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Introduction

Acute disseminated encephalomyelitis (ADEM) is an autoimmune, demyelinating disease affecting the central nervous system (CNS) [1–3]. Children are more commonly affected than adults. The disease is often triggered by bacterial or viral infections, and rarely vaccinations [4]. Many cases are reportedly preceded by bacterial and viral upper respiratory tract infections (URTI). Like many

autoimmune diseases, it is believed that a combination of genetic predisposition and environmental factors (including infections) acts synergistically to induce autoimmunity. In multiple sclerosis (MS), bacterial and viral agents have also been implicated as triggers of autoimmunity, disease flares and disease progression and are also implicated as potential causes of concomitant autoimmune disease [5, 6]. It is well recognised that multiple autoimmune conditions often co-exist in a patient, which raises the question of common triggers between these conditions.

ADEM is characterised by multiple inflammatory lesions in the brain and spinal cord, predominantly in the white matter. These lesions are morphologically indistinguishable from those seen in MS [7]. ADEM often presents as a monophasic condition with multiple neurological signs and symptoms, as well as encephalopathy [1–3]. Magnetic resonance imaging (MRI) of patients suffering ADEM shows subcortical white matter lesions and lesions in the deep grey matter of the thalami and basal ganglia [8]. The diagnosis of ADEM is based on clinical and radiological findings, with differential diagnoses including MS and the clinically isolated syndrome (CIS), transverse myelitis and neuromyelitis optica [8]. Bacterial and viral meningitis and encephalitis must also be excluded. Relapsing cases and the appearance of new lesions are suggestive of multiphasic ADEM or MS. It is often difficult to differentiate between ADEM and MS, with some cases of ADEM progressing to MS without explanation [8, 9].

This review examines the possible roles of infectious agents in inducing the progression of ADEM to MS through mechanisms such as loss of self-tolerance to specific myelin peptides via molecular mimicry and cross reactivity, in genetically and immunologically susceptible individuals. We also focus on possible methods for detecting and characterising the many infectious agents that may be involved during the protracted disease progression.

Autoantibodies: a clue to molecular mimicry and cross reactivity?

The pathogenesis of ADEM has not been fully elucidated, nor have its autoantigenic determinants. Implicated antigens include myelin basic protein, proteolipid protein and myelin oligodendrocyte glycoprotein (MOG) [8, 10]. T-cell reactivity to myelin basic protein is tenfold greater in ADEM patients compared to patients with encephalitis or healthy control patients [1]. Several studies have reported some ADEM patients with high titers of anti-MOG antibodies [11–16]. Di Pauli et al. [12] found that 44 % of ADEM patients had high titer anti-MOG IgG and noted that anti-MOG titers decreased with clinical improvement

in a longitudinal analysis of 266 patients. Similar results were reported by Brilot et al. [11] who found anti-MOG IgG in 40 % of ADEM/CIS patients. Lalive et al. [13] found that anti-MOG antibodies were highly reactive in children with ADEM, and that they were also present in MS. Probstel et al. [16] followed 25 children with anti-MOG-positive ADEM over 5 years. They found that anti-MOG antibodies declined rapidly in 16 monophasic ADEM cases and in one CIS case. Interestingly, anti-MOG antibodies persisted and even increased in six of eight cases who later developed paediatric MS [16]. Adult and paediatric controls were negative for anti-MOG. Six percent of adult MS patients were also found to have low titers of anti-MOG antibodies [16]. Probstel et al. [16] proposed that anti-MOG may therefore be present at the onset of inflammation in early MS, but may decline over time. A study by Menge et al. [17] found that correctly folded antibodies against MOG are found in paediatric MS and ADEM, but not in adult MS. The authors suggest that these differences may be related to molecular mimicry and cross reactivity [17], findings that raise the question of whether common infectious agents are shared between ADEM and MS. It is possible that specific infectious agents cause MS and/or ADEM in isolation and that certain infections lead to a form of ADEM which progresses to MS in a minority of cases.

Infectious triggers in multiple sclerosis

MS is an autoimmune disease characterised by chronic inflammation, nerve demyelination and gliosis in the CNS [18, 19]. Periods of relapse and remission are common and typify the most common form of the disease [18, 19]. Inflammatory lesions with areas of demyelination in the CNS characterise the gross pathology of MS [20]. The lesions are composed of mononuclear cell infiltrates (largely T and B lymphocytes, plasma cells, macrophages and microglia) in the perivascular spaces that develop into plaques [18, 21]. The peripheral regions of the plaques stain positive for IgG [18, 21]. Furthermore, 90 % of MS patients show intrathecal IgG synthesis in cerebrospinal fluid (CSF) [18]. The risk for developing MS is typically spread over a long period of time [22–24], although several studies indicate that children as young as 11 may be susceptible to the disease [25]. Although MS is primarily diagnosed in young adults, paediatric MS has been recognised [26].

Multiple viruses have been implicated in the pathogenesis of MS and disease flares [18, 19, 27–32]. Viruses can damage infected cells directly or trigger autoimmune reactions that cause demyelination. It is believed that autoimmunity develops due to bystander activation,

epitope spreading, molecular mimicry and cross reactivity between viral and self-peptides such as those in myelin [33–36]. Although multiple viruses have been implicated with varying degrees of evidence (reviewed in [37]), Epstein–Barr virus (EBV) and human herpes virus (HHV) (specifically HHV6) are most strongly implicated [18, 19, 29, 30, 37–40].

The relapse-remittance pattern of chronic HHV infection is similar to the clinical pattern of MS [19], and HHV pools have been found in brain tissue [41, 42] and the CSF of MS patients [43, 44]. Infection with HHV6 in childhood is associated with an increased risk of developing MS [40]. It has also been demonstrated that HHV6 is capable of infecting most glial cell-types [45]. Moreover, increased HHV6 DNA has been found in MS plaques, and monoclonal antibodies were able to detect HHV6 antigen in brain tissue from MS plaques but not control brain tissue [38, 39]. Molecular mimicry has been indicated, as sequence homology has been found between myelin basic protein and HHV6 encoded U24, and cross-reactive T cells responding to both protein types are found to be increased in MS patients [46].

EBV has been strongly associated with autoimmunity and specifically with MS. EBV has been shown to be highly prevalent in MS patients [47, 48], and a higher prevalence in paediatric MS cases compared to paediatric controls [49]. Although EBV is ubiquitous, the incidence of MS is higher among individuals with histories of symptomatic infectious mononucleosis [50]. Also, initial infection of B lymphocytes with EBV could account for the presence of increased oligoclonal bands from proliferating cell clones [51]. EBV-IgG has been noted in a cohort of MS patients up to 20 years prior to the onset of MS [52], and MS patients have been reported to have increased CD4+ T cells against EBV nuclear antigens [53]. Interestingly, myelin antigens were found to be cross reactive with EBV nuclear antigens and specific CD4+ T cells in cell studies [54, 55]. It has also been proposed that EBV may infect and immortalise autoreactive B cells, although no definitive conclusions have been drawn on whether EBV-infected B cells are present in brain tissue of MS patients [56–60]. A recent study by Pender et al. [61] reports defective cytotoxic CD8+ T-cell control of EBV which may contribute to the development of MS, as autoreactive B cells infected with EBV would accumulate in the CNS [61]. Interestingly, in the same study, MS patients were treated with in vitro expanded autologous EBV-specific CD8+ T cells against viral proteins, with subjective and objective clinical improvement in symptoms [61]. Several other infectious agents have been implicated in the pathogenesis of MS, but these have a weaker evidence base. A small number of these have also been implicated in ADEM, including EBV, coronavirus, cytomegalovirus (CMV), measles virus, and varicella zoster virus (VZV).

Viruses common in ADEM and MS

Most cases of ADEM are preceded by infection, yet often the infection has cleared before neurological signs and symptoms develop. Tissues samples from ADEM lesions are rarely obtained due to the good prognosis of the condition [7]. Several bacteria and viruses have been identified in ADEM patients.

The role of EBV has been well studied in MS and has also been implicated in ADEM, and in some cases of ADEM progressing to MS. Banwell et al. [26] examined the clinical features and viral serologies of 137 paediatric MS patients and 96 controls. A first MS attack that resembled ADEM was reported in 16 % of patients. Those patients tended to be younger with polyfocal or monofocal presentations [26]. Seropositivity for EBV was found in 86 % of cases compared to 64 % of controls, irrespective of geographical location suggesting that EBV may play a role in paediatric MS [26]. Fujimoto et al. [62] identified 10 cases of CNS syndromes following infectious mononucleosis in patients between 1984 and 2002. Two of these cases were ADEM with both having EBV detected in the CSF by PCR [62]. ADEM was observed in two of these patients. Both had EBV titers detected in the CSF by PCR. The remaining cases of ADEM linked with EBV are largely comprised of individual case reports and small studies [63–81].

Coronavirus is capable of infecting neural cells and has been implicated in MS [82, 83] and ADEM [84], although the evidence for this is weak. Yeh et al. note that coronavirus can induce a chronic demyelinating disease resembling MS in a murine model [84]. There are also few studies relating CMV to MS [85] and to ADEM [77, 86–88]. Brok et al. [86] demonstrated that the human CMV major capsid protein shares sequence similarities with the MOG-34-56. Rhesus monkeys, immunised with MOG-34-56, were found to develop neurological disease resembling human ADEM, and the mononuclear cell infiltrates in the demyelinating lesions were predominantly MOG-34-56 [86] T cells. MOG-34-56 reactive CD4+ and CD8+ T cells were also induced in monkeys immunised with human CMV major capsid protein [86].

Measles virus has been loosely linked with both MS and ADEM [32, 89–97]. Hagiwara et al. [91] report a case of ADEM following *Mycoplasma pneumonia* infection complicated with measles and comment on the potential involvement of multiple infectious agents in the pathogenesis of ADEM. VZV has been isolated in the CSF of MS patients and has also been identified during MS flares

[98–100]. A small number of case reports also note VZV infection in ADEM cases, with several reporting the presence of VZV in the CSF [101–110].

Although several viruses are associated with ADEM and MS, very little research has specifically focused on the progression from ADEM to MS. Indeed, most published accounts are case reports rather than formal clinical or epidemiological studies.

Respiratory tract infections preceding MS and ADEM

A history of URTI frequently precedes cases of ADEM and has been documented in several studies of MS patients. A prospective study of paediatric ADEM patients from January 2009 to January 2011 found that 57 % of patients had a history of URTI preceding their disease, with three cases showing infection with HSV and EBV [67]. There were no differences between cases and controls with respect to other viral infections such as CMV, parvovirus B19, VZV or HSV [26]. A case–control study of 225 MS cases and 900 controls by Marrie et al. [50] set out to determine whether URTIs are related to the onset of MS symptoms using the General Practice Research Database in the United Kingdom. Mean rates of respiratory tract infection were compared at intervals of 5 weeks, 3 months and 12 months prior to the onset of first symptoms. They found an increased frequency of URTI preceding MS onset, with significantly increased MS risk. Additionally, they demonstrated that a history of infectious mononucleosis was associated with a fivefold increased risk of developing MS.

Future prospects

The factors contributing to the development of MS, the various MS types and disease flares are unclear. Likewise, why some, particularly paediatric, cases of ADEM progress to develop MS is poorly understood. It is likely that inherent immunological and genetic factors contribute to this progression, although further research is needed [111–115]. Infectious agents are also probably involved in the progression of ADEM to MS, especially since both conditions are implicated with shared infections and that there are similarities with certain autoantibody profiles. Specific infectious agents may play a role in ADEM and MS in isolation, while others lead to progression of ADEM to MS. The lack of more implicated infectious agents may be due to a paucity of research rather than negative findings. The recent introduction of the infectome model may allow researchers to identify infectious agents involved in ADEM to MS progression, or indeed, infections that may be protective [5, 6]. The infectome model is based on

geographical, epidemiological, serological and molecular evidence of the presence and co-occurrence of infectious agents associated with autoimmunity [5, 6]. In the case of ADEM, regular monitoring and sampling of patients to detect infections preceding progression to MS could be implemented. Follow-up and sampling of MS patients may also elucidate the role of infectious triggers to disease flares.

Conflict of interest   There are no conflicts of interest.

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