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REVIEW

Infectious agents and different course of multiple sclerosis: a systematic review

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Abstract

Multiple sclerosis (MS) causes demyelination of white matter of central nervous system and neuro-degeneration due to inflammation. Different types of MS, as well as disease progression, come with different pathology and pathophysiology. The objective of this study was to evaluate the possible association between different micro-organisms and the relapse or progression of MS. Studies indexed in Medline/PMC, Scopus and Web of Science published without time and language limitation until March 2017 were identified through the search terms "infection" or "infectious" and "multiple sclerosis". A total of 20878 abstracts were identified through the initial search terms. Selection of articles and assessment of their quality was done based on Cochrane library guidelines. Full texts were reviewed for 33 articles out of which 14 articles met the criteria for inclusion. Different micro-organisms are known to play roles in the pathogenesis of MS and its relapse; including Human herpesvirus 6 (HHV-6), Human herpesvirus 7 (HHV-7), Epstein–Barr virus (EBV), *Chlamydia pneumoniae* and Torque teno virus (TTV). But in this review only HHV-6, *C. pneumoniae* and TTV have been considered to play a role in disease progression in some studies and not all of them. This review concluded that some micro-organisms such as HHV-6, *C. pneumoniae* and TTV have been considered as cofactors to make MS a progressive type. It should be considered that these findings do not necessarily rule out the role of other pathogens in MS progression but may represent population differences or different sensitivity of the technique used.

Keywords Infection · Multiple sclerosis · Relapsing–remitting · Progressive

Introduction

Multiple sclerosis (MS) causes demyelination of white matter and neurodegeneration of central nervous system (CNS) and is the most common demyelinating disease of CNS [1–10]. Relapsing–remitting (RR) form which is characterized by exacerbations with subsequent complete or partial recovery of symptoms is the most common type of MS (80%); some of which transform into a secondary progressive (SP) course (SPMS type) with or without superimposed relapses. Primary progressive (PP) form with no history of relapse or remission is less prevalent (20%), which usually causes a more rapid disability than the other forms [11–14].

MS is considered a disease by autoimmune inflammatory mechanism. Some different factors have been introduced as provocative factors for inflammation in MS including genetic and environmental factors [11, 13, 15–17]. There is an inclination among researchers to assess the role of infectious agents in neurological disorders [18–22]. In MS also infectious agents are the most interested candidates to have a role in provoking inflammation [23, 24].

Several viruses and bacteria have been associated with MS [25]. Among viruses; herpes viruses [26], human herpes virus 6 (HHV-6) [27–30], Epstein–Barr virus (EBV) [30–32], varicella zoster virus (VZV) have been evaluated

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for a possible causal association with MS [33, 34]. The bacterial pathogens associated with MS are *Chlamydia pneumonia* [30, 35], *Helicobacter pylori* [36] and *Borrelia burgdorferi* [30, 37].

Emerging hypotheses propose that the progression of MS maybe due to infectious agents expressing antigenic molecules mimicking the structure and glycoproteins and glycolipids on the surface of the CNS cells [17, 38, 39]. This molecular mimicry could lead to activation of auto reactive lymphocytes and thereby induction of inflammation in CNS. Although an antibody-mediated demyelination mechanism in MS is debated and no specific antibodies have been found in immunoassay in MS patients [17, 40–42].

There are different pathology and pathophysiology for different types of MS. Therefore, the present systematic review aims to generally evaluate the role of infectious agents in MS patients and identify which ones are involved in the MS recurrence or in RRMS type, and which ones are involved in the progression of MS or in SPMS and PPMS types.

Materials and methods

Search strategies

The entire studies addressing MS in the world were collected from world-wide databases including Medline/PMC (via PubMed), Web of Science, and Scopus. The databases were thoroughly searched for documents with no time and study type limit, until 25 March 2017. Presumably, the search was carried out without language limitation. The search terms which have been used and containing Medical Subject Headings (MESH) or keywords in text, title, and abstract with the help of Boolean operators were ("and" or "or"): "multiple sclerosis" and ["infection" or "infectious"].

The search strategy was modified and customized for every database. Google search engine was used as sources of grey literature.

Exclusion criteria

1. Animal model.
2. Case report.
3. Opinion study.
4. Demyelinating disorders except MS.
5. Other neurological diseases.
6. Communities with less than 50 samples.

Quality assessment

For quality assessment of articles we used the STARD (Standards for Reporting of Diagnostic Accuracy) which included the standards for the quality of completeness and transparency of reporting of diagnostic accuracy studies [43]. Quality assessment was only carried out for those studies which met the inclusion criteria for the review. The methodological quality (risk of bias) of the studies was assessed independently by two reviewers using the criteria of Downs and Black [44]. Any disagreements were resolved by consensus and checked by a third reviewer.

Data extraction

Data were extracted using an extraction form independently and in duplicate by two investigators. The following data were extracted from the chosen articles: the first author's name, the year of publication, the location of the studies, the mean age, the number of cases participated, course of MS, case group, control group, diagnosis test used for microorganism, infection type, and main results concern correlation between infection and MS in patients. The articles found by the search strategy were reviewed by two authors for eligibility based on title and abstract. Differences in data extraction between authors were resolved by consensus.

Results

Translucently, a total of 20,878 reports were screened for the analysis of patients with MS and infection. After eliminating the duplicate articles 15,966 articles were obtained for this review. After removing 15,610 unrelated records, 33 full texts were assessed for eligibility. Figure 1 demonstrated the search strategy based on the PRISMA Flow Diagram. The summary of the selected articles are presented in Table 1.

Discussion

Herpes viruses

In assessing the role of herpes viruses in the process of MS, the reaction occurs among T cells against patient's CNS antigens including myelin, brain homogenate, cell lysates of apoptotic oligodendroglia cells and neurons. Considering the MS type and the pattern of its progression; among progressive MS patients, intrathecal T cell proliferation is not proportionate to cytokine production of herpes virus-specific T cells. Although there is diminished intrathecal T cell proliferation but the cytokine production related to herpes virus increases. Therefore, additional immunologic mechanisms may influence this process [46].

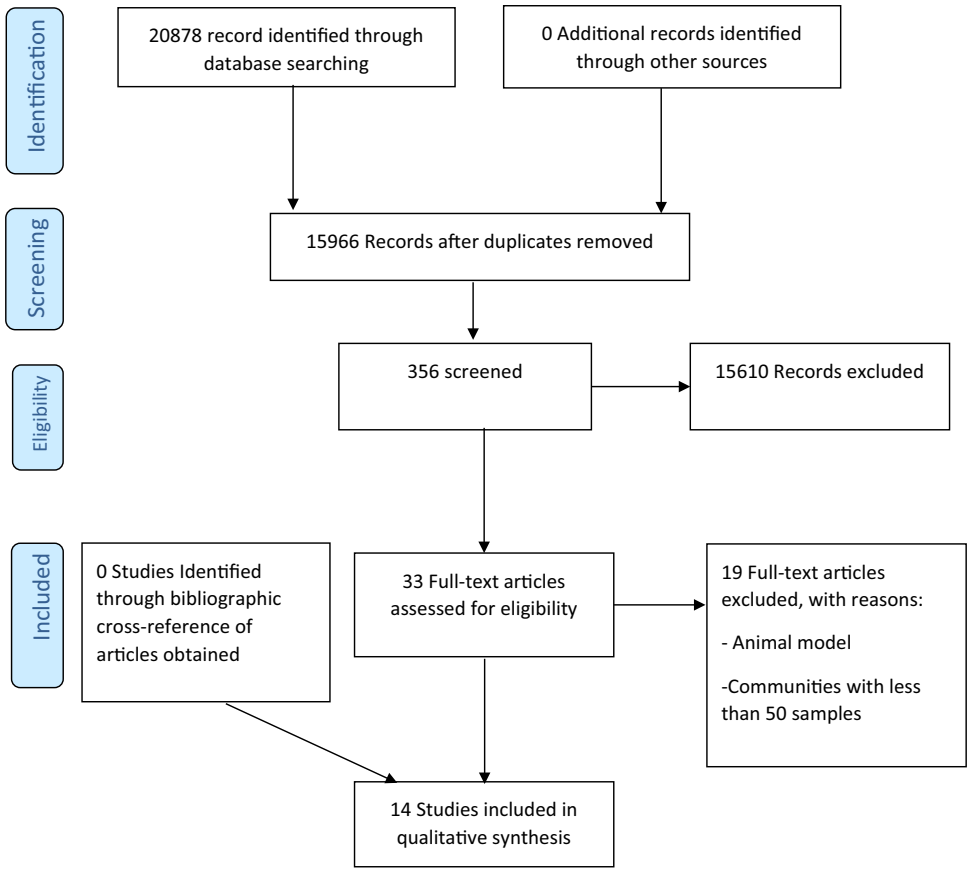

Fig. 1 Flow diagram of the literature search and study selection

Herpes simplex virus (HSV)

A few number of studies assessed HSV with different results that were not conclusive and none of them assessed its role in disease progression [47, 48].

Human herpesvirus 6 (HHV-6)

HHV-6 is a common pathogen (more than 80% HHV-6 seropositivity among adults) and one of its specificity remains in immune cells, neurons, and oligodendrocytes in a latent state [49, 50]. Its association with MS and its progression is controversial. HHV-6 produces neurotoxic behavior in some glial cells with some specific mechanisms. HHV-6, enters cells, by mediating CD46 and inducing the production of interleukin-1β and, interleukin-17. HHV-6 encodes a viral version of the CCR2 ligand, which acts as a chemo-attractant for monocytes and macrophages. Besides, this virus can activate other latent herpes viruses and human endogenous retroviruses (HERV) which have the components with pro-inflammatory, neurotoxic and gliotoxic properties either [51]. Also this virus increases the death of neurons, astrocytes, and oligodendrocytes, interfering with the correct phosphorylation of myelin basic protein, and/or increasing cerebrospinal fluid glutamate levels [52]. The concentration of HHV-6 antigen has been demonstrated in oligodendrocytes by immunohistochemical assays of MS plaques [53].

Simpson et al. [43] found an association between relapse risk and MS course and anti-HHV-6 IgG titers which is dose-dependent. In the study by Garcia-Montojo et al. Quantitative real-time PCR has been used to detect HHV-6 genomes among MS patients who received interferon (IFN)-beta 1b for 2 years. Presence of HHV-6 in blood increased the risk of severe relapses, bad responses, less reduction in the relapse rate, lower proportion of responders and poorer response to IFN-beta. Based on these results; active replication of the virus induces reaction of the immune system and causes inflammation and demyelination. Besides; HHV-6 could insolently interfere with remyelination process. Also an association was found between the changes in HHV-6 viral load and progression of EDSS score. Patients with confirmed progression had more changes in HHV-6 viral load during 24 months visit rather than non-progressing patients ($p=0.01$) [52].

Behzad-Behbahani et al. demonstrated that along the 6 months' follow-up the viral DNA was detected in 41% of RRMS samples, 14% of SPMS samples, and none of the primary progressive MS. No significant difference was found ($p=0.36$) between RRMS and the SPMS group in viral DNA load. HHV-6 viral load during active phase was

Table 1 Main characteristics of studies examining infectious agents role in different course of multiple sclerosis

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Behzad-Behbahani et al. [53], Iran	Original	70: 30 MS (21 F, 9 M) patients and 40 controls [20 OND (11 F, 9 M) and 19 healthy subjects (10 F, 10 M)]	RRMS ($n=22$) SPMS ($n=7$) PPMS ($n=1$)	–	MS: 33 (18–45) OND: 32(18–48) Healthy subjects: 28 (18–35)	MS patients	20 individuals with OND, and 20 randomly selected healthy blood donors	Nested polymerase chain reaction, enzyme-linked immunosorbent assay (PCR-ELISA) and DNA-enzyme-linked immunosorbent assay (DELISA) for quantifying HHV-6 DNA molecules Enzyme immunoassay for detection of IgG antibodies to HHV-6 MRI and clinical status of the patients for disease activity according to the criteria of Poser et al. [45]	Human herpesvirus-6 (HHV-6)	There was not any significant difference ($p<0.36$) between RRMS and the SPMS group. HHV-6 viral load during active phase was significantly greater ($p<0.001$) than remission The average antibody index for the MS was 2.68 versus 1.4 for both the control groups ($p<0.001$)
Nora-Krukle et al. [56], Latvia	Original	28 (21 F, 7 M)	RRMS ($n=14$) SPMS ($n=14$)	–	37 (16–59)	MS patients	–	Detection of HHV-6 and HHV-7Genomic Sequences by nested Polymerase Chain Reaction Detection of HHV-6 and HHV-7mRNA Transcription by Reverse Transcriptase-Polymerase Chain Reaction Enzyme-linked immunosorbent assay (ELISA) kit to measure the concentration of IL-12 (p70) and TNF-α	Human Herpesvirus 6 and 7 (HHV-6 and HHV7)	Active HHV-6 and HHV-7 infection may play at least a cofactor role in the activation or relapse of both RRMS and SPMS not in its progression

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Sotelo et al. [58], Mexico	Original paper	74: 53 MS patients, (19 M/34 F) 21 non MS patients (9 M/12 F)	MS in relapse ($n=31$;11 M/20 F) MS in remission ($n=16$;6 M/10 F) Progressive MS ($n=6$;2 M/4 F)	–	MS in relapse (31 ± 2) MS in remission (30 ± 2) Progressive MS (41 ± 2)	MS patients	21 patients with inflammatory or functional neurological disorders	VZV-DNA quantified (absolute quantification) in PBMC (peripheral blood mononuclear cells) and in CSF by real-time PCR	Varicella zoster virus (VZV)	DNA from varicella zoster virus was found in the CSF from all MS patients studied during relapse and in the PBMC from 28 of them (90%)
Farrell et al. [76], UK	Original	100	RRMS ($n=25$) PPMS ($n=25$) CIS ($n=50$)	At baseline CIS: 1.18 (0–2.5) RRMS: 1.17 (0–2.5) PPMS: 4.87 (3.5–6.5)	CIS: 32.5 (17–49) RRMS : 36.3 (26–48) PPMS: 45.4 (25–62)	MS patients	–	Quantitative real-time PCR for EBV- DNA in blood EBV serology for anti-Epstein–Barr virus nuclear antigen 1 (EBNA-1) immunoglobulin G (IgG), anti-viral capsid antigen (VCA) IgG, and anti-EBV IgM MRI: T1 gadolinium-enhanced scans and T2-weighted scans	Epstein–Barr virus (EBV)	All subjects had serologic evidence of previous EBV infection, but no lytic reactivation was detected Significant differences in EBNA-1 IgG titers were found between subgroups, highest in the RRMS compared with PPMS and CIS Gad-enhancing lesions on MRI correlated with EBNA-1 IgG and EBNA-1: VCA IgG ratio. EBNA-1 IgG also correlated with change in T2 lesion volume and EDSS score An association was between EBV infection and MS disease activity

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Ingram et al. [80], UK	Original paper	100: 75 MS (51 F, 24 M) 25 controls (11 F, 14 M)	PPMS ($n=25$) Stable-RRMS ($n=25$) Active RRMS ($n=25$)	Total MS: 4.4 ($\pm$2.1) PPMS: 6.0 ($\pm$1.6) S-RRMS: 2.8 ($\pm$1.9) A-RRMS: 4.3 ($\pm$1.5)	Mean age (39.9 $\pm$ 11.2) Control: 49.4 $\pm$ 20.6 Total MS: 39.9 $\pm$ 11.2 PPMS: 49.0 $\pm$ 11.6 S-RRMS: 37.4 $\pm$ 7.7 A-RRMS: 33.4 $\pm$ 7.1	MS patients	25 non-related healthy subjects with no personal or family history of neurological disease	Assessing serum anti-EBNA-1 IgG using both the Liaison quantitative chemiluminescent assay and Bio-test ELISA Anti-EBNA-1IgG tested via Liaison was considered negative if <5 U/ml, equivocal if 5–20 U/ml and positive if >20 U/ml. and via Bio-test was considered negative if 20% lower than the negative control supplied plus 0.2 U/ml	Epstein–Barr virus (EBV)	No difference in quantitative analysis of serum anti-EBNA-1 IgG levels between disease subgroups was found and no correlation with phenotypic characteristics including age at onset, disease duration, EDSS. Thus, there is not a clinical value for serum anti-EBNA-1 IgG levels in MS or to confirm reported association with disease course and clinical disease activity There was only moderate correlation between the two test methods used (intraclass correlation coefficient 0.67; 0.56–0.78) suggesting potential problems with test interpretation

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Garcia-Montojo et al. [52], Spain	CME article	54 (35 F, 19 M)	RRMS ($n=50$) SPMS ($n=4$)	0–5.5 for RRMS and 0 to 6.5 for SPMS Baseline mean 1.97 ± 1.36	35.35 ± 9.14 (16–55)	MS patients from 12 Spanish hospitals treated with IFN-beta 1b, (Betaferon, for 2 years)	–	Quantitative real-time PCR	Human herpesvirus-6 (HHV-6)/ Epstein–Barr virus (EBV)	Any association between EBV and clinical parameters could not be found HHV-6 was detected more frequently during relapses than in remission in blood and in serum Patients with HHV-6 in blood had a higher risk of relapse, severe relapses and bad response. An association was between HHV-6 viral load and progression in EDSS score
Simpson et al. [51], Australia	Original paper	198 (137 F, 61 M)	RRMS ($n=149$) PPMS ($n=9$) SPMS ($n=40$)	3.7 ± 2.3 (0–9)	Total MS: 48.2 ± 11.4 (21–77) RRMS:45.5 (10.4; 21–76)	MS patients	–	Serum anti-HHV-6 IgG titers were measured using indirect immunofluorescence assay (IFA) Serum anti-EBV (VCA and EBNA) IgG titers were measured using an analogous assay	Human herpesvirus-6 (HHV-6)/ Epstein–Barr virus (EBV)	HHV-6 infection or the immune response to HHV-6 antigens may have an effect on the risk of MS relapses and possibly on progressive courses of MS

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Wandinger et al. [48], Germany	Original	271: 108 MS patients (M/F: 41/67), 163 control (74/89)	RRMS ($n=65$) SPMS ($n=24$) PPMS ($n=12$) RPMS ($n=7$)	–	MS patients: 37.9 ± 10.3 (20–57) Controls: 36.2 ± 11.8 (19–56)	Patients with MS	Healthy subjects	ELISA for antibody against(HSV-1)/ Herpes simplex virus (HSV-2)/ Epstein–Barr virus (EBV)/Cytomegalovirus PCR for EBV-DNA	Herpes simplex virus type 1 (HSV-1)/Herpes simplex virus type 2 (HSV-2)/ Epstein–Barr virus (EBV)/ Cytomegalovirus	An association only between EBV reactivation and disease activity in MS was found ($p=0.002$, Chi square test)
Villoslada et al. [50], Spain	Original paper	201: 151 MS patients (100 F, 51 M) 50 controls (34 F, 16 M)	CIS ($n=53$; 35 F, 18 M) RRMS ($n=49$;32 F/17 M) SPMS ($n=49$;33 F/16 M)	CIS: 2.4 ± 1.3 RRMS: 1.5 ± 1 SPMS: 6.8 ± 1.7	CIS: 28.4 ± 7.6 RRMS: 32.1 ± 7.1 SPMS: 45 ± 9.7 Controls: 28.7 ± 6	MS patients	50 healthy subjects	ELISA PCR	Human herpesvirus type 6 (HHV-6)/ Epstein–Barr virus (EBV)/*Chlamydia pneumoniae* (CP)	An immune response against herpesviruses such as HHV-6 and EBV is associated with early MS No association was found between the levels of serum antibodies against CP and MS No detection of DNA of these micro-organisms The presence of this antibody to HHV is not specific to MS
Aghaei et al. [82], Iran	Original	135: 85MS patients and 50 control subjects	RRMS ($n=69$) SPMS ($n=16$)	2.5 ± 1.80	MS group: 33.8 (9.96) years Control group: 33.9 (10.7) years	MS patients	healthy people(age- and sex-matched)	Serum analysis by ELISA, using *Chlamydia pneumoniae* IgG and IgM kit (Euroimmun, Germany): *C. pneumoniae* IgM positive > 1.1 RU/mL and *C. pneumoniae* IgG positive > 22 RU/mL	*Chlamydia pneumonia* (CP)	No association was observed between MS and *Chlamydia pneumoniae* in Iranian MS patients

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Contini et al. [85], Italy	Original	143: 71MS patients (51 F, 20 M), 72 controls[(32 OIND (18 F, 22 M, 40 NIND (18 F, 22 M)]	RRMS ($n=46$) SPMS ($n=14$) PPMS ($n=11$) 39 clinically active (32 RR and 7 SP =/65%) and 21 clinically stable disease (14 RR and 7 SP = 35%) with clinically stable disease	3.2 ±/1.3(0–6)	Mean age: MS: 40.3 ± 11.4 OIND: 50 ±/15.8 NIND: 47.77 ±/17.61	MS patients	Patients with OIND or NIND	CSF analysis Touchdown nested polymerase chain reaction (n-PCR) for *C. pneumoniae* with primer sets which amplify target sequence genes encoding the major outer membrane protein (MOMP), the 16S rRNA and the Hsp70 protein	*Chlamydia pneumoniae* (CP)	CSF CP-specific DNA detection can occur in a subset of MS patients with clinical and MRI active RR form not in progressive form
McKay et al. [47], Canada	Systematic review	–	PPMS RRMS	–	–	20 observational studies (case–control or cohort)	–	–	Epstein–Barr virus (EBV)/human herpesvirus-6 (HHV-6)/*Chlamydia pneumoniae* (CP)/Herpes simplex virus (HSV)/Varicella zoster virus (VZV)	Exposure to Epstein–Barr virus (EBV) appeared to increase the risk of RRMS, but its association with PPMS was less clear HHV-6, HSV and CP were not consistently associated with a specific disease course The risk of RRMS was increased in people with a history of VZV infection but not for PPMS

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Agostini et al. [90], USA	Original	171: 94MS patients and 77 control subjects	RRMS ($n=13$)/ RPMS ($n=34$)/ Chronic progressive ($n=47$)	–	–	MS patients	Individuals without MS or PML	PCR on urinary DNA: Primers JLP-15 and 16 were utilised as described (Agostini et al. 1997a). The positive samples were then subjected to amplification with primers JRR-25 and 28 for analysis of changes in the archetypal regulatory region sequence (Agostini et al. 1997b) PCR on CSF: using the Qiagen Tissue Kit (Kit no. 29304) according to the manufacturer's protocol. Primers JLP-15 and 16 were used to amplify a 215-bp fragment in the 5′-end of the VP1 gene for genotyping (Agostini et al. 1997a).PCR utilised Turbo Pfu DNA polymerase (Stratagene) with the specificity of the reaction enhanced with Perfect Match (Stratagene)	Human polyomavirus (JCV)	The excretion of JCV in MS patients is similar in both genotype and frequency to that of control individuals No association was found between MS disease activity (stationary, progression, or clinical relapse) and JC virus excretion Failure to detect JCV DNA(JLP-15 and 16 fragment) in CSF of MS patients

Table 1 (continued)

References, country	Study type	Number of participants	Course of multiple sclerosis	EDSS	Age (year)	Case group	Control group	Diagnosis test for microorganism	Infection agent	Main results
Rasmussen et al. [91], UK	Original paper	210: 110 MS, 100 control	RRMS ($n=72$) SPMS ($n=16$) PPMS ($n=22$)	–	–	MS patients (white Caucasians)	100 healthy subjects(white Caucasians)	Determination the HRES-1 haplotype Genotyping at three polymorphic sites of HRES-1 by enzymatic amplification and treatment of amplified products with Hind III, Eco57I and NciI, after which haplotypes were deduced on the basis of the known allelic associations	Four human T-cell lymphotropic virus (HTLV)-related endogenous sequence, (HRES-1)	Endogenous retrovirus HRES-1 haplotype 1 is associated with MS. There is no significant difference in the distribution of HRES-1 haplotypes between relapsing remitting MS and the primary progressive form of the disease

RRMS relapsing–remitting MS, *SPMS* secondary progressive MS, *RPMS* relapsing progressive MS, *PPMS* primary progressive MS, *S-RRMS* stable relapsing remitting MS, *A-RRMS* active relapsing remitting MS, *CIS* clinically isolated syndrome, *ELISA* enzyme-linked immunosorbent assay, *RT-PCR* reverse transcriptase polymerase chain reaction, *PCR* polymerase chain reaction, *OCB* Oligo Clonal Bands, *IFA* Immunofluorescence antibody test, *OIND* other inflammatory neurological diseases, *OND* other neurological disorders including motor neuron disease dizziness, cerebrovascular disease, migraine, meningitis, and febrile seizure, *NIND* non-inflammatory neurological disorders

significantly greater rather than during the remission phase ($p < 0.001$). They demonstrated that this virus is only a predisposing factor for relapse in each RRMS and SPMS type with no influence in its progression [53]. But some studies rejected the association between MS and HHV-6. McKay et al. [47] in their systematic review found only one study which represented the association between HHV-6 and a specific disease course. A Jordanian case–control study demonstrated negative results and no association was found between HHV-6 DNA, relapse risk and progression of MS. 24% (6/24) of RRMS patients, 40% (2/5) of SPMS patients, and 24.2% (8/33) of controls were HHV-6 positive ($p > 0.05$) [54].

Human herpesvirus 7 (HHV-7)

HHV-7 is an enveloped double-stranded DNA beta-herpes virus that is closely related to HHV-6. Like other herpes viruses, HHV-7 can remain in neural and oligodendroglia cells in latent phases after primary infection and can be reactivated later [55, 56].

Nora-Krukle assessed the relation between the reactivation of both HHV-6 and HHV-7 and disease activity in RRMS and SPMS using genomic sequencing and mRNA transcription of the viruses in a widespread study. They demonstrated that active HHV-6 and HHV-7 infection may additionally be a cofactor in disease activation or relapse of both RRMS and SPMS and had no longer any impact on disease progression [56].

Varicella zoster virus (VZV)

In the systematic review, McKay et al. [47] reported a study in which the risk of RRMS had increased in people with a history of VZV infection (OR: 3.89; 2.05–7.36), but not for PPMS (OR: 1.26; 0.52–3.03) [57]. Sotelo et al. [58] also demonstrated in both CSF (100%) and PBMC (90%), VZV-DNA was found in clinical exacerbation of MS with low amounts in chronic courses and progressive forms of MS. For the latter form the number of cases was small and were not conclusive for its role in disease progression.

Epstein–Barr virus (EBV)

B-lymphotropic EBV is found to be related to MS based on serological and also epidemiological studies [59]. EBV might be indirectly involved in the pathogenesis of MS [48]. It infects the CNS-infiltrating B cells which are found in plaques of MS [60]. Early lytic EBV antigens elicited CD8-mediated immune responses, triggering strong cytotoxic effects on brain tissues [61]. Interestingly, the most active cortical MS plaques are crowded with CD8 + T cells and contain few B cells or plasma cells, suggesting cortical lesions which are responsible for progression of MS and not a result of EBV-infected B/plasma cells [62]. Acute inflammation in both white and gray matter in relapse phase is due to EBV reactivation combined with the ensuing cytotoxic antiviral responses [63].

EBV infects native human B cells causing clonal expansion of these cells and subsequent lifelong latent infection in mature memory B cells [64]. EBNA-1 is a protein consistently expressed in dividing EBV-infected B cells of healthy carriers [65] and is a dominant antigen for both humoral and cellular immune responses. There are sequential homologies between EBNA-1 and heat shock protein αB crystalline expressed by B cells and infected by EBV and myelin proteins [66]. The other mechanisms are increased production of pro-inflammatory cytokines, elevated serum levels of neopterin and soluble human leukocyte antigens (HLAs) [67–69], activation of autoreactive T cells by various viral or bacterial peptides with or without molecular similarity which maybe a result of a more potency of microbial antigens as ligands for the autoreactive T cell, generation of antibodies that cross-react with neuroglial antigens, [70–72] activating myelin basic protein-specific T-cell clones by The EBV DNA polymerase [71]. The susceptibility of some EBV seropositive individuals to develop MS is due to differences in the genetically determined affinity and the stimulatory potency of the specific trimolecular complexes of encephalitogenic T cells consisting TCR, major histocompatibility complex (MHC) class II molecule, and auto antigenic peptide [72]. Furthermore, the T-cell pool in MS patients might contain a considerably higher number of preactivated EBV-specific memory T cells [73].

In agreement with abovementioned mechanisms; Colby et al. [74] suggested a reduction of EBV replication by acyclovir might likewise have influence on the outcome of the MS patients. Also Weiner suggested vaccination against EBV for children who are at a high risk of MS development with strong family history of MS [75].

Most studies points to EBV infection as being a prerequisite for the development of MS and its activation during relapses, but not in its progression as followed, but the last three studies do not agree with its role in induction and activation of this disorder and its progression and determining the patterns of MS.

Farrell et al. in a large MS/CIS cohort study found the absence of significant lytic reactivation of EBV in the periphery either by direct detection of viral DNA in plasma or serologic evidence of reactivation, defined by VCA IgM response or significant fall in EBNA-1 IgG in MS.

Median titers (U/mL) and interquartile ranges of the EBNA-1 IgG was found in 478 (108–1155), 727 (491–3188), 225 (73–462) in CIS, RRMS, PPMS subgroups, respectively, and 48.5 (0–540) in 20 healthy controls ($p = 0.003$); highest in the RRMS compared with PPMS ($p < 0.001$) and

CIS ($p < 0.001$) and higher in CIS patients converting to CDMS within 5 years than non-developing to CDMS {780 [interquartile range (IQR) 400–3500]}. Also higher titer of EBNA-1 IgG was found to be associated with the development of gadolinium enhanced lesions in MRI in all subgroups increased T2 lesion volume ($r^2 = 0.26$, $p = 0.035$) and EDSS progression ($r^2 = 0.3$, $p = 0.004$). Although the latter was not significant for PPMS. The results demonstrate that EBNA-1 IgG and its ratio to VCA IgM are related to RRMS or the changes in this pattern but not related to PPMS. All subjects support the hypothesis that previous EBV infection may be a necessary cofactor for developing MS and relapse or its activity and progression of CIS to CDMS but they did not demonstrate the progression to SPMS or induction of PPMS [76].

Wandinger et al. found that antibodies against EBV were present in 100% of MS patients. A serologic pattern of reactivation was found in 15.5% of patients with a relapse or disease progression and in 12% of the stable patients. Although EBV reactivation phase was not definitely contemporaneous with the disease activity, but in following patients for 1 year, increased immunoglobulin IgM and IgA responses to EBV early antigens (p54 + p138) which showed that the active viral replication has been demonstrated only in patients with clinically active disease. Evidence of increased viral activity (anti-EA-IgG OD value), was seen in 54.5% of patients with exacerbations but in only 12.5% of patients in remission ($p < 0.08$). Positive serum DNA was seen in 72.7% of patients with exacerbations and in none of the patients with clinically stable disease. The results demonstrated an association between EBV reactivation and relapse of the disease but not in disease progression [48].

In Villoslada et al. study, the increased levels of EBV EBNA IgG in early MS was found; so that the patients with CIS and RRMS had higher levels of EBNA IgG antibody titers than the controls ($p = 0.041$) and CIS higher than controls and SPMS groups ($p = 0.012$ and 0.037) which indicates a decrease in the prevalence of such antibodies with longer disease period (15 years). So MS could be primarily triggered by viral antigens from latent EBV in immunized individuals but its progression or changes in its pattern to SPMS is not related to this virus [50].

McKay et al. introduce the modifiable risk factors associated with these different clinical courses of MS in a systematic review. In this review, EBV has been shown to increase the risk of RRMS, but its effect on PPMS is not definitely demonstrated [47]. Five studies were found which examined the association between Epstein–Barr virus (EBV) and risk of developing relapsing or progressive-onset MS [50, 76–79]. As a component of a 5-year longitudinal MRI study based in the UK, the sera of 25 RRMS and 25 PPMS patients were analyzed for EBV activities [76]. Significantly increased median titers of anti (EBNA-1) IgG were found in RRMS compared to PPMS (670 versus 267 U/mL, $p < 0.001$). The opposite was true for median levels of EBV viral capsid antigen (VCA), which were lower in RRMS compared to PPMS (297 versus 530 U/mL, $p < 0.05$) [76]. Antibody levels against EBV were compared between 46 RRMS, 11 SPMS, and 21 PPMS patients in Iran [77]. Seroprevalence to anti-EBV IgG levels was significantly higher among RRMS (93.5%) and SPMS (100.0%) compared to PPMS (81.0%, $p < 0.001$ for both comparisons). Furthermore, RRMS (15.2%) and SPMS (36.4%) showed more anti-EBV IgM reactivation than PPMS (0%, $p < 0.001$ for both comparisons) [77]. Serum samples collected prior to MS symptom onset were compared to age, sex, and ethnicity-matched controls from the USA's Department of Defense Serum Repository (DoDSR) for activity to EBV. An increased risk of RRMS was associated with a fourfold increase in anti-EBNA1 IgG serum antibody titers (RR: 2.3; 1.7–3.2) based on 122 cases and 234 controls. An increased risk of RRMS was also associated with a fourfold increase in anti-EBNA complex serum antibody titers (RR: 3.3; 2.3–4.7) based on 164 cases and 315 controls [78].

Based on the above-mentioned, it seems that it increases the risk of RRMS and SPMS but not PPMS. But in the other studies in McKay et al. [47] systematic review, no association was found between disease activation and progression. In this case–control study in Spain no significant difference was found between RRMS, SPMS, and healthy controls for anti-EBV EBNA IgG (no p value given) [50].

As in the last study mentioned above; Ingram et al., assessed Anti-EBNA-1 IgG by two methods of Bio-test and Liaison with independently high specificity and sensitivity and moderate agreement (ICC 0.67; 0.56–0.78) between them. The unreliable markers and phenotypic characteristics of disease include age at onset, disease duration, EDSS or MSSS. No convincing difference was demonstrated in serum levels of anti-EBNA-1 IgG in MS subgroups [PPMS, stable RRMS and active RRMS (Bio-test $p = 0.35$, Liaison $p = 0.25$)] [80]. In the study by Garcia-Montojo et al., on patients who received IFN-beta 1b for 2 years no association was found between EBV and clinical parameters of MS including response to treatment, progression in EDSS score, relapse rate and progression of MS to SPMS (for all parameters $p > 0.05$) [52].

Chlamydia pneumoniae

It is postulated that neural system cells may be sensitive to *C. pneumonia* [81] which can play a role in the pathophysiology of MS [82]. An association was found between *C. pneumonia* IgA titer and cerebral atherosclerosis which can cause ischemic stroke [18, 19] through infecting vascular endothelium. This pathogen can cause an alteration in the junctional complex proteins and also cause fenestrating

vasculitis. Peripheral blood mononuclear cells (PBMCs) are infectious elementary bodies for dissemination of this infection in CNS vascular system. Rindfleisch for the first time in 1863 suggested the vascular inflammation in venous system as a pathogenic process preceding neural damage [83]. Infected migratory macrophages might directly enter the CNS in response to inflammation caused by an infectious trigger and/or an autoimmune process [84]. *C. pneumoniae* induces the immune system almost mediated by some stress response proteins including Hsp 60 and 90. The results of studies are in contrast and cannot reach a mutual consent on the possible role of *C. pneumoniae* in MS activation and progression [30].

A serum analysis has been conducted by Aghaei et al. in 2011 in Iran on 85 MS patients (69 RRMS, 16 SPMS) and 50 controls with no significant difference in the serum *C. pneumoniae* IgM and also IgG level ($p = 0.66$, $p = 0.8$) between groups. No correlation was found between *C. pneumoniae* IgG and IgM and EDSS, the number of attacks and disease duration. Also CP-IgG in RRMS and SPMS was identical ($p = 0.8$). It not only is not considered as an associated factor with MS, but also is not related to disease progression or patterns including relapsing or progressive forms [82].

In another study Contini et al. [85] who analyzed the CSF of MS patients, nested PCR for *C. pneumoniae* was not different between MS patients, other inflammatory neurological disorders (OIND) and non-inflammatory neurological disorder (NIND) patients, ($p > 0.05$). But it was significantly more frequent in relapsing–remitting (RR) than secondary progressive (SP) ($p < 0.001$) and primary progressive (PP) MS ($p < 0.05$). It was more frequent in clinically active rather than clinically stable MS ($p < 0.05$) and in MRI active than in MRI inactive MS ($p < 0.001$). The gene expression analysis of *C. pneumonia* in CSF showed that Major Outer Membrane Protein (MOMP) was significantly more frequent in relapsing MS patients ($p < 0.05$) and PCR positivity for MOMP and 16S rRNA genes were more frequent clinically and radiologically active MS patients ($p < 0.05$). Also CSF PCR positivity for Hsp-70 gene was observed in only three active RR MS patients. CSF CP-specific DNA detection can occur in clinical and MRI active RR form and not in progressive forms. This study did not support a major role for *C. pneumoniae* in the pathogenesis of MS but suggested the possible involvement of *C. pneumoniae* in relapsing remitting type of MS and not in progressive types [85].

In a systematic review, McKay et al. and Aghaei et al. [82] concluded that *C. pneumoniae* is not consistently associated with a specific disease course by explaining four case–control studies: in a Spanish study no significant difference was found between RRMS, SPMS, and healthy controls for anti-*C. pneumonia* antibodies [50]. Using data from the prospective Nurse's Health Studies (NHS and NHSII), prior infection with *C. pneumonia* was not associated with a significantly increased risk of RRMS (1.7; 0.9–3.2). However, when progressive MS patients (SPMS or PPMS = 32) were included, MS risk was associated with *C. pneumonia* seropositivity (OR: 1.7, 1.1–2.7) [86].The same research group studied US Army personnel and found no association between *C. pneumonia* and the risk of RRMS (OR: 0.8; 0.4–1.7) or PPMS (OR: 1.0; 0.3–3.7) compared to healthy controls [87]. In an Austrian study *C. pneumonia* seropositivity was not statistically significant different between the MS groups (RRMS 59.1%, SPMS 46.4%, OIND 64.1%, and ONIND (75.0%) [88].

In contrast to many studies and micro-organisms, a statistical elevation of serology against *C. pneumonia* [86] and specific intrathecal IgG [89] is found in progressive but not in relapsing–remitting disease.

Human polyomavirus (JCV)

The results of Agostini et al. failed to determine the association between JCV and MS type according to its pattern of progression and activity. They assessed JCV by PCR in urine (by frequent analysis) and CSF DNA of 94 MS patients with different types of MS including relapsing remitting, relapsing progressive, and chronic progressive, and 77 control subjects. Positive urine test (overall) was similar in frequency (near 50%) and genotype (type 1 was more frequent than type 2A/C, 2B, 3, 4, 5 and 6) compared to the control individuals. Analysis of 84 CSF samples failed to provide evidence for viral involvement in the MS brain (all were negative) [90].

Human T-cell lymphotropic virus (HTLV1)

Limited studies searched about HTLV1 and failed to provide any strong evidence of association between this virus and MS disease or its MS type, activity or progression.

Rasmussen et al. assessed the frequency of four HTLV1-related endogenous sequences, (HRES-1) in MS. The haplotype distributions in MS subgroup of relapsing–remitting MS was the same as primary progressive MS [chi-squared value ($T_1 = 5.89$, $p = 0.12$)] with higher frequency of haplotype 1 (43%) in both groups. This study provided no evidence for the association between a haplotype of HRES-1 and MS activity or progression [91].

Torque teno virus (TTV)

Torque teno virus is a common virus that generally affects young children but is not currently known to be related to any specific disease symptomology [92]. It has been shown to increase the production of pro-inflammatory cytokines and thus was investigated for its role in MS [93]. Serum and

cerebrospinal fluid (CSF) samples were obtained from 104 RRMS, 31 PPMS, and 93 healthy controls from Italy. Levels of TTV viremia were significantly lower in RRMS patients compared to healthy controls (4.6 versus 5.4 log10 copies/mL, $p < 0.0001$). PPMS patients had significantly higher levels than the RRMS patients (5.8 versus 4.6 log10 copies/mL, $p = 0.0008$) [94].

Conclusion

Although some infection microorganism are proposed to have role in MS pathogenesis, a few number of agents such as HHV6, *C. pneumoniae* and TTV have been determined as cofactors to make MS a progressive type. Also it should be considered that these findings do not necessarily rule out a role of other pathogens in MS progression but may represent population differences or different sensitivity of the technique used in the detection of micro-organisms' markers in the study. Also the pathophysiology of MS progression is not only infection dependent. Different factors including genetic and other environmental factors and their interaction play roles in disease progression by producing different products or toxins or by different gene expressions.

Suggestions

- For better clarity in this systematic review, we need a meta-analysis.
- We would suggest not to use the sample size of the study as an exclusion criterion, especially when focusing on progressive MS. Because most of the large-size studies focus on RR-MS and therefore, smaller studies with progressive MS patients could be missed.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors.

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