# New insights on the link between Epstein-Barr virus infection and cognitive decline in neurodegenerative diseases (Review)

THOMAS GABRIEL SCHREINER[1,2], CONSTANTIN ROMANESCU[3], OLIVER DANIEL SCHREINER[1,4] and FARAI NHAMBASORA[5]

[1]Faculty of Medicine, University of Medicine and Pharmacy 'Gr. T. Popa', 700115 Iasi, Romania; [2]Department of Electrical Measurements and Materials, Faculty of Electrical Engineering and Information Technology, Gheorghe Asachi Technical University of Iasi, 700050 Iasi, Romania; [3]Clinical Section IV, 'St. Parascheva' Infectious Disease Hospital, 700116 Iasi, Romania; [4]Department of Medical Oncology, Regional Institute of Oncology, 700483 Iasi, Romania; [5]Department of Obstetrics and Gynecology, St. Luke's Hospital, R95 FY71 Kilkenny, Republic of Ireland

Received February 16, 2024; Accepted August 16, 2024

DOI: 10.3892/etm.2024.12702

**Abstract.** Cognitive decline is a frequent complaint in healthy controls and neurological patients, regardless of the underlying pathology. Whilst cognitive impairment can be easily diagnosed in the more advanced stages of neurodegenerative diseases, early detection can be challenging. This is mainly the consequence of the incomplete understanding of the underlying pathophysiological mechanisms. In addition, currently available neurological treatments do not specifically target cognitive decline, since other motor and non-motor symptoms, such as bradykinesia, tremor, autonomic disturbances and depression, are of greater relevance from a therapeutic perspective. In this context, prospective studies must address a number of issues, including the risk factors associated with cognitive deficits in neurodegenerative diseases. The present review aims to offer a novel perspective on the association between Epstein-Barr virus infection and cognitive decline found in patients with neurodegenerative disorders. Specifically, relevant epidemiological studies and clinical trials explaining this connection were reviewed, focusing on the most frequent neurodegenerative disorders. They are namely Alzheimer's disease, Parkinson's disease and multiple sclerosis. Despite their limitations, possible underlying pathophysiological mechanisms that explain the impact of Epstein-Barr virus infection on cognitive decline are expected to offer novel study directions on this clinically relevant topic.

*Correspondence to:* Dr Thomas Gabriel Schreiner or Dr Oliver Daniel Schreiner, Faculty of Medicine, University of Medicine and Pharmacy 'Gr. T. Popa', 16 Universității Street, 700115 Iasi, Romania
E-mail: schreiner.thomasgabriel@yahoo.com
E-mail: schreiner.oliver-daniel@email.umfiasi.ro

*Key words:* Epstein-Barr virus, cognitive decline, multiple sclerosis, Alzheimer's disease, Parkinson's disease, neurodegeneration, neurodegenerative disorders

**Contents**



## 1. Introduction

Cognition refers to the mental process of knowledge acquirement using thought, senses and experience (1). It is a broad term that includes all facets of intellectual actions and functions, including perception, attention, imagination, memory, problem-solving, decision-making, comprehension and language production (2). Cognitive decline is defined as a partial or total loss of the aforementioned mental functions, which has been a highly discussed clinical topic in neurologically relevant patients over the past decade (3). Whilst initially considered a hallmark of advanced stages of neurological disorders, cognitive impairment was demonstrated to be present even during the early stages of several neurological diseases, including multiple sclerosis and stroke, as an important symptom (4-6).

Cognitive decline can have a significant negative impact on personal, populational and socioeconomic levels. In addition, cognitive impairment can negatively impact the quality of life of patients and their relatives, because patients with cognitive impairments tend to have low adherence to treatment and self-care, which then accelerates the deterioration of their underlying disorder (7). Furthermore, despite not being directly associated with the severity of other functional limitations (motor deficits, walking problems) secondary to neurological disorders, cognitive deterioration has been demonstrated to influence the onset and progression of different neurological symptoms, such as depression (8), anxiety (9) and motor deficits (10). A number of studies have previously addressed the

topic of depression in association with mental impairment in the context of neurodegenerative disorders (8), while the association between cognitive decline and anxiety (9), or motor limitations (10), have also been extensively discussed.

At the population level, figures characterizing cognitive decline incidence and prevalence vary according to the study population. A previous systematic review summarized data from 80 studies and showed that cognitive impairment prevalence ranged between 5.1 and 41.0%, with a median of 19.0% in individuals aged >50 years worldwide (11). There were also slight differences among the age groups of the included subjects and the world regions in which data were collected. The number of available studies regarding the annual incidence of cognitive impairment is much lower compared to the research conducted on its prevalence. According to the 11 studies included in another previous systematic review, cognitive decline incidence ranged between 22 and 215 per 1,000 person-years, with a median of 56.5 per 1,000 person-years worldwide (11). Comparing the different age groups and regions, age was the only parameter to be statistically significantly correlated with the cognitive decline.

An enormous financial burden is also associated with cognitive impairment. The financial repercussions of cognitive deficits are currently the subject of intense research, which aims to address both the direct and indirect expenses, in addition to their effects on the healthcare system and society (11,12). All forms of cognitive damage, ranging from mild cognitive impairment (MCI) to severe dementia, have been carefully examined from an economic perspective. Data from 2020 reported by the World Health Organization and Alzheimer's Association estimated that Alzheimer's disease (AD) alone will pose a financial burden of >$300 billion per year in the United States, >€230 billion in Europe and >$950 billion globally (12). Furthermore, these costs are expected to rise within the next few decades because of the rising frequency of AD due to general population aging and rising per patient expenditures (12). However, MCI, whilst itself not debilitating, carries a significant risk of progressing onto AD, which has far-reaching consequences for the healthcare system, caregivers and society overall. Like other diseases that can cause dementia, MCI can incur direct expenses due to the increased frequency of medical examinations, diagnostic testing and symptomatic treatment, whilst also incurring indirect costs from caregiver stress and productivity loss (13).

Parkinson's disease (PD) remains to be the second most frequent neurodegenerative disease, posing a significant epidemiological burden. According to the latest figures from 2021, ≤2 per 1,000 individuals are affected at any time, with prevalence increasing with age and totalling 1% in individuals aged >60 years worldwide (14). By contrast, multiple sclerosis (MS) is the most common inflammatory demyelinating disease in young adults, with an incidence of 35.9 per 100,000.0 individuals, with a worldwide total of 2.8 million individuals according to the latest estimates from 2020 (15).

Epstein-Barr virus (EBV), also known as the Human Herpesvirus 4, is a *Gammaherpervirus* that belongs to a double-stranded DNA member of the *Lymphocryptovirus* genus and was first isolated and described in 1964 by Epstein, Barr and Achong (16). EBV DNA encodes >85 genes and is enclosed in a protein capsid of 120-180 nm in diameter. It presents glycoproteins on its external surface that are important for the entrance and infection of host cells (17). Epithelial and immune B cells are the primary targets for EBV, with the virus entering B cells through contact with the CD21 protein of the host cell or through a mechanism involving HLA class II molecules (18). When symptomatic, EBV leads to systemic infection symptomatology, including headache, fever, sore throat, splenomegaly and lymphadenopathy. This is the result of the EBV entrance in the B cells and epithelial cells in the oropharynx, which is facilitated by the different EBV's glycoproteins, such as glycoprotein gp350/220 and glycoprotein gp42 (19). Another possibility of EBV's pathogenicity is the induction of a persistent cell infection (latency state), in which no viral activity can be detected. EBV can establish three different types of latency (type I latency-expression of the viral EBNA1, EBERS and BART genes; type II latency-expression of additional viral genes; type III latency-activation of the C promoter) according to host B cell behaviour and characteristics for acute or chronic pathologies (19). According to recent literature, EBV has been frequently associated with several pathological conditions, including AD, MS, or PD. EBV's capacity to replicate in the central nervous system (CNS) and crosstalk with structures of the blood-brain barrier can potentially explain their association with neurological disorders characterized by neuroinflammation and neural damage (20).

With accumulating evidence that EBV can serve a role in the onset and evolution of cognitive decline associated with several neurodegenerative disorders (NDDs), the present review aims to offer novel insights into this potential link. Specifically, observational studies that explained the EBV-cognitive impairment association, focusing on AD, PD, PD dementia and MS, are discussed. Subsequently, possible pathophysiological mechanisms are presented in detail, where the role of EBV in cognitive degradation may also offer novel insights into the elusive mechanisms of neurodegeneration. In addition, novel research directions with promising perspectives are suggested based on the current knowledge and missing data. Compared with previous reviews, such as that by Zhang *et al* (20), which focused on the pathogenesis and the potential molecular targets of neurodegenerative diseases, the present review highlights the most relevant aspects of the EBV-neurodegeneration association, in addition to its impact on future diagnostic and therapeutic practice. There are differences in the scope of the two reviews in the methodology of article inclusion, updated data to 2024 and future research suggestions.

## 2. Materials and methods

Given the relatively limited data on the impact of EBV in the onset and amplification of cognitive deficit related to NDDs, the existing literature was considered in the form of a scoping review to create a broad picture of the topic, with subsequent insights into the potential underlying pathophysiological mechanisms. A systematic search was conducted in the most relevant online databases, namely PubMed/Medline (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/) and ScienceDirect (https://www.sciencedirect.com/), for the following three different NDDs considered: AD, PD and MS. Different combinations of the following

Table I. Literature search strategy and final papers yielded.

| A, Search strategy | |
|---|---|
| Search | Key words |
| #1 | 'Epstein Barr virus' OR 'EBV' |
| #2 | 'Alzheimer's disease' OR 'Alzheimer's dementia' OR 'Dementia' |
| #3 | 'Parkinson's disease' OR 'Parkinson's disease dementia' |
| #4 | 'Multiple sclerosis' |
| #5 | #1 and #2 |
| #6 | #1 and #3 |
| #7 | #1 and #4 |
| **B, Final results** | |
| Identified records | PubMed, N=980; Google Scholar, N=5,650; ScienceDirect, N=3,036 |
| Excluded records (duplicates, not eligible) | 9,651 |
| Included records in the review | 15 |

terms were used in the search: 'Epstein Barr virus', 'EBV', 'Alzheimer's disease', 'Alzheimer's dementia', 'Parkinson's disease', 'Parkinson's disease dementia', 'Multiple sclerosis', 'Neurodegenerative disease', 'Neurodegenerative disorder', 'Neurodegeneration', 'Cognitive decline' and 'Dementia'.

The inclusion criteria were comprised of original, peer-reviewed English language studies conducted on patients, *in silico*, *in vitro* and *in vivo* models, published between 2000 and the present. In addition, narrative and systematic reviews, short communications and editorials were excluded. After the screening process, 15 relevant papers were selected for the current scoping review. The search strategy and the final results are outlined in Table I.

## 3. EBV infection - AD association

Despite being described >100 years ago (21), AD remains to be incompletely understood today, with its aetiology and causative pathophysiological mechanism yet to be fully determined (22). A considerable number of studies have been conducted, with a number of diverging hypotheses being proposed. The role of the cholinergic deficit (23), chronic neuroinflammation (24), the negative influence of pathological amyloid β accumulation (25) and the effect of other misfolded proteins, such as Tau protein (26), have all been intensely debated. Additionally, the role of viral pathogens in the onset and development of AD-related neurodegeneration is becoming an increasingly plausible theory, according to the multiple-hit hypothesis (27). EBV-triggered infection is one of the possible viral risk factors for AD, considering also the results from the literature that suggest a possible association between the two phenomena (28-32). Table II summarizes the studies included and analysed within the present review.

Carbone *et al* (28) was among the first to analyse the possible EBV-AD association. Conducted on a group of 93 patients with AD and a control group of 164 healthy individuals, its main aim was to assess an EBV-AD relation by detecting the presence of EBV in the peripheral blood leukocytes using quantitative PCR. EBV DNA positivity and a significant increase in IgG-specific levels were observed in the peripheral blood of patients with AD included in the study, opening the pathway for similar studies in the following years. In this context, Shim *et al* (29) then analysed plasma levels of IgG specific for EBV comparatively in healthy and amnestic mild cognitive impairment (aMCI) individuals, with a clear association found between EBV and cognitive decline based on the CERAD score and Clinical Dementia Rating scale. Furthermore, this previous study then proposed the potential biomarker role of anti-EBV antibodies for evaluating the risk of developing aMCI and associated cognitive impairment (29).

The EBV-AD association was demonstrated more recently in larger cohorts, such as a previous Mendelian randomisation study by Huang *et al* (30). With data for stage 1 of the International Genomics of Alzheimer's Project, including 63,926 individuals (21,982 AD cases and 41,944 cognitively normal control individuals), a significant association between mononucleosis, an EBV-triggered pathology, and an increased risk of AD was demonstrated (30). Additionally, this previous study showed a link [odds ratio (95% CI) = 1.392 (1.061, 1.826), P=0.017] between mononucleosis and a positive family history of AD (30).

Considering the previously presented epidemiological associations, in recent years there has been an increased focus on deepening the understanding of the mechanisms of the EBV-AD association. Despite not being completely known, the generally accepted hypothesis is that the latent EBV infection can constantly activate the host immune system, leading to a chronic inflammatory state, which is a characteristic feature of AD and other neurodegenerative disorders (such as PD and amyotrophic lateral sclerosis) characterised by cognitive impairment (31). Tiwari *et al* (32) previously brought novel insights into the mechanisms linking EBV infection to amyloid β pathological aggregation, one of the significant hallmarks of AD. After using an *in silico*

Table II. Studies reporting a possible role of EBV in the pathogenesis of AD.

| First author, year | Aim of the study | Study design/materials and methods | Results/main conclusion | (Refs.) |
|---|---|---|---|---|
| Sun *et al*, 2022 | To determine the potential association between EBV infection and AD | Bioinformatics analysis of 5,066 differentially expressed genes examined through weighted gene co-expression network analysis, then clustered in modules; KEGG pathway enrichment analysis of the turquoise module | EBV infection associated with the KEGG pathways of the module turquoise, potential link with AD | (38) |
| Tiwari *et al*, 2021 | To determine the mechanistic details of EBV in AD | *In silico* study using online algorithms NetChop ver. 3.1 and Pcleavage; *in vitro* analysis using Congo red, Thioflavin-S assay and Raman spectroscopy | Increased tendency for aggregates forming from a peptide derived from EBV glycoprotein M; gained a deeper understanding of the mechanisms involved in EBV-derived peptides influencing amyloid-β aggregation cascade | (32) |
| Huang *et al*, 2021 | To evaluate the causal relationship between EBV and AD | Two-sample Mendelian randomization analysis; GWAS summary statistics from the International Genomics of Alzheimer's Project | A significant association between mononucleosis (caused by EBV) and the risk of AD; a significant association between mononucleosis and family history of AD | (30) |
| Shim *et al*, 2017 | To identify biomarkers for the development of aMCI | Analysis of plasma IgG levels against EBV in aMCI and normal cognitive subjects | EBV infection or its related host immune response is linked to cognitive decline; anti-EBV antibody level may be a potential biomarker for aMCI development risk | (29) |
| Carbone *et al*, 2014 | To detect the presence of EBV in the peripheral blood of patients with AD | Quantitative PCR and genotyping of peripheral blood leukocyte samples | Significantly increased IgG-specific levels for EBV and EBV DNA positivity in peripheral blood leukocyte samples in patients with AD | (28) |

AD, Alzheimer's disease; EBV, Epstein-Barr virus; aMCI, amnestic mild cognitive impairment; GWAS, genome-wide association studies.

model based on the online algorithms NetChop ver. 3.1 (https://services.healthtech.dtu.dk/services/NetChop-3.1/) and Pcleavage (http://www.imtech.res.in/raghava/pcleavage/), an *in vitro* analysis using Congo red, Thioflavin-S assay and Raman spectroscopy was then performed. Based on these models, an increased tendency for aggregates consisting of a peptide derived from the EBV glycoprotein M form was found, suggesting the importance of EBV-derived peptides in the modulation of the amyloid-β aggregation cascade (32). In addition, EBV has been reported to aggravate inflammation by infecting monocytes and mononuclear cells, which should be considered when studying neurodegenerative disorders (33). EBV was demonstrated to alter the immune system by triggering a cytotoxic $CD8^+$ T cell-dependent immune pathological response in AD, leading to pathological autoimmune responses that may favour neurodegeneration, according to data obtained from a cohort of 164 subjects with AD (34).

EBV has also been documented to modulate the cell cycle. As an oncogenic virus, EBV can alter the cell cycle directly at various stages, by interfering with protein-protein interaction and protein redistribution (35). Neurons affected by AD typically display a dysregulation of the physiological cell cycle, frequently resulting in exit from quiescence and re-entry into the cell cycle, potentially predisposing them to neurodegeneration. Since mature neurons do not re-enter the cell cycle under physiological conditions, this form of aberrant re-entry can cause malfunctions in DNA replication and chromosome distribution, axon disruptions and hindered communication, by inhibiting insulin signalling and inducing mTORC1 activation, finally resulting in neuronal cell death (36). Specifically, markers of mitotic dysfunction, such as hyperactivation of Ras-mediated signalling pathways and decreased expression of cell cycle proteins (such as cyclin D, CDK-4 and premature chromosome separation), have been observed in AD-affected neurons (37). EBV infection has emerged as a potential contributor to neurodegeneration in AD, with evidence suggesting that adaptive immune changes (including the increased presence of specific T cells that target EBV) and mitogenic signalling induced by EBV (by triggering cellular growth signals) serve a role in disease progression (37). These findings underscore

the importance of understanding the complex interactions between cell cycle dysregulation and viral infections that can lead to neurodegeneration. EBV can also indirectly regulate the cell cycle by indirectly expressing latent genes, grace to the molecular mimicry (structural similarity between different antigens) and by favouring encouraging conditions for cell cycle progression (35). However, it is likely that other still to be determined molecular pathways are also impacted by EBV during subsequent cognitive decline. Complex bioinformatic analyses and artificial intelligence-based technologies may prove valuable as tools for such future studies (38).

The impact of the genetic background on the EBV-AD association should not be neglected. Besides apolipoprotein E genetic mutations, other genetically regulated factors, such as nectin-2 (NC-2) (39), complement receptor-1 (CR-l) (40) and CD33 (41), may produce a genetic profile that can influence an individual's susceptibility to aging-related EBV infection in the brain, subsequently leading to inflammation, amyloid buildup and neuronal death, which is also encountered in AD. NC-2 serves as a mediating factor for human herpesvirus 6 (HHV-6) entry, the knockout of which has been previously reported to associate with significantly decreased HHV-6 activity (42). Although this previous study (42) is not directly associated with EBV, EBV and HHV-6 are similar viruses, both being members of the Herpesviridae family (42), suggesting that NC-2 may serve a key role in EBV's cerebral infection. CR-1, particularly the rs1408077 variant, has been reported to negatively regulate the complement cascade and inhibit both the classic and alternative pathways of the immune system (40). Specifically, the rs1408077 variant of CR-1 was demonstrated to be an AD risk allele in healthy, middle-aged adults (43). By contrast, CD33 regulates microglial activation in physiological conditions. In AD, CD33 was previously found to be overexpressed, resulting in pathological conversion to pro-inflammatory microglia, which is associated with amyloid β and Tau protein hyperaccumulation (44).

## 4. EBV infection - PD association

As the second-most common neurodegenerative disorder and the most common movement disorder in adults, PD has a continuously increasing prevalence, affecting >1% of individuals aged >65 years in 2021, which is expected to double in the following decades (45). The classical form of PD can be characterized by motor and non-motor signs, with a significant proportion (>75%) of patients with PD having no cognitive decline despite advanced stages of the disorder (46). However, cognitive impairment can be a common finding in patients with PD and involves heterogeneous deficits, from attention to visuospatial and memory (47). Dementia associated with PD is an umbrella term that remains to be an intensely discussed topic, with current opinions unable to clearly differentiate between PD dementia and dementia with Lewy bodies (48). In the present review, the focus remains on cognitive decline in PD, and the unequivocal distinction among different PD-related diagnoses is beyond the scope of the present review.

To the best of our knowledge, available studies on the potential EBV-PD-cognitive decline association remain scarce and old. A previous study by Woulfe *et al* (49) was relevant for elucidating the pathophysiological mechanisms of PD onset and evolution, with the infectious hypothesis (including the role of EBV) also addressed. Using ELISA and Western blotting techniques, Woulfe *et al* (49) demonstrated a cross-reactive mechanism between latent EBV infection and α-synuclein, one of the major proteins that pathologically accumulate in the brain of patients with PD. Subsequently, Bu *et al* (50) conducted a study that sustained the role of EBV in PD pathogenesis by comparatively measuring the EBV-antibody titres in the serum of patients with PD and normal controls (healthy individuals) using ELISA, detecting an increased titre in patients with PD. Regarding the underlying mechanisms explaining the EBV-cognitive decline in patients with PD, known molecular pathways are even more elusive compared with AD. Despite a thorough search, no study comparing the severity of PD with and without EBV infection could be found in the present review. Genetics may yet serve a role in the EBV-PD, particularly in the early-onset PD forms. Mutations in the *PARK7*, *LRRK2*, *SNCA*, *PINK1* or *PRKN* genes have been documented in the familial forms of PD (51). However, to the best of our knowledge, genes associated explicitly with the EBV-PD connection remain to be determined, since no studies focusing on viral infections in young patients with genetic PD have been performed. Based on the scarce existing data (summarized in Table III), it can be assumed that EBV is one of the pathogens that can sustain the infectious theory of PD.

## 5. EBV infection - MS association

MS is the most common inflammatory disease of the CNS (35.9 per 100,000 population). It has recorded a significant increase in incidence (2.1 per 100,000 persons/year) and prevalence (over 2.8 million MS patients) worldwide in recent years (52). In addition, MS remains to be the leading cause of disability among young individuals, having a significant socio-economic impact at individual and healthcare system levels (53).

From the clinical point of view, the neurological symptoms and signs of MS are highly diverse and can include motor deficits, visual symptoms, sensory problems, bowel and bladder dysfunction and cognitive impairment, even at the early stages of the disease (54). The clinical progression of MS is also variable, with different evolutions being possible: Relapsing-remitting MS, primary progressive MS and secondary progressive MS (55). Additionally, clinically isolated syndrome and radiologically isolated syndrome concepts have been garnering attention over the past decade (56).

Despite the numerous studies performed, the exact aetiology of MS remains unknown. However, several genetic and environmental factors have been proposed to be potential triggers for the neuroinflammatory changes that occur during MS (57). Among them, viral pathogenesis, mainly EBV infection, remains a constant (58). Table IV summarizes the most relevant studies that explored this association from the epidemiological, immunological and virological points of view.

A clear epidemiological association between EBV infection and an increased risk of MS has only been recently demonstrated. This was possible based on a previous study on a large cohort of young US military adults by Bjornevik *et al* (59), highlighting the leading role of EBV infection in the onset of MS. In this previous epidemiological study (59), serum samples from 955 young adults with MS active in the US military were

Table III. Studies reporting a possible role of EBV in the pathogenesis of PD and PD dementia.

| First author, year | Aim of the study | Study design/materials and methods | Results/main conclusion | (Refs.) |
|---|---|---|---|---|
| Bu *et al*, 2015 | To examine the association between EBV infection and PD | ELISA measured EBV-antibody titres in the serum of 131 patients with PD and 141 normal controls | The infectious burden of EBV, along with other common pathogens (*Borrelia burgdorferi*, *Helicobacter pylori*), was associated with PD | (50) |
| Woulfe *et al*, 2000 | To elucidate infectious or autoimmune mechanisms in PD | Using antibodies generated against latent membrane protein 1 of EBV, ELISA and western blotting techniques were used to assess cross-reactivity with α-synuclein | Latent EBV infection can trigger autoantibodies that cross-react with α-synuclein | (49) |

EBV, Epstein-Barr virus; PD, Parkinson's disease.

analysed, showing a 32-fold risk of MS after EBV infection, based on the increased serum levels of neurofilament light chain only after EBV seroconversion detected using the virome-wide screening technique. This finding was explained by ruling out the association of confounding factors, such as homozygosity for the HLA-DR15 allele or environmental factors, whilst excluding the possibility of false-positive seroconversion results (59). However, results from several other studies remain important when considering the underlying mechanisms that may explain the EBV-MS association. In this sense, another previous study reported the importance of the abnormal immune response triggered by EBV in patients with MS, with $CD8^+$ and $CD4^+$ serving significant roles (60). These T cell subtypes serve major roles in both acute MS relapses and chronic neurodegenerative phases, promoting inflammatory and cytotoxic attacks. Furthermore, naïve B cells can be effectively reprogrammed by EBV infection to follow a developmental pathway that replicates the germinal centre response, clonal growth and differentiation into a memory B cell phenotype that sustain long-term pathological immune response (60). EBV infection may also trigger an abnormal autoreactive peptide presentation and promote the development of inflammatory B cells, by increasing their binding specificity and proinflammatory gene (interleukins, tumour necrosis factor α) programming (61). All these aforementioned events sustain the exacerbated $CD20^+$ B cell population, which was demonstrated to play a significant role in sustaining MS-related neurodegeneration.

Additionally, with accumulating evidence favouring the role of B cells in MS pathogenesis, recent studies have also provided insights into the impact of the EBV-B cell crosstalk in MS onset and evolution (62-64). Long-lasting latent EBV infection may enhance the formation of anti-Epstein-Barr nuclear antigen 1 IgG-secreting B cells through molecular mimicry, with the exact viral proteins involved in this autoimmune process barely discovered (62). There have also been attempts to understand the role of genetic factors in the occurrence of MS. Previous genome-wide association studies that investigated the transcriptomes of EBV-infected B-cells showed commonly dysregulated genes (EBNA2, TRAF3) that indicate a strong link between EBV and MS mainly via the CD40 pathway (59,63).

While the precise mechanisms explaining cognitive deficit in patients with MS have remained elusive, to the best of our current knowledge is relatively more advanced compared with other neurodegenerative pathologies, such as AD or PD. MS-related cognitive impairment is multifactorial, since both CNS lesions and alterations in the immune system with subclinical impact can serve relevant roles. Previous studies were conducted to screen for factors associated with cognitive decline in patients with MS, with the most pertinent being a higher Expanded Disability Status Scale score (64), MS onset and duration (65), the number of MRI-detected brain lesions (66), atrophy of specific CNS regions (such as the hippocampus) (67) and the impact of other MS-related symptoms (such as fatigue and depression) (68). In addition, EBV has been demonstrated to modulate the immune system, sustaining the clinical and imagistic evolution (emergence of new demyelinating lesions) of MS, which indicates a highly active disease form with an increased number of relapses and brain lesions (69). The role of latent EBV infection has also been discussed in the context of depression and fatigue, even in healthy individuals (70). In this regard, among the other NDDs, MS can be differentiated by the increasing number of studies that attest to an association among pathology, cognitive deficit and EBV infection (71-73). However, the current knowledge on MS is relatively more advanced compared to AD or PD when referring to the underpinning pathophysiological mechanisms, mainly based on the T and B cell dysregulations likely triggered by EBV infectious-immune modalities. This hypothesis is also indirectly sustained by the therapeutic impact of anti-CD20 therapies in MS patients, which seem to be effective mainly due to the removal of circulating EBV-infected memory B-cells that drive CNS inflammation, mediating more of an anti-viral than an immuno-modulatory effect (74). CD20 is a B lymphocyte cell-surface non-glycosylated protein that acts as a natural ligand for the major histocompatibility complex class II, B-cell receptor and CD40. CD20 is also expressed by the majority of B cells, including late pre-B lymphocytes, and is a key factor in the development and differentiation of B-cells

Table IV. Studies reporting a possible role of EBV in the pathogenesis of MS.

| First author, year | Aim of the study | Study design/materials and methods | Results/main conclusion | (Refs.) |
|---|---|---|---|---|
| Bjornevik *et al*, 2022 | To assess the causality between EBV infection and MS onset | Epidemiological study using serum samples from 955 young adults (79% under 26 years) with MS, active in the US military | EBV is the leading cause of MS (after ruling out the association of confounding factors and excluding the possibility of false-positive seroconversion results) | (59) |
| Lanz *et al*, 2022 | To demonstrate high-affinity molecular mimicry between the EBV transcription factor EBNA1 and the central nervous system protein glial cell adhesion molecule | Single-cell sequencing of the paired-chain B cell repertoire of MS blood and CSF and protein microarray-based testing of recombinantly expressed CSF-derived antibodies against MS-associated viruses | Molecular mimicry between EBNA1 and CNS antigens represents a mechanistic link for the association between EBV and MS | (71) |
| van Langelaar *et al*, 2021 | To determine the association of B-cell EBV DNA load with CXCR3$^+$ memory B-cell development | EBV DNA load was determined using a multiplex RT-qPCR assay in peripheral blood mononuclear cells from patients with MS; quantification of anti-EBNA-1 IgG antibodies in memory B-cells | EBV DNA load positively correlated with the frequency of CXCR3$^+$ class-switched B cells; latent EBV infection corresponded to enhanced *in vitro* formation of anti-EBNA1 IgG-secreting plasma cells under GC-like conditions | (62) |
| Afrasiabi *et al*, 2019 | To understand the genetics behind the EBV-MS association | Computational GWAS; Investigation of the B cell transcriptomes and EBV-infected B cells at latency III | In total, 47 gene pairs were over-represented in dysregulated B cells and B cell transcriptomes, being also target loci of the EBV transcription factor EBNA2 | (63) |
| Harley *et al*, 2018 | To facilitate the understanding of the genetics behind the EBV-MS association | Computational GWAS | EBV transcription factor EBNA2 and its associated human transcription factors occupy a significant fraction of autoimmune risk loci; NF-κB is essential in the mechanisms that confer risk in MS; EBV-infected B cells are a possible site for EBNA2 pathological modulation at selected loci in MS | (72) |
| Pender *et al*, 2017 | To analyze the T-cell response to EBV in MS | Using flow cytometry and intracellular IFN-γ staining, measurement of T-cell responses to EBV-infected autologous lymphoblastoid cell lines and pools of human leukocyte antigen-class-I-restricted peptides from lytic EBV in 95 patients and 56 EBV-seropositive healthy subjects was performed | Decreased CD8$^+$ T-cell response to lytic EBV; increased CD8$^+$ T cells directed against EBV latent antigens but reduced cytokine polyfunctionality, T-cell exhaustion; expansion of EBV-specific CD4$^+$ and CD8$^+$ T-cell populations during attacks; anti-EBNA1 IgG titre correlated inversely with the EBV-specific CD8$^+$ T-cell frequency | (60) |
| Virtanen *et al*, 2014 | To investigate EBV-reactive oligoclonal bands and viral DNA in the intrathecal compartment in MS | Detection of reactive oligoclonal bands in the serum and CSF samples from 37 patients with MS and comparison with MRI aspects | EBV-reactive oligoclonal bands in patients with MS; MS patients with viral DNA in CSF had more contrast-enhancing lesions | (73) |

Table IV. Continued.

| First author, year | Aim of the study | Study design/materials and methods | Results/main conclusion | (Refs.) |
|---|---|---|---|---|
| Angelini *et al*, 2013 | To postulate that EBV infection serves a role in MS aetiopathogenesis | Assessment of the prevalence and magnitude of $CD8^+$ T-cell responses to latent and lytic EBV antigens in 113 relapsing-remitting patients with MS; detection of an association between the EBV-specific $CD8^+$ T cell response and disease activity (defined by clinical evaluation and MRI); post-mortem analysis | Changes in the immune control of EBV replication are associated with the active and inactive phases of MS; treatment of relapsing-remitting patients with MS with IFN-β and natalizumab is associated with marked changes in the $CD8^+$ T-cell response to viral antigens; detection of EBV BZLF1 in MS lesions post-mortem | (74) |

EBV, Epstein-Barr virus; EBNA, EBV nuclear antigen; MS, multiple sclerosis; CSF, cerebrospinal fluid; GWAS, genome-wide association study; CXCR3, C-X-C motif chemokine receptor 3; BZLF1, BamHI Z fragment leftward open reading frame 1; RT-qPCR, reverse transcription-quantitative PCR.

into plasma cells. It links to B-cell receptor signalling and facilitate microenvironmental interactions (75). In addition, CD20 is an important therapeutic target in MS, since $CD20^+$ B cells localized in the perivascular space have been shown to correlate with active lesions (more abundant in perivascular infiltrates in these MS patients) (76). $CD20^+$ B cells may also be among the memory B-cells involved in EBV-triggered CNS inflammation and neurodegeneration, explaining the beneficial impact of their elimination (77). Regarding AD and PD, the impact of $CD20^+$ B cells in the onset and evolution of neurodegeneration remains poorly understood. Therefore, no anti-CD20 treatment strategies are considered in the other neurodegenerative disorders.

## 6. Conclusions and future research directions

Cognitive decline is a constant complaint in patients suffering from NDDs, even in the early phases of the disease. AD, PD and MS remain to be the most frequent and intensely studied of the NDDs, with studies increasingly being focused on the negative influence of cognitive impairment on patient quality of life and its impact on a socioeconomic level. This is because cognitive problems have been ignored in favour of other motor and non-motor symptoms.

Despite the incomplete knowledge, several hypotheses have been intensely discussed when trying to explain the neurodegenerative process, with the viral infection hypothesis, such as the EBV infection, gaining traction. In the context of new results reported during the recent years, the present review summarized the most relevant data explaining the role of EBV infection in the cognitive decline encountered in NDDs. The most prolific domain was associated with the research conducted on patients with MS, with a multitude of epidemiological, virological and immunological studies being conducted over the last decade. Therefore, it can be hypothesised that the most important discoveries were made in the field of MS, since it was only recently that the primary role of EBV in MS onset in populations at risk has been demonstrated (59). Additionally, with a deeper understanding of the underlying immunopathological mechanisms found in MS, the influence of EBV on cognition may become more transparent. The current conclusion suggests a crosstalk between latent EBV infection and pathologically dysregulated immune cells (mainly T-cells and B-cells).

An abnormal long-term immune response secondary to the EBV infection also appears to be the key to understanding the impact of this virus on AD onset. Chronic neuroinflammation triggered by autoimmune dysfunctionality is, however, one piece of a more complex puzzle, where previous studies stressing the role of the direct influence of EBV on the amyloid β aggregation pathway, on the pathological misfolding of other relevant proteins (such as the Tau protein) or even on the progression of the cell cycle have been performed. With the quantity of unanswered questions and no curative treatment, future research must continue exploring the multiple processes disturbed by a prior EBV infection in the pathogenesis of AD.

Finally, whilst extensive research has been conducted in the field of AD and MS, only a number of studies on the role of EBV in PD pathogenesis have been performed. Therefore, extensive cohort epidemiological studies are mandatory in both patients with AD and those with PD to clarify a potential link to prior EBV infections. With one older study demonstrating the cross-reaction between EBV and α-synuclein, the interaction between EBV and other misfolded proteins encountered in PD would also be a valuable starting point for future experiments.

Despite the incompletely understood genetic and molecular pathways explaining the impact of EBV in NDDs, a promising future research direction is possibly the use of probiotics in the management of mental illnesses. Probiotics have the ability to modulate the gut microbiota and subsequent immune responses (78,79), becoming a potential adjunctive therapeutic strategy for managing NDDs. Since alterations in gut microbiota composition have been previously associated with EBV chronic infection and neurodegeneration, there is growing interest in the modulation of gut dysbiosis as a potential limiting factor for disease progression (80). In this context, probiotics may restore the gut microbial balance, reduce inflammation,

promote clearance of pathological protein aggregates and potentially mitigate neurodegeneration. Furthermore, the relationship between probiotics and EBV infection underscores the complex interplay between microbial, viral and host factors in NDD occurrence and evolution. Whilst further research is needed to elucidate the specific mechanisms and clinical implications of probiotics in NDDs, exploring the gut dysbiosis-EBV infection-neurodegeneration continuum offers promising avenues for therapeutic interventions aimed at preserving neurological function and slowing disease progression.

**Acknowledgements**

Not applicable.

**Funding**

No funding was received.

**Availability of data and materials**

Not applicable.

**Authors' contributions**

TGS, CR and ODS contributed equally to the study design and data collection (search and selection of studies). TGS, CR and FN contributed to data analysis and interpretation (final selection and inclusion of the studies). TGS, CR and ODS prepared the first draft of the manuscript, whilst TGS and FN reviewed, edited and wrote the final version of the draft. Data authentication is not applicable. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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