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Review

Alzheimer's disease as a viral disease: Revisiting the infectious hypothesis☆

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A B S T R A C T

Alzheimer's disease (AD) represents the most frequent type of dementia in elderly people. Two major forms of the disease exist: *sporadic* - the causes of which have not yet been fully understood - and *familial* - inherited within families from generation to generation, with a clear autosomal dominant transmission of mutations in Presenilin 1 (*PSEN1*), 2 (*PSEN2)* or Amyloid Precursors Protein (*APP)* genes. The main hallmark of AD consists of extracellular deposits of amyloid-beta (Aβ) peptide and intracellular deposits of the hyperphosphorylated form of the tau protein. An ever-growing body of research supports the viral infectious hypothesis of sporadic forms of AD. In particular, it has been shown that several herpes viruses (i.e., HHV-1, HHV-2, HHV-3 or varicella zoster virus, HHV-4 or Epstein Barr virus, HHV-5 or cytomegalovirus, HHV-6A and B, HHV-7), flaviviruses (i.e., Zika virus, Dengue fever virus, Japanese encephalitis virus) as well as Human Immunodeficiency Virus (HIV), hepatitis viruses (HAV, HBV, HCV, HDV, HEV), SARS-CoV2, Ljungan virus (LV), Influenza A virus and Borna disease virus, could increase the risk of AD. Here, we summarized and discussed these results. Based on these findings, significant issues for future studies are also put forward.

1. Introduction

Alzheimer's disease (AD) represents the most common form of dementia in elderly people (Breijyeh and Karaman, 2020). The main clinical manifestations include cognitive decline and several other symptoms involving perception, mood, personality, and basic functioning, known as Neuropsychiatric or Behavioral and Psychological Symptoms of Dementia (BPSD) (Altomari et al., 2022; Laganà et al., 2022). Based on the age of onset AD can be classified into Sporadic AD (sAD) - whose causes could be related to several hypotheses (Bruno et al., 2022) - and Familial AD (fAD) - inherited within families from generation to generation even with a clear autosomal dominant transmission of mutations in Presenilin 1 (*PSEN1*), Presenilin 2 (*PSEN2)* or Amyloid Precursors Protein (*APP)* genes (Abondio et al., 2021).

The main neuropathological hallmarks of this disease are represented by extracellular deposits of amyloid beta (Aβ) peptide (*amyloid plaques*) and intraneuronal aggregates of hyperphosphorylated and misfolded tau (*tangles or neurofibrillary aggregates*) (Serrano-Pozo et al., 2011; Skaper, 2012). Aβ peptides originate from the Amyloid Precursor Protein (APP) which is a membrane glycoprotein, characterized by a large N-terminal glycosylated domain on the extracellular side and a smaller intracellular C-terminal domain (Müller et al., 2017). Under physiological conditions APP is subject to two processing pathways, one non-amyloidogenic (α-secretase pathway) and one amyloidogenic (β-secretase pathway), the latter driving the production of Aβ peptides (Kojro and Fahrenholz, 2005). More specifically, β-site amyloid precursor protein cleaving enzyme 1 (BACE1) is the β-secretase enzyme that cleaves the transmembrane portion of APP and, together with

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γ-secretase, generates Aβ species that in AD form increasingly large and conformationally complex, soluble, regionally deposited brain aggregates (Hampel et al., 2021; Kojro and Fahrenholz, 2005; Nalivaeva and Turner, 2019; Zhao et al., 2020). In AD patients, amyloid plaques and neurofibrillary tangles are accompanied by diffuse cerebral atrophy, manly in the limbic structures, frontal, temporal and parietal lobes (Perl, 2010; Thompson and Vinters, 2012), astrogliosis (Jain et al., 2015), microgliosis (Hansen et al., 2018), neuronal and synaptic loss (DeTure and Dickson, 2019) and neuroinflammation (Heneka et al., 2015).

Several hypotheses have been formulated in the attempt to explain how these neuropathological features are causally related to each other, underpinning the pathogenesis of AD, such as the amyloid cascade hypothesis (Hardy and Higgins, 1992), the cholinergic hypothesis (e.g., Terry and Buccafusco, 2003), the inflammation hypothesis and the infectious hypothesis (Komaroff, 2020; Bruno et al., 2022). Among these, the infectious hypothesis (Naughton et al., 2020) has recently received considerable attention due to increasing evidence supporting the association between pathogens, the production and aggregation of Aβ peptide (Bruno et al., 2022; Ezzat et al., 2019; Robinson and Bishop, 2002), the documented increased risk of developing AD after contracting infections (Itzhaki et al., 2020) and the reported presence of viruses in the brains of AD patients.

A virus is an obligate intracellular parasite capable of living and reproducing only within living cells. Viruses tend to be diverse in terms of the diseases they cause and the organs they attack, however, all viruses have a unity of structure and consist of proteins and nucleic acids (Taylor, 2014). To protect the nucleic acid from the external environment, the virus surrounds its nucleic acid with a protein shell, called the capsid. Together, the nucleic acid and the capsid form the nucleocapsid of the virion (Louten, 2016). Viruses are also unique because they contain either RNA or DNA as genetic material. Nevertheless, viruses do not contain ribosomes, mitochondria, or other cell-like organelles. Since they cannot replicate without the metabolic processes of the host cell, they are genetic parasites (Taylor, 2014). The classification of viruses is not simple, considering there are over 2800 different viral species with very different properties. The main classifications are based on virion size, capsid structure, type of nucleic acid, physical properties, host species, or disease caused (Taylor, 2014).

The idea that infections could underlie AD was first proposed in 1907 by Oskar Fischer, Alois Alzheimer's "rival" (Allnutt and Jacobson, 2020). This hypothesis has been confirmed in 1991 by Jamieson and colleagues (Jamieson et al., 1991) who detected the presence of Herpes Simplex Virus 1 (HSV-1) DNA in AD brains. During the last 30 years, an increased number of viruses has been associated to the increased risk of AD, such as: other herpesviruses, flaviviruses, human immunodeficiency virus (HIV), hepatitis viruses, Ljungan virus, Borna virus and influenza A virus (Fig. 1, Table 1) (Chan and Valcour, 2022; Chemparthy et al., 2021; Chu et al., 2021; Filgueira et al., 2021; Jha et al., 2020; Lingel et al., 2020; Magaki et al., 2022; Murphy et al., 2021; Nir et al., 2021; Ojeda-Juárez and Kaul, 2021; Yin et al., 2022). To our knowledge, the potential role of many of these viruses in the pathogenesis of AD has been marginally reviewed and discussed. Here, we comprehensively summarize and review the current experimental evidence on this topic. Based on the findings, significant issues for future studies are then put forward.

2. Herpesviruses and AD

Herpesviruses are double-stranded DNA viruses with icosahedral symmetry, belonging to the family *Herpesviridae* (Roizmann et al., 1992). All herpes viruses are responsible for productive and lytic infections, which, after a more or less long florid phase depending on the reactivity of the infected subject, turn into latent infections. The site of latency is different for each subfamily of herpes viruses, but these are always areas of the body protected from constant aggression by the immune system, which makes the eradication of these viruses from the infected subject practically impossible. Eight human herpesviruses (HHV) are currently known, including HHV-3, also known as Varicella Zoster Virus (VZV), HHV-4 also known as Epstein–Barr Virus (EBV), and HHV-5, also known as Cytomegalovirus (CMV) (Carneiro et al., 2022). All of these viruses, except HHV-8, have been associated with AD (Ashraf et al., 2019; Barnes et al., 2015; Bernstein et al., 2020; Jeong and Liu, 2019; Polk et al., 2002). The main studies carried out in recent years on this topic are described in the following sub-paragraphs.

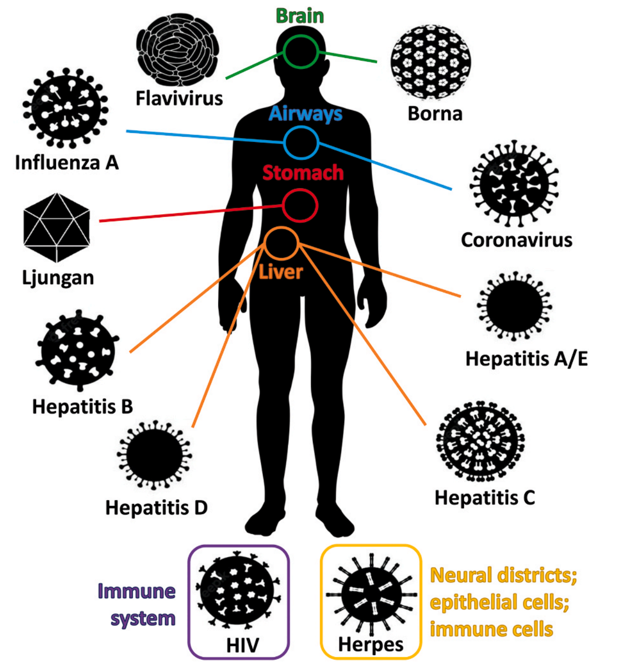

Fig. 1. Districts mainly involved in viral infection for the specific viruses/families.

2.1. HHV-1 and HHV-2

HHV-1 and HHV-2 are two closely related species of virus in the genus *Simplexvirus* and family *Herpesviridae* (Carneiro et al., 2022; Duarte et al., 2019). Viruses of the genus *Simplexvirus* have an enveloped capsid, with variable shapes and geometries and a diameter of 150–200 nm; genomes are linear, around 152 kilobases (kb) in length, and often carry overlapping genes that are transcribed by alternative splicing (Carneiro et al., 2022; Duarte et al., 2019). Entry into the host cell is achieved by attachment of the viral surface proteins to host cell receptors, which mediate endocytosis; replication happens in the cell nucleus, while translation takes place by leaky scanning (i.e. the actual starting position for protein synthesis can be bypassed, and translation may happen further downstream along the sequence) (Carneiro et al., 2022; Zhu and Viejo-Borbolla, 2021). The virus is primarily lysogenic and exits the host cell by nuclear egress (i.e., transiting through the nuclear membrane, instead of the nuclear pores), budding, and microtubular transport (Carneiro et al., 2022; Zhu and Viejo-Borbolla, 2021).

HHV-1 tends to reside in the trigeminal ganglia and most often manifests in the form of cold sores around the mouth and on the lips, that heal spontaneously in a few days or weeks (Cohen, 2020; Duarte et al., 2019). It is very common: about 67% of the world population under the age of 50 has HHV-1 (James et al., 2020). It is also highly contagious, so much so that HHV-1 is most often acquired orally and during childhood (James et al., 2020). It may also be sexually transmitted when infected saliva is involved, such as in kissing and mouth-to-genital contact (James et al., 2020). This species appears to be particularly damaging to the nervous system, and some research has attributed HHV-1 infection to an increased risk of developing AD,

Table 1
General characteristics of the viruses associated to the increased risk of AD.

Family	Genus	Species	Name	Type of genome
Hepersviridae	*Simplexvirus*	*Herpes alphaerpevirus 1*	Human Herpesvirus 1 (HHV-1)	Double-strand DNA
		Herpes alphaerpevirus 2	Human Herpesvirus 2 (HHV-2)	
	Varicellovirus	*Herpes alphaerpevirus 3*	Human Herpesvirus 3 (HHV-3) or Varicella-Zoster Virus (VZV)	
	Lymphocrayptovirus	*Herpes gammaerpevirus 4*	Human Herpesvirus 4 (HHV-4) or Epstein-Barr Virus (EBV)	
	Cytomegalovirus	*Herpes betaherpevirus 5*	Human Herpesvirus 5 (HHV-5) or Cytomegalovirus (CMV)	
	Roseolovirus	*Herpes betaherpesvirus 6*	Human Herpesvirus 6 A and B (HHV-6A and HHV-6B)	
		Herpes betaherpesvirus 7	Human Herpesvirus 7 (HHV-7)	
Flaviviridae	*Flavivirus*	*Zika virus*	Zika Virus (ZIKV)	Single-strand RNA
		Dengue virus	Dengue Virus (DENV)	
		Japanese Encephalitis virus	Japanese Encephalitis Virus (JEV)	
Retroviridae	*Lentivirus*	*Human Immunodeficiency virus 1 and 2*	Human Immunodeficiency Virus (HIV-1 and HIV-2)	Single-strand RNA
Picornaviridae	*Hepatovirus*	*Hepatovirus A*	Hepatitis A Virus	Single-strand RNA
		Hepatovirus B	Hepatitis B Virus	Double-strand DNA
		Hepatovirus C	Hepatitis C Virus	Single-strand RNA
		Hepatovirus D	Hepatitis D Virus	Single-strand RNA
		Hepatovirus E	Hepatitis E Virus	Single-strand RNA
Coronaviridae	*Betacoronavirus*	*Severe acute respiratory syndrome-related coronavirus*	Severe Acute Respiratory Syndrome C oronavirus 2 (SARS-CoV-2)	Single-strand RNA
Picornaviridae	*Parechovirus*	*Parechovirus B*	Ljungan Virus (LV)	Single-strand RNA
Bornaviridae	*Orthobornavirus*	*Mammalian 1 orthobornavirus*	Borna Disease Virus (BDV)	Single-strand RNA
Orthomyxoviridae	*Alphainfluenzavirus*	*Influenza A virus*	Influenza A Virus (IAV)	Single-strand RNA

especially in APOEε4 carriers (Wu et al., 2020; Zhang et al., 2020). This was further sustained by the observation that viral DNA could be localized with much higher frequency in the amyloid plaques of AD brains (90% of the amyloid plaques contained 72% of the total viral DNA) with respect to aged normal brains (only 24% of the viral DNA was found in amyloid plaques; p-value < 0.001) (Wozniak et al., 2009). However, recent studies discredited the possibility that HHV-1 could influence the expression of aberrant Aβ and hyperphosphorylated tau proteins, as neither preferentially co-localizes with viral DNA in infected trigeminal ganglia and brain of AD patients or controls (Tran et al., 2022). Then again, *in vitro* experiments with H4-N human brain cell lines did suggest a mechanistic involvement of HHV-1 in initiating APP endocytosis, cleavage, and Aβ production, which may stimulate AD onset through exocytotic Aβ deposition (Ge and Yuan, 2022). Moreover, an analysis of the cerebrospinal fluid of several patients (n = 128, mean age of 48, range 43–54, 28% female) with HIV but no neurological conditions has indicated an inverse relationship between chronic HHV-1 coinfection, blood-brain barrier (BBB) permeability and concentration of Aβ, with more significant associations if the subject had at least one symptomatic reactivation of HHV-1 (Trunfio et al., 2023). This suggests a role for HHV-1 infection as a modulating risk factor for AD and dementia symptoms, rather than a direct cause, as well as the involvement of environmental and host factors in determining the neurological outcome of the infection. Indeed, it has been suggested that chronic viral infection has a more prominent role in general cognitive disturbances that do not necessarily escalate in dementia (Murphy et al., 2021). Furthermore, an experimental study in murine hippocampal neurons and glioblastoma cells has introduced the hypothesis that protein buildup in the brain may be an immediate (as mediated by neurofibrillary aggregates) or long-term (by Aβ accumulation) reaction to viral infection/reactivation (Vojtechova et al., 2022), driven both by the presence of the virus and the consequent antiviral immune response (Powell-Doherty et al., 2020). Interestingly, several studies have also reported that the use of antiviral medications may reduce accumulation of amyloid plaques and neurofibrillary aggregates in the brain, opening the way for drug discovery and pharmacological treatment of AD-related cognitive impairment and dementia when HHV-1 is involved (Arrué et al., 2022; Lehrer and Rheinstein, 2022; Protto et al., 2022; Vojtechova et al., 2022). Indeed, evidence for an explicit connection between HHV-1 and AD is mixed, and several lines of inquiry are being pursued to shed more light on the challenges and therapeutic opportunities of this relationship.

The closely related HHV-2 most often presents itself in the form of genital herpes and is primarily a sexually transmitted infection (Cohen, 2020). The virus tends to reside in the sacral ganglia, from where it is periodically shed in the human genital tract, most often asymptomatically, increasing the chance of unnoticed sexual transmission (Schiffer et al., 2014). Asymptomatic reactivation is characterized by hard-to-notice symptoms that are not visible as signs of infection, so acquiring the virus is possible even if no blistering is present in the affected area (Johnston et al., 2011). Over the last 40 years, several antiherpetic drugs have been produced, tested, and successfully commercialized (Krishnan and Stuart, 2021; Majewska and Mlynarczyk-Bonikowska, 2022). For example, the efficacy of a 1 g/day dose of *valaciclovir* was tested for 60 days via a randomized study on HHV-2 positive but asymptomatic individuals. Some of the subjects received the antiherpetic drug (n = 36, mean age of 39 ± 13, 24% female), while others a placebo (n = 37, mean age of 36 ± 11.5, 29% female). A daily swab was collected and tested for HHV-2 by PCR. The study highlighted a 71% reduction in asymptomatic viral shedding in individuals receiving *valaciclovir* when compared to the placebo (p-value<0.001) (Sperling et al., 2008). Interestingly, another study on 911 couples with discordant partners (one infected, one not) showed that the transmission rate was approximately 5 per 10000 sexual contacts, with a marked impact on HHV-susceptible women during unprotected sex, and a sex-biased transmission during protected sex (i.e., infected women were more likely to transmit the virus to uninfected sexual partners, even when using condoms) (Magaret et al., 2015). In the central nervous system (CNS), HHV-2 has been most often associated with meningitis and meningoencephalitis, with severe consequences on neonates in particular (Berkhout et al., 2022; Jakobsen et al., 2022; Li et al., 2022b), but there is limited evidence of its involvement in dementia-like symptoms or AD both *in vitro* and *in vivo* (Bergström et al., 2021; Kristen et al., 2015).

2.2. HHV-3 (VZV)

HHV-3 or VZV is a DNA virus belonging to the *Herpesviridae* family (Arvin, 1996). It can remain latent and reappear in moments of debilitation or decline in the immune system. In this context, VZV can give two different infections: a primary one, chickenpox, and a secondary one, which can appear even many years after the first, i.e., herpes zoster (HZ), commonly called "shingles" (Arvin, 1996; Gershon et al., 2015).

Chickenpox is a highly contagious disease, typical but not exclusive of childhood, which consists of the appearance of a skin rash comprising vesicles scattered throughout the body (Dunkle et al., 1991). In a first phase, the virus is contagious both by air (therefore by sneezing, kissing, coughing) and by direct contact with the vesicles. This mode of transmission is due to the life cycle of the virus. After infecting the T cells of the nasal mucosa or regional lymph nodes, it multiplies and from there passes through the blood to the liver, spleen, and other lymph nodes. In these organs the virus multiplies again and subsequently reaches the skin and mucous membranes. At this point the viruses that have migrated to the skin produce maculopapular lesions, which will then become serum-containing vesicles. This serum, initially clear, then becomes cloudy once the vesicle enters its terminal stage, the pustule, which will eventually evolve into a crust. In children, the complications of chickenpox can be hemorrhagic manifestations, encephalitis and bacterial superinfections involving the blood, bones, lungs and skin (Gershon et al., 2015).

As mentioned above, VZV can remain latent in the neurons of the cranial nerve ganglia, dorsal root ganglia and enteric and autonomic ganglia, and its reactivation can cause HZ. The highest incidence of shingles occurs among individuals over the age of 50 or among immunocompromised patients, especially those with HIV/AIDS (Yawn et al., 2007). HZ is characterized by a vesicular eruption with a unitary dermatomal distribution, often associated with severe pain. Dermatomes between T3 and L3 are frequently affected. If the ophthalmic branch of the trigeminal nerve is involved, *ophthalmic zoster* (HZO) manifests itself with the appearance of an erythema and involves the presentation of blisters gathered in “clusters”. The eruption affects a limited area of the eyelids, where the virus had remained latent in the nerve. Characteristic is the pain, which begins as a tingling, then becomes burning and difficult to bear. Later, the infection can spread to the conjunctiva and cornea (Sampathkumar et al., 2009).

The most frequent complication of HZ is *postherpetic neuralgia* (PHN), a viral disease characterized by the appearance of vesicular rashes, accompanied by intense, continuous, and burning pain even after healing from HZ (Kost and Straus, 1996; Sampathkumar et al., 2009). The pain is often exacerbated violently by even slight contacts of the injured area, then perceived explosively for a period much longer than normal; for example, simple contact with clothes, nocturnal movements or even sudden changes in temperature, loud noises, or emotional stress, can trigger a violent and excruciating pain that can seriously compromise the quality of life. However, the intensity of pain is still considered subjective (Baron et al., 2009). The most important risk factor is, also in this case, adulthood. Generally, in fact, people over 50 are more prone to this disease than young people (Yawn et al., 2007).

Previous studies have shown that considerable cerebrovascular pathology is present in AD (Chen et al., 2009; O`Brien et al., 2003); in fact, cerebral hypoperfusion and ischemia phenomena are very frequent with consequent angiogenesis, which synergizes with Aβto produce AD. Especially in older and immunocompromised patients, VZV is the only human virus to replicate in cerebral arteries and produce vascular disease, subsequently damaging brain cells (Gilden et al., 2009; Kleinschmidt-DeMasters and Gilden, 2001). Therefore, a link between increased risk of dementia and VZV-induced vasculopathy is a testable hypothesis.

Tsai and colleagues (2017) sought to verify the relationship between HZO and risk of dementia following infection. They identified a group of patients diagnosed with HZO (n = 846, mean age of 62.2 ± 12.5, 50.3% female) and a control group (n = 2538, mean age of 61.4 ± 13.3, 49.1% female) for a total of 3384 study participants. Starting from the date of the first diagnosis of HZO for the first group and from the first use of medical services in the same period for the control group, the participants were followed up individually for 5 years in order to identify individuals who would have a diagnosis of dementia (Tsai et al., 2017). Therefore, dementia was diagnosed in the follow-up period in 4.61% of patients with HZO compared with 1.65% of patients without HZO. Furthermore, the study showed that HZO significantly increased the risk of subsequent dementia (hazard ratio [HR] = 2.83, 95% confidence interval [CI] = 1.83–4.37, p-value<0.001); this risk was found to be 1.4 times greater for male than female (HR = 3.35, 95% CI= 1.79–6.28, p-value< 0.001 *vs* HR= 2.40, 95% CI= 1.31–4.41, p-value< 0.01) (Tsai et al., 2017).

A direct link between VZV and AD was indeed found by Ukraintseva and colleagues, who estimated that the risk of AD after receiving a diagnosis of herpesviruses (including HZ) significantly increased by approximately 30% in individuals over the age of 65. However, in the same study, it was found that vaccination against these viruses did not result in a significant reduction in the risk of AD in this sample (Ukraintseva et al., 2017). However, antiviral treatment could be effective in preventing dementia (HR = 0.55, 95% CI= 0.40–0.77, p-value<0.05) according to the study by Chen and colleagues in which 78410 subjects, including 39205 patients with HZ, were examined. During a mean follow-up period of 6.22 years, 4204 subjects were diagnosed with dementia, suggesting a potential involvement of HZ in the development of dementia (HR = 1.11; 95% CI =1.04–1.17, p-value<0.05) (Chen et al., 2018).

More recent findings by Bae and colleagues are also consistent with what reported by Chen and colleagues in 2018 (Bae et al., 2021). Their study involved 195089 healthy subjects (mean age of 61.7 ± 9.4, 54.7% female) and 34505 Hz patients (mean age of 60.3 ± 8.1, 61.3% female), of whom 28873 (mean age of 66.9 ± 8.1, 61.3% female) received antiviral treatment. In patients with HZ the risk of AD in terms of HR was 1.11 (95% CI =1.04–1.19, p-value = 0.003); in addition, the incidence of dementia after HZ in untreated and treated patient groups was respectively 12.26 per 1000 person-years (95% CI =10.87–13.65, p-value<0.001) and 9.36 per 1000 person-years (95% CI= 8.20–10.52, p-value<0.001), with a HR of 0.76 (95% CI= 0.65–0.90, p-value<0.001) for the risk of dementia in the treated patients (Bae et al., 2021). Conversely, Choi and colleagues highlighted that HZ did not increase the risk of dementia in individuals of any age and of both sexes (Choi et al., 2021a). Recently Cairns, Itzhaki and Kaplan, not having found an involvement of HZ in the pathogenesis of AD, hypothesized an indirect effect of VZV, which may drive the reactivation of HSV-1 (Cairns et al., 2022). Another study from the same year would seem to exclude the possibility that HZ could contribute to the development of dementia, therefore vaccination, in this last case, would not be effective in preventing this condition (Schmidt et al., 2022). However, the results regarding a direct link between VZV and AD are still conflicting, and new studies may be needed to clarify these aspects.

2.3. HVV-4 (EBV)

The Human Herpesvirus 4, also known as Epstein Barr Virus (EBV), is a *Gammaherpervirus*, a member of the genus *Lymphocryptovirus*, with a double-stranded DNA, about 172 kbp long and encoding more than 85 genes. DNA is enclosed in a protein capsid and a viral matrix is interposed between these proteins and the virus membrane (Odumade et al., 2011). A mature virion usually has a diameter between 120 and 180 nanometers (nm) and presents glycoprotein on its external surface, which are paramount for entering and infecting the host cell (Hoover and Higginbotham, 2023).

EBV has been first isolated in 1964 by Epstein, Barr and Achong from Burkitt's lymphoma tissue (Epstein et al., 1964). This was the first case of a tumor-associated virus to be described, so that its discovery introduced the hypothesis of a viral origin for some forms of cancer (Esau, 2017).

EBV primarily infects epithelial and immune B cells through contact between the viral protein gp350 and the CD21 protein of the host cell (Speck et al., 2000); another mechanism involves the viral protein gp42 and HLA class II molecules (Odumade et al., 2011). The number of infected B cells decreases after the symptoms appear; however, it seems impossible to completely eliminate them from the organism (Hadinoto et al., 2008). When attacking epithelial cells, the BMRF-2 viral proteins interact with integrins avb1 (Tugizov et al., 2003), while the viral membrane proteins gH/gl merge to the epithelial cell by interacting with integrins avb6/8 (Chesnokova et al., 2009). EBV has two subtypes, distinguishable by their nuclear antigens (EBNA2 and EBNA3A-B-C) (Sample et al., 1990). The first subtype is dominant in Asia, Europe and North America, while both subtypes co-exist in Africa (Fields et al., 2007); the subtypes also differ for their spontaneous ability to stimulate cell lysis, therefore inducing cell death (Buck et al., 1999).

EBV, however, can also induce state of persistent cell infection (latency), in which no viral activity can be detected (Odumade et al., 2011). According to which genes are expressed during this state, three types of latency are established for this virus, each characterized by a different influence on immune B cell behavior (Cohen, 2020; Murata, 2014). For example, in Burkitt's lymphoma, a type 1 latent infection can be detected, characterized by the expression of *EBNA1*, *EBERS* and *BART* genes in immune B cells (Rowe et al., 1987). Type 2 latency can be found in nasopharyngeal carcinoma (Raab-Traub, 2002). Type 3 latency is characteristic of various pathologies (Young et al., 1989). Lastly, a type 0 latency exists, in which no viral genes are expressed in memory B cells (Babcock et al., 2000).

Several risk factors for EBV manifestation exist, such as young age, lower socioeconomic status, and reduced hygiene conditions (Bakkalci et al., 2020; Higgins et al., 2007). EBV is mainly transmitted orally through saliva, as it is associated with mononucleosis in at least 50% of the cases affecting young adults (Dunmire et al., 2018). Infants can contract the virus through the practice of premastication, which consists in a parent chewing solid food to break it down for an infant or toddler before transferring it to their mouth (Bakkalci et al., 2020; Dunmire et al., 2018). Clinically, EBV is the main cause of mononucleosis infection; subjects infected with EBV have a high chance of developing symptoms such as fever, fatigue, and sore throat, but lymphadenopathy, splenomegaly and hepatomegaly have been diagnosticated as well (Dunmire et al., 2018; Son and Shin, 2011).

EBV has been already linked with several neuropathologies (Zhang et al., 2022). In fact, several studies have revealed that EBV can replicate in the CNS, compromising the integrity of the BBB. Lesions involving the BBB have been associated with neurocognitive decline, neural damage and neuroinflammation (Liu and Cohen, 2016; Meyding-Lamadé and Strank, 2012; Van Gent et al., 2014). The main neuropathologies associated with EBV infection are Parkinson's disease (PD), multiple sclerosis (MS), acute cerebellar ataxia, meningitis and acute diffuse encephalomyelitis (Zhang et al., 2022).

AD also appears to be associated with EBV infection. A 2014 study (Carbone et al., 2014) tried to detect the presence of EBV and other herpesviruses in subjects diagnosed with AD ($n = 93$, mean age of 83.89 ± 6.89, 75.25% female) when compared with a control group ($n = 164$, mean age of 77.44 ± 5.26, 46% female). By analyzing peripheral blood leukocytes, they demonstrated that 45% of patients with AD, as well as 31% of the control subjects, were affected by EBV (odd ratio [OR]= 1.843, 95% CI=0.976–3.480; moreover, by stratifying the subjects according to the ε4 isoform of the APOE gene, they demonstrated that the ε4 allele is associated to EBV positivity only in the control group and that IgG levels for EBV antigens did increase in subjects who developed AD during the follow-up (Carbone et al., 2014). Therefore, this study highlighted how EBV infection can act as a risk factor for AD development.

A longitudinal study by Shim and colleagues analyzed the levels of anti-EBV igGs in blood plasma in a Korean cohort of subjects ($n = 36$, mean age of 66.6 ± 3.9, 60% female) who did not present cognitive dysfunction at the baseline visit but developed amnestic MCI within two years (Shim et al., 2016). These subjects were compared to an identically matched healthy control group and tested with the Korean version of mini-mental state examination (MMSE), the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD) and the Clinical Dementia Rating (CDR) Scale, while anti-EBV IgGs antibodies were analyzed through a commercial enzyme-linked immunosorbent assay (ELISA) kit (Shim et al., 2016). Research results showed that the subjects prone to develop MCI had higher anti-EBV IgG levels, and that these levels were correlated with both CDR (beta = 0.244, p-value = 0.049) and CERAD-K (beta = –0.177, p-value = 0.036) scores. No significant correlation was identified between IgG levels and K-MMSE scores (Shim et al., 2016). This study further suggests that EBV infection may be a risk factor for the development of cognitive decline, even of limited entity.

In a more recent study, Huang and colleagues discovered, through a Mendelian randomization study design, a significant association between mononucleosis (caused by EBV infection) and the risk of AD (OR=1.634, 95% CI= 1.092–2.446, p-value=0.017, false discovery rates [FDR]-adjusted, p-value = 0.034) in a large cohort of individuals with at least 97% European ancestry, highlighting that the same illness is associated with a familial history of AD (OR = 1.392, 95% CI= 1.061–1.826, p-value=0.017) (Huang et al., 2021).

However, a previous study by Tornianien-Holm and colleagues did not find any relationship between EBV infection and cognitive decline, both in the healthy adult and in the elderly population (Torniainen-Holm et al., 2018). In particular, their longitudinal study of a Finnish cohort ($n = 6554$, mean age of 53.0 ± 0.4, 52.5% female) in which cognitive abilities were measured through several neuropsychological tests, showed that IgG levels against CMV and EBV (detected through a solid-phase immunoassay method) were not associated with cognitive performances and, therefore, to a cognitive decline (Torniainen-Holm et al., 2018).

The molecular mechanisms underpinning the association between EBV infection and AD manifestation are still largely obscure. Several authors hypothesized that, given the latent nature of EBV, the immune system is constantly activated after the first infection and it has been verified that a chronic inflammatory state can induce AD-like phenotypes with age (Carbone et al., 2014; Krstic et al., 2012; Leonardo and Fregni, 2023). Moreover, a spike in cytokine levels, as well as other early markers for inflammation, such as alpha 1-antichymotrypsin, have already been associated with AD and age-driven cognitive decline (Carbone et al., 2014).

Given the discordant nature of the studies on this topic, further analysis is required to better understand whether a clear association between AD and EBV exists. If this is demonstrated, it would be paramount to determine if EBV is a direct cause of AD and of its neurobiological phenotypes.

2.4. HHV-5 (CMV)

HHV-5 or CMV is a widespread virus that has infected from 60% to 90% of the world population, with a seroprevalence in developing countries and areas with poor socio-economic conditions (Fowler et al., 2022; Zuhair et al., 2019). CMV is a double-stranded DNA virus with an envelope, has a mostly spherical shape and measures approximately 150–200 nm in diameter; under the envelope, it presents the classic viral capsid, whose symmetry is icosahedral. It has been estimated that CMV virion contains about 30–40 proteins (Varnum et al., 2004). During the infection phase, CMV enters the cells through an endocytosis mechanism and exploiting its characteristic glycoproteins; once inside the attacked cells, it goes to localize itself in the nucleus of the latter and, here, it begins to replicate using the host's nuclear enzymes (Crough and Khanna, 2009). Transmission of CMV to a new host can occur in various ways: through direct contact with oral-pharyngeal, vaginal or spermatic secretions, clearly belonging to an infected subject or with infection in progress; through breast milk, in a post-pregnancy lactation context; transplacentally, in the context of a pregnancy; by transfusion of infected blood or blood products; following a bone marrow or organ transplant (Sia and Patel, 2000). In healthy people, CMV tends to cause at most a mildly symptomatic infection; in those rare cases in which CMV is responsible for a substantial and evident symptomatology, the symptoms of the infection in progress are very reminiscent of those of a common flu; in fact, they generally consist of fever equal to or higher than 38 °C, chills, general malaise, sore throat, tiredness, muscle aches, enlarged lymph nodes, articular pain and loss of appetite (Crough and Khanna, 2009; Gandhi and Khanna, 2004). Sometimes, the symptoms resulting from a CMV infection are confused for the typical symptoms of mononucleosis.

Congenital CMV infection can have various consequences, including premature birth, low birth weight, jaundice, presence of an enlarged and poorly functioning liver, skin rash characterized by purple spots all over the body, microcephaly, presence of an enlarged spleen, pneumonia and epilepsy (Adler et al., 2007; Crough and Khanna, 2009). In people with an inefficient immune system (e.g., HIV/AIDS patients), CMV infection can affect the function of various organs, including the eyes, lungs, liver, esophagus, stomach, intestines and brain, and symptoms such as loss of vision following inflammation of the retina, digestive problems, encephalitis, and pneumonia (Rubin, 2007). The immune system can efficiently counteract the spread of CMV infection but is often unable to eradicate the virus permanently; this inability means that CMV remains clinically latent in the bone marrow cells of the infected subject until a temporary general weakening of the immune system (for example, due to stress) reactivates CMV, giving rise to a secondary infection (Forte et al., 2020). In a healthy individual, the reactivation phenomenon does not cause problems. Conversely, in an immunosuppressed individual, the reactivation of CMV has a high probability of causing the same serious consequences reported in the case of primary infections in people with an inefficient immune system. In essence, while secondary CMV infection is clinically irrelevant in healthy subjects, it is a particularly feared and dangerous event for immunosuppressed individuals (Luscalov et al., 2016; Ong et al., 2022; Prösch et al., 2000).

There have been numerous studies analyzing the relationship between CMV infection, the immune response to CMV and AD (Honjo et al., 2009). Barnes and colleagues verified ethnic differences in the incidence of CMV seropositivity and tested the link between CMV serostatus and incident AD and cognitive function decline of elderly African American (AA) and European American (EA) individuals, examined annually for an average of 5 years (Barnes et al., 2015). They also assessed whether ethnicity/ancestry modified this association. Among the participants of the study (n = 849, mean age of 78.6 ± 7.2, 25% black, 76% female), 73.4% (n = 623) were tested positive for CMV infection, and CMV antibody levels were significantly higher in AA than in EA individuals (89.0% *vs* 68.2%; p-value < 0.001) (Barnes et al., 2015). Also, after an average of 5 years of observation, n = 93 people developed AD and CMV seropositivity was associated with a 2-fold increase in the relative risk (RR) of AD onset (RR = 2.15; 95% CI =1.42–3.27, p-value < 0.001) and a faster rate of cognitive decline that was independent of the subjects' ethnic/ancestry background (Barnes et al., 2015).

Lurain and colleagues showed how CMV reactivations can lead to higher percentages of CD8 + T cells (known to destroy viruses with a cytotoxic effect) with associated CD28-/CD57 + phenotype in seropositive subjects, which are associated with cell senescence and a pathological diagnosis of AD; similarly, an increase of CD4 + T cells (which help produce antibodies) with the same phenotype was noted to correlate with accumulation of Aβ in infected individuals. Additionally, the study found a significant association beetween CMV-specific serum IgG antibody levels and neurofibrillary aggregates and of cerebrospinal fluid IFN-γ with CMV serostatus with neurofibrillary aggregates (Lurain et al., 2013).

An increase in the inflammatory response, especially in IFN-γ levels, was also found in a study by Westman and colleagues in CMV seropositive patients with AD compared to AD CMV seronegative subjects (n = 26 *vs* 4, mean age of 78.3 ± 6.54, 43% female) (Westman et al., 2014). It is therefore hypothesized that in the immunology of AD, IFN-γ has a considerable role as an inflammatory promoter; however, further studies examining subjects with prodromal disease are needed.

Moreover, Bu, (Bu et al. (2015) suggested a significant association between the infectious burden of CMV and AD onset (OR = 2.33, 95% CI=1.140–4.766, p-value=0.020) when comparing healthy controls (n = 102, mean age of 69 ± 9, 63% female) with AD patients (n = 114, mean age of 70 ± 10, 69% female), whereas Lövheim and colleagues did not find a direct link between CMV and the development of AD, but they suggested that CMV associated with herpes could facilitate the pathogenesis of AD (Lövheim et al., 2018).

Given the contradictory results presented in this paragraph, other studies are needed to demonstrate whether CMV seropositivity, alone and/or together with other infections, can facilitate the onset of AD.

2.5. HHV-6

HHV-6 is the collective name used to describe the two very similar species human betaherpesvirus 6 A (HHV-6A) and human betaherpesvirus 6B (HHV-6B). HHV-6A and HHV-6B are double-stranded DNA viruses within the *Betaherpesvirinae* subfamily and of the genus *Roseolovirus* (Carneiro et al., 2022). HHV-6A and HHV-6B infect almost all the human populations that have been tested. HHV-6B primary infection is the cause of the common childhood illness *exanthema subitum* (also known as *roseola infantum* or sixth disease) (Carneiro et al., 2022). It is passed on mainly from child to child, so it is uncommon for adults to contract this disease as most people have had it by *kindergarten*, and once contracted, immunity arises and prevents future reinfection (Carneiro et al., 2022). HHV-6A has been described as more neurovirulent, and as such is more frequently found in patients with epilepsy and neuroinflammatory diseases such as MS (Bahramian et al., 2022; Dunn et al., 2020; Santpere et al., 2020). HHV-6 levels in the brain may also be elevated in people with AD, although an explicit relationship between infection and illness is still to be unequivocally established. Indeed, limited and contradictory evidence has been found around this topic, with several studies dismissing this harmful association (Agostini et al., 2015; Allnutt and Jacobson, 2020; Chorlton, 2020; Hemling et al., 2003; Westman et al., 2017), while others find supporting evidence of immune system susceptibility and response to infection (Carbone et al., 2014; Licastro et al., 2015; Lin et al., 2002; Readhead et al., 2018; Rizzo et al., 2019; Wozniak et al., 2005). Although these results cannot be generalized, several studies on local communities have nonetheless highlighted a relationship between HHV-6 transcript presence and neurocognitive impairment. For example, a Chinese study on people infected with HHV-6 (n = 290, mean age of 67.1 ± 5.3, 52.4% female) revealed that, when compared with a healthy cohort of sex- and age-matched control individuals, there is a significant inverse linear correlation between HHV-6 copy number and tasks of orientation, attention-calculation, and language (all p-values < 0.05), and a non-linear dose-response correlation for the same tasks (p-value < 0.045) (C. Huang et al., 2022). Several recent publications have introduced novel viewpoints and critical interpretations of the results collected so far, trying to offer general criteria to link infectious neurotrophic agents with neurological diseases (Athanasiou et al., 2022; Komaroff et al., 2020; Romanescu et al., 2022), but extensive experimental research, supported by an international public health effort and a multidisciplinary approach, is necessary to provide a more complete framework around the relationship between HHV-6 and the brain, which remains extremely contradictory at this moment in time.

2.6. HHV-7

Human Herpesvirus 7 (HHV-7) is a *Roseolovirus* in the subfamily *Betaherpesvirus* (Ablashi et al., 1995; Staheli et al., 2016). HHV-7 has been isolated from the human host by Frenkel and colleagues, specifically from T cells of a healthy donor (Frenkel et al., 1990). Later, Berneman and colleagues reported the isolation of HHV-7 in peripheral blood mononuclear cells (PBMCs) from a patient with chronic fatigue (Berneman et al., 1992). HHV-7 is one of the most widespread viruses in the human population, and it seems likely that first contact happens during infancy, but the infection lasts a lifetime and immunocompromised individuals have a higher risk of developing severe clinical conditions upon virus reactivation (Wang et al., 2007; Wyatt et al., 1991).

HHV-7 virion size is approximately 200 nm; the most external part is a complex of membrane glycoproteins, while a dense matrix and a nucleocapsid protect the genetic material of the virus (Ablashi et al., 1995). The genome of HHV-7, which codes for over 70 proteins, consists of a single 145 kb region, delimited at the extremities by a repetitive DNA sequence of 10 kb in length (Kosuge, 2000; Staheli et al., 2016). After first infection by HHV-7, the salivary glands become a reservoir for the virus, as these are the anatomical sites where it is most abundant (Yadav et al., 1997). There, HHV-7 infiltrates CD4 + T lymphocytes and epithelial cells (Payne, 2017).

From a clinical standpoint, HHV-7 has been associated to the sixth disease, *roseola infantum* (Tanaka et al., 1994). There have been reports of hepatitis, respiratory infections and acute childhood hemiplegia (a rare neurodevelopmental disorder characterized by repeated episodes of weakness or paralysis that affect one side of the body) associated to HHV-7 infection as well (Kosuge, 2000).

HHV-7 can also induce neurological disorders in both adult and pediatric individuals. In a study by Schwartz and colleagues, polymerase chain reaction was employed to detect HHV-7 DNA fragments in the cerebrospinal fluid of several adolescent subjects (n = 2972, mean age of 2.3, range 0–17.99, 45% female) (Schwartz et al., 2014). Indeed, viral DNA was found in 57 subjects (1.9%). In three of these cases, primary HHV-7 infection was the actual cause of the neurological disease they presented: two patients developed viral encephalitis, the remaining one the Guillain-Barré syndrome (GBS). Eighteen other adolescents showed neurological conditions (encephalitis, meningitis, demyelination) possibly related to herpesvirus infection. Similar neurological diseases have been found in a cohort of adult subjects (n = 251, mean age of 55, range 15–89, 48.21% female) infected with HHV-7 (Corral et al., 2018). It has also been verified that HHV-7 can trigger acute encephalopathy in immunocompromised children. Foiadelli and colleagues recently described a group of patients (n = 12, mean age of 9.5 years ± 4.5, 50% female) with acute encephalopathy and an active HHV-7 infection: the viral DNA was detected in the CSF through real-time PCR and revealed from 20 to 3500 DNA copies per mL of CSF. Seven patients showed symptoms of meningoencephalitis, while the remaining five had acute neuropsychiatric symptoms (Foiadelli et al., 2022).

A recent study by Readhead and colleagues revealed that HHV-6 and HHV-7 are significantly increased in the brain tissue of AD patients when compared to a control group (Readhead et al., 2018). The investigation was carried out using four independent multiomic datasets including individuals with AD and healthy controls. Moreover, they have identified associations between herpesvirus abundance *APP* gene mutations. Specifically, to evaluate the presence of virions in brains with and without AD, they performed an RNA sequence analysis on two cohorts (i.e., AD patients and a healthy control group) from the Mount Sinai Brain Bank. Then, they performed a transcriptomic analysis of four cerebral areas (superior temporal gyrus, n = 137, anterior prefrontal cortex, n = 213, inferior frontal gyrus, n = 186, and parahippocampal gyrus, n = 107). Results showed that a higher presence of both HHV-6 and HHV-7 could be detected for the first two cerebral areas in AD patients. Furthermore, by comparing AD patients with subjects with Progressive Supranuclear Palsy, the authors revealed that levels of HHV-7 and HHV-6A are not equally distributed among neurodegenerative diseases but were influenced by the considered illness (Readhead et al., 2018). However, a detailed re-analysis of the same data by Jeong and colleagues points towards the absence of an actual association between AD and viral load in the original study, without excluding the tested hypothesis (Jeong and Liu, 2019). Moreover, a 2022 study (Bigley et al., 2022) evaluated the impact of members of the genus *Roseolovirus* on Aβaccumulation, using the 5XFAD mouse model infected with murine *Roseolovirus* (correlated to the human one). By analyzing viral load, neuropathogenesis and virus-Aβ interactions via electron microscopy, they showed that direct viral infection was the cause of neuroinflammation in mice, but Aβdeposition was not driven either by the virus, or by the inflammatory episode. Similarly, by analyzing viral RNA presence in the CNS of AD patients (n = 350), and a control group (n = 31), which is a subset of sample retrieved from the Charles F. and Joanne Knight Alzheimer's Disease Research Center (Knight-ADRC), they did not find any direct association between *Roseolovirus* infection and AD (Bigley et al., 2022).

These observations suggest that several mechanisms linking HHV-7 and the neuro-bio-behavioral phenotypes are typical of AD, although the relationship with Aβdeposition and inflammation is not clear (Fig. 2). Consequently, extensive functional studies may be required to determine the relationship between HHV-7 and AD.

3. Flaviviruses

Flaviviruses are a genus of single-stranded RNA viruses belonging to the family *Flaviviridae* (Westaway et al., 1985). This genus comprises 86 viruses, of which 73 are grouped into 53 species (King et al., 2011). At least 40 flaviviruses are known to be pathogenic to humans and other vertebrates causing a variety of different illnesses such as hepatitis, vascular shock syndrome, encephalitis, acute flaccid paralysis, congenital abnormalities and fetal death (King et al., 2011; Pierson and Diamond, 2020). Some of these viruses, such as Zika virus, Dengue virus, and Japanese encephalitis virus have been linked to AD (Chu et al., 2021; Lingel et al., 2020; Yin et al., 2022). The main studies carried out in recent years on this topic are described in the following sub-paragraphs.

3.1. Zika virus

Zika virus (ZIKV) is an arthropod-borne virus (arbovirus) in the genus *Flavivirus* and the family *Flaviviridae* (Musso and Gubler, 2016). The ZIKV has a spherical shape with a diameter not exceeding 40 nm and, like all other viruses belonging to the *Flaviviridae* family, it has a single-stranded RNA genome enclosed in an icosahedral capsid, with a positive polarity and about 11,000 bases long, encoding for three structural proteins: capsid (C), pre-membrane/membrane (prM/M) and envelope (E). The genome is flanked by two untranslated regions, 5′-UTR and 3′-UTR. Non-structural proteins, which function is mainly to drive viral replication, are NS1, NS2a, NS2b, NS3, NS4a, NS4b, NS5 with the latter being the RNA-dependent RNA polymerase protein (Kuno and Chang, 2007). Phylogenetic analysis showed that Zika virus can be classified into distinct African and Asian lineages (Plourde and Bloch, 2016; Sirohi and Kuhn, 2017). ZIKV was first isolated in 1947 from a febrile rhesus macaque monkey (*Macaca mulatta*) in the Zika forest (Uganda) and then identified in *Aedes Africanus* mosquitoes from the same forest (Dick et al., 1952). In humans was first described in Nigeria (Africa) in 1954 (MacNamara, 1954). Over the years, ZIKV infection has been reported all over the world. In 2007, the first major outbreak of Zika fever took place in the federated states of Micronesia (Duffy et al., 2009), then two other outbreaks took place in 2013 and 2014 in French Polynesia (Cao-Lormeau et al., 2014). Furthermore, in 2015 another outbreak was detected in Brazil (Campos et al., 2015), and then in other countries of the American continent (Hennessey et al., 2016) and in Europe (Plourde and Bloch, 2016). ZIKV is transmitted thought the bite of infected mosquitoes (Musso and Gubler, 2016) and with less frequency through other non-vector modes such as sexual activity, hospitalization, by transfusion or organ transplantation and from mother to child (Musso and Gubler, 2016). Clinically, 18% of the people infected by ZIKV develop various symptoms such as fever, arthralgia, maculopapular rash, conjunctivitis and, less frequently, headache, vertigo, myalgia, vomiting, and diarrhea (Agumadu and Ramphul, 2018; Estofolete et al., 2016). Furthermore, ZIKV could lead to neurological complications such as GBS (Sejvar et al., 2011) and microcephaly (Li et al., 2016). In 2020, a case of ZIKV-induced rapidly progressive dementia has been described in Brazil and reported at the 2020 meeting of the American Academy of Neurology by Osvaldo Nascimento and

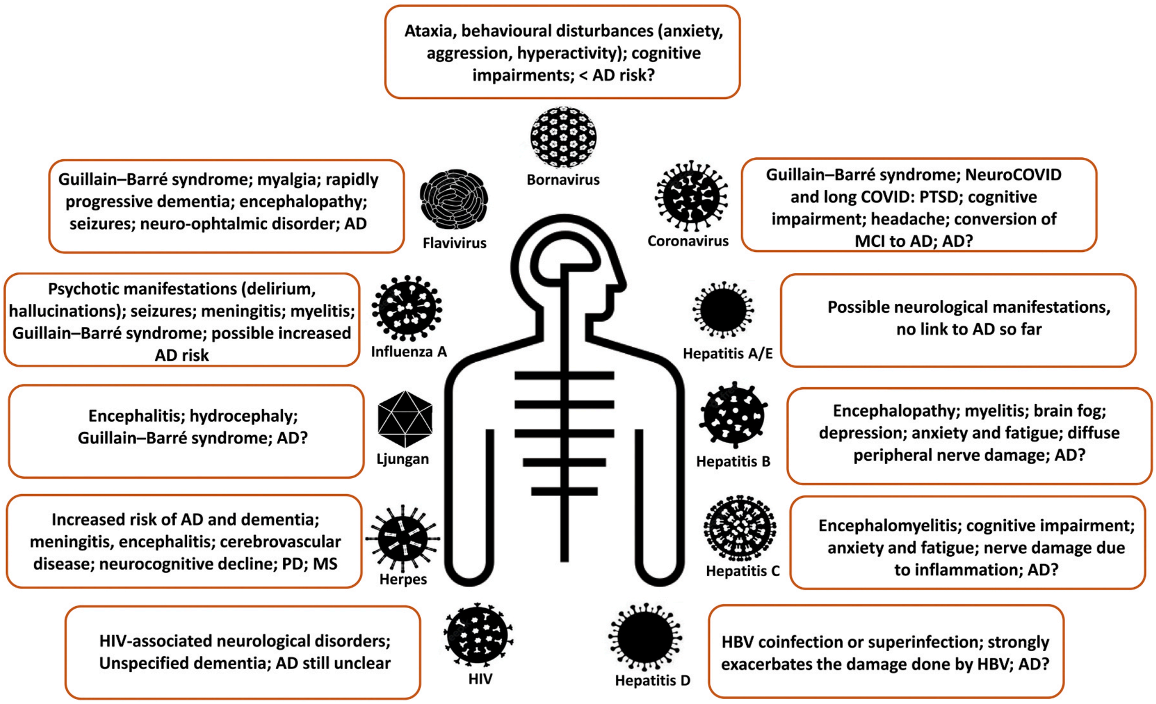

Fig. 2. Main manifestations of neurotropic and non-encephalotropic viral infections in the nervous system.

colleagues: over 6 months after ZIKV infection, a 27-year-old woman, with no significant medical history, presented a clinical picture characterized by ideomotor apraxia, dyscalculia, and severe short-term memory loss. Deep tendon reflexes were symmetrically brisk through all extremities and episodes of dystonic contraction of the left hand were also observed (Nascimento et al., 2020). According to several reports, AD pathology could be related to ZIKV infection. A 2020 article reported that ZIKV could intracellularly interact with APP by blocking the BACE1-binding site for APP cleavage and, consequently, increasing APP expression. In turn, APP would seem to represent a negative regulator for ZIKV replication in both human neural progenitor/stem cells and neonatal mouse brain cells, thus playing a protective role in ZIKV-mediated brain injuries (Lingel et al., 2020). On the other hand, ZIKV infection could induce Aβ accumulation through an increase of BACE1 abundance and an overactivation of PERK due to an activated endoplasmic reticulum stress, as well as an upregulation of tau phosphorylation through GSK3α/β affected by PERK-eIF2α pathway in human organoids model (Lee et al., 2022). Moreover, it has been shown that ZIKV promotes the differential expression of CASP3, a protein also linked to AD, in human mesenchymal stem cells (Beys-da-Silva et al., 2019). Therefore, while APP appears to protect against ZIKV infection damages, by contrast, ZIKV appears to increase the accumulation of proteins (Aβ and hyperphosphorylated tau) implicated in the pathogenesis of AD. The relationship between ZIKV and AD was also demonstrated by Costa, who reported that the blockade of N-Methyl-d-Aspartate receptors by memantine, an FDA-approved drug for treating the symptoms of AD, could moderate ZIKV-induced neuronal damage (Costa et al., 2017). Other studies are needed to better characterize the molecular mechanism of ZIKV underlying AD and to understand if having contracted that virus represents a risk factor for the onset of AD.

3.2. Dengue

Dengue is the most important arthropod-borne viral disease, first isolated in 1943 in Japan, with frequently occurring outbreaks in Southeast Asia, the Western Pacific area, Latin America, Africa, and Eastern Mediterranean regions (Chang et al., 2012; Ho et al., 2013). The mature Dengue virus (DENV) is a spherical virion of approximately 50 nm in diameter that comprises three structural proteins - C, prM/m and E - a lipid envelope and a positive polarity single-stranded RNA (ssRNA) of 10.7 kb. This capped RNA is composed by a long open reading frame (ORF) flanked by two untranslated regions (5'-UTR and 3'-UTR) (Perera and Kuhn, 2008). The 3'-UTR is important for DENV replication and modulates viral growth and RNA synthesis in mammalian cells (Tajima et al., 2007). Based on the differences in their viral structural and nonstructural proteins, a distinction can be made between four antigenically different serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 (Murugesan and Manoharan, 2020). DENV is mainly transmitted to humans by *Aedes aegypti* and *Aedes albopictus* mosquitoes (Harapan et al., 2020); nonetheless, the eradication of DENV is challenging due to its other non-vector transmission modalities such as blood transfusion, bone marrow transplant, intrapartum and perinatal transmission (Chen and Wilson, 2016). The most important factors related to DENV severity are female sex (Huy et al., 2013) and European (Figueiredo et al., 2010) or Chinese ancestry (Pang et al., 2012). It has been estimated that there are at least 100 million cases of symptomatic DENV each year in the world population (Bhatt et al., 2013). These cases are characterized by a wide range of clinical manifestations starting from mild dengue fever, in less severe cases, to dengue hemorrhagic fever and dengue shock syndrome, which are potentially lethal (Cui et al., 2018). Neurologically, DENV infection has been associated with dengue encephalopathy (Hendarto and Hadinegoro, 1992), encephalitis (Solomon et al., 2000), neuro-ophthalmic disorders (Somkijrungroj and Kongwattananon, 2019; Xie Cen et al., 2023) and immune-mediated syndromes, including acute transverse myelitis, acute disseminated encephalomyelitis, GBS (Carod-Artal et al., 2013) and dengue muscle dysfunction (Gulati et al., 2020). Interestingly, in 2020 Mohammed and colleagues reported the case of a 64-year-old hypertensive woman that developed seizures and progressive dementia after DENV infection (Mohammed et al., 2020). In the same manner, Mathew and colleagues, documented the case of a 32-year-old man that developed rapid-onset dementia, characterized by multidomain cognitive impairment and apraxia of speech associated with reversible splenial lesions of the corpus callosum, after a severe DENV infection (Mathew et al., 2021).

Recently, Chang and colleagues have identified Taiwan adults (n = 398, mean age of 56.0 ± 10.7, 55.5% female) without a familiar history of dementia who received a dengue fever diagnosis and compared their risk of developing dementia with a control non-DENV group (n = 1592, mean age of 55.7 ± 11.1, 55.4% female) (Chang et al., 2021). The authors found that individuals with dengue fever had a 71% increased risk of developing dementia than those without dengue fever (HR= 1.71; 95% CI= 1.03–2.83, p-value <0.05). The incidence rate of dementia was higher in female (4.91 per 1000 person-years) than in male (4.28 per 1000 person-years). Higher risks of dementia were observed in the elderly population: participants aged 60–69 years had a HR of 3.80 (95% CI= 2.08–6.93, p-value <0.001) and those aged at least 70 years had a HR of 12.8 (95% CI= 6.66–24.7, p-value <0.001). A similar result was found in participants with comorbidities, including cerebrovascular accident (HR= 2.83, 95% CI= 1.66–4.83, p-value <0.001) and depression (HR= 3.77; 95% CI= 2.08–6.84, p-value <0.001). Furthermore, the authors examined the association between dengue fever and dementia in different follow-up periods (1–3 years; 4–6 years; >6 years). Individuals in the dengue group who were followed up for more than 6 years had a significantly increased risk of developing dementia (HR= 3.11, 95% CI= 1.59–6.08, p-value <0.001), whereas individuals who were followed up for a short (1–3 years) and an intermediate (4–6 years) period did not have an increased risk of dementia (HR= 1.11, 95% CI= 0.30–4.13; HR= 1.79, 95% CI= 0.62–5.15, respectively) (Chang et al., 2021). Moreover, Chu and colleagues have longitudinally characterized DENV patients (n = 816, mean age of 59.66 ± 9.64, 52.1% female) and controls (n = 8160, mean age of 59.63 ± 9.65, 52.1% female) recruited in Taiwan from 1997 to 2012 and followed until the end of 2013, finding that patients after a DENV infection had a higher risk of developing dementia (HR= 2.23, 95% CI= 1.51–3.28, p-value <0.001) and in particular AD (HR=3.03, 95% CI= 1.08–8.45, p-value <0.001), and unspecified dementia (other types of dementia, especially diagnosis of AD with any evidence of cerebrovascular lesion), when compared to the control group (HR= 2.25, 95% CI =1.43–3.53, p-value <0.001) (Chu et al., 2021). This association remained statistically significant after adjusting for demographic variables and comorbid diseases.

Regarding the pathophysiology underlying the association between DENV and AD, preliminary data indicated that neuroinflammation could be the lead actor. In fact, the DENV can enter the CNS via the hematogenous route through plasma leakage, BBB injury, and infiltration of infected monocytes and macrophages (Guzman and Harris, 2015) inducing neuroinflammation. Indeed, it has been reported elevated levels of pro-inflammatory cytokines, including interleukin-6, interleukin-10, and tumor necrosis factor-alpha, in patients with a severe DENV (Guzman and Harris, 2015). Moreover, pro-inflammatory cytokines activate microglia and astrocytes (Liddelow et al., 2017), and the development of a vicious circle between microglia and proinflammatory cytokines represents a key pathological component of AD (Wang et al., 2015). Additionally, after inflammation, the enzyme indoleamine dioxygenase is activated and metabolizes tryptophan to kynurenine rather than serotonin (Roman and Irwin, 2020) and loss of serotonin may play a role in memory decline and drive the progression of AD (Smith et al., 2017), possibly influencing Aβ deposition (Smith et al., 2023). Additionally, DENV reduces the lipoprotein receptor-related protein 1 (LRP-1) expression *in vitro* (Tree et al., 2019). LRP-1 has been identified as an Aβ clearance receptor in the cerebral vascular smooth muscle cells, and the alteration of this pathway contributes to chronic inflammation, Aβ accumulation, and cerebral amyloid angiopathy (CAA) and thus could be considered involved in the pathogenesis of both AD and CAA (Kanekiyo et al., 2012). Interestingly, DENV can directly infect human microvascular endothelial cells, inducing apoptosis (Vásquez Ochoa et al., 2009). To date, the only studies that analyzed an association between AD and DENV were conducted in Taiwan, so further studies should explore the existence of this association in other countries. Moreover, additional studies are needed to better underline the molecular mechanisms that could explain this association in humans.

3.3. Japanese encephalitis virus

The Japanese Encephalitis virus (JEV) has a single-stranded RNA genome that codes for three structural proteins – i.e., C, prM/M, and E - and seven non-structural proteins - NS1, NS2A, NS2B, NS3, NS4, NS4B, and NS5 (Poonsiri et al., 2019). JEV is particularly widespread in South and Southeast Asia and affects about 69,000 people every year (Turtle and Solomon, 2018). Clinically, JEV infection can manifests with fever, coryza, diarrhea or rigors, accompanied by encephalitis and other symptoms such as pulmonary oedema, hepatomegaly, splenomegaly, and thrombocytopenia (Kumar et al., 2006). JEV infections have been also related to cognitive impairments (Campbell et al., 2011; Heffelfinger et al., 2017) and cases of dementia (Ayukawa et al., 2004; Nakashima et al., 1999; Shoji et al., 1994, 1990). Moreover, Yin et al. (2022) have recently analyzed the CSF proteomic profiling of JEV1 and JEV 2 patients (JEV1, n = 14, mean age of 44.1 ± 19.1, 14% female; JEV2, n = 12, mean age of 54.1 ± 14.7, 50% female), and control subjects (n = 33, mean age of 37.6 ± 15.1, 34% female), finding that the levels of several AD proteins were significantly increased (i.e., APOE, SPARCL1, fibrinogen alpha chain precursor, Serum amyloid A-1 protein; SAA1) or decreased (i.e., APP and Amyloid-like protein 1; APLP1) in JEV patients, respectively (Yin et al., 2022). Finally, German et al. (2006) reported an accumulation of β-APP in damaged axons in the inflamed region of mice infected with JEV (German et al., 2006), warranting further exploration of the possible relationship between JEV infection and AD in humans.

4. Other viruses linked to AD

Beyond herpesviruses and flaviviruses, also viruses belonging to other families have also been associated with AD. The scientific evidence will be described in the following sub-paragraphs.

4.1. Human Immunodeficiency Virus

Human Immunodeficiency Virus (HIV) is a collective name for two strains of retrovirus (HIV-1 and HIV-2) belonging to the family *Lentivirus*, that specifically infects humans and is responsible for the development of the Acquired Human Immunodeficiency Syndrome (AIDS) (Weiss, 1993). The virus is transmitted as a single-stranded, positive-end RNA segment enveloped in a protein capsid, which is surrounded by a fluid matrix and a lipid membrane taken from the host cell during reproduction. Specifically, the HIV virion contains two RNA strands from which 9 (sometimes 10) viral genes produce 12 structural proteins, 2 essential regulatory elements, and 4 accessory elements through a highly regulated system of RNA splicing and polyprotein processing (Engelman and Cherepanov, 2012; Gelderblom et al., 1989; German Advisory Committee Blood (Arbeitskreis Blut), Subgroup 'Assessment of Pathogens Transmissible by Blood, 2016).

HIV targets and reproduces in vital cells of the host immune system, particularly $CD4^+$ T cells, macrophages, and dendritic cells, leading to the inactivation or destruction of the infected cells (as well as uninfected bystander cells) through several direct and induced apoptotic mechanisms (Powell et al., 2016). It is also known that HIV can spread to new cells through both the classic cell-free route (in which the virion leaves a cell, travels through the extracellular fluid, and reaches another cell) and the recently recognized cell-to-cell spread, in which either a viral synapse or a virus-as-surface-antigen mechanism favors a more efficient diffusion of HIV, especially in the lymphoid organs (Bai et al., 2022; Han et al., 2022). In any case, the result of an untreated infection is a depletion of lymphocytes over a variable period of multiple weeks to several years, with an increasing impairment of the immune system and consequent premature death, mainly caused by opportunistic pathogenic conditions (Powell et al., 2016). However, in recent years the development of efficient antiretroviral treatments has reduced the infection rate of HIV, to the point that an undetectable condition (in which the affected individual has a viral load < 50 copies/mL) corresponds to the impossibility of transmitting the virus (Eisinger et al., 2019; Rodger et al., 2019). This, in turn, implies that progression into AIDS can be avoided, and drug-managed HIV infection has become a chronic condition, since the viral reservoir in the infected immune cells makes it impossible to eliminate the virus from the host (Bai et al., 2022). Indeed, extensive research has highlighted cognitive, motor, and behavioral manifestations like those seen for AD in infected patients, as part of HIV-associated neurological disorders (HAND); moreover, it seems like the chronicization of the infection in immune cells localized in the brain is related to the worsening of AD-like symptoms with aging (Chan and Valcour, 2022; Chemparthy et al., 2021; Filgueira et al., 2021; Jha et al., 2020; Magaki et al., 2022; Nir et al., 2021; Ojeda-Juárez and Kaul, 2021).

Esiri and colleagues (1998) arguably carried out the first study to investigate the prevalence of amyloid plaques in the frontal and temporal lobes of a cohort of 97 individuals who died of AIDS between the ages of 30 and 69 years, comparing it with an age-matched cohort of 125 non-HIV infected controls (Esiri et al., 1998). By classifying the cohorts in four age classes (30–39, 40–49, 50–59 and 60–69 years old), the authors showed a general trend for both cohorts consisting in a significant proliferation in amyloid plaques with increasing age (p-value = 0.005 and 0.048 for the control and AIDS group, respectively). However, there was a significantly greater prevalence of plaques in the AIDS group as a whole when compared to the whole control group (39% and 13% respectively; p-value < 0.004), as well as when focusing on individuals in the fourth decade age group (18% in HIV-infected cases and 0% in controls; p-value = 0.014) (Esiri et al., 1998). Two recent works by Jennifer Lam and colleagues aimed at comparing dementia risk (Lam et al., 2021), as well as incidence and prevalence (Lam et al., 2022) in people with (PWH) and without HIV infection (PWOH) and undergoing antiretroviral therapy (ART). Indeed, in the United States, the prevalence of HIV-associated dementia has declined to 1–2% in the ART era, and a drop in incidence has been noted (Brew and Chan, 2014; McArthur et al., 2010). However, ART protection against neurocognitive impairment is not well understood and up to 50% of HIV infected individuals show HAND symptoms (Brew and Chan, 2014; McArthur et al., 2010). In the first observational cohort study, Lam and colleagues identified 5381 PWH (mean age of 57 ± 7, 9% female) and 119022 (mean age of 58 ± 9, 10% female) demographically matched PWOH between 2013 and 2017, and followed them until 2019: the authors reported that, by age 80, 25.8% of PWH and 13.8% of PWOH have been diagnosed with dementia (HR= 1.58, 95% CI = 1.31–1.92, p-value<0.05) and highlighted a 58% higher risk of dementia for PWH, despite ART treatment for HIV (Lam et al., 2021). The second study included a cohort of 13296 PWH on ART (mean age of 53.9 ± 5.5, 11% female) and 155354 PWOH (mean age of 53.5 ± 5.5, 12% female) with dementia records obtained between the years 2000 and 2016. The authors report a reduction in dementia incidence over time for both groups, but higher in PWH (−8% per period) than in PWOH (−3.1% per period) as a possible effect of the ART treatment. However, adjusted dementia incidence (aI = 1.80, 95% CI = 1.60–2.04) and prevalence (aP = 1.86, 95% CI = 1.70–2.04) remained higher in PWH, and they were similar irrespective of sex (P-interaction=0.84 for aI; 0.39 for aP) or ethnicity (P-interaction= 0.36 for aI; 0.31 for aP) and until the last studied year (aI = 1.58, 95% CI = 1.18–2.12; aP = 1.75, 95% CI = 1.56–1.97, respectively) (Lam et al., 2022).

Recent studies have also highlighted a sex-biased impairment of perception, movement and cognitive functions (Duarte et al., 2021): women with HIV demonstrate significant sensorimotor deficits and reduced neuron integrity when compared to both healthy women and men (irrespective of their status), suggesting a stronger immune inflammatory response (Liang et al., 2021). Another observational study on American individuals by Sundermann and colleagues (2018) also highlighted that, in a comparison among 1362 HIV positive and 702 HIV negative subjects (204 and 214 women, respectively) for 15 neuropsychological tests, HIV-associated neurocognitive impairment was more prevalent in women and these results were mirrored in people of African ancestry, while in general the sex difference in HAND manifestations was variable in other ancestries (Sundermann et al., 2018). They conclude that women of African ancestry compose the group with the highest risk of developing HAND, and this may be mediated by differences in educational quality, so that biopsychosocial models and intersectional frameworks of inequality may be applied to describe the exacerbation of neurocognitive symptoms. A successive multicenter study on 429 HIV positive and 281 HIV negative women, as well as a matched number of men, sought to elucidate the role of sex, seropositivity and depressive symptoms on neurocognitive impairment (NCI) (Rubin et al., 2019). Results revealed that, while depression did exacerbate NCI across multiple domains both in seropositive and seronegative cohorts, HIV positive depressed women were significantly impacted in terms of executive function, both when compared to HIV negative women and to HIV positive men and proposed that treating depression may improve cognition in HIV infected patients.

Several mechanisms may be deemed responsible for the display of neurocognitive impairment in HIV-infected patients. Recently, it has been shown that intracellular Aβ aggregations could be detected in neurons of the dorsolateral prefrontal cortex and hippocampus, both in aged HIV-1 infected patients with HAND and in transgenic rats; however, no extra-neuronal amyloid plaques (typical of advanced AD) were found in either case (Li et al., 2022a). Furthermore, it is revealed that the virus exerts neurotoxic properties by downregulating the enzyme ADAM10, a secretase responsible for the correct processing of the Aβ, therefore favoring the production of the damaging Aβ in neurons (Lichtenthaler et al., 2022; Lopez Lloreda et al., 2022). Although in some cases the exact molecular mechanism remains unknown, several proteins produced by the virus also induce remodulation of protein aggregation and clearance in the brain. For example, HIV-Tat, a viral transcriptional regulator, can come into direct contact with Aβ polymers in the extracellular matrix and stimulate their accumulation into a more neurotoxic fibrillar composite (Hategan et al., 2017) which is not detected for clearance or phagocytosis (Hategan et al., 2019). Similarly, tau phosphorylation can be stimulated through a number of pathways by HIV surface glycoproteins (Sathler et al., 2022; Vijayan et al., 2022), enhancing the pathogenic effect of this protein in the brain. Indeed, both Aβ and tau appear to be greatly influenced by the same HIV protein products in terms of aggregation, distribution, clearance alteration and behavioral response in the patient (Bhargavan et al., 2021; Ditiatkovski et al., 2020; Hategan et al., 2019; Trunfio et al., 2023). Several authors also report that cognitive damage may be caused by a persistent low-grade neuroinflammatory state induced by virally suppressed HIV, especially in old subjects, where HAND and AD may be distinct and unconnected to Aβ burden (Canet et al., 2018; Howdle et al., 2020; Jha et al., 2020), while other conditions, such as depression, may come into play (Afridi and Suk, 2021; Mudra Rakshasa-Loots et al., 2023, 2022).

Extensive literature can also be found describing how APOE can interact with HIV to modulate cellular invasion and infectivity, and how this may reflect on the attainment of longevity (Abondio et al., 2019). APOE is, in fact, a protein that binds fats and cholesterol and is responsible for their redistribution and clearance; in the brain, it is highly expressed in the astrocytes, who are the major source of cholesterol for neurons: there, it is responsible for cholesterol transport between these cell types, as well as cell signaling (Mederos et al., 2018; Montague-Cardoso, 2021; Shan et al., 2021; H.Wang et al., 2021). Numerous studies have shown how APOE isoforms (alternative forms of the same basic protein) influence viral production in different directions, sometimes inhibiting infectivity when its overexpression is induced in macrophages (Siddiqui et al., 2018), sometimes failing at reducing internalization of viral glycoproteins (Khan et al., 2018) and accelerating disease progression (Burt et al., 2008; De Vlieger et al., 2022; Olivier et al., 2018) especially in correlation with the aging process in long-lived individuals with chronic HIV infection (Chang et al., 2014, 2011; Geffin and McCarthy, 2018; Valcour et al., 2004).

4.2. The Hepatitis group

Hepatitis virus is a collective name used to identify five main unrelated virus species (indicated with letters from A to E) that specifically cause inflammation of the liver (Nagra et al., 2022; Odenwald and Paul, 2022). These are called "hepatotropic" viruses as they thrive and multiply in the liver cells (Lanini et al., 2019; Xiang et al., 2022), in contrast to non-hepatotropic ones, such as the Epstein-Barr virus, which mainly infect other districts of the body, but are known to occasionally cause liver failure, especially in children (Gupta et al., 2015; Kelgeri et al., 2022; Wang and Xie, 2022). This event may present itself as a recent, acute infective episode with rapid onset (Alves, 2018; Manka et al., 2016) or as a chronic condition for which diagnosis, treatment and therapeutic strategies are still evolving with the knowledge of the pathogen and the illness it produces (Abu-Freha et al., 2022; Ma et al., 2022; Metin et al., 2022; Phillips et al., 2022).

Hepatitis A and E viruses induce a form of self-limiting acute and mild liver inflammation that may present itself up to 6 weeks from initial infection and last up to 8 weeks, although there have been reports of recurrent symptoms for about 6 months (Langan and Goodbred, 2021; Migueres et al., 2021; Pintó et al., 2021). The infection itself may not even be symptomatic and, when it does, is rarely conducive to liver failure. After first contact with the virus, the subject is immune for the rest of their life and there are in place preventative measures, such as simple daily hygiene and the hepatitis A vaccine, which has a protective effect for at least 20 years (P.H. Almeida et al., 2021; A. Almeida et al., 2021; Cao et al., 2021; Castaneda et al., 2021). As these conditions are supposed to prevent the latency of the virus and its spread to the nervous system, there have been no reports to date of dementia-like symptoms or AD related to hepatitis A and E; however, several studies have pointed out the ability of HEV to overcome the BBB (Shi et al., 2016; Tian et al., 2022, 2019), highlighting the possibility of extrahepatic and neurological manifestations (Jha et al., 2021; Lhomme et al., 2021; Mclean et al., 2017; Pischke et al., 2017) even though the specific mechanisms are not yet understood.

Hepatitis B can cause both acute and chronic liver inflammation, which can degenerate towards cirrhosis, fibrosis and hepatocellular carcinoma, for which liver transplant may be recommended (P.H. Almeida et al., 2021; A. Almeida et al., 2021; Castaneda et al., 2021; Datfar et al., 2021). However, antiviral medications for chronic infections and prompt vaccination are measures put in place to avoid the spread of the virus through contagious blood and bodily fluids (horizontal transmission) or from mother to newborn during childbirth (vertical transmission) (Bassit et al., 2021; Fung et al., 2022; Phillips et al., 2022). A similar set of conditions can be observed for hepatitis C, the main difference being that there is difficulty in developing a vaccine for this infection (although therapy with direct-acting oral antiviral drugs appears extremely efficient) (Abu-Freha et al., 2022; Campollo et al., 2022; Rafati et al., 2022). Interestingly, both acute and chronic infections from these viruses (and particularly the hepatitis C virus) have been associated with numerous extrahepatic manifestations, often mediated by a generalized immune response and inflammatory state (Dash et al., 2020; Larrubia, 2014; Popa and Popa, 2022). Secondary neurological and psychiatric disorders include cerebrovascular events, encephalopathy, myelitis, encephalomyelitis, cognitive impairment, brain fog, depression, anxiety, and fatigue, with peripheral nerve damage also reducing motor and sensory abilities (Abutaleb et al., 2018; Faccioli et al., 2021; Tian et al., 2022). It is suggested that chronic inflammation and metabolic disruption may ultimately induce neurotransmitter alterations, neuronal apoptosis and demyelination, which in turn are responsible for manifestations of neurodegeneration (Moretti et al., 2021; Redwan et al., 2022; Suhail et al., 2022), although the specific neurotropic mechanisms of HBV and HCV have still to be fully elucidated and their relationship with dementia and AD may be contradictory (Bassendine et al., 2020; Choi et al., 2021b; L. Huang et al., 2022; Piekut et al., 2022).

Hepatitis D virus presents itself as a satellite virus of HBV, as it depends on it to infect and propagate in the liver (Dandri et al., 2022; Khalfi et al., 2023; Robinson et al., 2023). Transmission can progress either by simultaneous infection with HBV (coinfection), or by HDV infecting a person with already existing chronic hepatitis B (superinfection) (Dandri et al., 2022; Khalfi et al., 2023; Robinson et al., 2023). Double infection by HDV greatly enhances the risk of cirrhosis, liver cancer and death; however, nothing has emerged so far about its possible neurological impact.

4.3. SARS-CoV-2

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is a viral strain identified in February 2020 and responsible for the Coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a positive-sense single-stranded RNA virus, with a single linear RNA segment and four protein structures known as: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. Experiments suggested that the virus has affinity to the receptor angiotensin converting enzyme 2 (ACE2) and uses these to enter cells (Naqvi et al., 2020). Even though the COVID-19 pandemic is still ongoing, and thousands of people continue to be infected by SARS-CoV-2 every day. It is mainly transmitted via droplets and aerosols from an infected person (Hui et al., 2020). Diagnosis is made through molecular testing or rapid antigen tests to detect SARS-CoV-2 and confirm the presence of the infection (Naqvi et al., 2020).

COVID-19 induces a series of symptoms that vary according to its severity, from the absence of symptoms (asymptomatic) to presenting with cough, sore throat, cold, fever, weakness, fatigue, and muscle pain. Other common symptoms may include headache, breathing difficulties, chills, vomiting and/or diarrhea, loss of sense of smell (anosmia) and taste (ageusia), rash, conjunctivitis (Adhikari et al., 2020). Interestingly, an increasing body of evidence suggested that about 36% of cases also developed neurological symptoms of which 25% can be attributed to the direct involvement of the CNS (Mao et al., 2020). In addition, a good portion of those who have been affected by COVID-19 continue to have signs and symptoms related to the infection and for this reason, the syndrome is known as "long COVID". The symptoms of long COVID include fatigue, dyspnea, cardiac abnormalities, symptoms of post-traumatic stress disorder, gastrointestinal disorders as well as neurological symptoms such as cognitive impairment, sleep disturbances, concentration problems, headache, muscle pain and, more rarely, GBS (Crook et al., 2021).

An increasing number of studies put forward the possibility that SARS-CoV-2 could cause damage in the CNS; therefore, it could accelerate brain aging favoring the development of neurodegenerative diseases, including AD (de Erausquin et al., 2021). Ciaccio and colleagues (2021) have hypothesized a link between AD and COVID-19; first, several risk factors and comorbidities such as older age, APOEε4 genotype, diabetes, gender, and hypertension are shared by both AD and COVID-19 (Ciaccio et al., 2021). It is interesting to note that anosmia, a very frequent symptom of COVID-19, has also been found to be related with the conversion of MCI to AD (Lennon, 2020). In addition, it has been reported an upregulation of ACE2 protein in the brain of AD patients which could facilitate the entry of the virus into the body and consequently increase the risk of contracting COVID-19 (Ciaccio et al., 2021; Ding et al., 2021). Other factors linked with the increased risk of COVID-19 in people with AD are of a social nature. During the lockdown some individuals with AD were unable to follow the recommendations of public health authorities to reduce transmission of COVID-19 (e.g., sanitize hands, wear face masks; keep physical distance from others and isolate themselves), due to apathy, depression and memory impairment

(Brown et al., 2020).

Interestingly, a recent hypothesis goes in the opposite direction of the previous one and posited that SARS-CoV-2 could increase the risk of the onset of AD. In particular, Wang and colleagues reviewed the medical records of over 6.2 million men and women who had received medical treatment in the United States between February 2020 and May 2021; the sample was subsequently divided into two groups: people who had contracted (n = 410748, mean age of 73.7 ± 7.75, 53.6% female) and people who had not contracted (n = 5834534, mean age of 73.0 ± 7.34, 55.6% female) COVID-19 in that period of time (Wang et al., 2022). The authors reported that people infected by SARS-CoV-2 had an increased risk of new diagnosis of AD within about 1 year after the COVID-19 diagnosis (HR=1.69, 95% CI= 1.53–1.72, p-value<0.05). This risk increases significantly in people aged ≥ 85 years (HR= 1.89, 95% CI= 1.73–2.07, p-value<0.05) and in women (HR= 1.82, 95% CI: 1.69–1.97, p-value<0.05). Given these preliminary data, further retrospective and longitudinal studies conducted in other cohorts of people, are needed to confirm the possibility to correlate COVID-19 infection with the development of AD or other neurodegenerative diseases.

4.4. Ljungan virus

Ljungan virus (LV) is a positive-stranded RNA virus belonging to the *picornavirus* family of the *parechovirus* genus (Tolf et al., 2009). This virus was first isolated from bank voles of the Ljungan Valley (Sweden) and then in rodents of Denmark and United States (Krous and Langlois, 2010; Niklasson et al., 1999). The viral RNA genome of LV is about 7.6 kb long, the virion is 27 nm in diameter, and the protein sequences encoded by the RNA are known (Johansson et al., 2002). Based on the genome sequence analyses and phylogenetic relationships, the eight strains of LV up to now isolated and sequenced, were grouped into four genotypes: LV-87–012 and LV-174 F (genotype 1), LV-145SL, LV342 and LV340 (genotype 2), M1146 (genotype 3) and LV-7855 (genotype 4) (Pounder et al., 2015; Tolf et al., 2009). Clinically, LV has been associated with several human diseases such as type I diabetes mellitus, myocarditis, fetal death (Niklasson et al., 2007; Tolf et al., 2009), as well as neurological diseases such as encephalitis (Krous and Langlois, 2010), Guillain–Barré syndrome (Niklasson et al., 1998), hydrocephaly and anencephaly (Niklasson et al., 2009). More recently, Niklasson and colleagues have immunohistochemically analyzed the presence of LV in postmortem hippocampus tissues of 18 AD cases and 11 age-matched controls (mean age of 74, SD not reported, 52.4% female) obtained from the brain bank of University of Lund (3 cases and 2 controls) and from the Netherlands Brain Bank (15 cases and 9 controls): interestingly, the LV viral antigen was detected in the hippocampal sections of all cases with AD and in none of the control subjects (Niklasson et al., 2020). Although these results are intriguing, further studies on other cohorts of subjects are needed to better investigate the possible role of the LV in the onset of AD, as well as to elucidate the molecular mechanisms underlying this possible association.

4.5. Borna disease virus

The genetic material of the Borna disease virus (BDV) is a negative-sense RNA that encodes for N, P, M, G, L, and p10 proteins; they may be glycosylated (M and G) or phosphorylated (P and L), and often associate to form heterocomplexes (Briese et al., 1995; Dittrich et al., 1989). BDV, so named because of the German town where an epidemic of infectious encephalitis caused many equine deaths in 1885 (Carbone, 2001), has a largely known epidemiology (Eisermann et al., 2021). Clinically, BDV infections are characterized by ataxia and behavioral disturbance such as anxiety, aggression, cognitive defects, and hyperactivity (Carbone, 2001; Zhai et al., 2018). A first study conducted in 1996 reported the presence of BDV genome in hippocampi of 5 patients with hippocampal sclerosis (mean age of 84 ± 5, no sex/gender ratio reported) harbored BDV but not of AD patients (n = 26, mean age of 77 ± 1.5, no sex/gender ratio reported) (De La Torre et al., 1996). One year later, Salvatore and colleagues reported the absence of BDV *P* gene mRNA in 19 postmortem brain samples of North American and European people with AD (Salvatore et al., 1997). In 1999, similar results were found by Czygan and colleagues through the examination of the presence of BDV in 14 brains of AD patients (Czygan et al., 1999). Moreover, Igata and colleagues have not found the BVD RNA genome and antibodies in peripheral blood mononuclear cells of AD patients (n = 10, mean age of 85.8, range 71–94, 60% female) (Igata et al., 1998). Taken together these results indicate that BDV infection is not implicated in the pathogenesis of AD. However, preliminary animal and human data suggested that BDV could reduce the accumulation of Ab (Sakai et al., 2018; Stahl et al., 2006) suggesting the use of BDV vectors may be a promising treatment strategy for AD.

4.6. Influenza A virus

The type A influenza virus (IAV) genome consists of 8 single-stranded negative RNA segments encoding for 11 proteins, including the surface glycoproteins haemagglutinin (H) and neuraminidase (N) (Bouvier and Palese, 2008; Dou et al., 2018). These two proteins are crucial for the infection of target cells as they are essential for the adhesion of the virus to the cell receptor and for its release once the replication process is completed, respectively (Kosik and Yewdell, 2019; F. Wang et al., 2021). Influenza virus has one gene (HA, segment 4) that codes for 1 of 16 possible hemagglutinins and another (NA, segment 6) that codes for 1 of 9 possible neuraminidases. Subtypes H1, H2, H3, N1 and N2 – paired only in three (AH1N1, AH2N2 and AH3N2) of the 144 possible combinations (16Hx9N = 144HN) – were found in viruses adapted to humans and therefore capable of causing seasonal epidemics or pandemics (e.g. the 1918 “Spanish Flu”, 1977 “Russian Flu” and 2009 “Swine Flu” from subtype AH1N1; the 1957 “Asian Flu” from AH2N2; the 1978 “Hong Kong Flu” from AH3N2) (Belshan et al., 2014; Bouvier and Palese, 2008; Harrington et al., 2021; Piret and Boivin, 2021; Ray et al., 2017). Nevertheless, rare zoonotic IAV infections from other subtype combinations have been recently reported as cause of sporadic cases and fatalities among humans (e.g., Avian influenza subtypes AH5N1, AH5N8 and AH7N9), that are less contagious among humans, but more deadly as they infect the lung tissue, instead of the upper respiratory tract (Amer et al., 2021; Chang et al., 2023; De Vries et al., 2015; Rafique et al., 2023). The flu is generally characterized as an acute infection with numerous sudden non-specific symptoms, such as fever, chills, myalgia, cough, sore throat, and headache, so much so that many non-focalized illnesses are frequently categorized as “common flu” and their correct diagnosis may be delayed, sometimes with adverse outcomes (Jutel and Banister, 2013). Indeed, it is customary among individuals outside of the healthcare professions to self-misdiagnose influenza based on “influenza-like symptoms”, particularly because there seems to be no definite consensus on a specific definition and unique symptomatology for IAV-borne illness (Cedraschi et al., 2013; Jutel, 2019; Mayrhuber et al., 2018). Several testing methodologies exist, such as rapid antigen tests, flu PCR and multiplex PCR, or respiratory viral panels, with different sensitivities and specificities for each diagnostic test (Merckx et al., 2017; Ravina et al., 2023; Rodriguez et al., 2022). Epidemiological studies reveal that, across all age groups, people hospitalized with influenza-like respiratory symptoms are infected by subtype AH1N1 twice as often as AH3N2, but people between 40 and 65 years of age are infected five times as often; that AH1N1 affects all age groups over the age of 40 at a similar rate, while AH3N2 affects people over 65 significantly more often than individuals between 40 and 64 years; and that AH1N1 has the highest rate of infection in people between 18 and 65 years (P.H. Almeida et al., 2021; A. Almeida et al., 2021; Belazi et al., 2021; Lytras et al., 2020; Wong et al., 2019).

Neurological complications of viral flu and their association to respiratory pathologies have been revealed both in children and adults (Bohmwald et al., 2018; Froggatt and Heaton, 2022; Goenka et al., 2014;

Paksu et al., 2018; Popescu et al., 2017), with clinical outcomes ranging from neuropsychiatric disorders, like delirium and hallucinations (Manjunatha et al., 2011; Mizuguchi, 2013), to seizures (Paksu et al., 2018), meningitis (Liang et al., 2018), encephalitis (Newland et al., 2003), myelitis (Ruisanchez Nieva et al., 2017; Shafiq et al., 2022; Xia et al., 2014) and GBS (Grisanti et al., 2021; Sivadon-Tardy et al., 2009; Yamana et al., 2019). A specific link between IAV infection and AD progression has been established only recently in a transgenic mouse model (APP/PS1) of the disease, where long-term peripheral infection with AH3N2 (starting at 2 months of age) was induced (Hosseini et al., 2021). The study revealed that infected transgenic mice had more pronounced microglia activation, Aβ deposition and cognitive impairments, and dendritic spine density was reduced, despite a similar number of neurons in wild-type and transgenic mice. The authors conclude that peripheral AH3N2 infection could stimulate the immune response by triggering activation of the microglia and exacerbate symptoms of AD (Hosseini et al., 2021). However, a previous publication had already elucidated the role of Aβ in inhibiting the spread of IAV in the neuronal cell and facilitating its uptake by lymphocytes, also reducing viral protein synthesis and interleukin production in monocytes (White et al., 2014). Indeed, large cohort studies report no direct association between influenza infection and increased AD risk (Imfeld et al., 2016) but confirm a reduction in AD risk with repeated instances of vaccination against IAV, particularly for people over the age of 65 (Bukhbinder et al., 2022; Wiemken et al., 2021). These results suggest an indirect role of the pathogenic infection on AD, given that the IAV vaccine may reduce risk of dementia by training the immune system and reducing the chance of a long-term inflammatory response (Wiemken et al., 2021).

5. Conclusions

Infectious viral diseases are among the most common and widespread human illnesses in the world. Many of these, especially if maintained in a condition of latency (spontaneously or through pharmacological therapy), may have an impact on the central and peripheral nervous system either directly (in the case of neurotropic viruses, such as members of the *Herpesvirus* group), by dysregulating the immune system (for example, HIV), or by stimulating a state of constant immune activation and inflammation. Although research around some of these viruses is still contradictory, it seems that they are involved in numerous psychiatric (loss of consciousness, hallucinations, detachment from reality, delirium) and neurological complications (seizures, myalgia, neuralgia, headaches, encephalitis, myelitis, meningitis and GBS, among others), as well as behavioral and psychological impairments that can develop into full-fledged dementia. Limited but compelling evidence has been presented for the involvement of several neurotropic and non-neurotropic viruses with amyloid plaques and neurofibrillary aggregates, sustaining a role in the onset (but more probably the exacerbation) of AD, especially in older and immunocompromised individuals who can be more susceptible to multiple and opportunistic infections. Further investigation for virus genomes in postmortem brain samples from controls and AD patients and on the possible viral pathways that may impact neurodegeneration are needed, to better clarify the possible contribution of viruses to the pathogenesis of this neurodegenerative disease. Nonetheless, an increasing wealth of evidence is shedding new light on the potential use of vaccines and anti (retro)viral therapies as novel pharmacological treatments for dementia and AD, as well as for other neurodegenerative disorders, as it appears that vaccination against common viral illnesses significantly reduces the risk of dementia and neural deterioration at a later age (Ali and Shaikh, 2022; Bukhbinder et al., 2023, 2022; Lehrer and Rheinstein, 2022; Wiemken et al., 2022, 2021; Wu et al., 2022). Further studies will be needed to understand whether this effect is directly linked to the limitation of incident infection, or if the training to which the immune system is subjected to through immunization can determine a lower impact of immune activation and reduce long-term inflammation in this context.

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Declaration of Competing Interest

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Data Availability

No data was used for the research described in the article.

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