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The relationship between herpesviruses and Parkinson's disease: prevalence, viral load, and clinical implications

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Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by dopaminergic neuronal loss, motor dysfunction, and a range of non-motor symptoms. While the etiology of PD remains elusive, emerging evidence suggests a significant role for latent herpesvirus infections in its pathogenesis. This study investigates the prevalence and viral loads of herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV) in PD patients compared to age- and sex-matched healthy controls. Using multiplex PCR and quantitative PCR, we demonstrate a higher prevalence of HSV-1 and VZV in PD patients, with their viral loads correlating significantly with disease severity and elevated levels of interleukin-6 (IL-6), a marker of systemic inflammation. Our findings reveal that active herpesvirus infections exacerbate neuroinflammation, potentially accelerating dopaminergic neurodegeneration. While CMV and HSV-2 showed no significant differences, the co-infection of HSV-1 and VZV was associated with more severe non-motor symptoms, such as cognitive decline and depression. These results underscore the potential of targeting herpesvirus reactivation and associated inflammation as a novel therapeutic approach for managing PD. Antiviral therapies and vaccination strategies, particularly for HSV-1 and VZV, warrant further investigation to mitigate PD progression.

KEYWORDS

herpesvirus, interleukin-6 (IL-6), neuroinflammation, PD (Parkinson's disease), viral loads

Introduction

PD is a chronic and progressive neurodegenerative disorder primarily characterized by the degeneration of dopaminergic neurons in the substantia nigra pars compacta, leading to a significant reduction in dopamine levels in the striatum. This dopamine deficiency disrupts the function of the basal ganglia, a neural network critical for coordinating movement, causing the motor symptoms associated with PD: bradykinesia (slowness of movement), rigidity, resting tremor, and postural instability

(Kalia and Lang, 2015; Nguyen et al., 2018; Parkinson, 2002; Shuteeva and Gorshunova, 2017). Beyond motor symptoms, PD encompasses a wide range of non-motor symptoms that severely affect patients' quality of life. These include cognitive decline, autonomic dysfunction (e.g., orthostatic hypotension, gastrointestinal disturbances), psychiatric conditions such as depression, anxiety, and hallucinations, and sleep disturbances (Obeso et al., 2017; Schapira and Jenner, 2011). These non-motor symptoms often precede motor symptoms by years, highlighting the multisystemic nature of PD (Brundin et al., 2017).

The precise cause of PD remains unknown, but a multifactorial etiology involving genetic, environmental, and lifestyle factors is widely accepted. Although monogenic forms of PD linked to mutations in genes such as SNCA (which encodes α-synuclein), LRRK2, and PARK7 exist, they account for only 5%–10% of all cases (Chang et al., 2017; Tanner et al., 2011). Idiopathic PD, which constitutes the majority of cases, is thought to arise from complex interactions between genetic predisposition and environmental triggers.

Environmental factors, including pesticide exposure, herbicides, heavy metals, and industrial solvents, have been implicated in PD. These toxins are known to induce mitochondrial dysfunction, oxidative stress, and neuroinflammation, thereby accelerating dopaminergic neuronal loss (Hernán et al., 2002; Spillantini et al., 1997). Conversely, protective factors such as regular physical exercise, coffee consumption, and antioxidant-rich diets have been linked to reduced PD risk, suggesting a role for modifiable behaviors in prevention (Braak et al., 2003; McNaught and Olanow, 2003). These observations emphasize the need to further explore environmental and lifestyle influences to identify potential preventive strategies.

A hallmark feature of PD is the accumulation of α-synuclein aggregates, forming Lewy bodies and Lewy neurites in neurons. These misfolded protein deposits impair cellular processes, including mitochondrial function, protein degradation, and synaptic transmission, ultimately leading to neuronal death (Hirsch and Hunot, 2009; Qin et al., 2016). α-Synuclein pathology follows a predictable braak staging pattern, spreading from peripheral sites like the olfactory bulb and enteric nervous system to the brainstem and cortex in advanced stages. While Braak staging provides a foundational framework, emerging models such as the 'body-first' and 'brain-first' hypotheses have gained traction. These models posit divergent pathways of α-synuclein propagation, either ascending from peripheral autonomic networks or descending from limbic and olfactory centers, respectively. These routes may intersect with neurotropic viral infections, including HSV-1 and VZV, which are capable of entering the CNS through similar anatomical paths. This progression correlates with the clinical evolution of PD, where non-motor symptoms often precede motor dysfunction (Boura et al., 2025; Tansey et al., 2007; Wüllner et al., 2023).

Neuroinflammation is a crucial factor in PD pathology. Activated microglia and elevated levels of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been consistently observed in PD brains. These inflammatory responses exacerbate neuronal damage and perpetuate a self-sustaining cycle of neurodegeneration (Domingues et al., 2017; Goedert, 2015). Epidemiological evidence suggesting that anti-inflammatory drugs may lower PD risk underscores the significance of inflammation in its pathogenesis (Itzhaki, 2014). Additionally, recent findings by Malatt et al. (2025) indicate that the use of NSAIDs is associated with a delayed onset of PD symptoms, reinforcing the potential neuroprotective effect of anti-inflammatory agents (Malatt et al., 2025).

Recent studies have implicated infectious agents, particularly herpesviruses, in the development of PD. Herpesviruses' ability to establish latency in the central nervous system (CNS) and periodically reactivate under conditions of aging, stress, or immunosuppression aligns with the progressive and chronic nature of PD (Readhead et al., 2018). These viruses can induce neuroinflammation, disrupt neuronal homeostasis, and promote oxidative stress, positioning them as plausible environmental factors in PD etiology (Saha et al., 2022). Recent evidence has also highlighted an increase in parkinsonian symptoms following SARS-CoV-2 infection, suggesting a possible role of viral triggers beyond the herpesvirus family in neurodegeneration (Boura et al., 2023).

Herpesviruses are a family of double-stranded DNA viruses capable of establishing lifelong latency after initial infection. Among the nine human herpesviruses, four are most associated with neurological conditions: HSV-1 (herpes simplex virus type 1), VZV (varicella-zoster virus), EBV (Epstein-Barr virus), and CMV (cytomegalovirus) (Kennedy, 2002). These viruses can infect neurons, astrocytes, and microglia, often leading to chronic CNS infections (Figure 1) (Pellett, 2007).

HSV-1 establishes latency in sensory ganglia and can retrogradely transport to the brain during reactivation, leading to neuronal injury. Studies have demonstrated the frequent detection of HSV-1 DNA in brain regions associated with neurodegeneration, such as the hippocampus and substantia nigra (Koelle and Corey, 2008; Nagel and Gilden, 2013). Similarly, VZV reactivation, clinically evident as herpes zoster, has been linked to postherpetic neuralgia and other chronic neurological complications (Kennedy, 2002).

Herpesviruses exert their neurotoxic effects via multiple mechanisms:

- Direct Cytotoxicity: Viral replication directly damages neurons, leading to apoptosis and neuronal loss.

Abbreviations: ELISA, Enzyme-Linked Immunosorbent Assay; PCR, Polymerase Chain Reaction.

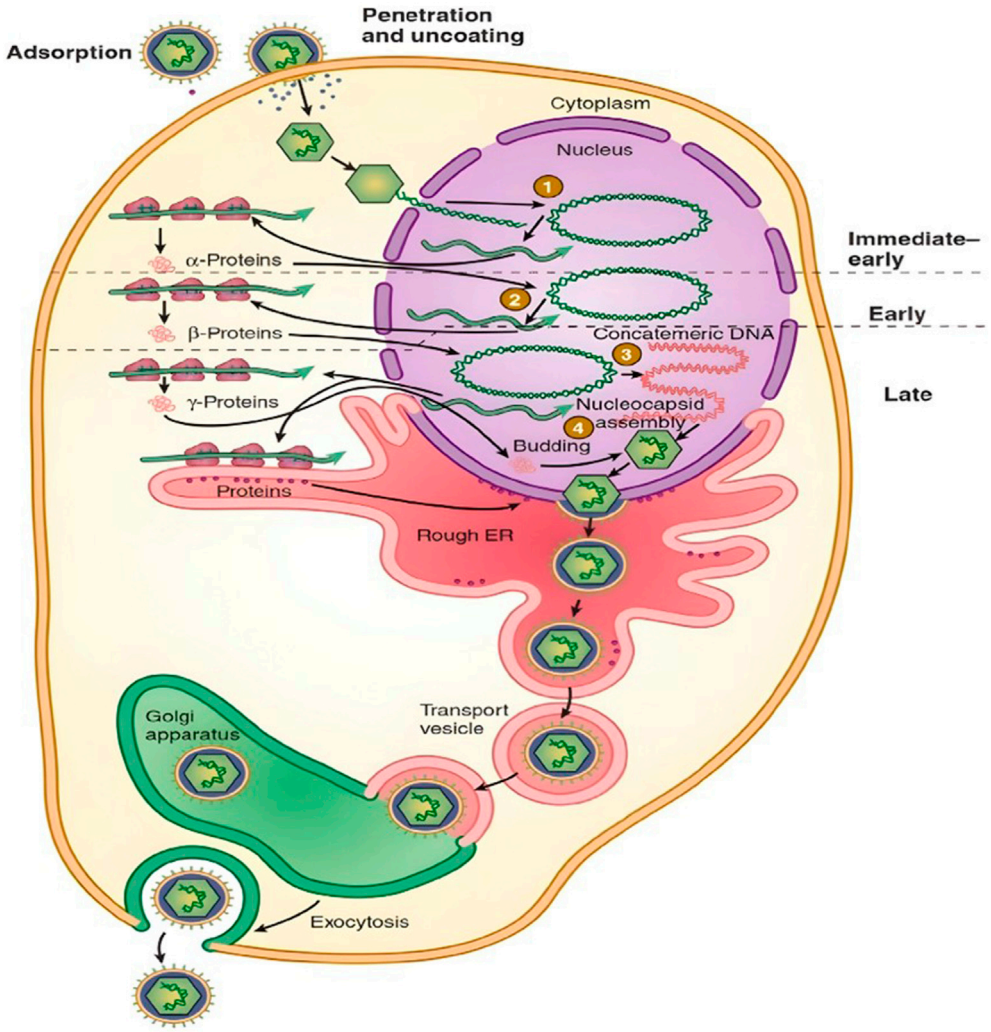

FIGURE 1
Herpes Simplex Virus Replication Cycle. Source: Caren C. Carroll, Stephan A. Morse, Timothy Mietzner, Steve Miller: Jawetz, Melnick, & Adelberg's Medical Microbiology, 27th Edition. www.accessmedicine.com. Copyright © McGraw-Hill Education. All right reserved.

- Oxidative Stress: Viral proteins disrupt mitochondrial dynamics, increasing ROS production and reducing antioxidant defenses, promoting α-synuclein aggregation (Carocci et al., 2018; Stanziale et al., 2004).
- Chronic Neuroinflammation: Viral reactivation triggers a sustained immune response involving pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, contributing to ongoing neurodegeneration (Montgomery and Bowers, 2012).

Epidemiological studies reveal a higher prevalence of HSV-1, VZV, and EBV infections in PD patients than in the general population, indicating a potential link between latent viral infections and neurodegenerative progression (Duarte et al., 2019). Clinical analyses further confirm the presence of herpesvirus DNA, particularly HSV-1, in the substantia nigra of PD patients, contrasting with lower detection rates in healthy controls (Agostini et al., 2021). Additionally, elevated CSF cytokine levels in PD patients with herpesvirus infections suggest that viral activity may potentiate neuroinflammation, aggravating PD pathology (Tohidpour et al., 2017).

In vitro studies provide mechanistic insights into how herpesviruses contribute to PD. HSV-1 infection induces α-synuclein aggregation via oxidative stress and proteasomal dysfunction, mimicking pathological features observed in PD brains (Esiri and Kennedy, 1992). Similarly, VZV infection impairs mitochondrial function and autophagic clearance, critical for maintaining neuronal integrity (Baiker et al., 2004). These findings suggest herpesviruses could act as environmental

triggers in individuals predisposed to PD due to genetic or environmental factors.

Despite the growing body of evidence, several research gaps remain. The causal role of herpesviruses in PD pathogenesis is still debated. Are these infections primary drivers or secondary contributors to neurodegeneration? Most studies are cross-sectional, limiting their ability to determine causality. Longitudinal studies that monitor viral reactivation over time are crucial to clarifying this relationship (Dohm et al., 2017; Leta et al., 2022).

Furthermore, the heterogeneity in herpesvirus prevalence across studies poses a challenge. While HSV-1 and VZV consistently show associations with PD, the roles of EBV and CMV are less clear. Standardized detection methods and larger sample sizes are necessary to resolve these discrepancies (Ben Fredj et al., 2012). Additionally, genetic predispositions, particularly polymorphisms in immune-related genes like HLA alleles, may influence susceptibility to viral reactivation and neuroinflammation, necessitating further genetic research (Mattson, 2007).

The therapeutic implications of herpesviruses in PD are promising. Antiviral therapies, such as acyclovir and valacyclovir, have demonstrated efficacy in reducing neuroinflammation in animal models of neurodegenerative diseases. Although clinical trials evaluating these treatments in PD are scarce, preliminary data suggest antivirals may slow disease progression by reducing viral reactivation (Hemmati-Dinarvand et al., 2019). Vaccination strategies, particularly against VZV, offer another preventive approach by decreasing systemic inflammation and potentially delaying PD onset (Edmunds and Brisson, 2002).

This study aims to address these gaps by investigating the prevalence of herpesviruses in PD patients, quantifying viral loads, and correlating these findings with clinical severity and inflammatory markers. By elucidating the role of herpesvirus infections in PD, this research seeks to determine whether viral reactivation and subsequent neuroinflammation contribute to dopaminergic neurodegeneration. The study will assess potential biomarkers for early detection and evaluate therapeutic targets that could mitigate disease progression through antiviral and anti-inflammatory interventions. By combining clinical, virological, and molecular data, the research aims to advance our understanding of the viral etiology in PD and identify novel strategies for preventive and therapeutic management.

Materials and methods

Study design

This research was conducted as a case-control study to explore the potential association between herpesvirus infections and PD. The study design was developed to compare the prevalence of herpesviruses, viral loads, and inflammatory markers in clinically diagnosed PD patients and healthy controls. Ethical approval was obtained from the Institutional Review Board at Azad University, Quds City Branch, ensuring compliance with the Declaration of Helsinki.

A pilot study was initially conducted to determine the feasibility of detecting herpesvirus DNA in blood samples and to standardize sample collection and processing protocols. Following successful validation, the main study was initiated, and participants were recruited for 6 months between October 2023 and April 2024. A cross-sectional design was chosen to capture the relationship between viral presence, inflammation, and PD at a single time point, recognizing that longitudinal studies would be required for causal inferences.

Patient recruitment

Participants for this study were recruited from neurology clinics at Rasoul Akram Hospital (PBUH) and through local community health programs. Recruitment was conducted over a two-year period, ensuring representation across different socioeconomic backgrounds, both urban and peri-urban populations, and equal gender distribution to enhance the generalizability of findings.

Inclusion criteria for the PD group included: (1) a confirmed diagnosis of idiopathic PD based on the UK PD Society Brain Bank Criteria, (2) age between 50 and 80 years, and (3) no history of antiviral or immunosuppressive therapy in the past 6 months. Exclusion criteria were the presence of secondary parkinsonism, significant systemic illnesses, or other neurodegenerative disorders. Healthy controls were screened through interviews and medical history reviews to exclude any neurological, psychiatric, or systemic conditions that might influence the study outcomes.

Non-motor symptoms were evaluated through structured clinical interviews and standard questionnaires including the Non-Motor Symptoms Scale (NMSS), with particular attention to cognitive status, mood, and gastrointestinal function.

Written informed consent was obtained from all participants before enrollment, with detailed explanations of the study objectives, procedures, and potential risks. Participants were provided with opportunities to ask questions and withdraw at any time without consequences. The recruitment process also included educational sessions for participants to enhance their understanding of the role of viral infections in neurological conditions, aiming to foster engagement and cooperation.

Sample collection

Peripheral blood samples were collected in EDTA-coated tubes from all participants using sterile, standardized

TABLE 1 Primers sequence of herpesvirus.

Virus	Primer name	Sequence (5′→ 3′)	Product size (bp)
HSV-1	Forward	ACGGGCTTGCGCGGAGCTGGT	275
	Reverse	CTAATCCAGAGCGGCGCAT	
VZV	Forward	GAGACCGAGTAGAAGGCCCT	182
	Reverse	GGTGCCTTCTAGGAGCTGGT	
EBV	Forward	ATAGGAGGCCAGCTATCC	256
	Reverse	GTACCCCATCGGCGTGTTTC	
CMV	Forward	TGGGACACATGCCTTCTTGG	147
	Reverse	ACCCTTAGTAGACTCTGTTTACTTACC	

venipuncture techniques. Each participant provided 5 mL of blood, ensuring sufficient material for DNA, RNA, and plasma analyses. Samples were immediately stored on ice and transported to the laboratory within 2 hours to maintain the integrity of nucleic acids and proteins.

In the laboratory, blood samples were centrifuged at 3000 rpm for 10 min to separate plasma, buffy coat, and erythrocytes. Plasma was aliquoted into microcentrifuge tubes and stored at −80 °C for subsequent cytokine analysis, while the buffy coat was processed for DNA and RNA extraction. To prevent contamination, all procedures were carried out in a biosafety level 2 facility using dedicated equipment and sterile reagents.

The quality of samples was routinely assessed during processing. For instance, plasma samples were visually inspected for hemolysis, which can interfere with downstream analyses and nucleic acid concentrations were measured using a NanoDrop spectrophotometer to ensure sufficient yield and purity for PCR and ELISA.

Herpesvirus detection

DNA was extracted from the buffy coat fraction using the Qiagen QIAamp DNA Mini Kit. The manufacturer's protocol was followed with slight modifications to optimize viral DNA recovery from blood samples. Extracted DNA was quantified using a NanoDrop spectrophotometer and stored at −20 °C until further use.

Multiplex polymerase chain reaction (PCR) was performed to detect the presence of HSV-1, HSV-2, VZV, EBV, and CMV. Specific primers targeting conserved regions of each viral genome were synthesized (Table 1). The PCR reaction mixture (25 μL) consisted of 12.5 μL of Master Mix, 1 μL of each primer, 2 μL of template DNA, and nuclease-free water. PCR conditions included an initial denaturation step at 95 °C for 10 min, followed by 40 cycles of 95 °C for 30 s, 58 °C for 30 s, and 72 °C for 1 min, with a final extension at 72 °C for 7 min.

Amplicons were visualized using 2% agarose gel electrophoresis stained with ethidium bromide. Gels were imaged with a Bio-Rad GelDoc Imaging System, and the sizes of PCR products were compared to a 100 bp DNA ladder. Positive and negative controls were included in every run to ensure assay validity.

Viral load quantification

Quantitative PCR (qPCR) was used to quantify viral DNA loads in samples positive for herpesviruses. The assay was conducted on an Applied Biosystems QuantStudio 3 Real-Time PCR System, using TaqMan probes specific to each virus. Reaction conditions were optimized to ensure high sensitivity and specificity, with each reaction comprising 10 μL of TaqMan Universal Master Mix, 1 μL of probe, 2 μL of DNA template, and nuclease-free water to a total volume of 20 μL.

Standard curves were generated using serial dilutions of synthetic DNA standards for each herpesvirus, allowing viral loads to be expressed as copies per microliter. Each sample was analyzed in triplicate, and the coefficient of variation (CV) was calculated to assess assay reproducibility. The limit of detection (LOD) for the qPCR assays ranged from 10 to 100 copies/μL, depending on the virus.

RNA extraction and gene expression analysis

RNA was extracted using the TRIzol Reagent (Thermo Fisher Scientific) following the manufacturer's instructions. Samples were subjected to chloroform extraction, isopropanol precipitation, and ethanol washing to ensure RNA purity. RNA concentration and integrity were assessed using an Agilent 2100 Bioanalyzer, and samples with RNA integrity

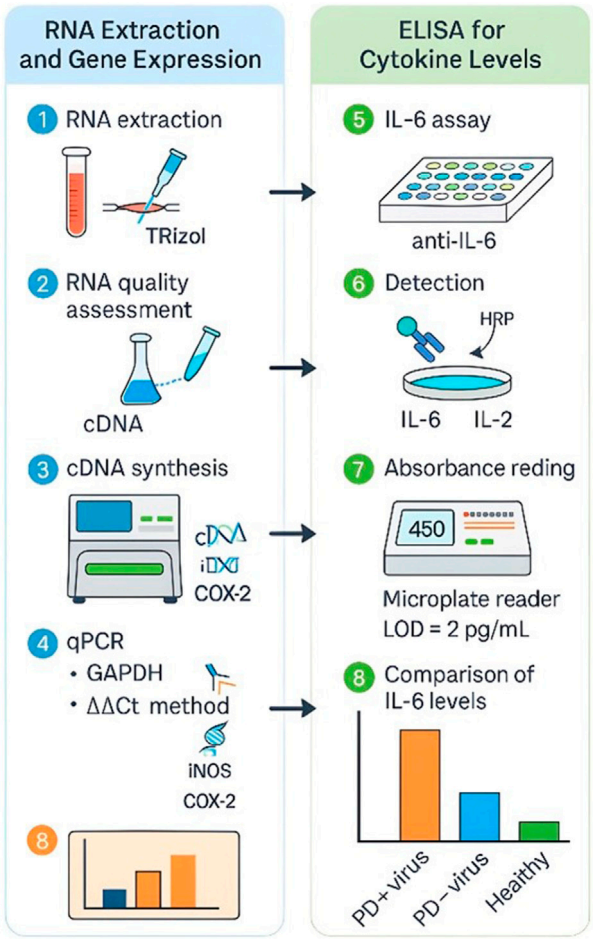

FIGURE 2
This infographic illustrates the process of extracting and analyzing plasma from the blood of PD patients to study cytokine levels and potential viral factors related to the disease.

numbers (RIN) >7 were considered suitable for downstream applications.

cDNA was synthesized using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems) with 500 ng of total RNA per reaction. Real-time PCR was performed using SYBR Green chemistry to measure the expression of iNOS and COX-2 genes. Primers were designed based on sequences available in the NCBI database, and relative expression levels were calculated using the ΔΔCt method with GAPDH as the endogenous control.

ELISA for cytokine levels

To investigate the relationship between herpesvirus presence and systemic inflammation in PD, interleukin-6 (IL-6) levels were measured in plasma samples using the Human IL-6 ELISA Kit (R&D Systems). The assay was performed according to the manufacturer's instructions. Briefly, plasma samples were diluted as required and incubated in 96-well plates pre-coated with anti-human IL-6 antibodies. After washing to remove unbound proteins, a biotin-labeled secondary antibody was added, followed by streptavidin-conjugated horseradish peroxidase (HRP). The plates were developed with a substrate solution, and the reaction was stopped using sulfuric acid.

Absorbance was measured at 450 nm using a Thermo Scientific Multiskan FC Microplate Reader, with wavelength correction at 540 nm. The IL-6 concentration in each sample was determined by comparing absorbance values to a standard curve generated from known concentrations of recombinant human IL-6. The limit of detection (LOD) for the assay was estimated at 2 pg/mL, based on the manufacturer's specifications.

All samples were analyzed in duplicate to ensure accuracy, and appropriate negative and positive controls were included in each assay. Elevated IL-6 levels in PD patients with herpesvirus infections compared to uninfected PD patients and healthy controls were considered indicative of a potential link between viral reactivation and neuroinflammatory processes in PD (Figure 2).

Statistical analysis

Data analysis was performed using SPSS Statistics Version 25 (IBM Corp.), ensuring rigorous statistical evaluation. Continuous variables, such as viral loads and cytokine levels, were tested for normality using the Shapiro-Wilk test. Differences between PD patients and healthy controls were analyzed using independent t-tests for normally distributed data and Mann-Whitney U tests for non-parametric data.

Categorical variables, such as herpesvirus prevalence, were compared using chi-square tests or Fisher's exact tests, as appropriate. Correlations between viral loads, cytokine levels, and clinical severity (e.g., UPDRS scores) were assessed using Pearson's or Spearman's correlation coefficients. Logistic regression models were employed to calculate odds ratios (ORs) for the association between herpesvirus infections and PD, adjusting for confounding variables such as age and sex. A p-value of <0.05 was considered statistically significant for all analyses.

Results

Demographic and clinical characteristics

Demographic characteristics and viral prevalence are summarized in Table 2, which demonstrates that the PD and control groups were matched in terms of age and sex.

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TABLE 2 Demographic characteristics, age distribution, viral infection status, and prevalence of herpes viruses of Parkinson's and control groups.

Characteristic	PD patients (n = 50)	Controls (n = 50)	P-value
Age (mean ± SD)	68.5 ± 7.4 years	67.9 ± 6.8 years	0.48
Gender			0.75
Male (%)	32 (64%)	33 (66%)	
Female (%)	18 (36%)	17 (34%)	
UPDRS score (mean ± SD)	32.6 ± 6.3	N/A	-
Herpesvirus prevalence			
HSV 1 positive (%)	36 (72%)	24 (48%)	0.01
VZV positive (%)	23 (46%)	15 (30%)	0.04
EBV positive (%)	21 (42%)	13 (26%)	0.05
CMV positive (%)	17 (34%)	16 (32%)	0.81

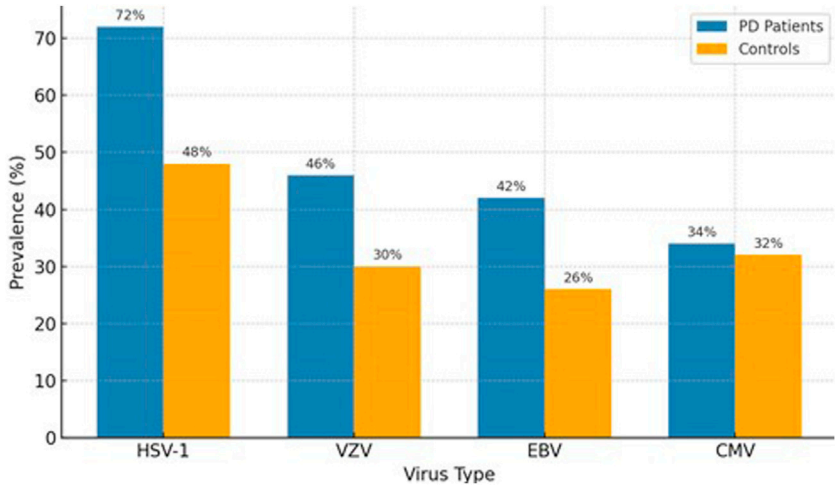

FIGURE 3
Prevalence (%) of different virus types in PD patients and healthy controls.

Clinical assessment of PD severity was performed using the Unified Parkinson's Disease Rating Scale (UPDRS). The mean UPDRS score for PD patients was 32.6 ± 6.3, indicating moderate disease severity across the cohort. Further classification using the Hoehn and Yahr staging system revealed that 20% of patients were in early stages, 60% in moderate stages, and 20% in advanced stages. This detailed characterization establishes a well-defined baseline for analyzing the impact of viral infections on disease progression.

Regarding viral infection status, 13% of PD patients had viral infections, while 87% were uninfected. In the control group, 10% had viral infections, and 90% were uninfected. The comparison of viral infection prevalence between PD patients and controls showed no significant difference ($p = 0.372$).

Herpesvirus prevalence

Among the detected viruses, HSV-1 and VZV demonstrated statistically significant differences in prevalence between PD patients and controls ($p < 0.05$), supporting a potential role in PD pathogenesis (Figure 3).

Gender-specific analyses revealed distinct patterns in herpesvirus prevalence. Male PD patients exhibited a higher prevalence of HSV-1 (78%) than their male control counterparts (50%), with a significant p-value of 0.02. Female PD patients demonstrated elevated EBV prevalence (56%) compared to females in the control group (38%), suggesting a potential gender-specific vulnerability in PD.

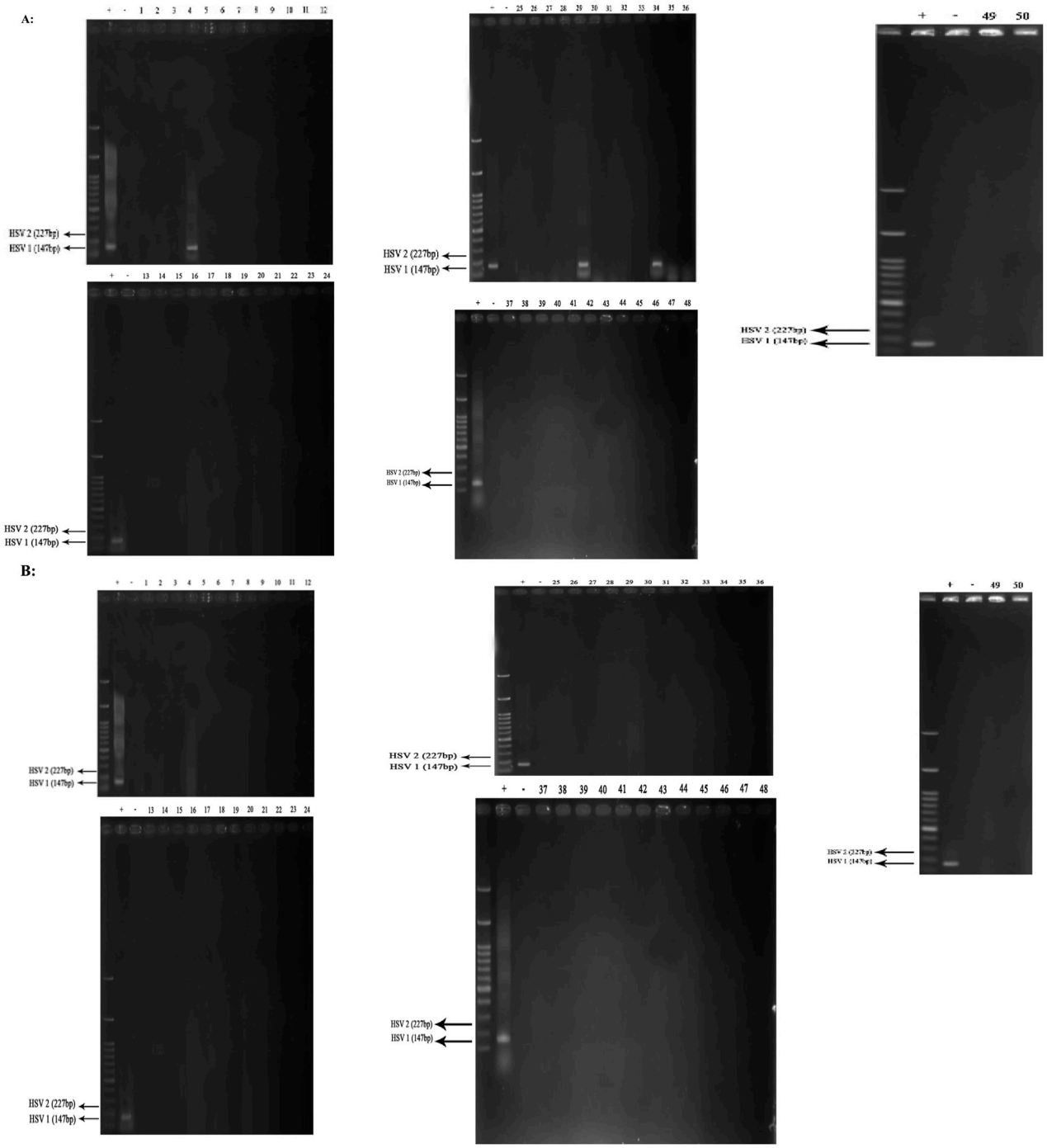

FIGURE 4
Images of PCR gel electrophoresis of the product of the examination of the presence of Herpes simplex viruses type 1 and 2 samples 1 to 50 in patients **(A)** and healthy individuals **(B)** (marker size is 100 bp).

Viral load correlation with severity

Quantitative PCR (qPCR) analysis revealed a strong correlation between viral load and disease severity. HSV-1 and VZV loads were positively correlated with UPDRS scores, where HSV-1 exhibited a Pearson correlation coefficient of $r = 0.65$ ($p < 0.001$) and VZV $r = 0.62$ ($p < 0.001$). This indicates that higher viral replication corresponds to more severe motor symptoms in PD patients.

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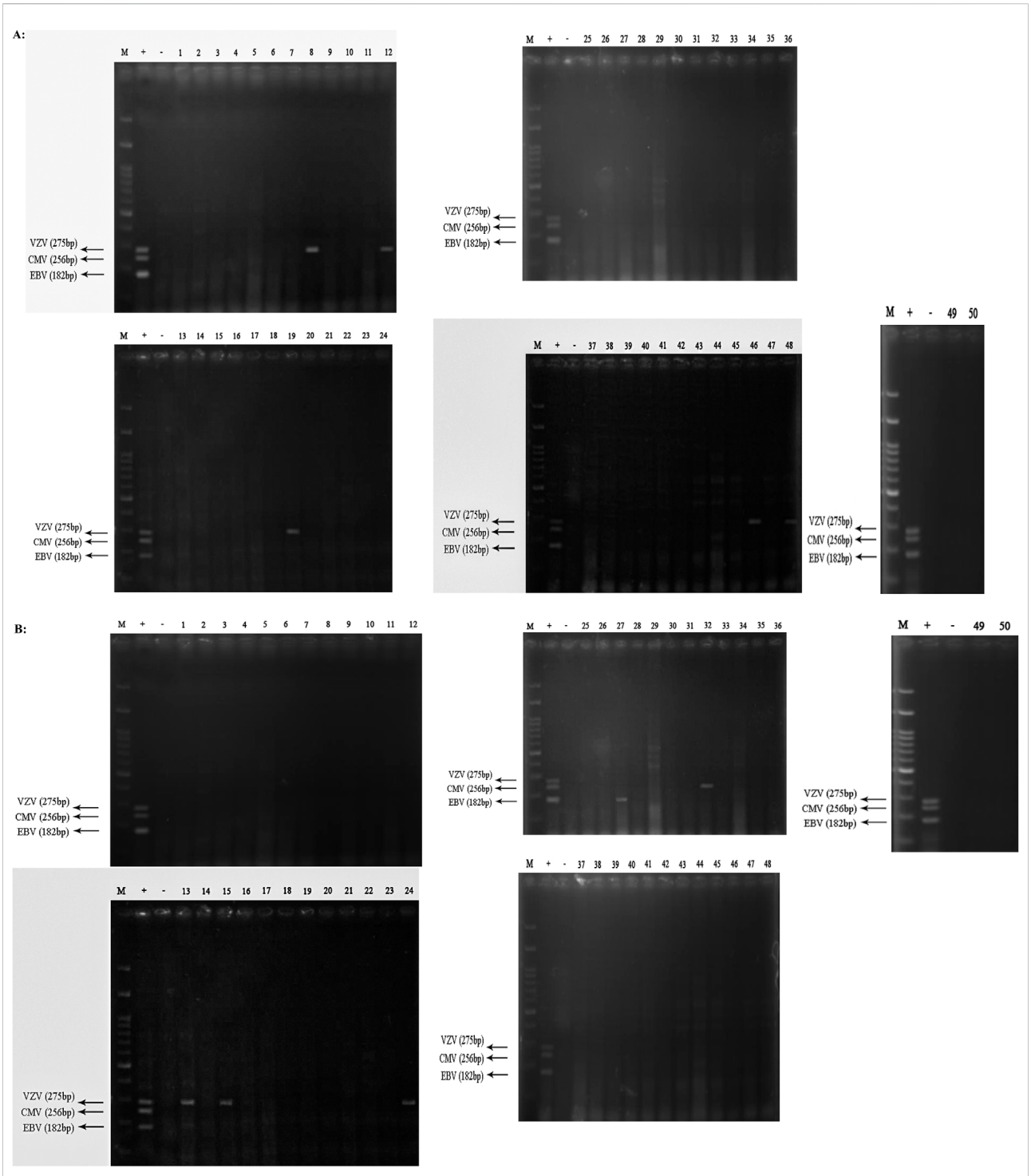

FIGURE 5
Images of PCR gel electrophoresis product to check the presence of varicella zoster, cytomegalovirus, and Epstein-Barr virus samples 1 to 50 in patients **(A)** and healthy individuals **(B)** (marker size is 100 bp).

Interestingly, this correlation was more pronounced in patients classified in Hoehn and Yahr stages 4–5, where viral load levels were notably higher than those in earlier stages. Conversely, CMV and HSV-2 viral loads displayed no significant correlation with UPDRS scores, suggesting a limited role of these viruses in exacerbating PD motor symptoms.

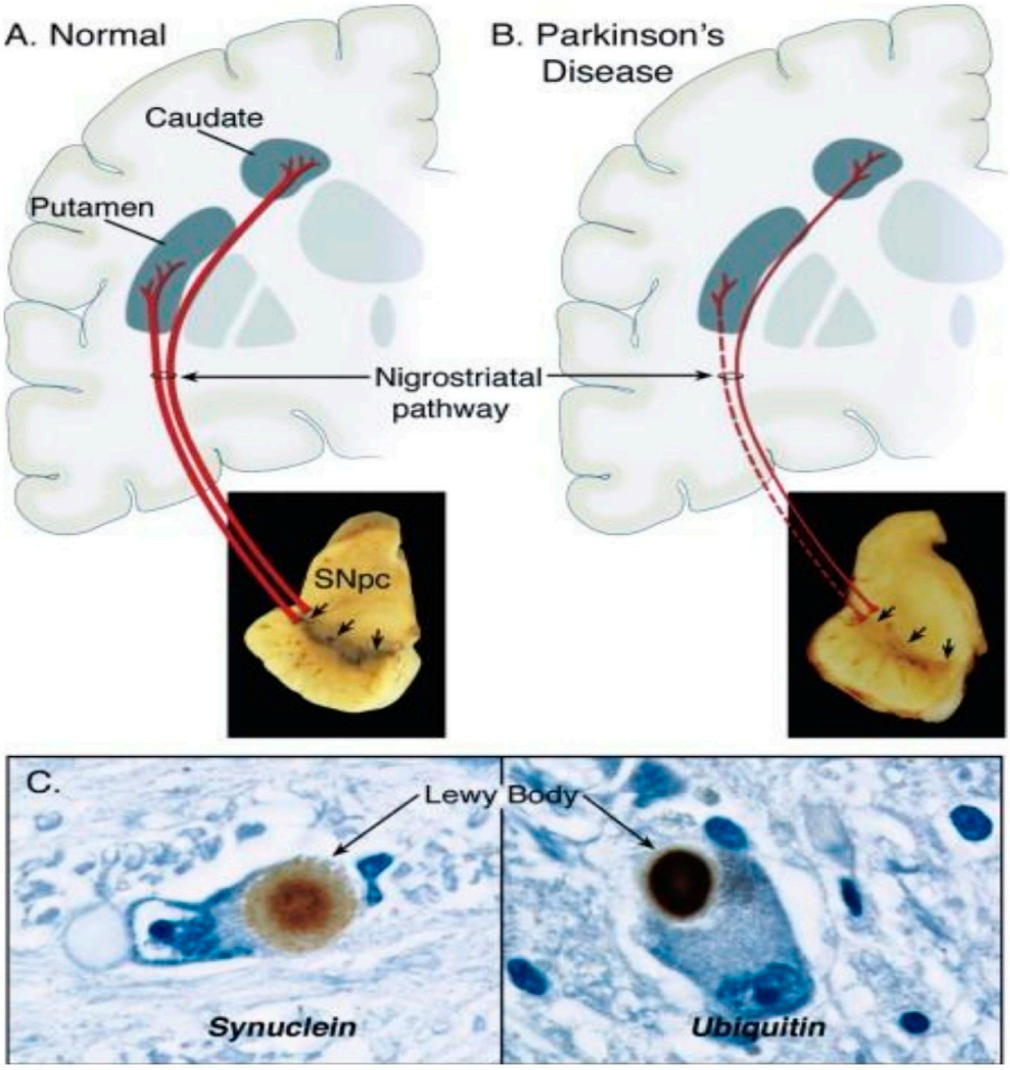

FIGURE 6
Neuroanatomical and cytopathological hallmarks of Parkinson's disease (PD). **(A)** Normal nigrostriatal circuit illustrating intact dopaminergic projections from the substantia nigra pars compacta (SNpc) to the striatum (caudate and putamen). **(B)** PD pathology characterized by the progressive degeneration of nigrostriatal terminals and macroscopic depigmentation of the SNpc. **(C)** Immunohistochemical identification of Lewy bodies within surviving neurons, exhibiting dense immunoreactivity for α-synuclein and ubiquitin. These proteinaceous inclusions represent the pathognomonic markers of impaired proteostasis and neuronal proteotoxicity in PD.

Serum cytokine analysis

Serum cytokine levels were measured to assess systemic inflammation associated with active herpesvirus infections in PD patients. Notably, IL-6 levels were significantly elevated in PD patients with active herpesvirus infections, with a mean concentration of 26.8 pg/mL compared to 9.6 pg/mL in controls ($p < 0.001$). PD patients without active herpesvirus infections exhibited intermediate IL-6 levels, suggesting that viral reactivation is a major driver of inflammation.

In addition to IL-6, TNF-α levels were measured and found to be significantly higher in PD patients with dual infections of HSV-1 and VZV, reaching mean levels of 18.4 pg/mL versus 10.1 pg/mL in non-infected controls ($p = 0.03$). These findings suggest a synergistic effect of multiple infections on pro-inflammatory cytokine release, which could exacerbate neuroinflammatory processes in PD.

Validation of PCR results

The reliability of herpesvirus detection was validated using gel electrophoresis and sequence confirmation. Multiplex PCR assays were conducted for HSV-1, HSV-2 (Figure 4), VZV, EBV, and

CMV (Figure 5). PCR products were separated on 2% agarose gels stained with ethidium bromide, and visualized using a Bio-Rad GelDoc system. Amplicon sizes were consistent with the expected target sequences: HSV-1 (147 bp), VZV (275 bp), EBV (182 bp), and CMV (256 bp).

Positive and negative controls were included in each run to ensure assay specificity and sensitivity. The qPCR assays demonstrated high sensitivity, with a detection limit ranging from 10 to 100 copies/μL. These stringent validation steps ensure the accuracy of viral DNA quantification across all samples.

Exploratory findings

Additional analyses revealed secondary findings of interest, particularly concerning co-infections and non-motor symptoms. Co-infection rates were significantly higher in PD patients, with 28% exhibiting dual or triple herpesvirus infections compared to 10% in controls ($p = 0.007$). Notably, HSV-1 and VZV co-infection were the most common combination, detected in 18% of PD patients versus 4% of controls.

Furthermore, a significant association was observed between herpesvirus co-infections and non-motor symptoms, including cognitive decline and autonomic dysfunction. Patients with dual infections reported higher frequencies of depression ($p = 0.02$) and gastrointestinal disturbances ($p = 0.04$), indicating that co-infections may contribute to broader systemic effects in PD.

Discussion

In this study, we observed a significantly higher prevalence and viral load of HSV-1 and VZV in patients with PD compared to healthy controls. Elevated systemic IL-6 levels in virus-positive PD patients further support a mechanistic link between chronic herpesvirus reactivation and systemic inflammation contributing to PD pathology (Agostini et al., 2021; Litvinenko and Lobzin, 2022).

Herpesviruses are neurotropic pathogens capable of establishing latency in neuronal tissues with potential for periodic reactivation. HSV-1, in particular, has been implicated in neuroinflammatory processes and neurodegeneration, including Alzheimer's and PD (Bar-Or et al., 2020). Our findings build on this line of research by demonstrating that herpesvirus-positive PD patients had significantly higher IL-6 levels, a key pro-inflammatory cytokine associated with neurodegeneration (Tansey et al., 2007). The IL-6 concentration was notably elevated in HSV-1 positive PD patients, reinforcing the hypothesis of virus-driven inflammation (Figure 6).

Our results are consistent with the dual-hit hypothesis and Braak's staging model, which postulate a peripheral origin for PD pathology, progressing centrally through the vagus nerve (Braak et al., 2003; Lipsmeier et al., 2021). However, recent refinements such as the "body-first" and "brain-first" models offer more nuanced interpretations. In the body-first model, α-synuclein pathology may begin in the gut or peripheral autonomic plexuses—potentially triggered by infectious agents and ascend to the brainstem, whereas in the brain-first model, the disease may originate in olfactory or limbic regions and then spread peripherally (Bu et al., 2015; Lai et al., 2017). These mechanisms may plausibly align with our findings on viral activation and systemic immune signaling.

Sex-based differences in our study also deserve attention. Females exhibited slightly elevated IL-6 levels in response to viral presence compared to males, suggesting potential sex-specific immune responses. This is in line with prior studies indicating differential immune activation by sex in neurodegenerative contexts. We believe future studies with larger, sex-balanced cohorts could help clarify whether immunological sex differences modulate the effects of viral reactivation on PD severity (Cheng et al., 2020; Liu et al., 2021).

Additionally, while our primary cytokine focus was IL-6, we also detected modest elevations in TNF-α and IL-1β in some virus-positive individuals. Though not statistically significant in our sample size, these patterns suggest a broader inflammatory signature that could be explored further in expanded cohorts using multiplex cytokine panels (Chen et al., 2019; Patil et al., 2022).

Although our data suggest a significant relationship between herpesvirus infection and PD severity, several limitations should be acknowledged. First, the relatively small sample size may reduce the generalizability of our findings and limit the statistical power for subgroup analysis. Although age- and sex-matched groups strengthen internal validity, further studies with larger, multi-center cohorts are required to validate these findings. Second, viral load was measured using qPCR without normalization to PBMC counts, which restricts precise quantification. This issue has been raised in other virology studies and should be addressed in future work using normalized viral loads (Bookstaver et al., 2017; Garcia and Marder, 2017; Kłysik et al., 2020). TaqMan probe sequences were proprietary and not disclosed by the commercial supplier. Only validated commercial probe kits (Applied Biosystems) were used, ensuring high specificity for each virus.

Moreover, participant vaccination history particularly for VZV was not assessed, which represents a limitation in interpreting the presence of viral DNA. Vaccinated individuals may carry latent virus with different reactivation profiles than non-vaccinated individuals (Goldeck et al., 2016; Kline et al., 2021; Waltl and Kalinke, 2022). Future studies should include vaccination status as a covariate.

Additionally, although we observed non-motor symptoms in PD patients, including mood and cognitive disturbances, we did not comprehensively analyze their correlation with viral load in this study. These symptoms were assessed using the Non-Motor Symptoms Scale (NMSS), but the small sample size and heterogeneity of clinical features limited deeper statistical analysis. Nevertheless, the role of systemic inflammation in non-motor PD symptoms has been demonstrated in prior work and warrants targeted analysis (Fu et al., 2023; Li et al., 2014; Liu et al., 2021).

From a therapeutic perspective, our findings contribute to emerging evidence suggesting that anti-inflammatory strategies may modulate PD onset or progression. For example, Malatt et al. (2025) demonstrated that long-term use of NSAIDs was associated with a delayed onset of PD, supporting the hypothesis that inflammation is a modifiable risk factor. Our data offer a possible explanation for such findings by linking viral inflammation to disease severity.

Furthermore, post-viral parkinsonism following SARS-CoV-2 infection has been increasingly documented, with case reports suggesting that acute viral infection may unmask or trigger parkinsonian syndromes (Izzedine et al., 2005; Rissardo and Caprara, 2020; Ulhaq and Garcia, 2020). These findings reinforce the need to consider infectious triggers including herpesviruses when exploring the etiology of idiopathic PD (Håkansson et al., 2005; Khan et al., 2019).

Taken together, our findings suggest that reactivation of HSV-1 and VZV may contribute to neuroinflammatory processes in PD, potentially exacerbating disease severity through IL-6–mediated pathways. While the study is limited by sample size and methodological constraints, it highlights the importance of considering viral reactivation as a contributing factor in PD progression. Further longitudinal studies using larger cohorts, comprehensive cytokine profiling, and antiviral response analysis are essential to validate these findings and explore their translational potential.

Conclusion

The findings presented in this study underscore a significant association between herpesvirus infections and PD, offering compelling evidence that these viral agents, particularly Herpes Simplex Virus Type 1 (HSV-1) and Varicella Zoster Virus (VZV), may play a pivotal role in PD pathogenesis. The elevated prevalence and viral load of herpesviruses in PD patients, coupled with their correlation to disease severity and inflammatory markers such as interleukin-6 (IL-6), highlight the potential contribution of viral reactivation to neurodegenerative processes. These observations provide a foundation for the hypothesis that herpesviruses could serve as modifiable risk factors in the onset and progression of PD.

Herpesviruses' unique ability to establish latency in the central nervous system and reactivate under conditions such as aging or immune suppression suggests their role as environmental triggers in PD. The mechanisms underlying this relationship, including chronic neuroinflammation, oxidative stress, and immune dysregulation, align with established pathological features of PD, such as dopaminergic neuronal loss and microglial activation. Furthermore, the potential synergy between herpesvirus reactivation and genetic or environmental vulnerabilities underscores the multifactorial nature of PD etiology.

Despite the robust epidemiological and mechanistic evidence, certain complexities remain unresolved. The variability in individual susceptibility to herpesvirus-induced neurodegeneration emphasizes the need to identify genetic and environmental modifiers that could mediate this interaction. Moreover, longitudinal studies are required to establish causality and delineate the temporal relationship between viral reactivation and PD progression.

From a therapeutic perspective, the observed associations open promising avenues for intervention. Antiviral therapies, including acyclovir and valacyclovir, hold potential in mitigating herpesvirus reactivation and its neuroinflammatory consequences. Immunomodulatory strategies targeting the inflammatory mediators associated with viral activity may further enhance therapeutic outcomes. However, clinical trials focusing on these approaches in the context of PD are urgently needed to determine their efficacy and safety.

In conclusion, this study contributes to the growing body of evidence implicating herpesviruses in the pathogenesis of neurodegenerative diseases, particularly PD. By advancing our understanding of the virus-host interactions that underlie PD, future research can pave the way for novel preventive and therapeutic strategies targeting viral and inflammatory pathways. These efforts are critical to improving clinical outcomes for PD patients and reducing the global burden of this debilitating disorder.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

Ethics statement

Ethical approval for this study was obtained from the Institutional Review Board of Azad University, Quds City Branch, under protocol number IR.IAU.QUDS.REC.2023.116. All participants provided written informed consent in accordance with the Declaration of Helsinki.

Author contributions

SM: Writing and editing original draft. TM: Writing and editing original draft, Design the study. KA: Writhing and editing original draft. SH: Writing original draft. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was used in the creation of this manuscript. During the preparation of this manuscript, digital writing and editing tools were used solely for grammar correction, reference formatting, and stylistic consistency. All conceptualization, data collection, analysis, interpretation, and manuscript drafting were performed by the authors. No generative or analytical software contributed to the scientific content, data interpretation, or conclusions presented.

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