· Review ·

# Advances in research on the role of autoimmunity in psychiatric sequelae of viral encephalitis

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## Abstract

The pathophysiological understanding of viral encephalitis is shifting from a paradigm of direct viral injury to one emphasizing combined infection–immune–mediated damage. This review focuses on how viral infection and autoimmunity act synergistically to promote encephalitis-related psychiatric sequelae. In addition to disrupting the blood–brain barrier and activating innate neuroinflammation, viral infections can induce neuron-specific autoantibodies, such as anti – N-methyl-D-aspartate receptor (NMDAR) antibodies, leading to sustained immune-mediated synaptic dysfunction and neuronal injury. These immunopathological processes preferentially affect the prefrontal cortex, temporal lobe, and limbic system, providing a mechanistic explanation for the high prevalence of acute and long-term psychiatric manifestations, including delirium, cognitive impairment, mood disorders, and psychosis. By integrating evidence from clinical phenotypes, cytokine signaling, exosomes, and neuroimaging, this review underscores the limitations of antiviral therapy alone and highlights the rationale for early combined immunomodulatory interventions to improve long-term neuropsychiatric outcomes following viral encephalitis.

**Keywords:** viral encephalitis, autoimmunity, neuroinflammation, herpes simplex virus, anti-NMDAR encephalitis, psychiatric symptoms, cognitive impairment

## Introduction

Encephalitis is a major global neurological disorder characterized by high morbidity and mortality, affecting individuals across all age groups, with children and older adults being particularly vulnerable. The condition is primarily caused by pathogen infection—most commonly viral—or by autoimmune-mediated mechanisms [1]. Among infectious etiologies, viral infections predominate [2]. Viral encephalitis(VE) refers to inflammatory lesions of the brain parenchyma resulting from infection with a range of neurotropic RNA or DNA viruses [3]. Common causative agents include herpes simplex virus type 1 and type 2, non-polio enteroviruses, and arthropod-borne viruses such as dengue virus, Zika virus, and chikungunya virus. In

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addition, seasonal influenza viruses, cytomegalovirus, Epstein–Barr virus, human herpesvirus type 6, and re-emergent measles virus have also been implicated [4]. Among these, herpes simplex virus type 1 exhibits marked neuroinvasiveness and causes particularly destructive brain infections [5]. Given the high sensitivity of the central nervous system to pathogenic insults and its limited regenerative capacity, immune-mediated injury frequently results in irreversible neurological deficits [6].

The clinical manifestations of viral encephalitis are heterogeneous and depend on the severity of inflammation, the extent of viral dissemination, and the specific brain regions involved. Typical features include acute fever, headache, altered consciousness, seizures, and focal neurological deficits. Notably, survivors often experience severe neuropsychiatric sequelae [7–9]. This review focuses on recent advances in the understanding of viral encephalitis and its associated psychiatric manifestations.

## The "Dual-Hit" mechanism and the central role of neuroinflammation

### *The "Dual-Hit" mechanism*

The pathogenesis of VE is multifactorial rather than driven by a single insult. Using herpes simplex virus (HSV) infection as an example, CNS injury evolves through a stepwise process involving direct viral cytotoxicity, induction of inflammatory responses, and subsequent activation of virus-specific immune responses, ultimately leading to sustained damage to the central nervous system (CNS). Crucially, viral infection and the subsequent autoimmune response it triggers act synergistically, delivering a "dual-hit" to the CNS. This combined assault progressively disrupts the blood – brain barrier (BBB), promotes irreversible injuries like neuronal necrosis, and ultimately leads to long-term neurological deficits.

### *The central role of neuroinflammation*

The neuroinflammation hypothesis is now widely accepted, with neuroinflammation—defined as inflammation centered within the CNS—considered a common biological basis for diverse neuropathological alterations [10]. Within the CNS parenchyma, microglia, the resident innate immune cells, maintain their population through local proliferation. They express a broad array of pattern recognition receptors, enabling continuous surveillance of the microenvironment and rapid immune responses, thereby constituting the first line of CNS immune defense. Upon activation, microglia release cytokines and chemokines, subsequently activating astrocytes and recruiting peripheral immune cells to sites of injury, collectively amplifying the inflammatory cascade [11–13]. Activated microglia exhibit macrophage-like functional plasticity and can polarize toward pro-inflammatory (M1) or anti-inflammatory/repair (M2) phenotypes, thereby profoundly influencing the trajectory of neuroinflammation [14].

Emerging evidence has identified specific immune cell subsets that drive inflammation in herpes simplex encephalitis (HSE) [15]. Immune cell infiltration into the CNS, together with BBB disruption, further exacerbates neuroinflammation during HSE, creating a vicious cycle [16]. Similarly, in Japanese encephalitis (JE), a well-recognized mechanism involves Japanese encephalitis virus (JEV) breaching the BBB and robustly activating microglia and astrocytes, triggering intense neuroinflammatory responses that culminate in neuronal injury [17]. BBB dysfunction increases its permeability, facilitating the entry of inflammatory mediators and peripheral immune cells into the brain

parenchyma, thereby directly promoting neuroinflammation and the development of associated psychiatric symptoms [18].

During CNS viral infection, microglia play a pivotal protective role by initiating both innate and adaptive immune responses. However, this process may become dysregulated. Aberrant interactions between microglia and T cells can drive pathological synaptic stripping (synapse engulfment) and promote neuronal apoptosis, ultimately contributing to neurocognitive impairment [9]. In particular, stimulation by T-cell-derived cytokines such as interferon-γ (IFN-γ) can enable microglia to directly or indirectly induce neuronal loss and disrupt neural architecture. Whether these detrimental microglial effects represent a passive consequence of neuroinfection or an active amplification of inflammatory injury during VE remains an important question requiring further investigation.

## Immunopathological mechanisms

### *Core components of immune-mediated injury*

Recent studies increasingly demonstrate that viral-induced damage to the central nervous system (CNS) extends far beyond direct viral cytotoxicity. Immune-mediated neuroinflammation plays a central role in driving long-term neuropsychiatric sequelae. Key pathological events involve three interconnected processes: (1) the persistent aberrant activation of microglia; (2) the emergence of pro-inflammatory cytokine storms (e.g., IL-6, IL-1β, TNF-α); and (3) the production of autoantibodies against neuronal surface antigens, notably the N-methyl-D-aspartate receptor (NMDAR) [19]. Collectively, these immune responses lead to functional impairment of brain regions critical for emotion and cognition, including the limbic system and prefrontal cortex.

This immune-mediated process is highly complex. It involves extensive interactions among diverse elements, including cytokines, genetic factors, microRNAs (miRNAs), exosomes, and numerous cellular and subcellular components. Direct viral infection of microglia, astrocytes, or neurons can profoundly reshape the cerebral immune microenvironment, exacerbate inflammatory states, and induce secondary cellular injury. Such immune dysregulation–driven pathology may cause clinical manifestations to evolve from early neurocognitive or motor deficits to severe autoimmune encephalitis（AE), such as anti-NMDAR encephalitis, and may ultimately result in death [20–23].

### *Transition from HSE to autoimmune encephalitis*

Clinically, disease relapse occurring in patients with HSE after antiviral therapy is often not attributable to viral reactivation, but rather driven by newly emerging autoimmune responses. These responses specifically target synaptic antigens within the CNS, most notably NMDAR and the γ-aminobutyric acid type B receptor ($GABA_B$ R). Evidence indicates that HSV infection of the CNS not only induces anti-NMDAR antibodies [24], but may also trigger autoimmune responses associated with anti-$GABAB_B$ R antibodies [25]. The presence of these autoantibodies in the cerebrospinal fluid (CSF) is closely correlated with disease relapse and progression, underscoring the decisive role of immunopathological mechanisms in the long-term outcomes of HSE.

Prospective clinical studies have shown that up to 27% of patients with HSE develop AE following the acute phase, a process commonly associated with the generation of neuronal surface antibodies, particularly anti-NMDAR antibodies, and typically occurring within two months after initial HSE treatment [27]. Notably, these autoantibodies are usually absent during

the acute phase of HSE, strongly suggesting that their production represents a secondary immune response triggered by viral infection. Although the precise mechanisms remain incompletely understood, two main hypotheses have been proposed: (i) virus-induced neuronal injury leading to antigen release, and (ii) molecular mimicry between viral proteins and neuronal antigens such as NMDAR. While the detection of antibodies against multiple neuronal antigens in patients lends greater support to the antigen release hypothesis, the possibility of molecular mimicry cannot be entirely excluded [26].

It is important to emphasize that AE triggered by viral infections differs significantly from non-viral infection-induced AE. Viral Infection-Induced AE: This type, often referred to as post-infectious autoimmune encephalitis, is clinically characterized by a definite history of viral infection, typically presenting with prodromal symptoms such as fever and headache. Non-Viral Infection-Induced AE: This category is usually associated with tumors (e. g., ovarian teratoma, small cell lung cancer). It represents an onconeural or paraneoplastic response where the immune system, generated against the tumor, mistakenly attacks the brain. In these cases, evidence of infection is generally lacking, CSF pathogen tests return negative results.

In clinical practice, differentiating between these two scenarios involves the following key steps: history taking, CSF analysis (the core method), and tumor screening. Early Stage: Detect the presence of viral nucleic acids (e. g., HSV-DNA) in the CSF using methods such as PCR. A positive result supports the diagnosis of viral encephalitis. Convalescent Phase: If the CSF viral test turns negative but specific autoantibodies (e. g., anti-NMDAR antibodies) become positive, this finding strongly suggests a diagnosis of post-infectious autoimmune encephalitis.

### *Key immune mediators: IFN-γ and the interferon pathway*

Within virus-triggered immune cascades, IFN-γ produced by lymphocytes plays a complex and pivotal role. Traditionally, IFN-γ has been regarded as an auxiliary factor that amplifies pro-inflammatory microglial responses. However, emerging evidence indicates that IFN-γ exerts distinct and direct effects on microglial activation. Specifically, IFN-γ can drive microglial proliferation (microgliosis), mediate pathological synaptic elimination, and induce nitric oxide production, changes that are sufficient to impair synaptic transmission, disrupt neuronal oscillations (such as gamma rhythms), and compromise cognitive function [28]. More importantly, IFN-γ promotes the polarization of Toll-like receptor (TLR)–activated microglia toward a neurotoxic phenotype, thereby triggering metabolic dysfunction, oxidative stress, profound disruption of neural network activity, and ultimately neuronal death [29].

The biological effects of interferons are mediated through the regulation of a broad family of interferon-stimulated genes (ISGs), whose functions extend well beyond antiviral defense to encompass extensive immunomodulatory roles. During infections of the nervous system, ISGs act in a cell-type- and region-specific manner to precisely restrict viral invasion and replication within the CNS [30]. These findings highlight the existence of a finely tuned balance within the interferon signaling pathway, mediating both antiviral protection and immune-driven neuropathology.

### *Exploration of potential biomarkers*

Advances in understanding immunopathological

mechanisms have also driven the search for relevant biomarkers. Studies have shown that in patients with neuroinflammation-associated schizophrenia, there is an increased density of perivascular $CD163^+$ macrophages in the brain, which correlates with distinct cytokine profiles, including elevated interleukin levels and TNF-α concentrations [31].

In parallel, neurofilament light chain (NfL), a marker of axonal injury, has been demonstrated to hold significant value for the diagnosis, differential diagnosis, and prognostic assessment of AE. Although current studies remain heterogeneous, NfL shows substantial promise as an objective and effective adjunctive clinical biomarker [32]. The proposed sequential relationship between viral infection, immune dysregulation, neural injury, and psychiatric sequelae is summarized in Figure 1.

## The role of exosomes in autoimmunity

Recent studies have revealed that exosomes—membrane-bound nanovesicles generated via the endocytic pathway—play a critical role in immune-mediated injury associated with viral encephalitis [18,19]. Using HSV infection as an example, its pathogenic mechanisms extend well beyond direct viral cytotoxicity. HSV infection has been shown to induce the release of neuron-derived exosomes that carry viral microRNAs as well as neuronal surface antigens, such as the NMDAR. As highly efficient mediators of intercellular communication, exosomes can deliver these cargoes to the immune system, thereby initiating and amplifying immune responses directed against self-neuronal antigens. This mechanism provides a crucial new perspective for understanding neuronal injury and secondary autoimmune responses following HSE [33].

Exosomes can be released locally into the brain parenchyma and may also enter the peripheral circulation,

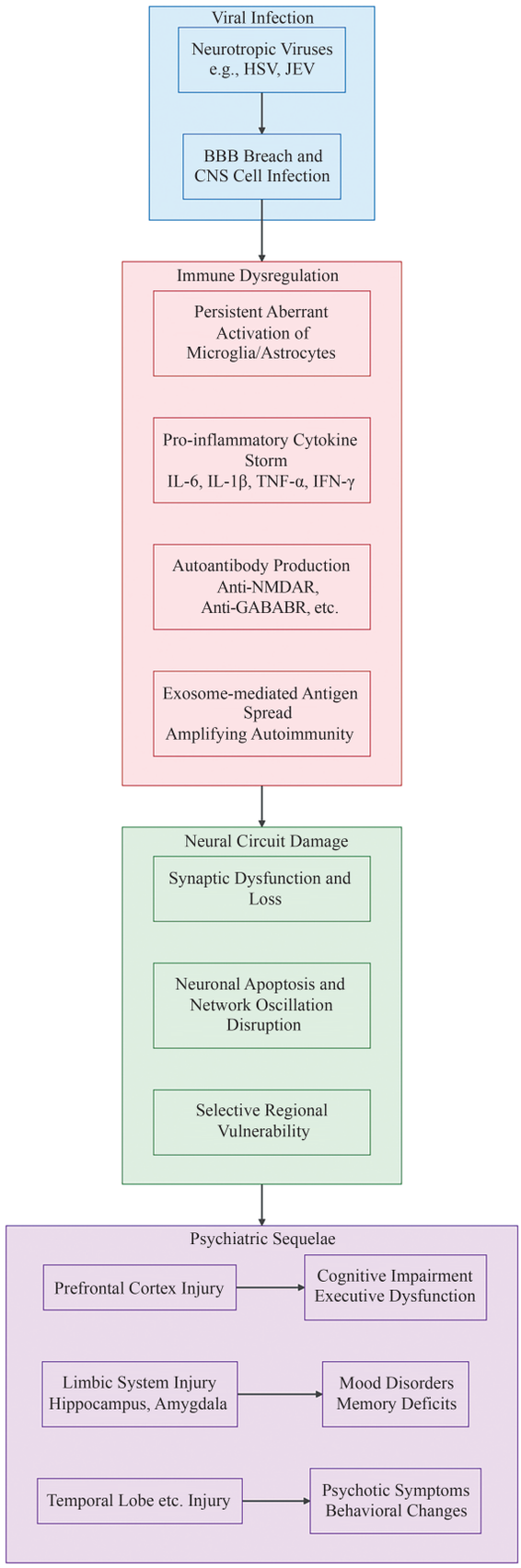


**Figure 1. Proposed pathogenic mechanisms linking viral encephalitis to autoimmune-mediated psychiatric sequelae.**

suggesting that they can function as systemic immune triggers [24]. Importantly, by presenting self-antigens on their membrane surfaces, exosomes are capable of directly activating immune cells, thereby serving as central mediators in the induction of CNS autoimmunity and neuroinflammation. This concept is supported by clinical evidence demonstrating the presence of disease-specific exosomes in the cerebrospinal fluid of patients with autoimmune encephalitis [34]. Collectively, current data indicate that virus-induced release of autoantigen-bearing exosomes represents a novel and critical pathological pathway linking viral infection to the subsequent development of autoimmune encephalitis.

## Psychiatric and behavioral disturbances in encephalitis

### *Epidemiology and clinical spectrum of psychiatric symptoms*

Psychiatric and behavioral abnormalities represent some of the most prominent clinical manifestations of encephalitis, spanning the acute phase—manifesting as delirium and cognitive impairment—and extending into long-term sequelae. Large-scale clinical studies indicate that psychiatric symptoms are highly prevalent among patients with encephalitis. An analysis of more than 600 patients with encephalitis reported that while the incidence of psychiatric symptoms was highest in AE (94.3%), more than one-third of patients with infectious encephalitis also developed such symptoms, with approximately 40% of patients with HSE being affected. Psychiatric manifestations in encephalitis fall into five major domains: behavioral abnormalities, psychotic symptoms, mood disorders, sleep disturbances, and catatonia [35].

Another study demonstrated that approximately 81% of patients with VE experience varying degrees of psychiatric disorders, with symptoms emerging at different stages of the disease course [36]. These organic psychiatric disorders are primarily characterized by cognitive decline, attentional deficits, perceptual disturbances, alterations in thought content, and changes in mood and personality. A key distinguishing feature is the frequent presence of altered consciousness, which differentiates these conditions from functional psychiatric disorders, such as primary schizophrenia [37]. Due to overlapping clinical features, encephalitis-related psychiatric symptoms are often misdiagnosed as schizophrenia, with reported misdiagnosis rates as high as 45% [38]. Accordingly, heightened clinical vigilance and careful differential diagnosis are essential to reduce diagnostic errors [39–42]. At present, reports of psychiatric symptoms associated with chronic viral encephalitis remain limited, with such manifestations occurring predominantly during the acute phase of the disease.

### *Psychiatric symptom profiles across different etiologies of encephalitis*

The distribution and predominant features of psychiatric symptoms vary according to the etiology of encephalitis. For example, patients with anti-NMDAR encephalitis exhibit not only an extremely high prevalence of psychiatric symptoms but also greater phenotypic diversity, with catatonia being particularly prominent. This feature is useful in distinguishing anti-NMDAR encephalitis from HSE and other forms of AE. In addition, different viral families are associated with distinct patterns of neurological sequelae: encephalitis caused by herpesviridae (e. g., HSE) more commonly affects cognitive and psychiatric domains, whereas flavivirus-associated encephalitis (such as infections with West Nile virus or Japanese encephalitis virus) more frequently involves motor neuronal dysfunction in addition to psychiatric manifestations [43].

***Clinical features of HSE and the risk of transition to AE***

As a major neurological complication caused by α-herpesviruses, HSE demonstrates age-dependent clinical characteristics. In children, HSE predominantly presents with movement disorders (such as chorea and athetosis) and seizures. In adults, the disease is more commonly characterized by psychiatric and behavioral disturbances, cognitive impairment or memory loss, aphasia, seizures, and altered consciousness, with severe cases progressing to coma [44,45]. Importantly, in light of the aforementioned mechanism whereby viral infection triggers autoimmunity, HSE carries a well-recognized risk of progression to AE. Studies indicate that approximately 25% of patients with HSE develop AE-related symptoms within 1–2 months following infection [4], while some cases may present with delayed-onset AE months or even years later [46]. This transition substantially increases the risk of complex and treatment-refractory psychiatric symptoms, most of which are associated with secondary anti-NMDAR encephalitis.

## Cognitive impairment

Cognitive dysfunction is one of the most common and severe sequelae of VE, with its manifestations and impact varying according to the causative pathogen and the brain regions involved. Cognitive impairment is also a core deficit in schizophrenia, in which patients typically exhibit marked declines across multiple domains, including memory and executive function [47]. This overlap suggests that cognitive dysfunction represents a transdiagnostic neuropsychiatric phenotype, underpinned by highly complex relationships between brain structure and function.

In VE, distinct pathogens give rise to different patterns of cognitive impairment. For instance, patients with HSE frequently experience prominent and persistent cognitive sequelae. A longitudinal follow-up study reported that 30.3% of HSE survivors exhibited long-term memory impairment [48]. In contrast, neuroinvasive disease caused by West Nile virus (WNV) displays a different clinical profile. A prospective study indicated that WNV infection primarily affects the basal ganglia, spinal cord, and cerebellum, resulting in more pronounced motor dysfunction, while global cognitive function often remains within the normal range [49]. Nevertheless, the long-term impact of WNV infection should not be underestimated, as approximately 70% of patients reported persistent disability 5.5 years after infection [50].

Notably, other studies suggest that post-WNV cognitive impairment may be more prevalent than previously recognized [51]. One clinical observation found that during the acute phase of WNV infection, 93% of patients exhibited significant neurological deficits; at 90-day follow-up, nearly half of the patients demonstrated clear cognitive impairment. Specifically, 42% reported attentional deficits and subjective memory difficulties, 27% showed impaired comprehension, and 25% experienced confusion and decision-making difficulties, respectively [52]. These findings indicate that cognitive impairment following WNV infection may exhibit domain-specific vulnerability and underscore the need for systematic cognitive assessment after the acute phase.

## Neuroanatomical and neuroimaging basis of encephalitis-related psychiatric disorders

***Brain regions involved in emotion and cognition***

Psychiatric manifestations secondary to encephalitis have a well-defined neuroanatomical basis, with clinical

symptoms closely linked to inflammation or injury in specific brain regions. Neuroimaging studies have demonstrated that emotional processing and regulation primarily depend on the cortico–limbic system, with key structures including the prefrontal cortex, amygdala, and hippocampus [53]. Among these regions, the prefrontal cortex is central to working memory, executive function, and emotional regulation. This is especially true for the dorsolateral prefrontal cortex (DLPFC). Dysfunction of this region can result in cognitive deficits, disorganized thinking, and even hallucinations and delusions, which are core pathological features of disorders such as schizophrenia [54,55].

Notably, basic research has shown that approximately 40% of patients with schizophrenia exhibit significantly elevated mRNA levels of immune-related markers in the DLPFC [56], suggesting that neuroimmune dysregulation may represent a shared mechanism underlying impairments in higher-order cognitive functions. When encephalitic lesions involve these emotion- and cognition-related brain regions, corresponding psychiatric, behavioral, and affective disturbances are likely to emerge.

### *Neurotropism of HSV and region-specific brain injury*

HSV exhibits marked neurotropism, preferentially invading the temporal lobes, frontal lobes, and limbic system, where it commonly induces hemorrhagic and necrotizing encephalitis [57–59]. This pattern of region-specific injury provides a direct explanation for the characteristic clinical manifestations of HSE. Involvement of the temporal lobe—particularly the hippocampus and amygdala—as well as other epileptogenic regions such as the orbitofrontal cortex, leads to a markedly increased frequency of seizures. Meanwhile, damage to the hippocampus, amygdala, and prefrontal cortex accounts for the frequent occurrence of cognitive deficits, memory impairment, language disturbances, and behavioral abnormalities observed in affected patients [49].

### *Neuroelectrophysiological and structural neuroimaging evidence*

Electroencephalography (EEG), as a sensitive tool for assessing brain function, can objectively reflect the severity and extent of brain injury in HSE. Studies have shown that 60.7% of patients with HSE exhibit abnormal EEG findings, typically characterized by diffuse high-amplitude slow waves in the frontal and temporal regions, often accompanied by spikes, sharp waves, or epileptiform discharges [57]. These electrophysiological abnormalities show a high degree of concordance with structural lesions in the frontotemporal regions observed on brain magnetic resonance imaging (MRI), together providing objective evidence to support the diagnosis of encephalitis [60]. It should be emphasized, however, that a normal EEG does not exclude HSE, and clinical diagnosis must rely on multimodal evidence [61].

The neuropathological alterations associated with encephalitis and its sequelae can also be revealed through structural neuroimaging. For example, a longitudinal study of HSV1-seropositive patients with schizophrenia demonstrated a significant reduction in gray matter volume of the posterior cingulate cortex over a one-year follow-up period, while prefrontal gray matter volume remained relatively preserved. These findings suggest that HSV1 exposure may be associated with posterior cingulate gray matter loss and concomitant declines in executive function in patients with schizophrenia [62]. Notably, similar reductions in posterior cingulate gray matter volume have been observed in HSV1 encephalitis survivors treated with

acyclovir, indicating that region-specific structural damage driven by infection or immune responses may persist even after viral clearance.

***Functional neuroimaging features***

Functional neuroimaging, particularly $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), provides a direct assessment of cerebral metabolic activity in different AE antibody subtypes and reveals highly distinctive metabolic patterns. Anti-NMDAR encephalitis is characterized by a typical "frontotemporal dissociation" pattern, featuring widespread hypometabolism in the frontal lobes with relative hypermetabolism or preservation in the medial temporal lobes, including the hippocampus [63,64]. In addition, hypometabolism of the occipital cortex, involving both medial and lateral regions, represents another prominent imaging hallmark of this disorder [65]. Case-based studies further suggest that psychotic symptoms may be closely associated with localized metabolic abnormalities in the anterior cingulate cortex [66].

In anti-LGI1 encephalitis, the characteristic pattern consists of unilateral or bilateral hypermetabolism in the medial temporal lobes, particularly the hippocampus, often accompanied by metabolic abnormalities in the basal ganglia. This hypermetabolic state is considered an imaging correlate of active inflammation and serves as an important diagnostic clue for anti-LGI1 encephalitis [67]. By contrast, anti-AMPAR encephalitis, a rare form of limbic encephalitis, typically demonstrates hypometabolism in the frontal lobes and posterior cingulate cortex on PET/CT imaging [68]. This metabolic pattern is consistent with its clinical presentation, which is dominated by short-term memory loss, seizures, and psychiatric disturbances, reflecting dysfunction of the limbic system.

## Neuropsychiatric outcomes and rehabilitation considerations after encephalitis

Neuropsychological and psychiatric outcomes following encephalitis exhibit marked etiological heterogeneity. With advancing research, the clinical spectrum of post-encephalitic psychiatric sequelae has become increasingly well defined. In addition to acute-phase manifestations such as delirium, mania, and psychotic symptoms, certain neuropsychological functions—particularly in patients with severe acute injury—may show partial improvement over time.

However, a range of long-term and subtle neuropsychiatric sequelae warrants sustained clinical attention. These include organic affective disorders such as depression and anxiety, organic personality and behavioral changes, and persistent cognitive impairments involving memory, attention, and executive function, as well as apathy and deficits in impulse control [48]. Such manifestations should be systematically incorporated into comprehensive rehabilitation assessment and intervention frameworks to optimize long-term functional outcomes.

Currently, clinical practice primarily relies on the following categories of biomarkers to aid in diagnosis and assessment: Diagnostic Biomarkers: Neuronal autoantibodies (detected in cerebrospinal fluid and serum) are the most core biomarkers for diagnosing AE. Examples include anti-NMDAR antibodies, anti-LGI1 antibodies, and anti-$GABA_BR$ antibodies. Auxiliary Biomarkers: Cerebrospinal fluid free light chains (e.g., NfL [32]) and oligoclonal bands (OCB) [69]. In addition, inflammatory cytokines in the cerebrospinal fluid—such as IL-6 and IFN-γ [28]—are elevated in some AE patients and represent a promising future research

direction.

Taking post-encephalitic depression and anxiety disorders as representative examples, their occurrence is closely associated with structural and functional alterations in specific brain networks. Neuroimaging studies have established that the key brain regions implicated in depression include the hippocampus, prefrontal cortex, amygdala, anterior cingulate cortex, insular cortex, and nucleus accumbens. Further functional connectivity analyses indicate that abnormal intra-prefrontal and interregional connectivity involved in executive control and emotion regulation may serve as neurofunctional signatures of depression, whereas dysfunction of the striatal–amygdala circuitry, which is related to reward processing and emotional learning, is more characteristically associated with anxiety disorders [70].

Structural imaging studies have consistently reported a significant reduction in hippocampal volume in patients with depression, and this anatomical change is positively correlated with the severity of depressive symptoms and accompanying cognitive impairment. These findings suggest that anatomical alterations—including cortical atrophy, white matter degeneration, and hippocampal volume loss—may directly contribute to the pathophysiology of mood disorders through multiple mechanisms, such as neurodegeneration, neuroinflammation, and neurotransmitter imbalance [71]. Of particular note, a bidirectional vicious cycle may exist between depression and neuroinflammation: depressive states may trigger or exacerbate neuroinflammatory responses, leading to further brain dysfunction, which in turn aggravates affective symptoms [72]. This framework provides an important theoretical perspective for understanding the chronicity and persistence of mood disorders following encephalitis.

## Treatment

***Prevention and early antiviral therapy***

The management of viral encephalitis remains highly challenging. Given the lack of specific antiviral therapies for many neurotropic viral infections, preventive strategies are of paramount importance. Vaccination has been proven to substantially reduce the incidence of certain forms of viral encephalitis; for example, a five-year Japanese encephalitis vaccination program resulted in a 78% reduction in cases in Nepal [4].

From a therapeutic perspective, early antiviral therapy remains the cornerstone of viral encephalitis management. Agents such as acyclovir can significantly improve clinical outcomes; however, delays in treatment are associated with mortality rates as high as 70%, and fewer than 3% of patients regain baseline neurological function [44,73]. These data underscore the critical importance of early diagnosis and timely intervention. Metagenomic next-generation sequencing (mNGS) enables rapid and precise detection of pathogen nucleic acids in cerebrospinal fluid, providing a powerful tool for the early diagnosis of HSE. This approach facilitates the initiation of targeted antiviral and immunomodulatory therapies, thereby helping to halt disease progression and improve prognosis [57].

***Rationale and strategies for immunomodulatory therapy***

Clinically, a subset of patients develop multiple autoantibodies following herpesvirus infection, predominantly HSV-1, suggesting the presence of post-infectious autoimmune responses [46]. These immune responses may initially spare the nervous system; however, in some cases they evolve into targeted attacks against specific neuronal receptors, such as NMDAR,

manifesting as relapsing or biphasic disease courses. A prospective multicenter study demonstrated that approximately 40% of patients with HSE developed neuronal surface antibodies during follow-up, nearly half of whom exhibited corresponding clinical symptoms. This phenomenon was observed across all age groups and both sexes [26]. These findings identify HSE patients as a high-risk population for autoimmune encephalitis, underscoring the need for long-term surveillance.

Accordingly, patients who develop chorea-like movements, marked psychiatric and behavioral changes, or clinical phenotypes suggestive of anti-NMDAR encephalitis after HSE should undergo testing for NMDAR antibodies and other neuronal surface antigens [33]. In cases with a high clinical suspicion of autoimmune encephalitis, early initiation of immunomodulatory therapy, such as corticosteroids and intravenous immunoglobulin (IVIG), may be considered even before antibody results become available [57].

In particular, post-HSE autoimmune encephalitis is often associated with more severe inflammatory responses and blood–brain barrier disruption, and may respond less favorably to standard immunotherapies compared with non-virus-triggered autoimmune encephalitis. Consequently, earlier and more aggressive use of second-line immunosuppressive agents, such as rituximab, may be required to achieve effective disease control in these patients [19].

## Prognosis

The prognosis of viral encephalitis is influenced by multiple factors and is generally poor. Predictors of unfavorable outcomes in acute viral encephalitis include immunocompromised status, altered consciousness at admission (such as a reduced Glasgow Coma Scale score), seizures, and delayed initiation of antiviral therapy. These factors have been consistently identified as independent risk factors significantly associated with moderate-to-severe neurological sequelae or mortality [74].

Beyond acute-phase determinants, psychosocial stress has also been recognized as an important trigger for reactivation of latent viruses, mediated through modulation of neuroendocrine–immune pathways. Catecholamines and glucocorticoids can suppress innate immune responses and interferon signaling, while simultaneously promoting viral replication. For instance, major psychological stressors, such as bereavement, may contribute to the reactivation of latent herpes simplex virus infection [40]. Accordingly, even after resolution of the acute infectious phase, patients require long-term follow-up and monitoring because of the ongoing risk of progression to chronic neuropsychological disorders [43].

In addition, individual susceptibility to viral encephalitis and its sequelae exhibits substantial genetic heterogeneity. Specific genetic variants can increase disease risk; for example, the HLA-DRB1*16: 02 allele may promote aberrant activation of autoimmune responses by influencing the binding efficiency of antigenic peptide–MHC complexes to T-cell receptors [75]. In contrast, individuals who do not carry such susceptibility alleles are less likely to develop misdirected immune attacks against the central nervous system, even after viral infection and antibody production. These observations highlight the critical regulatory role of genetic background in the pathogenesis of post-infectious autoimmune encephalitis.

## Conclusions and future perspectives

This review systematically elucidates the “dual-hit” mechanism underlying neuropsychiatric symptoms

following viral encephalitis, whereby viral infection and secondary autoimmune responses act in concert to induce widespread damage to the central nervous system through disruption of the blood–brain barrier, activation of the complement system, and T cell–mediated cytotoxicity. Accumulating evidence further reveals a complex interactive network linking neuroinflammation with psychiatric and behavioral disturbances, affective dysregulation, and cognitive impairment, involving multilayered dysregulation across the immune system, neurotransmitter signaling, and brain circuitry.

Future efforts should prioritize two goals: first, developing highly specific neuroinflammatory biomarkers for early diagnosis; second, exploring novel anti-inflammatory and immunomodulatory strategies that target key immunopathological pathways. This is especially critical for patients who respond poorly to conventional psychotropic treatments. In parallel, greater emphasis should be placed on personalized diagnostic and therapeutic approaches, integrating genetic susceptibility, inflammatory profiles, and environmental factors, while further elucidating the roles of critical brain regions, such as the cingulate cortex, in post-encephalitic neuropsychiatric sequelae. Moreover, prospective evaluation of combined anti-inflammatory and immunomodulatory interventions initiated during the acute phase of herpes simplex encephalitis to prevent long-term autoimmune complications and improve outcomes represents an important direction for future clinical research.

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## Author contributions

Wang JY drafted the manuscript. Shi K, Ji P, and Chen Y contributed to data collection and analysis. Li HW and Bian JW were responsible for study design and provided overall guidance. Han GT and Zhang D critically revised and proofread the manuscript. Ke Z provided technical support and secured funding. All authors read and approved the final manuscript.

## Conflict of interest

All authors declare no conflicts of interest.

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