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CASE STUDY

Herpesvirus-associated encephalitis: A literature review with an update on pathophysiology and treatment

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This article is dedicated to novel insights in the concept of herpesvirus-associated encephalitis (HAE) pathogenesis and treatment, obtained via performing a literature review of the publications within 2018-2024. Herein, we emphasize the gene's role in neuroinfection manifestation and outcome, especially such pathways as RIPK3, Fas/FasL, mTORC2, TRIF, TLR3, and Stat1. Additionally, significant attention was given to the molecular mechanisms of immune cell interactions and histopathological changes in the brain tissue under the circumstances of neuroinflammation. We also suppose studying the peculiarities of neurotransmitter exchange during HAE to be a perspective direction of future research, since it may expand understanding of the pathophysiology of this condition. Furthermore, we considered up-to-date options of the disease management, particularly the superiorities of using monoclonal antibody-based drugs such as HDIT101 and HDIT102. The article includes two tables, where the information regarding recent achievements in studying the pathogenesis and treatment network of HAE is summarized.

Keywords: herpesvirus-associated encephalitis, pathogenesis, treatment, genes role in neuroinfection manifestation and outcome, pecularities of neurotransmitter exchange, monoclonal antibody-based drug

Introduction

Nowadays, up to 90% of an adult population is considered to be infected with herpes viruses (HVs). These agents are known to have a significant tropism to the nervous tissue, triggering inflammatory processes in peripheral nerves and even the central nervous system (CNS). Fortunately, the normal immune system is capable of providing the human body with defense against them. Therefore, not all the carriers are likely to have encephalitis, meningitis, or meningoencephalitis. Despite this, HVs keep remaining the leading etiology of neuroinfection among adults (1). The last one is life-threatening and potentially disabling condition: having manifested, it's hard to be kept under control, hence lifelong consequences for patients. Overall, herpesvirus-associated encephalitis (HAE) is worth studying and elaborating algorithms of effective treatment and rehabilitation.

Methodology

Objective

The purpose of this work is to perform the data analysis regarding herpesviral encephalitis, evaluate the evolution of its concept within 2018–2024, structure the obtained information, and find out if there are possibilities or perspectives of optimizing its management.

Materials and methods

Comparison and analysis of information obtained via review of medical databases for the period of 2018–2024 were used to perform the study and make the conclusions.

Results and discussion

Herpesviridae is a diverse family of viruses. Although they have much in common in their structure (DNA, capsid, tegument, and viral lipid bilayer envelope), the peculiarities of their genome and glycoprotein (GP) organization help to distinguish different types of HVs. Thus, herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella zoster virus are the representatives of Alphaherpesvirinae; cytomegalovirus (CMV, HHV-5) and human herpesvirus 6 (HHV-6)—Betaherpesvirinae; Epstein-Barr virus (HHV-4, EBV), human herpesvirus 7 (HHV-7) and human herpesvirus 8 (HHV-8)—Gammaherpesvirinae.

However, GPs play a significant role not only for classification: they are capable of binding specific receptors in the human body, determining different clinical forms of infection. Herpesvirus entry mediator, 3-O-sulfated heparan sulfate, and Nectin-1 are the targets for HSV-1 and 2, and integrins are the targets for Varicella-Zoster virus (VZV). CMV binds neuropilin-2 and platelet-derived growth factor receptor α. HHV-6 is divided into HHV-6A and HHV-6B subgroups, and their targets are CD46 and CD134, respectively. Finally, human leukocyte antigen class II and ephrine type-A receptor 2 (EphA2) are specific for HHV-4; EphA2 and EphA4 are specific for HHV-8 (2, 3).

According to the foregoing information, not all the HVs have the same probability of resulting in full-fledged neuroinfection. The overwhelming number of HAE cases are caused by HSV-1 and HSV-2, sometimes by VZV. Less often, the disease is triggered by HHV-4, CMV, or HHV-6. Cases of CNS affected by HHV-7 and 8 are casuistic but not impossible (4).

Altogether, our research demonstrates the pathophysiology of HAE keeps remaining vague. The traditional explanation of it relates either to primary infection or to reactivation of latent HVs (what happens more often). Additionally, HVs are supposed to have some typical options of getting into the CNS: from the oropharyngeal region (via trigeminal and olfactory tracts), from a peripheral infection site, or by getting reactivated directly in the brain (1). However, such a description doesn't provide a comprehensive understanding of HAE: obviously, not all the carriers with activated HV or even a debilitated immune system end up with encephalitis. Fortunately, after processing the available resources, we managed to find the up-to-date data, giving an opportunity to expand the concept of HAE.

To start with, the possibility of genetics contributing in HAE manifestation should be mentioned. In 2018, the detailed research of hereditary role under the context of neuroinfection was conducted, which confirmed the idea of the existence of some "protective" genes (TLR3, Stat1, TRIF) determining CNS defense against viruses (5). The hypothesis was complemented with another observation made in 2021, where the TLR3-pathway was suggested to be involved in forming the response against infection. The authors assumed TLR3 could have an impact on interferon-β (IFN-β) production in cortex neurons, though it remains uncertain whether its synthesis is controlled at some basal level throughout all the time or in response to stimulus. One way or another, IFN plays a crucial role in overwhelming viral infection, especially at the first stages. This explains why the impairment of TLR3 can lead to an increased risk of occurrence and an unfavorable prognosis of HAE (6). Moreover, such a suggestion resonates with another finding. The animal research performed in 2023 showed genetic flaws in TLR3 and TRIF correlated with a severe disease course, which was explained by possible engagement of these pathways into activation of natural killers, IFN-I, and interleukin-15 synthesis (7).

Additionally, one more probable gene-dependent mechanism has already been exposed. It concerns apoptosis-related limiting of viral replication: when a programmed host-cell death occurs, the viral agent gets deprived of its development foundation. This process depends on the activity of receptor-interacting protein kinase 3 (RIPK3). Liu Z et al. demonstrated the deficiency of RIPK3 was associated with apoptosis impairment; therefore, active dissemination of the inflammatory process and unfavorable outcome (8). Oddly enough, the decreased function of another apoptosis-controlling pathway, Fas/FasL, can determine, vice versa, a better prognosis. The point is, its expression was associated not with the suppression of infected neurons but with the failure of immunity components (cytotoxic T-lymphocytes, monocytes, microglia, etc.) (9). Similarly, neuroprotective effects were observed due to antiapoptotic activity of mTORC2, contributing into optimal immune response (both innate and adaptive) and neuronal survival (10).

To sum up, nowadays we possess convincing data about the significant role of genes in HAE pathogenesis, particularly

TLR3, RIPK3, Stat1, TRIF, Fas/FasL, and mTORC2. However, further research is required.

Next, the mechanisms of restarting viral replication should be found out. Classic HSV-1 neuroinfection will be used as the example. Normally, promyelocytic leukemia nuclear bodies (PML-NB) and interferon-γ-inducible protein 16 (IFI16) restrain the virus from replication by heterochromatinization of its DNA, whereas neuronal stress response (NSR) facilitates reactivation. NSR can be provoked by a range of factors, such as lack of neurotrophines, inhibited activity of phosphoinositide 3-kinase (PI3K), fever, hormonal imbalance, ultraviolet, etc. Having arisen, it results in c-Jun N-terminal kinase (JNK) pathway activation, which is supposed to promote viral replication via serine phosphorylation (11). However, the mentioned data was obtained from animal studies; therefore, the possibility of some discrepancies with humans. Nevertheless, we consider these facts to be worth attention.

After manifestation, viral replication results into inflammation and host immune system response. Within the CNS these processes are known to involve astrocytes, microglia, and peripheral immunocytes (transported into the CNS across the blood-brain barrier [BBB] due to its increased permeability under the condition of inflammation) (12).

According to the publication of Patrycy M et al., microglia may play the crucial role in overwhelming viral activity. The evidence in favor of this assumption is the finding, obtained via animal experiments, that lower activity of microglia was associated with worse outcomes of neuroinfection. The mentioned fact is explained with an ability of these cells to phagocytosis, antigen presentation, and cytokine synthesis (TNF, IL-1β, IL-6 and 8, CCL-2, 3, 4, 5, CXCL-10). Such contributions are necessary for an adequate immune response to form and mediate of inflammation. Even when peripheral immunocytes get involved, they can't completely replace or take over their role. On the other hand, microglia activation can appear to be the link of the "vicious circle": when its function is excessive, it probably leads to neurotoxicity (12).

As mentioned above, not only microglia facilitates defense against viruses. It's usually complemented with astrocytes, which take part into sustaining normal BBB density, neurotrophine synthesis, promoting reparative processes, regulating synaptic activity, IFN producing, and also modulating inflammation via anti-inflammatory cytokines. In spite of such a significant contribution, excessive activation of these cells, resulting into further astrogliosis, can limit normal regeneration of the nervous tissue (13, 14).

Obviously, active CNS infection can't help having an impact on the peculiarities of neurotransmitter exchange. Unfortunately, the data regarding this aspect appeared to be limited: the metabolism of dopamine, gamma-aminobutyric acid, acetylcholine, glutamate, serotonin, etc. was predominantly highlighted for other viral agents but not HSV. Therefore, such a research direction is perspective for future expanding of knowledge about this neuroinfection. One thing is clear: HAE is associated with oxidative stress and increased production of nitric oxide (NO). Under the circumstances of encephalitis, NO facilitates not only neuroinflammation but also neurodegeneration (15, 16). This is a surprising finding, because there is a congruity at least between a few publications where the hypothesis of a possible connection between HVs and Alzheimer disease (AD) was expressed. The point is, HSV-1 neuroinfection is capable of triggering amyloid-β synthesis, underlying the mentioned type of dementia; hence such a correlation (2, 15, 16). One way or another, further studies are needed to confirm the theory and figure out other possible interconnections.

To finish with, besides neurodegeneration, autoimmunization can result from HAE. The accurate mechanisms of it remain unclear, although a few explanations have already been expressed. They include the hypothesis of non-specific activation of B-cells, molecular mimicry of viral particles, and neuronal antigen exposure. The new publication of 2024 supposes the last one to be the most plausible. The theory is based on the concept of the "immune privilege": the antigens of the CNS are concealed from the immune system by the BBB, serving its isolation and providing defense against peripheral immunocyte invasion. That's why autoimmune aggression doesn't occur in normal. When nervous tissue gets damaged, some neuronal proteins are likely to drain outside and be identified by immune cells, resulting into further full-fledged inflammation of the brain. Possible ways of antigens "escape" include arachnoid granulations, the olfactory nerve, and nasal and meningeal lymphatics (17).

All the foregoing information is summarized in **Table 1**, "An updated view on the pathogenesis of HAE, caused by HSV-1 reactivation," where the pathophysiology of the most "classic" variant of HAE is schematically described. Additionally, it should be mentioned that in reality all these processes may not be divided into separate "stages," but for better understanding the data in the table is organized in a "step-by-step" manner.

Such a presumptive pathogenesis leads to the specific, from a neurological perspective, clinical picture, including focal symptoms (consequence of organic lesion at the background of some localized area of inflammation among the brain tissue), general cerebral symptoms (result from generalized cerebral edema as a non-specific response to injury), and meningeal symptoms (arise at the background of irritation of meninges by intoxication and cerebral edema, or in case of transforming into meningoencephalitis—by direct inflammation of meninges). The significance of these components, as well as the prodromal period and intoxication syndrome, depends on the peculiarities of certain infectious agents and the host's health condition. Evaluating patient history and clinical

TABLE 1 | An updated view on the pathogenesis of HAE, caused by HSV-1 reactivation.

No.	"Stages"	Processes		Characteristics	Result
1	Stage of risk of HAE occurs	Unfavorable hereditary background	TLR3 and TRIF deficiency	↓ cytokine synthesis within CNS.	No "first line defense."
			Stat1-impairment	↓ ability of cells to block a potential viral replication.	
			RIPK3-impairment	↓ apoptosis of infected cells.	Absence of apoptosis-related defense.
			Excessive Fas/FasL pathway activation in response for infection	Facilitates apoptosis of peripheral immunocytes and microglia.	Immune response won't be capable of overwhelming infection.
			mTORC2-hypofunction	In normal, ↓ neuronal apoptosis and ↑ immune response.	Immune response won't be capable of overwhelming infection, ↑ neuronal death.
2	The onset of viral replication	I	The impact of unfavorable circumstances	Reactivation of the latent virus and beginning of its replication.	Risk of virus invading into CNS and resulting into encephalitis.
		II	NSR		
		III	JNK-pathway activation		
		IV	Serine phosphorylation		
3	Encephalitis	Microglia activation		Antigen presentation, phagocytosis, cytokine synthesis (TNF, IL-1β, 6 and 8, CCL2-5, CXCL-10).	If microglia response is ↑ - neuronal damage; if ↓ - compensatory infiltration with immune cells, progressing of disease. Medium activity—adaptive role.
		Peripheral immune cells infiltration			
		Neuronal changes	Viral invasion	Neurons become the substrate for viral replication	Spreading of viral infection
			Affecting by ↑ NO production	NO has both protective and damaging role, also induces peroxynitrite synthesis.	Under the context of encephalitis, predominantly of neurons via the mechanisms of inflammation, neurodegeneration, and oxidative stress.
			Affected by oxidative stress	Additional damage to neurons	
		Astrocyte activation		Sustaining BBB structure, reparation, and synaptic activity control. Synthesis of IFN-γ, TGF-β, and brain-derived neurotrophic factor (BDNF).	Predominantly adaptive role, but when it's excessive, further astrogliosis occurs.
4	Outcome	Astrogliosis		Astroglial scar replaces dead neurons.	Inability of full regeneration. Presence of neurological deficit depends on localization and the area of lesion.
		Neurodegeneration		Progression of neurological deficit. Possible risk group of AD.	
		Autoimmunization		Risk of repeat case of encephalitis, but because of autoimmune etiology.	

symptoms, accompanied with laboratory and instrumental findings (abnormalities of brain parenchyma and electrical activity, confirmed via MRI scans and electroencephalogram (EEG), respectively; changes in blood and cerebrospinal fluid tests according to the features of the etiological factor, etc.), is a key for making the right diagnosis (18). Altogether, our literature review demonstrates the availability of modern, reliable tools for HAE detection, even though each case is original and nuanced. In contrast to diagnostics, therapeutic approaches leave much to be explored.

Theoretically, nowadays we possess the facility of etiotropic treatment of classic HSV-1-associated

TABLE 2 | Up-to-date view on HAE management.

Drug	Characteristics
Acyclovir	After being converted into acyclovir triphosphate, it gets incorporated into viral DNA and inhibits DNA polymerase. Main standard of treatment of HSV and VZV-associated infection, including encephalitis.
Valacyclovir	Gets converted into acyclovir in the human body. It is similar to acyclovir but has higher bioavailability. However, it is not supposed to be the first-line treatment.
Gancyclovir	Gets converted into ganciclovir triphosphate, becomes incorporated into viral DNA, and inhibits viral DNA polymerase. Is likely to be effective against HHV-5 and 6. Cross-resistance with acyclovir is present (shouldn't be used for acyclovir-resistant HSV).
Foscarnet	Has a direct inhibiting impact on the DNA-polymerase of HVs. Supposed to be preferred for HHV-5, HHV-6, and acyclovir-resistant HSV. Also has a potential to overwhelm other types of HVs.
GCSs	Uncertain data about the superiority for their usage. Reduce inflammation as well as suppress immune response. Require individual decision-making.
Monoclonal antibodies (HDIT101, HDIT102)	Seems to be a novel promising option of HSV-associated infection by binding specifically to GPs of HSVs. However, the data regarding its usage for HAE is missing yet.
Polyclonal antibodies (human IgG)	Safe, but the superiority of its usage is unclear.
IFN	Has theoretical justification of administering, obtained via animal studies, but the relevant data about clinical usage for HAE in humans is missing.
Vaccines	Seem to be a relevant direction of future research; however, all the previous trials failed to develop an effective vaccine against HVs, except VZV.

encephalitis—acyclovir and acyclovir-like drugs. However, even appropriate antiviral treatment can't guarantee the absence of lifelong consequences and disability after HAE. This determines the necessity of an expanding variety of etiotropic drugs and complementing them with pathogenetic therapy.

To start with, we can't help pointing out the modern medical tendency to develop monoclonal antibody-based drugs. The advantage of such an approach is its high specificity to the certain targets of pathological processes without affecting other organs and systems. Therefore, we suppose them to be one of the most perspective ways of improving HAE outcomes. Such an assumption goes along with the last research conducted within 2022–2024. According to Seyfizadeh N et al., humanized IgG HDIT101 and HDIT102 are capable of suppressing HSVs activity via binding viral GPs. The immunoglobulins effects are connected with overwhelming virus spreading as well as improving of T-cells activity and phagocytosis (19). Moreover, the drug appeared to be safe for humans and well-tolerated (20). Similarly, the conclusion about the superiority of monoclonal antibody usage for HSV infection management was made by Backes IM et al. (21). Unfortunately, there are only a few trials concerning such an aspect of treatment. It also remains unclear whether antiviral antibodies could contribute more as a facility of treatment of acute herpesviral encephalitis or as a facility of its prevention. Besides that, the brain is isolated from the blood flow by BBB, so it's uneasy to anticipate if the patients with HAE benefit from monoclonal Ig administration. One way or another, further observations are needed.

In contrast to the previously mentioned, using IFNs and polyclonal Ig to improve host organism response or vice versa glucocorticosteroids (GCSs) to settle down its overreaction seems to be more realistic nowadays. At least, they are available for casual practice. As an example, Sakoulas G et al. showed that a combined therapy with acyclovir, intravenous immunoglobulin, and dexamethasone had promoted a good outcome for the patient with HAE (22). In spite of such a conclusion, using GCSs for neuroinfections keeps a controversial topic because of their ambiguous effects. On the one hand, they are likely to mitigate cerebral edema and inflammation-caused neuronal damage; on the other hand, their immunosuppressive qualities are not acceptable while the infectious process keeps going on. Thus, the German trial did not succeed in proving the benefits from GCS administration for HAE (23). Meanwhile, the results of another trial, "DexEnceph," haven't been published yet, so they can change the concept of dexamethasone usage in the future (24). As for now, our perspective on this problem is that prescribing GCSs shouldn't be a routine decision. It can be appropriate, for example, for severe disease course or in combination with Ig administration to avoid a pronounced immunosuppressive effect.

Back to the topic of IFN and Ig, only a few publications within the last year are present. Besides that, the data is predominantly limited with animal studies, although immunomodulatory therapy including IFNs is noticed as promising due to their crucial role in antiviral immunity. Decreasing mortality among experimental animals after recombinant human IFN-α administration for HAE is an argument in favor of its usage (25, 26). Another publication we managed to find was dedicated to IgG-based drugs

for encephalitis treatment. However, it wasn't focused exactly on herpesviral etiology. Moreover, the conclusions were ambiguous, and no certain correlation between IgG administration and the outcome was found, although the therapy was estimated as safe (27).

Including other categories of drugs (anticonvulsants, antipsychotics, etc.) into a therapeutic scheme depends on the significance of particular syndromes and requires making the decision individually. Therefore, they won't be considered in this article.

The data about relevant possible options of HAE management are summarized in **Table 2**, "Up-to-date approaches for HAE management" (28–33).

Recently, the amount of data has increased significantly about sirtuins, especially sirtuin 1 (34–36). Sirtuins are known to regulate the processes of aging, transcription, and apoptosis and play an important role in the response of organisms to stress (35). According to studies, the sirtuin 1 activator resveratrol reduced the level of metalloproteinase 9 (MMP9) in the cerebrospinal fluid, modulated neuroinflammation, and induced adaptive immunity. Activation of SIRT1 may be a viable target for the treatment or prevention of inflammatory and neurodegenerative diseases.

Conclusions

Studying the features of herpesviral encephalitis remains a challenge for modern medicine. Nevertheless, some progress has already been made. As an example, we possess the data about TLR3, TRIF, and Stat1 pathways role in providing defense against infection and RIPK3, Fas/FasL, and mTORC2's contribution into apoptosis regulation, which determines the viability of immunocytes and infected neurons. Therefore, we emphasize the necessity of future research to clarify the details of genetics impact on HAE manifestation and prognosis. Moreover, we need to understand the molecular mechanisms of immune cell coordination as well as interactions between the host organism and the viruses in order to develop facilities of treatment and prevention. As for now, studying monoclonal antibodies seems to be one of the most promising options. Additionally, it should be mentioned that the purpose of elaborating new approaches is not to replace or get rid of the previously used methods but to complement them, improving patient outcomes and optimizing their therapy.

For this reason, investigations concerning GCSs, IFNs, polyclonal antibodies, etc. keep staying relevant. The role of sirtuin 1 activators versus Sirtuin 1 inhibitors may determine brain disease and neuroinflammation with relevance to appropriate management of the disease. The plasma sirtuin 1 levels may need to be measured in infected individuals with relevance to neuroinfection and neurodegenerative disease.

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Author Contributions

Literature review of the publications within 2018–2024, with an accent on the gene's role in neuroinfection manifestation and outcome; considered up-to-date options of the disease management, particularly the superiorities of using monoclonal antibody-based drugs such as HDIT101 and HDIT102.

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