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Unveiling the clinical spectrum of herpes simplex virus CNS infections in adults: a systematic review

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Abstract

Background Herpes simplex virus (HSV) infections of the central nervous system (CNS) are associated with high morbidity and mortality. Prompt recognition and antiviral treatment are critical to improve patient outcomes. This systematic review of the literature aimed to aggregate the symptoms described with HSV infections of the CNS which may provide a framework to aid in early diagnosis.

Methods This review was registered (PROSPERO; CRD42022366036) and adheres to PRISMA guidelines. MEDLINE, Embase, and Cochrane databases were systematically screened for studies including adult patients with HSV infections confirmed by histopathology or polymerase chain reaction. Demographics, clinical characteristics, diagnostics, and outcomes were assessed.

Results Of 21 studies from 18 countries describing 1605 patients, the most frequently reported symptoms were fever (75%), headache (65%), neck stiffness (55%), and language/speech abnormalities (41%). Other common symptoms included seizures (36%) and gastrointestinal issues (35%). Information regarding a combination of symptoms was not provided. Diagnostics often included lumbar puncture and magnetic resonance imaging, revealing temporal lobe abnormalities in 88%. While mortality was 13%, 72% of survivors had good neurological outcomes. The risk of bias was high in most studies.

Conclusions Fever, headache, neck stiffness, and language/speech abnormalities were frequently reported clinical findings in patients with proven HSV infection of the CNS. Despite limited evidence, these symptoms warrant a high index of suspicion, prompting early empiric antiviral therapy, especially when alternative diagnoses lack strong support. The predictive value of these symptoms and their combination for diagnosing HSV infection of the CNS should be further investigated, as they could accelerate diagnostics and treatment.

Keywords Herpes simplex virus, Encephalitis, Neurocritical care

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Background

Herpes simplex virus (HSV) infections of the central nervous system (CNS) are associated with high morbidity and mortality [1–3]. HSV encephalitis, the most severe form of CNS involvement, can lead to devastating neurological outcomes and death if not adequately treated.

Early intervention with antiviral therapy is critical for mitigating these outcomes [4, 7, 8], making timely diagnosis and treatment pivotal. Research has consistently shown that one of the most critical determinants of patient outcomes is the interval between symptom onset and the initiation of antiviral treatment [4, 5, 7, 8]. However, diagnosing these infections can be challenging due to the highly variable and often nonspecific clinical presentation [5, 6, 9]. Patients may present with a range of signs and symptoms, including fever, altered mental status, seizures, or focal neurological deficits. These manifestations often overlap with other neurological disorders, such as autoimmune encephalitis, bacterial meningitis, or stroke, further complicating the diagnostic process [9–11]. As a result, delays in initiating appropriate antiviral therapy are not uncommon, potentially worsening clinical outcomes [4, 7, 8].

To address these challenges, experts in the field have proposed categorizing clinical signs and symptoms of HSV-related CNS infections into typical and atypical presentations [5]. However, the underlying body of evidence supporting this categorization remains limited. To bridge this gap, we conducted a systematic review to aggregate and analyze the clinical presentations reported in patients with confirmed HSV infections of the CNS as documented in the literature. Our objective was to identify the types and frequencies of symptoms and clinical findings associated with these infections, ultimately supporting healthcare providers in identifying key clinical features that should raise suspicion for HSV infections early in the disease course, thereby facilitating timely diagnosis and treatment.

Methods

Registration and reporting

This systematic review was registered on PROSPERO prior to the start of the screening process (PROSPERO 2022 CRD42022366036; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022366036).

Results are reported according to the PRISMA guidelines (http://www.prisma-statement.org).

Screening and data extraction

The digital databases MEDLINE (via the Ovid interface), Embase, and Cochrane were searched using a predefined search strategy. Details regarding the search strategy for each database are presented in Supplementary Table 1. The search results were systematically screened for inclusion by two reviewers (PG and TD) based on pre-defined inclusion and exclusion criteria. The definite inclusion of pre-selected studies was decided through a joint consensus between two reviewers (PG and RS). Studies meeting the following inclusion criteria were included in this systematic review:

1) Inclusion of adult patients (i.e., age ≥ 16 years)
2) Diagnosis of HSV infection either by histopathology from brain tissue (biopsy or autopsy) or by polymerase chain reaction (PCR) from cerebrospinal fluid (CSF)
3) Number of included patients > 10
4) Publication language English.

For studies including both pediatric and adult patients, data were only included in our review if the specific symptoms could be allocated to the individual patients or to the adult subgroup. Data regarding demographics, clinical, and neuroradiologic characteristics were extracted using a standardized data collection form. Details regarding inclusion and exclusion processes are outlined in Fig. 1.

Assessment of the level of evidence

The level of evidence was assessed for each study using the approach proposed by the **G**rading of **R**ecommendations, **A**ssessment, **D**evelopment and **E**valuation (**GRADE**) Working Group [12].

Risk of bias assessment

The risk of bias for each study was evaluated using the Risk Of Bias In Non-randomized Studies—of Exposure (ROBINS-E) tool [13], which is designed for the assessment of non-randomized studies. This tool was expanded by the authors to include the following four additional bias domains deemed particularly relevant to the selected studies: recall bias (errors in memory recall or selective reporting by patients and/or physicians regarding signs and symptoms of HSV infection), misclassification bias (incorrect classification of study participants), interobserver bias (variability in measurements or interpretations across different observers), and temporal bias (the influence of the timing of data collection on study outcomes). For temporal bias, a study period exceeding four years was, albeit somewhat arbitrarily, considered to represent an increased potential risk.

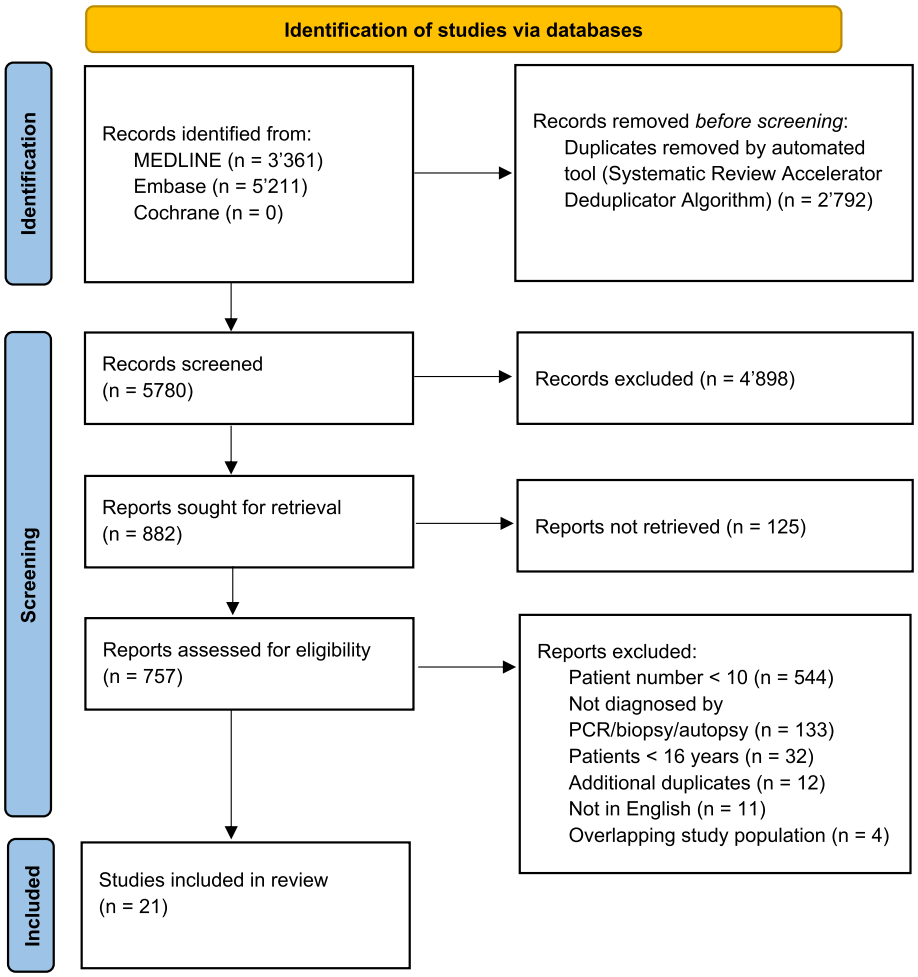

Fig. 1 Flow chart. Legend: PCR, polymerase chain reaction

Results

Screening and origin of studies

Of the 8572 studies screened, 21 met our inclusion criteria, comprising a total of 1605 patients. The main results regarding study design, demographics, microbiologic workup, and symptoms are outlined in Tables 1 and 2. All studies are retrospective in design, and the vast majority originate from Europe and North America. While 28.6% of studies included less than 20 patients each [10, 14–18], 14.3% of them comprised more than a hundred individuals [2, 19, 20]. The oldest study dates from 1982 [21], using brain biopsy or autopsy for detection of HSV, while the remaining 20 papers were published within the last 21 years and HSV infection was confirmed by PCR from CSF. Of the 13 studies that reported the type of HSV [2, 3, 8–10, 16–18, 21–25], two included HSV-2 positive patients only [22, 25], while eight reported individuals who were exclusively or predominantly infected by HSV-1 [2, 8–10, 16, 17, 21, 24]. Twelve out of the 21 studies reported on the patients' immune status [1, 3, 8, 9, 14, 17–19, 22, 24–26], with a median of 8.4% (interquartile range [IQR] 4.6–23.6%) of patients being immunocompromised.

Clinical signs and symptoms

Figure 2 summarizes the six most frequently described clinical signs and symptoms from the literature. In more detail, the most frequent symptoms and signs were fever, as reported in 18 studies [1–3, 6, 9, 10, 14, 16–21, 23–27], with a median frequency of 75% (IQR 62.2–82.9%), headache, as mentioned in 16 studies [1–3, 8–10, 14, 16–19, 21–23, 25, 27], with a median frequency of 65.1% (IQR 37.6–88%), and neck stiffness, as presented in 10 studies [1–3, 6, 9, 16, 18, 19, 22, 23], with a median of 54.5% (IQR 26.8–63.1%). Language/speech abnormalities were described in 10 studies [2, 9, 10, 15–17, 20, 21, 24, 27] (median 40.7%, IQR 33.8–49.3%), seizures in all but one study [25] (median 35.7%, IQR 18.6–51.1%), and gastrointestinal problems (i.e., nausea and vomiting) in 12 investigations [1, 3, 6, 8, 9, 16, 18, 21–23, 25, 27]

Table 1 Overview of demographics

Study	Year	Geographical origin	Number of HSV-positive patients reported	Age (years)	Sex female (%)	HSV type	Diagnostic proof	Immunosuppression (%)
Retrospective/multicenter								
Cag et al. [2]	2016	Europe/Middle East/North Africa	496	Median 50.5, IQR 33.3–63	53.6	351 HSV-1, 83 HSV-2, 62 not specified	PCR	NR
De Montmollin et al. [19]	2022	Europe	273	Median 64.6, IQR 55.5–73.7	49.8	NR	PCR	12.1
Poissy et al. [20]	2009	Europe	184	Median 58	44.6	NR	PCR	NR
Kaewpoowat et al. [16]	2016	North America	80	Median 40.5, range 18–82	62.5	NR	PCR	6.3
Chow et al. [19]	2015	North America	60	Mean 56.8, SD 19.2	50	57 HSV-1, 3 HSV-2	PCR	0
Omland et al. [22]	2008	Europe	49	Median 39, IQR 33–45	77.6	0 HSV-1, 49 HSV-2	PCR	6.1
Gennai et al. [6]	2016	Europe	36	Median 60, IQR 55–73	61.1	NR	PCR	NR
Afonso et al. [23]	2007	North America	20	Median about 40	majority female	1 HSV-1, 19 HSV-2	PCR	NR
Retrospective/monocenter								
Moon et al. [3]	2014	Korea	95	Median 34, range 16–85	54.7	21 HSV-1, 74 HSV-2	PCR	6.3
Mulatero et al. [24]	2022	France	76	Mean 55, range 16–92	51.3	72 HSV-1, 4 HSV-2	PCR	10.5
Singh et al. [8]	2016	North America	45	Median 66, IQR 53.5–78	71.1	33 HSV-1, 9 HSV-2, 3 not specified	PCR	22.2
Tan et al. [26]	2012	North America	29	Mean 55.1, SD 16.1, range 26–79	51.7	NR	PCR	48.3
Miller et al. [25]	2013	North America	28	Mean 38, SD 19–55	78.8	0 HSV-1, 29 HSV-2	PCR	0
Babaei et al. [27]	2021	Middle East	21	Mean 62.2	42.8	NR	PCR	NR
Esiri et al. [21]	1982	Europe	21	Mean 45.9, range 18–81	61.9	21 HSV-1, 0 HSV-2	brain biopsy or autopsy	NR
Bewersdorf et al. [14]	2019	Europe	18	Median 54.7, range 20–90	50	NR	PCR	27.8
Studahl et al. [15]	2009	Europe	17	Mean 57.8, range 32–90	41.2	NR	PCR	NR
Basaran et al. [16]	2019	Europe	16	Mean 53.37, SD 16.59	62.5	16 HSV-1, 0 HSV-2	PCR	NR
Alessandro et al. [17]	2018	South America	16	Median 38, range 22–84	31.1	9 HSV-1, 5 HSV-2, 1 both, 1 not specified	PCR	0
Momméja-Marin et al. [18]	2003	Europe	13	Median 37, range 29–77	38.5	7 HSV-2, 6 not specified	PCR	100
Oyanguren et al. [10]	2013	Europe	12	Mean 67.8	58.3	12 HSV-1, 0 HSV-2	PCR	NR

NR Not reported, *SD* Standard deviation, *IQR* Interquartile range, *PCR* Polymerase chain reaction

(median 34.9%, IQR 30.2–54.3%). Less commonly mentioned symptoms were photophobia [1, 6, 8, 18, 21–23, 25] (median 26.4%, IQR 7.2–45.4%), focal deficits [1, 2, 6, 8, 9, 14, 16, 18, 19, 21, 23, 26] (median 14.1%, IQR 10.5–42.9%), altered mental status [1, 3, 14, 16, 19, 23], altered consciousness [2, 9, 15, 22, 27], confusion [8–10, 21, 24],

Table 2 Overview of reported symptoms

Study	Symptoms (%)							
	Fever	Headache	Neck stiffness	Language/ speech abnormalities	Seizures	GI symptoms	Photophobia	Focal deficits
Retrospective/multicenter								
Cag et al.	78.4	67.7	63.1	22	19.8	NR	NR	1.4
De Montmollin et al.	83.9	33.7	6.6	NR	34.7	NR	NR	14.3
Poissy et al.	85	NR	NR	47.3	36.7	NR	NR	NR
Kaewpoowat et al.	50	91.3	61.5	NR	5	68.4	43.2	13.8
Chow et al.	80	51.7	32.1	33.3	54.5	36.5	NR	10.3
Omland et al.	NR	87.8	71.4	NR	2	59.2	44.9	NR
Gennai et al.	69.4	NR	19.4	NR	50	27.8	5.6	55.6
Afonso et al.	75	84.2	63.1	NR	15	52.6	78.9	10.5
Retrospective/monocenter								
Moon et al.	60	88.4	47.4	NR	10.5	65.3	NR	NR
Mulatero et al.	51.3	NR	NR	43.3	21.1	NR	NR	NR
Singh et al.	NR	22.2	NR	NR	46.7	31.1	4.4	40
Tan et al.	79.3	NR	NR	NR	58.6	NR	NR	51.7
Miller et al.	51	100	NR	NR	NR	31	47	NR
Babaei et al.	90.5	61.9	NR	38.1	61.9	33.3	NR	NR
Esiri et al.	52.4	28.6	NR	33.3	57.1	4.8	9.5	23.8
Bewersdorf et al.	72.2	38.9	NR	NR	22.2	NR	NR	72.2
Studahl et al.	NR	NR	NR	35.3	58.8	NR	NR	NR
Basaran et al.	75	62.5	25	68.8	43.8	25	NR	12.5
Alessandro et al.	68.8	87.5	NR	50	31.3	NR	NR	NR
Momméja-Marin et al.	92.3	100	76.9	NR	0	46.2	7.7	0
Oyanguren et al.	91.7	25	NR	66.7	41.7	NR	NR	NR

NR Not reported, *GI* Gastrointestinal

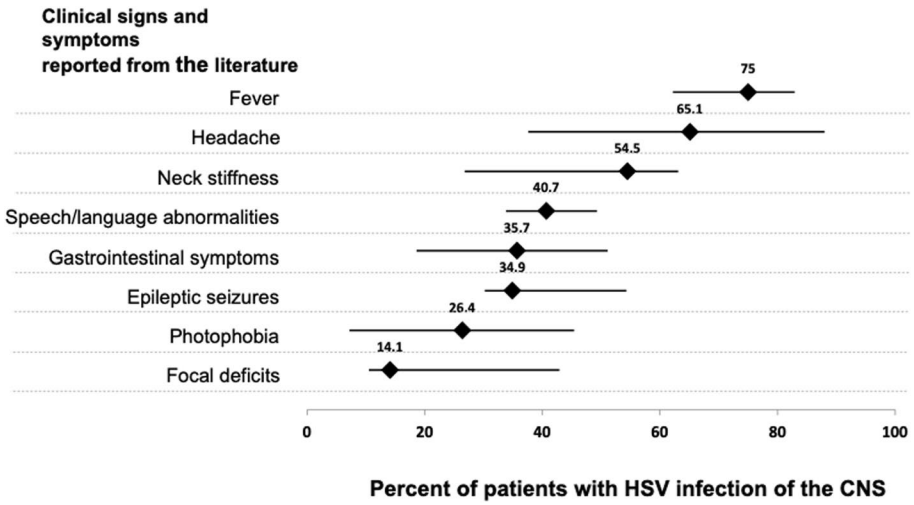

Fig. 2 Percentage and IQR of most frequently reported signs and symptoms of HSV infection of the CNS. Legend: HSV, herpes simplex virus; CNS, central nervous system; IQR, interquartile range

disorientation [2, 15, 16, 20], behavioral [6, 20, 27] and personality change [2, 21], hallucinations [2, 9], sensory impairment [17], meningeal syndrome [24], meningeal symptoms [17], psychosis [9], psychiatric symptoms [17], drowsiness [24], agitation [24], ataxia [9], encephalopathy [26], and memory impairment [3]. Details on the frequency of those less commonly reported symptoms are compiled in Supplementary Table 2.

Due to the retrospective nature of included studies coupled with a paucity of detailed information regarding the co-occurrence of specific clinical signs and symptoms, analysis of the potential predictive value for specific symptom clusters in diagnosing HSV infection of the CNS was precluded.

Information on diagnostics, treatment measures, and outcomes

Further information regarding results from diagnostic workup and outcomes are summarized in Table 3. Most studies describe results from lumbar puncture. Remarkably, normal white blood cell counts are reported in 5% of patients (IQR 0–15.7%). Nine out of the 21 studies contain information on magnetic resonance imaging (MRI) of the brain [1, 2, 6, 8–10, 14, 16, 26]. It was performed in 92.8% of patients (IQR 87–98.6%), with three percent (IQR 0–20.8%) having an unremarkable MRI. If MRI abnormalities were present, they mostly affected the temporal region (87.5%, IQR 78.1–93.5%).

In eight studies reporting the performance of an electroencephalogram (EEG) [1, 2, 8, 14, 16, 17, 22], a median of 81.7% (IQR 45.2–95.4%) of patients received an EEG, with a median of 56.3% (IQR 48.4–89.1%) being abnormal. Of note, the description of EEG abnormalities was very heterogeneous.

While 15 studies provide detailed information on the administration of antimicrobial drugs, data regarding the time from first symptoms to the initiation of medical treatment was analyzed in only four studies [17–19, 26], with very heterogeneous results describing a range of 0 to 55 days between symptom onset and the start of HSV-specific treatment.

Information on outcomes is found in all but three studies [6, 9, 10]. Overall, 13% of patients died (IQR 0–20.1%). Among survivors, 72.1% (IQR 51.6–89.3%) were reported to have a good neurological outcome with no or minor sequelae.

Level of evidence and risk of bias

The results of the GRADE assessment are compiled in Supplementary Table 3. The overall certainty was very low to low with only two studies reaching a moderate certainty.

Supplementary Table 4 outlines the most pertinent potential biases identified in the included studies, which are inherently associated with their retrospective and observational design. The most frequently observed potential biases were selection bias, confounding bias, and recall bias, with temporal bias also being an issue in many cases. Due to the high risk of these potential biases, the overall quality of evidence is considered to be low.

Discussion

In this systematic review of the literature including 1605 adult patients from 18 countries and four continents with proven HSV infections of the CNS, we focused on clinical signs and symptoms while applying rigorous predefined inclusion criteria for diagnosis (via PCR from CSF, brain biopsy, or autopsy). While this restriction to include cases with histologically or PCR-confirmed HSV infection of the CNS led to the exclusion of a considerable number of studies ($n=133$, i.e., 15% of the 861 theme-related studies initially identified, see Fig. 1), it ensures a high level of diagnostic accuracy and improves the quality of our systematic review.

The most frequently described clinical signs and symptoms identified in our review are rather unspecific, including fever, headache, and neck stiffness, as compiled in Fig. 2. Even though seven studies included patients presenting with signs and symptoms indicative of possible meningitis [1–3, 18, 22, 23, 25], this symptom was also reported in several studies claiming to present a cohort of patients with encephalitis [6, 9, 16, 19]. This finding suggests that HSV and/or its associated inflammatory response may extend beyond the brain to involve the adjacent meninges.

Since HSV has a predilection for the temporal lobes [9, 21], the frequent appearance of language/speech abnormalities does not seem surprising. Similarly, the relatively high incidence of epileptic seizures seems more than plausible and underscores the high susceptibility of the temporal region and the limbic system to epileptic seizures, particularly in the presence of structural abnormalities or irritation. While seizures were reported in all but one study with a median of 35% of patients affected, transformation into status epilepticus was only described in two studies [8, 24] with a frequency of 13.3–18.4%. Since recognizing non-convulsive or subtle status epilepticus is challenging [28, 29], underdiagnosis and underreporting seems more than likely [30] and calls for heightened clinical awareness in this context.

Our findings are mostly in line with a prior opinion paper by Rabinstein, suggesting the symptoms of headache, fever, confusion, language difficulties, focal deficits,

Table 3 Overview of diagnostics and outcome

Study	CSF results					Imaging studies			EEG		Outcome	
	WBC (cells/mm^3)	Normal WBC (%)	Protein (mg/dl)	Glucose (mg/dl)	Decreased glucose (%)	MRI performed (%)	MRI normal (%)	Temporal abnormalities (%)	EEG performed (%)	EEG abnormal (%)	Death (%)	No or minor sequelae (%)
Retrospective/multicenter												
Cag et al.		5	NR	NR		66.7	25.7	69.5	53.6	88.7	NR	88.7
De Montmollin et al.		15.8	NR	NR		NR	NR	NR	NR	NR	14.3	NR
Poissy et al.	median 83.5, IQR 21–195.5	NR	Median 67, IQR 50–100	NR		NR	NR	NR	NR	NR	19.9	NR
Kaewpoowat et al.	median 265, range 6–6400	0	Median 98.5, range 18–445	Median 52, range 35–169		86.3	78.3	NR	20	56.3	0	50
Chow et al.	median 50, IQR 22–76	NR	Median 75, IQR 48–105	Median 65, IQR 54–74		100	0	100	NR	NR	NR	NR
Omland et al.	mean 370, range 2–1174	NR	Median 122, range 36–273	Mean 56, range 25–81		NR	NR	NR	4.1	50	0	100
Gennai et al.	NR	NR	NR	Minimal 16		77.8	NR	NR	NR	NR	NR	NR
Afonso et al.	475.5, SD 317, range 100–1130	0	Mean 92.4, SD 32.3, range 24–139	65.7, SD 23.7, range 36–118		NR	NR	NR	NR	NR	NR	89.5
Retrospective/monocenter												
Moon et al.	range 6–4000	0	Range 25–335	Range 27–117		NR	NR	NR	NR	NR	0	84.2
Mulatero et al.	mean 151	NR	100	NR		100	NR	NR	100	89.5	11.6	42
Singh et al.	median 64, range 1–2508	15.6	Median 75, IQR 57.5–105	Median 61, IQR 50.3–72		88.9	NR	87.5	80	NR	15.6	65.9
Tan et al.		13.8	NR	NR		100	0	92.9	NR	NR	20.7	NR
Miller et al.	mean 504, SD 443, range 86–1860	0	Mean 146, SD 54, range 60–258	Mean 54, SD 12, range 32–80		NR	NR	NR	NR	NR	0	100
Babaei et al.	mean 65, range 12–520	0	Mean 145, range 60–500	NR	13.6	NR	NR	NR	NR	NR	25	75
Esiri et al.	NR	NR	NR	NR		NR	NR	NR	NR	NR	100	0
Bewersdorf et al.	mean 131, range 1–893	22.2	Mean 67.8, range 10–123	NR		94.4	5.9	94.1	83.3	100	5.6	38.9
Studahl et al.	NR	NR	NR	NR		NR	NR	NR	NR	NR	18.6	56.3
Basaran et al.	lymphocytes mean 142.71, neutrophils mean 6.14	NR	Mean 389.09, SD 255.63	Mean 68.25, SD 30.78		93.8	NR	86.7	93.8	46.7	0	NR
Alessandro et al.	median 97.5, range 0–890	25	Median 93, range 23–235	NR	25	NR	NR	NR	100	43.8	0	100

Table 3 (continued)

Study	CSF results					Imaging studies			EEG		Outcome	
	WBC (cells/mm^3)	Normal WBC (%)	Protein (mg/dl)	Glucose (mg/dl)	Decreased glucose (%)	MRI performed (%)	MRI normal (%)	Temporal abnormalities (%)	EEG performed (%)	EEG abnormal (%)	Death (%)	No or minor sequelae (%)
Momméja-Marin et al.	median 74, range 4–340	NR	Median 72, range 32–441	NR	53.8	NR	NR	NR	NR	NR	30.8	69.2
Oyanguren et al.F	mean 83, range 2–300	NR	Mean 81, range 52–140	Mean 63.7, range 47–90		91.7	0	100	NR	most	NR	NR

CSF Cerebrospinal fluid, *NR* Not reported, *SD* Standard deviation, *IQR* Interquartile range, *WBC* White blood cell count, *MRI* Magnetic resonance imaging, *EEG* Electroencephalogram

and seizures as typical manifestations of HSV encephalitis in adult patients [5]. In contrast to Rabinstein, our systematic review identified additional signs of meningitis, such as neck stiffness and photophobia. However, the author did not provide evidence for the categorization of symptoms as typical or atypical nor did he base these claims on a systematic review of the literature. Furthermore, he did not focus exclusively on confirmed cases of HSV infection of the CNS (i.e., by PCR or brain biopsy), which presents a major limitation.

A clear differentiation in the clinical presentation between monophasic and recurrent forms of HSV infections of the CNS—two distinct yet potentially overlapping entities—could not be conclusively established based on the findings of our review. Available yet limited evidence indicates that monophasic infections are commonly characterized by the acute onset of fever, headache, altered mental status, and focal neurological deficits. Conversely, recurrent infections, particularly HSV meningitis, may present with milder symptoms compared to the initial episode, potentially reflecting the involvement of complex immune-mediated mechanisms [31]. Nevertheless, the scarcity of larger studies centered on this distinction underscores the need for further research to elucidate these clinical differences. Similarly, the studies identified a lack of sufficient data to synthesize the clinical manifestations and severity of HSV infections involving myelitis or radiculitis. This is a significant limitation, as these presentations may exhibit distinct features and require specific diagnostic and therapeutic approaches. Limited reports suggest HSV-2 is more commonly associated with myelitis and radiculitis [32]. HSV-2 myelitis may present with acute back pain, rapidly ascending flaccid paralysis, sensory deficits, and autonomic dysfunction, such as urinary retention and constipation, differing markedly from the HSV infections in our review. Diagnosis may be supported by MRI findings of spinal cord swelling and tractopathy, and CSF analysis showing pleocytosis and elevated protein. Outcomes can remain poor despite early acyclovir treatment [32].

Another important, yet underinvestigated aspect is that PCR-confirmed cases of HSV infections of the CNS tend to show less severe manifestations compared to biopsy-proven cases, as evidenced by a study of almost 100 patients with HSV DNA-positive CSF, of which 17% had mild or atypical disease with slow progression and no focal findings even without antiviral therapy [33]. This likely reflects the higher sensitivity and specificity of PCR in detecting milder cases that might go undetected with biopsy. Additionally, biopsy-based studies often involve cohorts from the 1980s, the "pre-PCR era," when clinical awareness and treatment options were less advanced, acting as a potential confounder.

Due to the frequently nonspecific clinical presentation of patients and the absence of reported combinations of symptoms that would be inherently more specific, there is a significant risk of either a delayed or incorrect diagnosis of HSV infections of the CNS, leading to substantial delay in antiviral treatment. Unfortunately, exact information regarding the time from symptoms onset to the start of antiviral medication was lacking frequently with the exception of four studies [17–19, 26]. In eight studies [1, 8, 10, 14, 16, 20, 24, 27], the time from hospital admission to the beginning of specific treatment is mentioned, ranging from 1 h to 6 days. The heterogeneity of information on the timing of antiviral treatment among the studies included in our systematic review does not allow any further conclusion as to what extent delayed or missed diagnosis may impact the clinical courses and outcomes. However, it seems more than likely that delayed treatment does not come without costs. Early initiation of acyclovir has been shown to reduce mortality to approximately 15% and improve neurological outcomes as shown in a retrospective multicenter study that included 93 adult patients in whom HSE was diagnosed by PCR [4]. The clinical presentation of HSV encephalitis may overlap with other CNS infections and inflammatory conditions and the tests for definitive diagnosis (PCR or biopsy) may not yield immediate results. Additionally, early in the disease course, CSF findings can be nonspecific, and neuroimaging may not yet show characteristic abnormalities. Given the potential for rapid progression and irreversible brain damage in HSV encephalitis, initiating empiric acyclovir therapy while awaiting diagnostic confirmation is prudent. Acyclovir is generally well-tolerated, with nephrotoxicity as the main adverse effect, especially in patients with underlying renal impairment or receiving concurrent nephrotoxic agents [34]. Adequate hydration and dosing adjustments mitigate this risk [34]. The benefits of early antiviral therapy outweigh the risks, leading the Infectious Diseases Society of America (IDSA) to recommend acyclovir for all suspected encephalitis cases while awaiting diagnostic results [35].

Given the paucity of studies systematically evaluating the emergence and predictive value of specific symptom clusters for diagnosing HSV infection of the CNS, further research is warranted. We found only one study performing risk analyses and attempting to develop a score on the initial clinical presentation of infected patients [6]. Since additional workup involving CSF analysis and neuroimaging is time-consuming and may delay not only diagnosis but also treatment, there is a need for further research regarding rapid and reliable diagnostic methods for HSV CNS infection based on specific clinical signs and symptoms. Furthermore, there is evidence that PCR might be negative in up to four percent of patients in the first few

days of infection, so a multimodal approach comprising clinical signs and symptoms in addition to MRI and CSF results seems important to better assess the risk of infection and to avoid delays in treatment [19]. As a first step, future research should focus on evaluating the predictive value of models derived from the most frequent clinical signs and symptoms identified in this review.

While the focus of our review centered on the clinical presentation, we also collected information on diagnostics, treatment, and outcome of patients with HSV infections of the CNS, where provided. In line with the literature, cerebral MRI was commonly performed and revealed temporal lobe abnormalities in eight out of 10 patients [5, 36, 37]. However, the interpretation and reporting of MRI findings varied significantly. The same holds true for EEG findings; thus, no further analyses were possible.

Mortality rates and neurological outcomes varied among studies, reflecting differences in patient populations, disease severity, and possibly treatment practices. The overall mortality rate of 13% observed in our review, however, falls within the range found in the literature [4, 5, 8, 38]. Additionally, the 72% of survivors in whom the neurological outcomes were described as "good" (characterized by no or minor sequelae) is also consistent with previous reports, suggesting that a substantial proportion of patients can recover with no or limited long-term deficits if treated early [4, 5, 8, 38].

Strengths and limitations

This systematic review leverages several strengths. First, we employed a predefined search strategy aligned with the current PRISMA guidelines, ensuring comprehensive and unbiased identification of relevant studies and a careful assessment of several biases. Second, by restricting our analysis to studies investigating adult patients with histologically or PCR-confirmed HSV infections of the CNS, we ensured a high degree of diagnostic certainty. This methodological rigor strengthens the internal validity of our review and minimizes the potential for bias introduced by studies with less stringent diagnostic criteria. Third, our analysis encompasses a substantial dataset of 21 studies ($n=1605$ adult patients), spanning patients from 18 countries across 4 continents. This broad geographic representation enhances the generalizability of our findings.

Our review has several limitations, such as the retrospective observational design of the included studies that result in a high risk of bias and a low level of evidence. In addition, it is important to note that the vast majority of studies originate from Europe and North America, potentially limiting the generalizability of our results. Furthermore, the sample sizes of the included studies were highly variable, with more than a quarter of the studies including fewer than 20 patients. This variability could introduce additional bias and further affect the reliability of our findings. To mitigate this issue, we excluded case series (i.e., presenting less than 10 patients), aiming to enhance the robustness of our estimates.

A major limitation may come from the fact that most studies did not systematically assess clinical signs and symptoms as their main objective, resulting in heterogeneous assessment and reporting, as well as a potential recall bias. Lastly, our review was restricted to studies published in English, which might have led to the exclusion of relevant studies in other languages. However, given the predominance of English in scientific literature, we do not consider this as a major limitation to the comprehensiveness of our systematic review. Furthermore, and as discussed in detail above, due to insufficient data, it was not possible to conclusively differentiate between monophasic and recurrent forms of HSV CNS infections or to synthesize the clinical manifestations and severity of infections involving myelitis or radiculitis. The scarcity of large studies regarding these distinct presentations underscores the need for further research to clarify clinical features and inform diagnostic and therapeutic approaches. Finally, the restriction of our search of the literature to the three databases mentioned may pose a risk for an additional systematic bias. However, we believe that this potential bias is limited, as the screening of the three databases fulfills the requirement for Cochrane reviews [39].

Conclusion

Our systematic review compiled common clinical signs and symptoms in a large number of adult patients from 18 countries with histologically proven or PCR-confirmed HSV infection of the CNS. Fever, headache, neck stiffness, and language/speech abnormalities were the symptoms most frequently reported, followed by epileptic seizures, photophobia, and focal neurologic deficits. Despite a high risk of bias and limited evidence, these symptoms should prompt early empiric antiviral therapy, especially when alternative diagnoses lack strong support.

Symptoms such as neck stiffness and photophobia may misdirect clinicians and delay diagnosis and treatment. Significant knowledge gaps remain, particularly the predictive value of specific symptoms and their clusters for diagnosing HSV infection of the CNS. As prediction models based on the symptoms compiled in our review could provide measures for accelerated diagnosis and treatment, future research should be centered on these areas. In the meantime, clinicians should maintain a high index of suspicion for HSV infections of the CNS and consider early empirical treatment.

Abbreviations

CNS	Central nervous system
HSV	Herpes simplex virus
CSF	Cerebrospinal fluid
PCR	Polymerase chain reaction
IQR	Interquartile range
MRI	Magnetic resonance imaging
EEG	Electroencephalogram

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Authors' contributions
Pascale Grzonka: Major role in the acquisition of data, interpreted the data, and drafted the manuscript. Tamina Mosimann: Major role in the acquisition of data and revised the manuscript for intellectual content. Sebastian Berger, Simon A. Amacher, Sira M. Baumann, and Caroline E. Gebhard: Revised the manuscript for intellectual content. Gian Marco De Marchis: Designed and conceptualized the study. Tolga D. Dittrich: Major role in the acquisition of the data, designed and conceptualized the study, and revised the manuscript for intellectual content. Raoul Sutter: Major role in the acquisition of the data, designed and conceptualized the study, analyzed the data, and drafted the manuscript.

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Data Availability
The corresponding author has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data not provided in the article because of space limitations may be shared at the request of any qualified investigator for purposes of replicating procedures and results.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
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