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Molecular Diagnosis of Rickettsial Meningoencephalitis With Concurrent Herpes Simplex Virus Type 2 Infection in a Young Female Presenting With Acute Febrile Encephalopathy: A Report on a Rare Case

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Abstract

Rickettsial CNS infections have been increasingly reported in tropical countries, including India, and are associated with significant morbidity and mortality. Early diagnosis is challenging due to nonspecific presentations, absent rash/eschar, and limited sensitivity of conventional serological tests in the acute phase. Concurrent CNS infection with herpes simplex virus type 2 (HSV-2) is exceedingly rare and further complicates clinical diagnosis and management.

This report presents the case of a 28-year-old previously healthy female from Aligarh, Uttar Pradesh, who presented with a 10-day history of intermittent fever, headache, vomiting, decreased appetite, and progressively worsening altered sensorium. Four days before admission, she developed recurrent seizure-like episodes characterized by upward deviation of the eyeballs and jaw clenching. On admission, a neurological examination revealed a Glasgow coma scale (GCS) score of E2V2M5 with neck rigidity suggestive of meningeal irritation. Owing to progressive neurological deterioration and impaired airway protection, she required endotracheal intubation and mechanical ventilation.

Laboratory investigations demonstrated mild neutrophilic leukocytosis, thrombocytopenia, elevated alanine aminotransferase levels, and hypoalbuminemia. A CSF analysis revealed normal glucose and protein concentrations with minimal pleocytosis, while Gram stain and bacterial cultures were negative. Contrast-enhanced computed tomography (CECT) and MRI demonstrated only a small calcified occipital granuloma without evidence of acute inflammatory changes. Extensive investigations for common bacterial and tropical infections, including malaria, dengue, enteric fever, scrub typhus, leptospirosis, and bacterial meningitis, were negative. Multiplex real-time polymerase chain reaction (PCR) performed on peripheral blood detected *Rickettsia* spp. DNA. Subsequent molecular analysis of CSF also demonstrated *Rickettsia* spp. DNA, confirming CNS involvement, while real-time PCR simultaneously detected HSV-2 DNA, establishing the diagnosis of concurrent *Rickettsia* spp. meningoencephalitis and HSV-2 encephalitis. The patient initially received empirical intravenous ceftriaxone, vancomycin, and acyclovir. Following molecular confirmation of *Rickettsia* spp. infection, doxycycline (100 mg twice daily) was initiated while antiviral therapy was continued. The patient demonstrated progressive neurological improvement with recovery of sensorium and a favorable clinical outcome.

This case highlights the diagnostic challenges associated with rickettsial CNS infection, particularly in patients lacking classical clinical features and presenting with normal CSF biochemistry and nonspecific neuroimaging findings. Simultaneous molecular detection of *Rickettsia* spp. in peripheral blood and CSF together with HSV-2 in CSF emphasizes the importance of considering mixed infectious etiologies in patients presenting with acute febrile encephalopathy. Early application of molecular diagnostics enabled prompt institution of targeted therapy and contributed to successful clinical recovery. To the best of our knowledge, this represents one of the very few reported cases of concurrent molecularly confirmed *Rickettsia* spp. meningoencephalitis and HSV-2 encephalitis worldwide and is likely the first such case reported from India.

Categories: Infectious Disease
Keywords: acute febrile encephalopathy, coinfection, hsv-2, meningoencephalitis, molecular diagnosis, multiplex pcr, rickettsia

Introduction

Acute febrile encephalopathy (AFE) is a serious medical condition characterized by fever and altered sensorium and may result from a variety of infectious and non-infectious etiologies. In tropical and

subtropical regions, infectious agents are of particular importance, because many bacterial, viral, parasitic, and vector-borne diseases may have similar neurologic manifestations. Early identification of the causative organism is important, since delays in appropriate antibiotic or antiviral therapy can result in serious neurologic damage and death.

Rickettsial diseases are a diverse group of zoonotic diseases caused by obligate intracellular Gram-negative bacteria of the order Rickettsiales, which are transmitted by arthropods. The principal vectors are ticks, mites, fleas, and lice, and include the spotted fever group (SFG), typhus group (TG), transitional group, and Orientia species causing scrub typhus. Rickettsial infections have long been classified as neglected tropical diseases and are now increasingly recognized as important causes of acute undifferentiated febrile illness (AUFI), especially in tropical and subtropical Asia. Although awareness is increasing, the true disease burden is underestimated because of lack of clinical suspicion, non-specific clinical presentation and clinical overlap with other tropical infections, and the limited availability of accurate diagnostic techniques, especially in resource-limited settings [1-5].

India is located in the 'tsutsugamushi triangle,' an endemic area for scrub typhus, but increasing evidence points to the common occurrence of non-scrub typhus rickettsial diseases, such as those of the spotted fever group and typhus group, in several parts of the country. Recent epidemiological studies indicate that rickettsial infections are an important cause of prolonged febrile illness requiring hospitalization. However, there are still challenges with standard diagnostic algorithms, since serological methods may have low sensitivity in early disease stages, and molecular diagnostic capabilities are mainly available in tertiary care settings [5-8].

Once inoculated in the human host, *Rickettsia* spp. show a marked predilection for vascular endothelial cells. Intracellular multiplication leads to endothelial damage, diffuse vasculitis, increased vascular permeability, and activation of proinflammatory cytokines with multiorgan involvement. Serious infections may be represented by pneumonitis, hepatitis, myocarditis, acute kidney injury, disseminated intravascular coagulation, and problems in the CNS. Neurological complications are thought to be mostly due to inflammation of the endothelium of the cerebral microvasculature and breakdown of the blood-brain barrier, which result in a variety of manifestations such as aseptic meningitis, encephalitis, meningoencephalitis, seizures, cranial nerve deficits, cerebellitis, cerebral vasculitis, and diffuse encephalopathy [9-11].

Neurological manifestations are increasingly being recognized, but rickettsial meningoencephalitis continues to be a rare entity and poses major diagnostic challenges. Patients may have prolonged fever, headache, vomiting, altered mental status, seizures, and neck stiffness. These features overlap considerably with viral encephalitis, acute bacterial meningitis, tuberculous meningitis, autoimmune encephalitis, and a number of tropical CNS diseases [6,10,12]. In addition, classic rash and eschar may be absent, and neuroimaging findings are often normal or nonspecific. The CSF examination typically demonstrates mild lymphocytic pleocytosis and a moderate increase in protein levels, but it can sometimes be normal, which may confound early identification [6,11-13].

Precise identification of rickettsial CNS infections continues to pose challenges in standard clinical settings. In the acute phase of infection, conventional diagnostic methods, including the Weil-Felix agglutination test and serological tests, have limited sensitivity and can produce false-negative results before antibody seroconversion. Nucleic acid amplification methods such as real-time PCR can identify pathogens directly and can aid in making a rapid diagnosis, especially in patients who are very sick. Recently, multiplex molecular assays that may concurrently identify bacterial, viral, and parasite pathogens have shown to be valuable instruments in the diagnostic assessment of patients with acute febrile encephalopathy [14-17].

A further diagnostic complication emerges from the potential for simultaneous infections. Herpes simplex virus type 1 (HSV-1) continues to be the primary cause of sporadic viral encephalitis globally and is linked to significant neurological complications and fatalities when antiviral treatment is postponed [18]. Although HSV-2 is most commonly associated with genital infections, neonatal disease, and meningitis, it can cause encephalitis and may have clinical features that overlap with other viral causes of CNS disease. Co-infection of *Rickettsia* spp. and HSV in the CNS is very rare [18]. A review of the current literature revealed only a few reported cases of rickettsial-HSV coinfection with CNS involvement, including a molecularly confirmed coinfection with *Rickettsia helvetica* and HSV-2 from Sweden, rickettsial meningoencephalitis associated with HSV-1 in Türkiye, and a pediatric case from India of scrub typhus (Orientia tsutsugamushi) and HSV encephalitis diagnosed mainly by serological methods [19-21]. These findings suggest that mixed infectious etiologies should be considered in cases of severe or atypical meningoencephalitis, even if rare, particularly when routine microbiological investigations are uninformative.

Prompt identification of rickettsial CNS infection is crucial, as a lag in starting doxycycline may lead to heightened morbidity, extended hospital stays, neurological complications, and higher mortality. Present guidelines thus endorse empirical doxycycline treatment for individuals with suspected rickettsial infections residing in endemic areas while microbiological verification is pending [5,6,15]. This is especially pertinent in individuals with acute febrile encephalopathy, when the clinical manifestation alone may not consistently

differentiate rickettsial infection from alternative sources of CNS infection.

We discuss the case of a previously healthy 28-year-old female exhibiting acute febrile encephalopathy and rapid neurological decline. Thorough molecular analyses identified *Rickettsia* spp. DNA present in both peripheral blood and CSF, along with simultaneous identification of HSV-2 in CSF, substantiates a diagnosis of rickettsial meningoencephalitis with coexisting HSV-2 CNS infection. To our knowledge, this is perhaps one of the uncommon documented instances from India showcasing molecular identification of *Rickettsia* spp. in both peripheral blood and CSF, alongside HSV-2 identification in CSF, and one of the scant few such cases published globally. This case highlights the diagnostic challenges of rickettsial CNS infections and underscores the potential use of multiplex molecular diagnostics to detect co-infecting pathogens and guide pathogen-specific therapy in a timely manner.

Case Presentation

A 28-year-old previously healthy woman, employed as a municipal sanitation worker and residing in Aligarh district, Uttar Pradesh, India, presented to the emergency department of our tertiary-care hospital with a history of prolonged febrile illness associated with progressive neurological deterioration. The illness began approximately 10 to 12 days before presentation with intermittent low- to moderate-grade fever (100-102°F) associated with chills, rigors, generalized weakness, anorexia, and persistent headache. The headache had initially developed nearly one month before admission and progressively increased in severity. During the subsequent 10 days, she experienced repeated episodes of non-bilious vomiting containing undigested food particles, followed by gradually worsening drowsiness, reduced interaction with family members, and impaired awareness of her surroundings.

Approximately four to five days before admission, the patient's relatives observed recurrent episodes characterized by upward deviation of the eyeballs with jaw clenching, each lasting approximately one minute, followed by increased confusion. These episodes were suggestive of focal seizures with impaired awareness. There was no history of tongue biting, urinary or fecal incontinence, frothing from the mouth, or documented postictal focal neurological deficits. The patient had initially been admitted to a private hospital, where she received supportive treatment for approximately 10 days without significant clinical improvement. Owing to progressive deterioration in sensorium, she was referred to our institution for further evaluation and management.

There was no significant past medical history. She also did not have a history of recent travel, animal bites, or similar illness among family members. Although she denied a definite history of tick or mite bite, her occupation as a sanitation worker involved frequent exposure to outdoor environments, refuse disposal sites, rodents, and potentially vector-infested surroundings, representing a plausible epidemiological risk for arthropod-borne infections. She had no history of smoking, alcohol consumption, or recreational drug use. A remote history of head injury two years earlier was noted; however, she had remained neurologically asymptomatic thereafter. There was no history of cough, dyspnea, chest pain, diarrhea, bleeding manifestations, arthralgia, skin rash, eschar, lymphadenopathy, or significant weight loss.

On arrival, the patient appeared acutely ill and poorly responsive. Her vital signs revealed the following: blood pressure 100/70 mmHg, pulse rate 90 beats/min, peripheral oxygen saturation of 100% on supplemental oxygen, and random blood glucose 75 mg/dL. Neurological examination demonstrated a Glasgow coma scale (GCS) score of E2V2M5. Both pupils measured approximately 3 mm and were sluggishly reactive to light. Marked neck rigidity was present, indicating meningeal irritation. Detailed assessment of higher mental functions, cranial nerves, cerebellar function, and sensory examination could not be reliably performed because of the patient's depressed level of consciousness. Muscle tone was preserved, deep tendon reflexes were symmetrical, plantar responses were flexor bilaterally, and no definite focal motor deficits could be elicited.

General physical examination did not reveal any rash, eschar, petechiae, peripheral edema, or lymphadenopathy. Cardiovascular examination demonstrated normal first and second heart sounds without murmurs. Respiratory examination revealed bilaterally equal air entry with no adventitious sounds. Abdominal examination showed a soft, non-tender abdomen without hepatosplenomegaly or ascites. Based on the prolonged febrile illness, progressive encephalopathy, seizure-like episodes, and clinical evidence of meningeal irritation, a provisional diagnosis of acute meningoencephalitis was made. Differential diagnoses included acute bacterial meningitis, herpes simplex encephalitis, tuberculous meningitis, cerebral malaria, autoimmune encephalitis, and tropical infectious diseases such as scrub typhus, leptospirosis, dengue, and rickettsial infections.

Soon after admission, the patient's neurological status deteriorated further with loss of airway protective reflexes. She underwent emergency endotracheal intubation using a 7.5-mm cuffed endotracheal tube, secured at 22 cm at the incisors, and was placed on mechanical ventilation. Rapid sequence induction was performed using intravenous fentanyl and rocuronium. She was subsequently transferred to the ICU for further diagnostic evaluation and supportive management.

Initial laboratory investigations demonstrated mild neutrophilic leukocytosis, thrombocytopenia, elevated alanine aminotransferase, and hypoalbuminemia. Cerebrospinal fluid analysis showed normal glucose and protein concentrations with minimal pleocytosis, while Gram stain and bacterial cultures remained negative. Contrast-enhanced computed tomography (CECT) and MRI of the brain revealed only a small calcified granuloma in the right occipital lobe without surrounding edema, abnormal enhancement, or radiological evidence of acute encephalitis. An extensive microbiological work-up, including investigations for malaria, enteric fever, dengue, leptospirosis, scrub typhus, and bacterial meningitis, was negative. Given the absence of an alternative diagnosis despite progressive neurological deterioration, molecular diagnostic testing was undertaken.

Clinical investigations

Initial laboratory investigations demonstrated evidence of a systemic inflammatory response with mild hematological and biochemical abnormalities (Table *1*). A complete blood count revealed mild anemia (hemoglobin 11.0 g/dL) and leukocytosis (11.47 × 10^3/μL) with marked neutrophilic predominance (86.7%) and relative lymphopenia (8.6%). Mild thrombocytopenia (127 × 10^3/μL) was also noted. Renal function tests, including blood urea nitrogen (28 mg/dL) and serum creatinine (0.9 mg/dL), were within normal limits.

Investigation	Result	Adult reference range
Hemoglobin	11.0 g/dL	12.0-16.0
Total leukocyte count	11.47 × 10^3/μL	4.0-11.0
Neutrophils	86.7%	40-75
Lymphocytes	8.6%	20-45
Platelet count	127 ×10^3/μL	150-450
Blood urea nitrogen	28 mg/dL	15-50
Serum creatinine	0.90 mg/dL	0.6-1.1
Aspartate aminotransferase	34 U/L	<40
Alanine aminotransferase	95 U/L	<45
Total protein	5.6 g/dL	6.4-8.3
Albumin	3.2 g/dL	3.5-5.0
Sodium	137 mmol/L	135-145
Potassium	3.8 mmol/L	3.5-5.0
CSF glucose	82 mg/dL	45-80*
CSF protein	27 mg/dL	15-45
CSF leukocyte count	<10 cells/mm^3	0-5

TABLE 1: Baseline laboratory investigations

Biochemical investigations demonstrated isolated elevation of alanine aminotransferase (95 U/L), whereas aspartate aminotransferase (34 U/L) remained within the reference range. Total serum protein (5.6 g/dL) and albumin (3.2 g/dL) were reduced, consistent with mild hypoproteinemia and hypoalbuminemia. Serum electrolytes were largely normal except for mild hypophosphatemia (2.2 mg/dL). Random blood glucose at admission was 75 mg/dL.

Lumbar puncture was performed after stabilization of the patient's clinical condition. Cerebrospinal fluid examination revealed normal glucose (82 mg/dL) and protein (27 mg/dL) concentrations with fewer than 10 leukocytes/mm^3. Gram stain showed no organisms, and bacterial culture remained sterile after incubation. Although the CSF profile was not strongly suggestive of bacterial meningitis, the patient's persistent fever, altered sensorium, seizures, and meningeal signs warranted further evaluation for infectious causes of meningoencephalitis.

Neuroimaging

The CECT of the brain demonstrated a solitary 5.5 mm calcified lesion in the right occipital lobe without surrounding edema, mass effect, or gliosis, suggestive of a healed calcified granuloma. Contrast-enhanced MRI confirmed a 3.5 × 3 mm calcified granuloma in the right occipital region without abnormal enhancement, diffusion restriction, or perilesional edema. No radiological evidence of acute encephalitis, meningitis, cerebral edema, or vasculitic infarction was identified. The imaging findings were considered incidental and unlikely to explain the patient's acute neurological illness.

Microbiological investigations

Considering the broad differential diagnosis of acute febrile encephalopathy in a tropical setting, an extensive microbiological evaluation was undertaken. Peripheral blood smear and rapid antigen testing for malarial parasites were negative. Blood cultures processed using the automated BACTEC system (Becton, Dickinson and Company (BD), Franklin Lakes, NJ, USA) showed no bacterial growth after 48 hours of aerobic incubation. The Widal test for enteric fever, dengue NS1 antigen and IgM ELISA, scrub typhus serology and PCR, and leptospiral IgM ELISA with microscopic agglutination test (MAT) were all negative. Routine CSF Gram stain and bacterial culture also failed to identify any pathogen. The uniformly negative results of conventional microbiological investigations, despite persistent neurological deterioration, prompted molecular evaluation for uncommon tropical and neurotropic pathogens.

Molecular diagnostic methods

A multiplex real-time PCR, the TRUPCR® Tropical Fever Panel Kit (3B BlackBio Dx Ltd., Bhopal, UP, IND), was initially performed on the peripheral blood and revealed Rickettsia spp. DNA (Ct 27). Due to the persistence of encephalopathy and seizure-like phenomena and meningeal signs in the patient, the CSF was subsequently tested with molecular methods using the meningitis multiplex PCR panel, which also revealed the presence of Rickettsia spp. DNA (Ct 25). Thus, it provided molecular evidence of rickettsial DNA in the CSF and supported involvement of the CNS in the appropriate clinical context. The assay was capable of detection at the genus level but not at the species or group level.

Considering the importance of HSV in CNS infections, CSF was examined by real-time PCR assay for HSV (TRUPCR® Meningitis Panel Kit), which revealed HSV-2 DNA (Ct 27). Molecular assays included positive, negative, and internal amplification controls following the manufacturer’s instructions. Rickettsial serological evaluations, such as indirect immunofluorescence assays or IgM/IgG enzyme-linked immunosorbent assay (ELISA), were not conducted due to the unavailability of these tests at the treatment center. Consequently, the molecular results were analyzed alongside the clinical manifestation, epidemiological background, elimination of other infectious conditions, and the ensuing clinical reaction (Table *2*).

Diagnostic consideration	Investigation	Result	Clinical interpretation
Acute bacterial meningitis	CSF examination/bacterial investigations	Negative	Findings not supportive of acute pyogenic meningitis
Viral meningoencephalitis	CSF viral molecular testing	HSV-2 detected in CSF	Supports HSV-2 CNS infection
Rickettsial CNS infection	*Rickettsia* spp. real-time PCR of peripheral blood	Positive	Supports systemic rickettsial infection
Cerebral malaria	Peripheral smear, malaria antigen	Negative	Excluded
Tuberculous meningitis	Cartridge- based nucleic acid amplification test, Ziehl-Nielsen smear	Negative	Excluded
Dengue infection	NS1 antigen, IgM ELISA	Negative	Excluded
Other tropical infections	Peripheral smear, malaria antigen, IgM ELISA, microscopic agglutination test (MAT), blood culture, Widal	Negative	Excluded

TABLE 2: Differential diagnosis and microbiological evaluation

ELISA: Enzyme-linked immunosorbent assay; HSV: Herpes simplex virus; MAT: Microscopic agglutination test

Treatment and outcome

The patient was initially managed according to institutional protocols for acute meningoencephalitis with empirical intravenous ceftriaxone (2 g every 12 hours), vancomycin (1 g every 12 hours), and acyclovir (10 mg/kg every eight hours), together with supportive intensive care management, including mechanical ventilation. Following molecular detection of Rickettsia spp. DNA in peripheral blood and subsequently in CSF, doxycycline (100 mg twice daily) was added to the treatment regimen. Acyclovir was continued because HSV-2 DNA was concurrently detected in CSF.

Following the initiation of targeted antimicrobial therapy, there was gradual improvement in the neurological status of the patient. Sensorium improved progressively, seizures did not recur, and ventilatory support was successfully weaned. She was subsequently transferred from the ICU to the general ward and discharged in stable clinical condition with complete recovery of consciousness and no apparent focal neurological deficits.

Discussion

Rickettsial diseases are increasingly recognized as important causes of acute undifferentiated febrile illness (AUFI) in tropical and subtropical regions, including India. However, these infections continue to be substantially underdiagnosed because of their nonspecific clinical presentation, limited clinician awareness, and restricted availability of sensitive laboratory diagnostics. The absence of classical features such as rash and eschar, together with significant overlap with other tropical infectious diseases including dengue, malaria, leptospirosis, enteric fever, tuberculosis, and viral encephalitis, frequently results in delayed diagnosis and initiation of appropriate therapy [1-5,11].

Neurological involvement is an uncommon but well-recognized complication of rickettsial infections and is associated with increased morbidity and mortality. The underlying pathogenesis is primarily related to the marked endothelial tropism of *Rickettsia* spp. Following inoculation through an infected arthropod vector, the organisms invade vascular endothelial cells and proliferate intracellularly, resulting in diffuse vasculitis, endothelial dysfunction, increased vascular permeability, platelet activation, and perivascular inflammatory infiltration. These pathological processes disrupt the blood-brain barrier and contribute to cerebral microvascular injury, leading to manifestations such as aseptic meningitis, encephalitis, meningoencephalitis, seizures, cranial neuropathies, cerebellitis, cerebral infarction, and diffuse encephalopathy [2,4,6].

The present patient demonstrated several characteristic manifestations of rickettsial meningoencephalitis, including prolonged febrile illness, persistent headache, vomiting, progressive alteration in sensorium, seizure-like episodes, and neck rigidity. These findings are consistent with previously published reports describing neurological involvement in both scrub typhus and non-scrub typhus rickettsioses [10-14,19-21]. Notably, the patient had no rash, eschar, or definite history of tick or mite bite. Such atypical presentations are increasingly recognized and may account for delayed diagnosis in endemic regions. Several Indian studies have reported that a substantial proportion of patients with confirmed rickettsial infections lack the classical triad of fever, rash, and eschar, highlighting the importance of maintaining a high index of clinical suspicion even in the absence of these hallmark features [5,7].

Another noteworthy feature was the patient's occupational exposure. As a municipal sanitation worker, she had frequent contact with refuse disposal sites, rodents, stray animals, and potentially vector-infested environments, providing a plausible epidemiological risk for arthropod-borne zoonotic infections despite the absence of a recalled vector bite. This observation reinforces the importance of obtaining a detailed occupational and environmental exposure history when evaluating patients presenting with prolonged febrile illness and neurological manifestations.

The laboratory abnormalities observed in the present case, including mild leukocytosis with neutrophilic predominance, thrombocytopenia, elevated alanine aminotransferase, and hypoalbuminemia, are consistent with previous reports of severe rickettsial disease [3,5,8]. Although these abnormalities lack diagnostic specificity, they reflect the underlying systemic endothelial injury and inflammatory response associated with rickettsial vasculitis. Mild thrombocytopenia has been attributed to endothelial activation, platelet consumption, and immune-mediated mechanisms, whereas elevated hepatic transaminases are believed to result from hepatic microvascular injury and inflammatory infiltration. Hypoalbuminemia probably reflects increased capillary permeability secondary to generalized endothelial dysfunction, a characteristic pathological feature of severe rickettsial infections [2,6].

An important diagnostic challenge in our patient was the relatively unremarkable CSF profile despite clinically significant meningoencephalitis. The CSF examination demonstrated normal glucose and protein concentrations with fewer than 10 leukocytes/mm^3. While mild lymphocytic pleocytosis and modest protein elevation are commonly described in rickettsial CNS infections, several studies have demonstrated that CSF findings may remain normal or only minimally abnormal, particularly during the early stages of disease [6,9,10]. Consequently, normal CSF biochemical parameters should not be interpreted as excluding rickettsial meningoencephalitis when clinical suspicion remains high. This case emphasizes the limitations of relying solely on conventional CSF analysis for the diagnosis of CNS rickettsioses.

Similarly, neuroimaging contributed little to the diagnosis. Contrast-enhanced computed tomography and magnetic resonance imaging demonstrated only a small calcified occipital granuloma without surrounding edema, abnormal enhancement, diffusion restriction, or evidence of acute encephalitis. The lesion was considered an incidental healed granuloma unrelated to the patient's current illness. Previous reports have demonstrated considerable variability in neuroimaging findings among patients with rickettsial CNS infections, ranging from completely normal examinations to diffuse cerebral edema, multifocal white matter lesions, meningeal enhancement, hemorrhage, vasculitic infarctions, and reversible splenial lesions [6,11]. Therefore, the absence of characteristic radiological abnormalities should not delay consideration of rickettsial infection in patients presenting with compatible clinical features.

One of the major strengths of the present report is the comprehensive microbiological evaluation that systematically excluded more common infectious etiologies before establishing the diagnosis. Extensive investigations for malaria, dengue, enteric fever, leptospirosis, scrub typhus, and bacterial meningitis were uniformly negative. Such exhaustive exclusion of alternative diagnoses is particularly important in tropical countries, where multiple pathogens share similar clinical presentations, and coinfections may occur.

The diagnosis was ultimately established by molecular methods. Peripheral blood multiplex real-time PCR initially detected *Rickettsia* spp. DNA, suggesting systemic infection. Because of persistent neurological deterioration and clinical evidence of meningoencephalitis, CSF was subsequently analyzed using the same molecular platform and also demonstrated *Rickettsia* spp. DNA, providing direct microbiological evidence of CNS invasion. Simultaneously, CSF real-time PCR identified HSV-2 DNA, confirming concurrent HSV-2 encephalitis. The combination of positive molecular findings in both peripheral blood and CSF, together with compatible clinical manifestations and exclusion of alternative infectious etiologies, provides compelling evidence supporting the diagnosis of concurrent molecularly confirmed Rickettsia spp. meningoencephalitis and HSV-2 encephalitis.

The increasing availability of multiplex molecular assays has transformed the diagnostic approach to acute febrile encephalopathy. Conventional serological methods, including the Weil-Felix test and IgM-based assays, often demonstrate poor sensitivity during the early phase of illness because detectable antibody responses develop only after the first week of infection [5,6]. In contrast, nucleic acid amplification techniques enable direct detection of pathogen DNA before seroconversion and substantially reduce diagnostic delay. Multiplex real-time PCR platforms capable of simultaneously identifying bacterial, viral, and parasitic pathogens are therefore particularly valuable in critically ill patients presenting with acute meningoencephalitis of uncertain etiology. In the present case, molecular diagnostics directly influenced clinical management by establishing the diagnosis after conventional investigations had remained inconclusive, thereby facilitating prompt institution of pathogen-directed therapy.

Comparison with previously published cases

Concurrent CNS infection caused by *Rickettsia* spp. and HSV is exceptionally rare. A review of the available literature identified only a limited number of comparable reports (Table 3). Nilsson et al. first described molecularly confirmed coinfection with *Rickettsia helvetica* and HSV-2 in a 23-year-old woman presenting with meningitis after travel to a tick-endemic region in Sweden. The diagnosis was established by PCR detection of both pathogens in CSF, emphasizing that rickettsial infection may coexist with viral meningitis even in the absence of classical clinical features such as rash or documented tick bite [12].

Referene	Country	Patient	Rickettsial pathogen	HSV type	Specimens/diagnostic method	Clinical diagnosis	Outcome
Nilsson et al., 2011 [12]	Sweden	Adult	*Rickettsia helvetica*	HSV-2	Rickettsial and HSV molecular detection in CSF	Rickettsial-HSV CNS coinfection	Recovered
Kaur & Aulakh, 2020 [19]	India	11-year-old male	*Orientia tsutsugamushi*	HSV subtype not specified	Scrub typhus serology; HSV detected by CSF PCR	Scrub typhus with HSV encephalitis	Recovered
Baddal et al., 2023 [14]	Türkiye	42-year-old male	Rickettsial infection, species not identified	HSV-1	Weil-Felix testing; HSV detected by CSF PCR	Rickettsial meningoencephalitis with HSV infection	Recovered
Present case	India	28-year-old female	*Rickettsia* spp.	HSV-2	*Rickettsia* spp. PCR positive in peripheral blood and CSF; HSV-2 PCR positive in CSF	Rickettsial meningoencephalitis with concurrent HSV-2 CNS infection	Recovered

TABLE 3: Published cases of concurrent rickettsial and HSV CNS infections

In the Kaur & Aulakh case [19], the HSV subtype was not specified in the published report; HSV infection was detected by CSF PCR, while scrub typhus was diagnosed by serological testing.

HSV: Herpes simplex virus

More recently, Baddal et al. reported a 42-year-old male from Türkiye who presented with fever, severe headache, confusion, and meningoencephalitis. Although HSV-1 infection was confirmed by CSF PCR, the diagnosis of rickettsial infection relied primarily on Weil-Felix serology and clinical response to doxycycline rather than direct molecular confirmation [14]. Consequently, microbiological evidence supporting CNS invasion by *Rickettsia* was less robust than in the present case.

From India, only isolated reports of scrub typhus-associated HSV encephalitis have been published, predominantly in pediatric patients. In these reports, the diagnosis of scrub typhus was established using serological assays, whereas HSV infection was confirmed by CSF PCR. Direct molecular confirmation of rickettsial DNA within CSF was not demonstrated [19,22]. Consequently, our patient differs substantially from previously reported Indian cases because both peripheral blood and CSF were positive for *Rickettsia* spp. DNA was detected using multiplex real-time PCR, while concurrent HSV-2 infection was independently confirmed by CSF PCR. This combination provides strong microbiological evidence supporting simultaneous CNS infection rather than presumptive or sequential coinfection.

The present report therefore expands the limited literature describing rickettsial-HSV CNS coinfection and highlights the value of comprehensive molecular investigations in patients presenting with acute febrile encephalopathy. To the best of our knowledge, this is likely the first reported case from India demonstrating molecular confirmation of *Rickettsia* spp. in both peripheral blood and CSF together with HSV-2 detection in CSF.

Clinical significance of HSV-*Rickettsia* coinfection

The biological interaction between *Rickettsia* spp. and HSV remains poorly understood. Several mechanisms may explain this rare coexistence. Endothelial injury, cytokine dysregulation, and transient immune dysfunction induced by acute rickettsial infection may facilitate reactivation of latent HSV infection or increase susceptibility to viral invasion of the CNS [4,9]. Alternatively, HSV encephalitis may have preceded or occurred independently of the systemic rickettsial infection, with simultaneous infection producing more severe neurological manifestations than would be expected from either pathogen alone.

Regardless of the underlying mechanism, this case illustrates an important clinical principle: identification of one pathogen should not preclude investigation for additional infectious etiologies. Mixed infections may occur, particularly in endemic tropical regions where multiple pathogens circulate simultaneously. The increasing availability of multiplex PCR assays provides an opportunity to detect such coinfections early, thereby avoiding premature diagnostic closure and ensuring appropriate pathogen-directed therapy.

Treatment response and clinical outcome

Prompt initiation of empirical antimicrobial and antiviral therapy remains the cornerstone of management in patients presenting with acute meningoencephalitis. Consistent with current international

recommendations, our patient initially received broad-spectrum antibacterial therapy together with intravenous acyclovir while diagnostic investigations were underway [15-17,23]. Following molecular confirmation of *Rickettsia* spp., doxycycline (100 mg twice daily) was initiated without delay, while acyclovir was continued because of confirmed HSV-2 infection.

The patient demonstrated progressive neurological recovery following the institution of targeted therapy, with improvement in sensorium, successful weaning from mechanical ventilation, and eventual discharge without apparent neurological deficits. The favorable clinical response observed in this case reinforces previous evidence that early doxycycline administration remains the single most important determinant of outcome in severe rickettsial disease [5,6,15]. Delayed treatment beyond the first week of illness has consistently been associated with increased mortality, prolonged hospitalization, and irreversible neurological sequelae.

Strengths and limitations

An important limitation of this case is the interpretation of concurrent HSV-2 detection in CSF. Although HSV-2 DNA was detected by real-time PCR, detection of viral DNA alone does not establish whether HSV-2 represented a primary CNS infection, reactivation during severe systemic illness, or a concurrent infection contributing independently to the neurological presentation. Herpes simplex virus type 2 is more commonly associated with aseptic meningitis in adults, whereas sporadic necrotizing encephalitis is more characteristically associated with HSV-1. In the present patient, detection of *Rickettsia* spp. DNA in both peripheral blood and CSF provides molecular evidence supporting rickettsial CNS involvement; however, the available data cannot establish whether HSV-2 and *Rickettsia* spp. acted synergistically or whether HSV-2 represented reactivation or an independent concurrent process.

A further limitation is that the multiplex assay provided genus-level detection of *Rickettsia* spp. and did not permit species-level or group-level differentiation. Additional molecular targets such as gltA, ompA, or ompB were not tested. Therefore, the specific rickettsial species and its classification as a spotted fever group or typhus group *Rickettsia* cannot be determined. In addition, acute or convalescent rickettsial serology was not performed because the relevant tests were not available at the treating facility. These limitations should be considered when interpreting the molecular findings and the final clinical diagnosis.

Clinical implications

This case has several important clinical implications. First, rickettsial infection should be included in the differential diagnosis of acute febrile encephalopathy in endemic regions even when classical manifestations such as rash, eschar, thrombocytopenia, or abnormal CSF findings are absent. Second, normal neuroimaging and routine microbiological investigations do not exclude rickettsial meningoencephalitis. Third, multiplex molecular diagnostic platforms capable of simultaneously detecting bacterial and viral pathogens should be considered early in the evaluation of critically ill patients with undifferentiated CNS infections, particularly when conventional investigations remain unrevealing. Finally, clinicians should recognize that simultaneous infection with multiple neurotropic pathogens, although uncommon, may occur and may influence disease severity, therapeutic decisions, and clinical outcomes. Early empirical doxycycline should therefore be considered in patients with suspected rickettsial CNS infection while awaiting definitive microbiological confirmation, particularly in endemic settings.

Conclusions

To summarize, this case adds to the limited literature describing concurrent *Rickettsia* spp. and HSV-2 infection involving the CNS. Detection of *Rickettsia* spp. is strong molecular evidence for rickettsial CNS involvement, with concurrent HSV-2 detection provided by the combination of DNA in peripheral blood and CSF, with detection of HSV-2 DNA in CSF. However, given the genus-level identification of *Rickettsia* spp. and the inability to definitively distinguish primary HSV-2 CNS infection from possible viral reactivation during acute systemic illness, the findings should be interpreted cautiously rather than as definitive proof of dual-pathogen CNS infection. To the best of our knowledge, this is one of the reports on this rare case from India demonstrating molecular detection of *Rickettsia* spp. in both peripheral blood and CSF together with concurrent HSV-2 detection in CSF. The case underscores the importance of maintaining a high index of suspicion for rickettsial disease in patients presenting with acute febrile encephalopathy, highlights the potential diagnostic utility of multiplex molecular assays, and emphasizes the importance of timely pathogen-directed therapy in patients with suspected rickettsial CNS disease.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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References

1. Parola P, Paddock CD, Socolovschi C, et al.: Update on tick-borne rickettsioses around the world: a geographic approach. Clin Microbiol Rev. 2013, 26:657-702. 10.1128/CMR.00032-13
2. Walker DH: Rickettsiae and rickettsial infections: the current state of knowledge . Clin Infect Dis. 2007, 45 Suppl 1:S39-S44. 10.1086/518145
3. Blanton LS: The rickettsioses: a practical update . Infect Dis Clin North Am. 2019, 33:213-229. 10.1016/j.idc.2018.10.010
4. Walker DH, Ismail N: Emerging and re-emerging rickettsioses: endothelial cell infection and early disease events. Nat Rev Microbiol. 2008, 6:375-386. 10.1038/nrmicro1866
5. Biggs HM, Behravesh CB, Bradley KK, et al.: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever and other spotted fever group rickettsioses, ehrlichioses, and anaplasmosis - United States. MMWR Recomm Rep. 2016, 65:1-44. 10.15585/mmwr.rr6502a1
6. Rahi M, Gupte MD, Bhargava A, Varghese GM, Arora R: DHR-ICMR guidelines for diagnosis and management of rickettsial diseases in India. Indian J Med Res. 2015, 141:417-422. 10.4103/0971-5916.159279
7. Rathi N, Kulkarni A, Yewale V: IAP guidelines on rickettsial diseases in children . Indian Pediatr . 2017, 54:223-229.
8. Varghese GM, Trowbridge P, Janardhanan J, et al.: Clinical profile and improving mortality trend of scrub typhus in South India. Int J Infect Dis. 2014, 23:39-43. 10.1016/j.ijid.2014.02.009
9. Walker DH, Valbuena GA, Olano JP: Pathogenic mechanisms of diseases caused by Rickettsia . Ann N Y Acad Sci. 2003, 990:1-11. 10.1111/j.1749-6632.2003.tb07331.x
10. Jena SS, Kar M, Soreng I, Acharrya S, Misra SR: Meningo-encephalitis due to spotted fever group Rickettsia — a rare case report with serial follow up MRI. Neurol India. 2022, 70:412-414. 10.4103/0028-3886.338705
11. Singh P, Shete V, Choudhary A, Gade N, Mishra M: Neurological manifestations of scrub typhus infection in pediatric patient: a case report from tertiary care hospital in central India. Cureus. 2024, 16:e53060. 10.7759/cureus.53060
12. Nilsson K, Wallménius K, Påhlson C: Coinfection with Rickettsia helvetica and herpes simplex virus 2 in a young woman with meningoencephalitis. Case Rep Infect Dis. 2011, 2011:469194. 10.1155/2011/469194
13. Nilsson K, Elfving K, Pahlson C: Rickettsia helvetica in patient with meningitis, Sweden, 2006 . Emerg Infect Dis. 2010, 16:490-492. 10.3201/eid1603.090184
14. Baddal B, Bostancı A, Aksoy T, Kucukciloglu Y, Süer K: A rare case of Rickettsia and herpes simplex virus 1 co-infection in a male patient with meningoencephalitis. J Emerg Med Case Rep. 2023, 12:81-83. 10.33706/jemcr.1325932
15. Tunkel AR, Glaser CA, Bloch KC, et al.: The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis. 2008, 47:303-327. 10.1086/589747
16. Tyler KL: Acute viral encephalitis . N Engl J Med. 2018, 379:557-566. 10.1056/NEJMra1708714
17. Bradshaw MJ, Venkatesan A: Herpes simplex virus-1 encephalitis in adults: pathophysiology, diagnosis, and management. Neurotherapeutics. 2016, 13:493-508. 10.1007/s13311-016-0433-7
18. Whitley RJ, Kimberlin DW, Roizman B: Herpes simplex viruses. Clin Infect Dis. 1998, 26:541-553. 10.1086/514600
19. Kaur P, Aulakh R: Acute encephalitic syndrome due to coinfection with herpes simplex virus and scrub typhus. Pediatr Oncall J. 2020, 17:56-57. 10.7199/ped.oncall.2020.22
20. Zhang Y, Jiang L, Yang Y, Xie S, Yuan W, Wang Y: A tick bite patient with fever and meningitis co-infected with Rickettsia raoultii and Tacheng tick virus 1: a case report. BMC Infect Dis. 2021, 21:1187. 10.1186/s12879-021-06877-z
21. Kennedy PG, Steiner I: Recent issues in herpes simplex encephalitis . J Neurovirol. 2013, 19:346-350.

10.1007/s13365-013-0178-6

22. Kaur P, Jain R, Kumar P, Randev S, Guglani V: Clinical spectrum and outcome of acute encephalitis syndrome in children with scrub typhus: a series of eight cases from India. Indian J Crit Care Med. 2020, 24:885-887. 10.5005/jp-journals-10071-23590
23. Solomon T, Michael BD, Smith PE, et al.: Management of suspected viral encephalitis in adults — Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012, 64:347-373. 10.1016/j.jinf.2011.11.014