

Varicella Zoster Encephalitis in an Immunocompetent Traveler

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Abstract: Varicella-zoster virus (VZV) is a frequent cause of encephalitis in adults, particularly in elderly and immunocompromised individuals. In young immunocompetent patients without cutaneous manifestations, it represents a rare presentation. We report the case of a 35-year-old previously healthy man who developed VZV encephalitis during a ten-month trip across Latin America. While in Nicaragua, he presented with bitemporal and left suboccipital headache, pulsatile in nature, insidious in onset, daily, and with progressive worsening. After five days, he sought medical care due to language disturbance (paraphasia). He denied fever, seizures, paresis, or systemic symptoms. Physical examination revealed only language impairment, with no skin lesions. Magnetic resonance imaging demonstrated hyperintensity in the left temporal lobe. Cerebrospinal fluid analysis showed hypoglycorrhachia, hyperproteinorrhachia, and hyperlactatorrhachia. Molecular testing (PCR) detected VZV DNA. Intravenous acyclovir was initiated for eight days, followed by oral acyclovir for six days, resulting in complete resolution of symptoms without residual deficits. Investigation for immunodeficiency, including HIV testing, lymphocyte immunophenotyping, immunoglobulin levels, and complement assessment, was negative. As prophylaxis, vaccination with the recombinant inactivated herpes zoster vaccine was recommended. This case illustrates an atypical presentation of VZV encephalitis, reinforcing the importance of molecular testing in the investigation of acute neurological syndromes and of early antiviral treatment for a favorable prognosis.

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1. Introduction

Varicella-zoster virus (VZV) is a neurotropic, double-stranded DNA virus belonging to the Herpesviridae family and is primarily responsible for dermatological manifestations in humans. Primary infection usually occurs in childhood and is followed by a latent period, during which the virus persists for decades in peripheral autonomic neuronal ganglia [1]. Reactivation of the virus, known as herpes zoster, manifests as painful and pruritic vesicles distributed along peripheral nerves, respecting dermatomal patterns [2]. Both during primary infection and reactivation, VZV may involve the central nervous system, causing meningitis and encephalitis, with potentially severe outcomes [3].

VZV is among the leading causes of infectious encephalitis in adults, accounting for 21–31% of cases [4,5]. Among travelers, however, it is an uncommon etiology of encephalitis, representing only about 4% of reported cases [6]. It generally affects individuals over 55 years of age and immunocompromised patients [7–10]. Concomitant rash is present in 59–89% of cases [9–12]. Clinical outcomes are variable, with mortality rates reaching up to 36% and long-term sequelae occurring in as many as 45% of patients [9].

The present study aims to describe a rare case of varicella-zoster encephalitis in an immunocompetent traveler without cutaneous involvement, evaluated at a travel medicine service in São Paulo, Brazil, in July 2024, with a favorable clinical outcome.

2. Case Report

A 35-year-old man, previously healthy, attended a travel medicine clinic in Brazil in November 2022 for a pre-international travel consultation. His itinerary included Argentina, Uruguay, Chile, Bolivia, Peru, Ecuador, Colombia, Panama, the Dominican Republic, Costa Rica, and Nicaragua. He received counseling regarding vaccination (typhoid fever and rabies), food safety measures, mosquito bite prevention, and was prescribed azithromycin for potential traveler's diarrhea. The trip began in January of the following year. During the journey, the patient experienced recurrent episodes of diarrhea of probable foodborne origin, which were self-limited, characterized by loose stools (Bristol types 5 to 6), without systemic symptoms, pathological contents, or the need for antibiotic therapy.

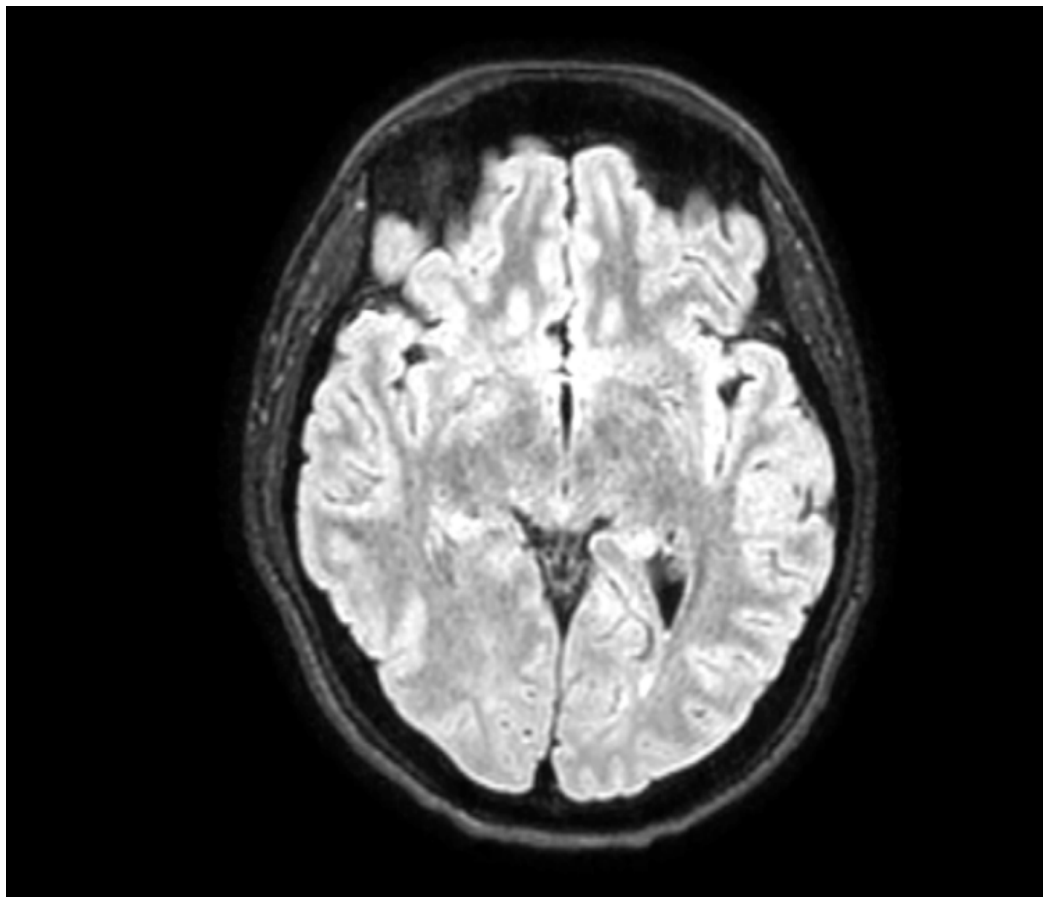
After ten consecutive months of travel, he sought medical care due to bitemporal and left suboccipital headache, pulsatile in nature, with insidious onset and daily frequency, lasting up to 24 hours and progressively worsening over the preceding five days. The pain did not resolve completely with intravenous analgesics. He reported associated nausea, vomiting, postural vertigo, photophobia, and phonophobia. The headache was exacerbated by physical exertion and the prone position. On one occasion, it was associated with paresthesias in the lower limbs, and from November 16 onward, with language disturbances characterized by literal and semantic paraphasias. He denied fever, seizures, paresis, ataxia, gait disturbances, or systemic symptoms. No cutaneous lesions compatible with herpes zoster were observed.

General physical examination revealed no abnormalities. On neurological examination, scores on the Mini-Mental State Examination (MMSE) [13] and the Montreal Cognitive Assessment (MoCA) [14] were 28/30, with impairment restricted to language. Higher cognitive functions were preserved. Cranial nerve examination was unremarkable, with no papilledema, nystagmus, facial paresis, or vestibular dysfunction. Muscle tone, strength, deep tendon reflexes, and sensation were preserved, with no Babinski sign. Cerebellar testing, assessment for meningeal signs, and evaluation of the autonomic nervous system were normal.

Brain magnetic resonance imaging with contrast demonstrated a poorly defined hyperintense area in the left temporal lobe (Figure 1). Complete blood count revealed normocytic, normochromic anemia (hemoglobin 11.9 g/dL, hematocrit 35.1%). Serum biochemistry was within normal limits. Cerebrospinal fluid analysis showed hypoglycorrhachia (32.7 mg/dL), hyperproteinorrhachia (122.01 mg/dL), and hyperlactatorrhachia (34.86 mg/dL). Cerebrospinal fluid culture was negative, and no *Cryptococcus* sp. antigen was detected. A multiplex polymerase chain reaction (PCR) test using the FilmArray Meningitis/Encephalitis Panel (BioFire Diagnostics, bioMérieux, Salt Lake City, USA) detected varicella-zoster virus (VZV) DNA in the cerebrospinal fluid. All other tested pathogens were negative, including *Escherichia coli* K1, *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, cytomegalovirus, enterovirus, human herpesvirus type 6, herpes simplex virus type 2, human parechovirus, and *Cryptococcus neoformans/gattii*.

Treatment was initiated with intravenous acyclovir (10 mg/kg per dose, three times daily) for eight days during hospitalization, followed by oral acyclovir for an additional six days after discharge. The patient showed complete resolution of neurological symptoms, with no residual deficits or clinical recurrence. Follow-up examinations, including brain magnetic resonance imaging, showed no abnormalities. Investigation for possible immunodeficiency, including HIV testing, lymphocyte immunophenotyping, and measurement of immunoglobulin and complement levels, was negative. As a prophylactic measure, the patient was advised to receive vaccination against herpes zoster with the recombinant inactivated vaccine.

Figure 1. Brain magnetic resonance imaging demonstrating a hyperintense lesion in the left temporal lobe on axial T2-weighted images.



3. Discussion

The reported case represents a rare occurrence of varicella-zoster encephalitis in a young, immunocompetent patient without associated cutaneous manifestations, occurring in the context of prolonged international travel. Although varicella-zoster virus (VZV) is a frequent etiologic agent of encephalitis in adults [4,5], the study by Picard L. et al. found a lower incidence among travelers, accounting for only 4% of encephalitis cases in this group [6]. Furthermore, the literature shows a predominance of cases in patients older than 55 years or in those with some degree of immunocompromise [7–10], which makes the present case even more atypical.

One of the most notable features of this case is the absence of cutaneous manifestations. Studies indicate that skin lesions are present in 59–89% of VZV encephalitis cases [9–12], constituting an important clinical marker for diagnosis. The absence of rash may hinder clinical suspicion and etiological diagnosis. The lack of cutaneous lesions in this case places it within the spectrum of presentations known as VZV sine herpete, in which viral reactivation occurs in a manner restricted to the central nervous system, without evident dermatological involvement [11,12]. The use of molecular methods, such as multiplex PCR in cerebrospinal fluid, as applied in this case, facilitates etiological definition even in atypical presentations.

From a radiological standpoint, the identification of hyperintensity in the left temporal lobe raises herpes simplex virus type 1 (HSV-1) encephalitis as the main differential diagnosis, as this condition is classically associated with temporal lobe involvement. However, in the present case, molecular testing of the cerebrospinal fluid was negative

for HSV-1 and HSV-2, while VZV DNA was detected. In addition, the clinical course without impaired consciousness, seizures, or signs of extensive hemorrhagic necrosis favors the diagnosis of VZV encephalitis [9,11,12].

The cerebrospinal fluid abnormalities observed, hypoglycorrhachia, hyperproteinorhachia, and hyperlactatorrhachia, are consistent with an inflammatory process of the central nervous system and are frequently described in cases of VZV encephalitis [8,9]. Although detection of viral DNA in cerebrospinal fluid alone does not allow differentiation between active infection and subclinical reactivation, its association with inflammatory CSF changes, suggestive neuroimaging findings, and a compatible clinical presentation strongly supports the diagnosis of active encephalitis in this patient [9]. The travel history across Latin America could raise the hypothesis of other regional infectious etiologies, such as neurotropic arboviruses. However, the absence of fever, systemic manifestations, myeloradiculopathy, or signs of multisystem involvement, together with the focal temporal pattern observed on magnetic resonance imaging and molecular identification of VZV in the cerebrospinal fluid, made these hypotheses less likely. The favorable clinical response to acyclovir further supports this interpretation.

The patient experienced recurrent episodes of diarrhea during travel, which could theoretically act as physical stressors. However, no laboratory evidence of transient immunosuppression, such as lymphopenia, was identified. Therefore, the association between physiological stress and viral reactivation should be interpreted with caution and remains speculative. The case is more appropriately understood within the spectrum of VZV reactivation restricted to the central nervous system in immunocompetent individuals without identifiable classical risk factors [11,12].

Despite the presence of literal and semantic paraphasias, scores on the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA) remained high. This finding may be explained by the limited sensitivity of these screening instruments for focal language impairments, particularly in young patients with preserved overall functioning [13,14]. A formal evaluation using specific aphasia tests was not performed, which represents a limitation of this report. The rapid initiation of acyclovir therapy was decisive for the favorable outcome, with complete symptom resolution and no residual neurological deficits during six months of clinical follow-up. Although VZV encephalitis may be associated with mortality rates of up to 36% and neurological sequelae in up to 45% of cases [9], reports involving immunocompetent patients suggest a more favorable prognosis when diagnosis is established early and antiviral therapy is promptly initiated [15–17].

In this context, the importance of molecular methods in the etiological diagnosis of central nervous system infections should be emphasized. In December 2024, the Brazilian Ministry of Health published Ordinance SECTICS No. 61 [18], which incorporated multiplex PCR testing for the detection of multiple infectious agents in cerebrospinal fluid into the Unified Health System (SUS), following a favorable recommendation by the National Commission for the Incorporation of Technologies in the SUS (CONITEC). This commission highlighted the technology's potential to reduce hospitalization time and unnecessary use of empirical antibiotics and antivirals, demonstrating cost-effectiveness [19]. Complementarily, in February 2025, the National Supplementary Health Agency (ANS) included this test in the List of Health Procedures and Events, making its coverage mandatory by health insurance plans [20]. These measures reinforce the consolidation of multiplex molecular diagnostics as a first-line tool in the etiological investigation of central nervous system infections, promoting faster diagnoses and targeted therapies, as exemplified by the present case.

Finally, vaccination with the recombinant herpes zoster vaccine was recommended on an individualized basis, considering the patient's history of severe neurological manifestation associated with VZV reactivation. Current guidelines prioritize this vaccine for individuals over 50 years of age or those who are immunocompromised. However, the

live attenuated VZV vaccine does not provide protection against viral reactivation in previously infected individuals. Therefore, the recombinant formulation was recommended as a strategy for secondary prevention after encephalitis, without the intention of extrapolating this approach to universal recommendations.

4. Conclusion

This report highlights a rare case of VZV encephalitis in a young, immunocompetent adult without cutaneous manifestations, occurring in the context of prolonged international travel. The absence of rash may hinder initial clinical diagnosis, reinforcing the importance of molecular testing for etiological identification in patients presenting with acute neurological syndromes. Early initiation of acyclovir therapy was decisive for complete recovery. This case contributes to expanding recognition of atypical presentations of VZV encephalitis, particularly in populations outside classical risk groups, such as young, immunocompetent travelers.

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