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CASE REPORT

A Case Report of Rabies in an HIV Patient: Diagnostic Challenges and Near-Miss Recognition

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Introduction: Rabies is a fatal viral zoonosis. It typically manifests as furious or paralytic encephalomyelitis. Diagnosis is challenging, especially with atypical presentations, low viral loads, or immunocompromise. HIV co-infection may further obscure the clinical picture.

Case Presentation: A 53-year-old man with well-controlled HIV presented with dizziness, fever, and headache, then rapidly developed right hemiparesis, dysarthria, and behavioral changes. On day 3, he acutely deteriorated, developing quadriplegia, dysphagia, and mutism. Repeat CSF mNGS detected 48 rabies virus reads; reanalysis of the initial CSF sample revealed only 9.

Conclusion: Early rabies diagnosis may fail when viral load falls below the detection limit of targeted assays such as tNGS. Even well-controlled HIV infection can predispose to atypical, rapidly progressive paralytic rabies. For acute encephalitis of unknown cause, clinicians should suspect rabies and repeat CSF testing using highly sensitive methods if initial tests are negative.

Keywords: rabies, next-generation sequencing, HIV, diagnosis, encephalitis

Introduction

Rabies, one of the world's most ancient infectious diseases and most lethal viral zoonoses of mammals, kills an estimated 59,000 people annually across large regions of the globe.[1,2] Rabies typically manifests initially with nonspecific prodromal symptoms, including low-grade fever, headache, malaise, and localized paresthesia or dysesthesia, often described as burning, pruritus, or tingling, at the site of viral inoculation. Subsequently, the rabies virus undergoes retrograde axonal transport along peripheral nerves to reach the central nervous system (CNS), where it replicates and triggers progressive, fatal encephalomyelitis. Clinical onset is marked by rapidly evolving neurological dysfunction, reflecting widespread CNS involvement.[3] Rabies presents in two principal clinical forms: furious (encephalitic) and paralytic (dumb). Furious rabies, accounting for over 80% of reported cases in the United States, is characterized by hyperactivity, agitation, confusion, hallucinations, autonomic instability, and hydrophobia—often precipitated by pharyngeal muscle spasms during attempted swallowing or even at the sight or sound of water. Paralytic rabies, comprising approximately 20% of cases globally (and more frequently observed in cases following bat exposures or in vaccinated individuals), is distinguished by ascending flaccid paralysis, areflexia, and rapid progression to coma without prominent behavioral disturbances.[4]

Notably, antemortem diagnosis of rabies remains challenging due to nonspecific early symptoms, limited accessibility of sensitive molecular assays, and the absence of a clear exposure history in many cases. In particular, immunocompromised states such as HIV infection may further obscure the typical clinical manifestations and complicate the early diagnosis of rabies.

Case Presentation

A 53-year-old man was admitted to our hospital, presenting with a 3-day history of dizziness accompanied by visual rotation and intermittent headache. The patient had a fever, with the highest temperature reaching 38.7°C. The treatment at the local community hospital was ineffective. Subsequently, the patient experienced nausea and vomiting several times, mostly of

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gastric contents. He felt weakness in the right limb, disordered speech, and abnormal behavior. The patient's MRA of the head showed no obvious abnormalities. Symptomatic treatment was ineffective, and the patient was transferred to our hospital by emergency for further treatment. Physical examination: Conscious, but in low spirits. Poor cooperation during the examination. Deaf (hearing assisted by a hearing aid, but the hearing aid is not functioning). Pupils are equal in size and round. Right limb muscle strength is 4+, left limb is grade 5. Muscle tone is normal.

On the day of admission, lumbar puncture was performed for further examination. Cerebrospinal fluid (CSF) laboratory results were as follows: adenosine deaminase (ADA) 0.6 U/L and lactate dehydrogenase (LDH) 20 U/L; CSF biochemistry revealed glucose 3.38 mmol/L, protein 444 mg/L, and chloride 119.1 mmol/L. The Pandy test was weakly positive, with a nucleated cell count of 3×10^6/L and red blood cell count of 3×10^6/L, while CSF lactic acid was 1.56 mmol/L. All related tests for the pathogens of common opportunistic infections that often coexist with HIV were negative (Table 1). No pathogen was detected in cerebrospinal fluid targeted next-generation sequencing (tNGS). The patient had a 10-year history of AIDS and had been receiving regular antiretroviral therapy. The count of CD4+ T cells was 335 IU/mL, and HIV RNA was below the detection limit.

On the second day of admission, the patient was capable of independent feeding, could communicate via written text, exhibited normal muscle strength, and experienced occasional episodes of restlessness. On the third day, the patient's condition took a sudden turn for the worse. The patient presented with sluggish response, difficulty in swallowing, quadriplegia, inability to speak, and urinary incontinence upon waking up in the morning. Physical examination revealed a soft neck without resistance, grade 0 muscle strength in all four limbs, decreased tendon reflexes, and no pathological signs elicited.

A lumbar puncture was performed again, and metagenomic next-generation sequencing (mNGS) testing of the cerebrospinal fluid detected 48 sequences of the rabies virus. Retesting the original CSF sample detected 9 rabies virus reads. At this point, the diagnosis of rabies was confirmed. Eventually, the patient's condition worsened. After the rabies diagnosis was fully communicated to the family, the patient was discharged against medical advice for palliative home care. The entire diagnosis of this case is presented on the timeline (Figure 1). According to the Jinhua Municipal Center for Disease Control and Prevention[5] (Zhejiang Province), following the diagnosis of rabies via CSF mNGS,

Table 1 Summary of Key Laboratory Findings on Admission

Parameter	Result	Reference Range (if Applicable)
Cerebrospinal fluid		
ADA	0.6 U/L	≤8U/L
LDH	20 U/L	10~30U/L
Candida antigen	Negative	Negative
Methylene blue staining	No Cryptococcus detected	Negative
Glucose	3.38 mmol/L	2.50–4.50mmol/L
Protein	444 mg/L	120–600mg/L
Chloride	119.1 mmol/L	120–132mmol/L
Pandy test	Weakly positive	Negative
Nucleated cell count	3×10^6/L	0
Lactic acid	1.56 mmol/L	–
Rabies virus (tNGS, LP1)	Not detected (9 reads retrospectively)	
Rabies virus (mNGS, LP2)	Detected (48 reads)	
Blood examination		
$CD4^+$ T-cell count	335 cells/μL	500~1600 cells/μL
HIV-1 RNA	<100 IU/mL	<100 IU/mL
Candida antigen	Negative	Negative
RPR	Negative	Negative
T-SPOT.TB	Negative	Negative

Abbreviations: ADA, Adenosine deaminase; LDH, Lactate dehydrogenase; CSF, cerebrospinal fluid; LP, lumbar puncture; mNGS, metagenomic next-generation sequencing; tNGS, targeted next-generation sequencing; RPR, Rapid plasma reagin.

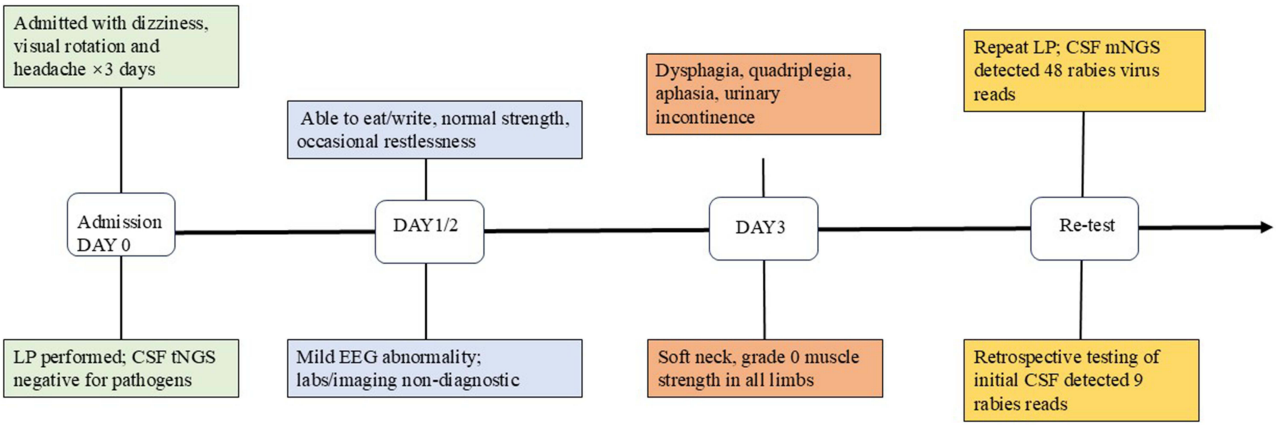

Figure 1 The timeline shows the entire diagnosis process of this case. Clinical timeline of a 53-year-old HIV-infected patient with rabies. Day 0: admission with dizziness and vertigo; initial CSF tNGS was negative. Day 3: rapid neurological decline (quadriplegia, dysphagia, aphasia); repeat CSF mNGS detected 48 rabies virus reads. A dog bite history was confirmed retrospectively after diagnosis.

Abbreviations: LP, lumbar puncture; CSF, cerebrospinal fluid; tNGS, targeted next-generation sequencing; EEG, electroencephalogram; mNGS, metagenomic next-generation sequencing.

a retrospective review of the patient's medical history revealed a dog bite exposure that occurred four months earlier in a rabies-endemic county. The bite inflicted by the patient's domestic dog resulted in bleeding from the index finger. No post-exposure prophylaxis was administered, and the dog was slaughtered and consumed shortly thereafter. No secondary human cases were identified following the exposure.

Discussion

The incubation period—the interval between exposure and the emergence of neurological signs—ranges from weeks to several months and is influenced by multiple factors, including the viral variant, the anatomical distance between the exposure site and the CNS, the viral inoculum size, and prior rabies vaccination status. Once clinical rabies develops, the disease is invariably fatal, with mortality approaching 100%; no proven antiviral therapy exists to halt CNS viral replication or reverse established neuropathology.

Rabies diagnostic test results can be affected by illness duration, clinical presentation, intermittent viral shedding (eg, in saliva), prior rabies vaccination, and patient immune status.[6] Serological diagnosis is defined as the detection of rabies virus-specific antibodies in cerebrospinal fluid (CSF) and/or serum, which has limited diagnostic utility in most rabies cases, owing to the disease's typically rapid and fulminant clinical course. Antibody responses generally emerge only in the late stages of illness, thereby reducing the sensitivity of serological assays for early diagnosis. In contrast, serology becomes diagnostically informative in patients who survive beyond 7–14 days, where a positive result provides strong confirmatory evidence.[7]

Just as in the case reported in this article, retesting the original CSF sample detected 9 rabies virus reads. The initial negative result was due to low viral load—below the NGS detection threshold—at first collection. By the second CSF test, the patient was comatose and clinically deteriorated, with viral load rising above the threshold, enabling reliable detection. In addition, in this report, the absence of an initial animal exposure history was a major clinical limitation, delaying early suspicion of rabies. Definitive autopsy or brain tissue viral isolation was not performed due to discharge against medical advice, although CSF mNGS is now widely accepted for diagnosis.

From the perspective of detection technology, consider the reasons for the initial missed diagnosis. (tNGS and mNGS were both performed in this study. tNGS adopts a pathogen-specific primer panel for targeted amplification and enrichment of common infectious pathogens, with a fixed detection spectrum covering major viruses, bacteria, and fungi. Rabies virus was included in the tNGS target panel; however, due to extremely low viral load in the clinical sample, the viral reads were insufficient for valid detection, resulting in a false-negative tNGS result. Different from tNGS, mNGS is an unbiased culture-independent sequencing strategy without primer-based targeted enrichment. It

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comprehensively detects all microbial and host nucleic acids in the sample. Raw sequencing reads were subjected to quality control, host sequence removal, microbial sequence alignment, and de novo genome assembly, which successfully captured rabies virus-related reads and enabled definite pathogen identification even under low viral load conditions. While tNGS is generally more sensitive than mNGS, stable detection requires pathogen levels above the assay's LOD; sub-threshold loads risk missed detection. Clinical vigilance for rabies and detailed exposure history taking are essential. While NGS is a valuable complementary tool for unclear encephalitis, it is limited by low or variable viral loads; sequencing also aids epidemiological tracing and source attribution.

The therapeutic impasse in rabies primarily arises from irreversible neuronal injury once clinical signs develop, rather than from extensive genetic or antigenic diversity of lyssaviruses. While lyssavirus diversity is relatively limited compared with many other viral families, distinct RABV variants circulate globally—including raccoon-, skunk-, and multiple phylogenetically distinct bat-associated lineages in the United States.[8] Beyond classical RABV, over a dozen other lyssaviruses are zoonotic and can cause fatal encephalitis clinically indistinguishable from classical rabies. Rabies epidemiology in China differs from that in the United States, with domestic dogs as the main reservoir. Importantly, current rabies vaccines and rabies immunoglobulin (RIG) provide robust protection against nearly all RABV strains. However, rare, highly divergent lyssaviruses may exhibit reduced susceptibility to standard prophylaxis, posing a potential challenge in exceptional cases.[9] Consequently, once clinical rabies encephalitis develops—whether due to failure of post-exposure prophylaxis (PEP), delayed presentation, or infection with a divergent lyssavirus—no effective antiviral therapy exists to halt CNS viral replication or reverse established neuropathology. Mortality remains effectively nearly100%.[10]

Reports of PLWH (people with HIV/AIDS) contracting rabies are extremely rare. The majority of reported cases to date have been among individuals without underlying health conditions. The presence of HIV infection as a basis may lead to atypical symptoms in some cases and a more rapid progression of the disease. The most reported rabies cases in HIV-infected individuals occur in the setting of severe immunosuppression. In contrast, our patient had well-controlled HIV with a CD4 count of 335 cells/μL and undetectable viral load, representing an atypical presentation. It is possible that even with effective ART, subtle defects in T-cell immunity or HIV-related chronic CNS inflammation may accelerate viral spread and mask the classic furious phenotype. Clinicians should maintain high suspicion for rabies and consider repeat CSF testing with a highly sensitive method if initial tests are negative.

Conclusion

Early rabies diagnosis may fail when viral load falls below the detection limit of targeted assays such as tNGS. Well-controlled HIV infection may alter the clinical phenotype, potentially predisposing patients to atypical, rapidly progressive paralytic rabies. This case underscores the risk of over-reliance on a single negative molecular test, as timing of sampling outweighs technical sensitivity for low-burden CNS infections. For acute encephalitis of unknown cause, clinicians should suspect rabies and repeat CSF testing using mNGS or RT-PCR if initial tests are negative.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation. For data inquiries, please get in touch with yll8324@163.com.

Ethics Approval and Consent to Participate

All procedures performed in the study involving human participants were in accordance with the ethical standards of the Ethics Committee of the Hangzhou Xixi Hospital. The ethics committee approved the waiver in this case report, based on the ethical standards to publish the case details. Written informed consent was obtained from the patient's next of kin for publication of this case report.

Consent for Publication

Written informed consent was obtained from the patient's guardian for the publication of any potentially identifiable images or data included in this article.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests for this work.

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