



Clinical and Laboratory Characteristics, Diagnosis, and Treatment of Patients with Neurosyphilis in Emergency Department: A Retrospective Study of 12 Patients

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Purpose: Syphilis, caused by *Treponema pallidum*, presents a diagnostic challenge due to its diverse clinical manifestations. Neurosyphilis has seen a resurgence in recent years, particularly among men who have sex with men and those living with HIV. Diagnosis of neurosyphilis in emergency settings is challenging due to its varied neurological presentations. This study aims to serve as a reference for dermatologists and neurologists in diagnosing and treating neurosyphilis.

Patients and Methods: This retrospective study analyzed patients who presented with neuropsychiatric symptoms and were ultimately diagnosed with neurosyphilis. These patients were collected from the emergency department in Peking Union Medical College Hospital between January 2018 and November 2023. The medical history, clinical symptoms, laboratory examinations, cranial MRI characteristics, and treatment regimens of these patients were investigated.

Results: Among the included 12 neurosyphilis patients, memory deterioration was observed in 8 out of the 12 neurosyphilis patients. Diagnosis often resulted in delays, with misdiagnoses mainly including Alzheimer's disease, stroke, and epilepsy. Neuroimaging revealed various abnormalities, predominantly affecting ventricular and temporal regions. Treatment with penicillin-based regimens varied in compliance, with only a minority of patients adhering to guidelines. Treatment outcomes were inconsistent, with some patients experiencing irreversible neurological damage and fluctuating serum rapid plasma reagin (RPR) titers.

Conclusion: Diagnosis of neurosyphilis in the emergency department remains challenging, necessitating awareness of its varied neurological presentations. Enhanced diagnostic strategies are imperative to accelerate treatment initiation and improve outcomes for affected individuals.

Keywords: neurosyphilis, emergency department, neuropsychiatric symptoms, cerebrospinal fluid, serologic tests

Introduction

Syphilis is a sexually transmitted infection caused by *Treponema pallidum*. Due to its myriad clinical manifestations, syphilis is known as the “great imitator” that poses a diagnostic challenge. In the past decades, syphilis has re-emerged as a public health concern, particularly in men who have sex with men and those people living with HIV (PLWH).¹ Syphilis can advance to neurosyphilis at any point after the initial infection. While the prevalence of neurosyphilis has significantly decreased since

the advent of antibiotics, recent years have witnessed a resurgence in reported cases.² Notably, PLWH are approximately twice as likely to develop neurosyphilis when compared to the immunocompetent population.³

Neurosyphilis, depending on its progression, can be categorized into early and late stages. Early neurosyphilis, in turn, can be divided into asymptomatic and symptomatic forms, with the latter including symptomatic meningitis and meningo-vasculitis. Late neurosyphilis manifests as dementia paralytica and tabes dorsalis. In recent times, new characteristics of neurosyphilis have emerged. Recent studies highlight that neurosyphilis can present in atypical forms, often with oligosymptomatic or asymptomatic features, complicating diagnosis and treatment. For instance, Ciccamese et al (2024) reported that atypical manifestations were observed in 30% of cases within their retrospective analysis, underscoring the diverse clinical presentations of the disease.⁴ Notably, cases such as recurrent ischemic strokes secondary to meningovascular syphilis illustrate how neurosyphilis can mimic other neurological conditions, often leading to misdiagnosis and delayed treatment.⁵ Additionally, depression with psychotic features has been identified as another atypical presentation, further emphasizing the polymorphic nature of neurosyphilis and its potential to masquerade as an affective disorder. Understanding these varied manifestations is crucial for timely intervention and effective management of syphilis-related complications.⁶ Currently, asymptomatic neurosyphilis and meningoenkephalitis are the most prevalent forms, although meningovascular syphilis was the most common in certain cohort studies.⁷ Additionally, there has been an increase in the incidence of ocular syphilis and otosyphilis according to recent research.^{8,9}

In recent years, cases of patients seeking emergency medical care due to syphilis have been reported. However, there remains a lack of systematic summarization of these cases.^{10,11} This study aimed to collect patients presenting with neuropsychiatric symptoms in the emergency department and subsequently diagnosed with neurosyphilis. A comprehensive examination was conducted of their demographic, clinical, laboratory, and radiographic profiles, along with an assessment of their responses to treatment. This study may enhance awareness and facilitate early diagnosis of neurosyphilis among emergency department physicians.

Materials and Methods

Study Subject

The study retrospectively collected patients who sought medical attention at the Emergency Department of Peking Union Medical College Hospital in Beijing, China, and ultimately received a diagnosis of neurosyphilis from January 2018 to November 2023. Investigations were conducted within the internal medical record system to enroll individuals whose diagnosis encompassed 'syphilis'. The records were retrieved and checked by two authors (J. Zhou and H. Zhang) and double-checked by a professor in dermatology (J. Li), to exclude cases unrelated to syphilis.

Based on the diagnostic criteria for syphilis,^{12–15} subjects included in this study must fulfill the following criteria, as depicted in Table 1. To diagnose neurosyphilis, subjects must satisfy all three criteria, including epidemiological history, clinical presentation, and abnormal cerebrospinal fluid (CSF) results in laboratory examinations. Specifically, we conducted qualitative and quantitative tests for *Treponema pallidum* particle agglutination assay (TPPA) and rapid plasma reagin (RPR) on serum samples at the initial evaluation in the emergency department, as well as after therapy, to establish a comprehensive diagnostic framework. Furthermore, a CSF analysis for white blood cell (WBC) counts, protein levels, TPPA, and RPR was performed post-treatment to assess for any abnormalities consistent with neurosyphilis.

Study Methods

For the included subjects, we collected data on demographics, medical and sexual history, clinical symptoms, disease progression, and prior medical interventions. We conducted thorough examinations, including physical assessments, cognitive tests, CSF laboratory analyses, and cranial MRI scans. The interpretation of MRI results was performed by a neurologist (C. Mao) and a radiologist (M. Li) to obtain the final results. The treatment plans and subsequent serum RPR evaluations were summarized. Treatment effectiveness for neurosyphilis was determined based on several criteria: a significant reduction (over fourfold decrease or complete negativity) in serum RPR titers within one-year post-discharge, or normalization of CSF (an evident decrease in WBC counts and normalization of protein levels) three

Table 1 Diagnostic Criteria for Neurosyphilis Patients Included in the Study

Criteria	Description	
Epidemiological History	History includes unsafe sexual practices, multiple sexual partners, sexual partner infection, or blood transfusion.	
Clinical Presentation	Clinical manifestations are consistent with asymptomatic early neurosyphilis, syphilitic meningitis, meningovascular syphilis, general paresis, and tabes dorsalis.	
Laboratory Examinations of CSF	A. White blood cell	>20*10 ⁶ /L (without concurrent HIV infection) >20*10 ⁶ /L (with concurrent HIV infection)
	B. Protein	≥ 0.5g/L
	C. RPR	Positive results in the CSF RPR test ⁺
	D. TPPA	Positive results in the CSF TPPA test
*The definition of abnormal CSF includes either C, A+D, or B+D, excluding other potential causes for these abnormalities.		

Notes: + The gold standard test for syphilis, the toluidine red unheated serum test (TRUST), is unavailable at our hospital. Consequently, we rely on RPR results as an alternative. Previous research suggests that RPR's sensitivity and specificity are comparable to TRUST, making them interchangeable for diagnosis.^{16,17}

Abbreviation: CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; RPR, rapid plasma reagin; TPPA, Treponema pallidum particle agglutination.

months after treatment. Improvement in clinical symptoms, as reported by both the physician and the patient, was also considered in the assessment of treatment effectiveness, especially as an auxiliary reference when lumbar puncture was not performed post-treatment.¹⁵

Patient Informed Consent

The committee determined that as this study was retrospective and all included patients remain anonymous, written informed consent from patients is not required for this study.

Results

Personal Profile and Baseline Characteristics

In the medical records, a total of 12 cases of neurosyphilis were identified. The gender distribution among these cases consisted of nine males and three females. The ages of the patients ranged from 30 to 67 years, with an average age of 52.3 years and a median age of 52.5 years. Of note, only one patient reported a history of prior syphilis infection upon inquiry. Regarding potential sources of infection, only three disclosed engaging in promiscuous or high-risk sexual behaviors. Among them, two males reported sexual encounters with sex workers, while one female attributed her infection to her husband's interaction with a sex worker. A smaller proportion (16.7%) mentioned drug abuse. The majority of patients (75.0%) denied any suspicious personal histories. Occupationally, the neurosyphilis patients encompassed various professions, including 41.7% who were clerks, 25.0% who were factory workers, 25.0% who were unemployed, and 8.3% who were artists. Furthermore, upon investigation of comorbidities of infectious diseases, only one patient was co-infected with HIV, CMV, and EBV (8.3%), while two patients had HBV infection (16.7%).

Clinical Manifestations and Disease Course

As shown in Table 2, the foremost initial manifestation frequently encountered among neurosyphilis inpatients is the decline in memory function, as evidenced by its occurrence in eight cases (66.7%). Additionally, dyskinesia (n = 2), dysesthesia (n = 1), and epilepsy (n = 1) were also reported as primary symptoms. Patients typically sought emergency neurological care due to exacerbation of symptoms: four patients experienced abnormal behavior following acute hallucinations, while three patients experienced grand mal seizures. Furthermore, three patients displayed exacerbated cognitive decline, characterized by non sequitur responses, and two patients presented with mobility impairment.

Table 2 showed a broader spectrum of symptoms during the disease progression, beyond those previously mentioned. Across different phases, memory impairment was noted in 11 individuals, while personality changes were observed in nine individuals, including irritability, euphoria, and apathy. Various cognitive deficits were identified, including impairments in calculative ability

Table 2 Neuropsychiatric Manifestations of Neurosyphilis Patients in Emergency Department

Manifestations	The Initial Stage of the Disease	The Entire Course of Disease Progression
Memory impairment	8 (66.7%)	11 (91.7%)
Personality changes	0	9 (75.0%)
Irritability	0	6 (50.0%)
Euphoria	0	2 (16.7%)
Apathy	0	1 (8.3%)
Impairments in calculative ability	0	7 (58.3%)
Abnormal behavior	0	7 (58.3%)
Comprehension difficulties	0	7 (58.3%)
Emotional disturbances	0	6 (50.0%)
Anxiety disorder	0	3 (25.0%)
Depression	0	2 (16.7%)
Mania	0	1 (8.3%)
Temporal or spatial disorientation	0	6 (50.0%)
Incomprehensible speech	0	5 (41.7%)
Dysarthria	0	5 (41.7%)
Dyskinesia	2 (16.7%)	4 (33.3%)
Epilepsy	1 (8.3%)	3 (25.0%)
Ataxia	0	2 (16.7%)
Sleep disorders	0	2 (16.7%)
Hypersomnia	0	1 (8.3%)
Hyposomnia	0	1 (8.3%)
Dysesthesia	1 (8.3%)	1 (8.3%)
Hypotonia	0	1 (8.3%)

(n = 7), emotional disturbances such as anxiety disorder, mania, depression, and suicidal tendencies (n = 7), abnormal behavior (n = 7), comprehension difficulties (n = 7), temporal or spatial disorientation (n = 6), incomprehensible speech (n = 5), dysarthria (n = 5), dyskinesia (n = 4), epilepsy (n = 3), ataxia (n = 2), sleep disorders such as hypersomnia (n = 1) and hyposomnia (n = 1), hypotonia (n = 1), and dysesthesia (n = 1).

The mean and median durations between symptom onset and seeking medical attention were 341.9 and 165.0 days, respectively. Following consultation, the mean and median durations until diagnosis were found to be 18.3 and 14.0 days, respectively. Before the definitive diagnosis, misdiagnosis or oversight occurred in 91.7% of cases (n = 11). The most prevalent misdiagnosis was Alzheimer's disease, accounting for 25.0% (n = 3) of cases. Other less common misdiagnoses included stroke (n = 2), epilepsy (n = 2), and encephalitis (n = 1). Furthermore, four patients in our cohort remained undiagnosed despite previous medical consultations.

Physical Examination and Assessment of Cognitive Condition

Pathological reflexes were evident in four neurosyphilis patients (33.3%) within the cohort, including positive Babinski's sign observed in three patients, along with positive findings for Gordon, Oppenheim, Chaddock sign, and palmomental reflex. Argyll Robertson's pupil was noted in three patients. Regarding cognitive assessments, one patient exhibited a Montreal Cognitive Assessment (MoCA) score of 22 and a Mini-Mental State Examination (MMSE) score of 24. The MMSE scores of two other patients were 23 and 8, respectively. Notably, general cognition assessments were lacking for the remaining patients.

Laboratory Tests

All enrolled subjects underwent serum RPR and TPPA testing at the time of admission, all demonstrating positive results in TPPA. For RPR serum tests, except for one case with a negative RPR result, all other patients showed positive results. Among those with positive RPR titers, values ranged from 1:32 to 1:256, with a median titer of 1:32.

Additionally, CSF analyses were performed, revealing CSF RPR titers that varied from negative to 1:128 positive, with levels $\geq 1:8$ observed in four patients (33.3%). TPPA tests conducted on CSF samples for all patients also exhibited reactivity, confirming the presence of *Treponema pallidum*. Leukocyte counts in patients diagnosed with general paresis ranged from 2 to 66×10^6 cells per liter. Seven patients exhibited CSF leukocyte counts exceeding 5×10^6 cells per liter. CSF protein levels ranged from 470.0 to 1050.0 mg, with an average of 766.7 mg, all surpassing the normal range for CSF protein levels.

Cranial MRI

Out of the 12 patients included in the study, cranial MRI examinations were performed on 11 patients. Figure 1 showed typical lesions at the bilateral medial temporal lobe in neurosyphilis patients. Among these patients, three individuals (27.3%) exhibited no significant cerebral abnormalities upon MRI evaluation. The most commonly affected structures were the ventricular and paraventricular areas ($n = 4$) and temporal lobes ($n = 4$), followed by the hippocampus ($n = 2$), frontal lobe ($n = 2$), cerebellum ($n = 2$), and brainstem ($n = 2$). Patchy or speckled hyperintensities were detected in seven patients. Additionally, common findings included cerebral atrophy ($n = 3$) and dilated ventricles and fissures ($n = 2$). Cerebral atrophy was reported in various locations, including the cerebellum and brainstem ($n = 1$), bilateral hippocampus ($n = 1$), and bilateral temporal lobe ($n = 1$).

Treatment and Response

Penicillin-based anti-syphilitic regimens were administered to 11 patients. Four patients received treatment under both the US CDC guidelines and the Chinese sexually transmitted infection guidelines for syphilis. This regimen involved intravenous aqueous crystalline penicillin at a dosage of 3–4 million units every 4 hours for 10–14 days; if necessary, followed by intramuscular benzathine penicillin at a dosage of 2.4 million units weekly for three weeks. Corticosteroids

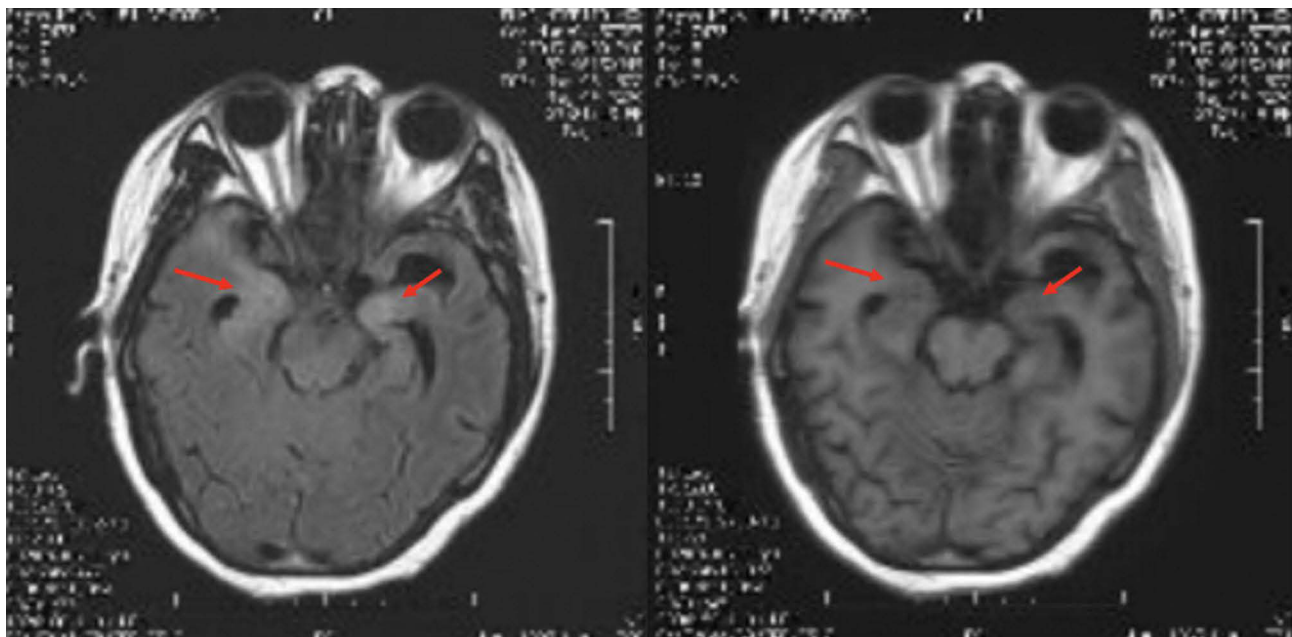


Figure 1 MRI findings of neurosyphilis in T2 and T1. A 48-year-old female patient was admitted to our hospital due to cognitive impairment and was diagnosed with neurosyphilis. MRI reported lesions at the bilateral medial temporal lobe (red arrow), showing a high signal on T2 (left) and a low signal on T1 (right).

were adjunctively prescribed to two patients to prevent the Jarisch-Herxheimer reaction. One patient experienced this reaction after receiving penicillin-based treatment without corticosteroids.

Post-treatment results of serum tests were available for eight patients revealing a range of RPR titers from 1:1 to 1:128. The median post-treatment titer was 1:8, compared to 1:32 pre-treatment. Notably, the RPR titer did not decrease in four patients (33.3%), among whom two had received adequate penicillin administration, while the remaining two exhibited poor treatment compliance, failing to adhere to the penicillin regimen adequately and on time.

Regarding CSF analysis, follow-up results indicated that CSF analysis was performed on 50% of post-treatment patients ($n = 5$). In the pre-treatment analysis, four patients (33.3%) had CSF RPR titers $\geq 1:8$, while post-treatment, only two patients exhibited titers $\geq 1:8$. None of the patients achieved complete serological conversion to negative RPR results. The limited follow-up rate was due to constraints in emergency evaluations and patients refusing a second lumbar puncture. Additionally, one HIV-positive patient exhibited poor improvement in neuropsychiatric symptoms, while three patients demonstrated only limited improvement.

Discussion

This study collected data from emergency neurosyphilis patients referred to a tertiary center in Beijing, China. It revealed the characteristics of neurosyphilis patients during emergency presentations, as well as highlighting issues and areas for improvement in their management in the emergency department. Currently, there is limited systematic analysis of patient cohorts diagnosed with neurosyphilis in the emergency setting. This study may serve as a reference for dermatologists and neurologists in diagnosing neurosyphilis.

The majority of patients seeking medical attention for acute neurosyphilis symptoms were middle-aged males. Only one individual acknowledged a history of past syphilitic infection and genital rash. 75% denied any suspicious personal history. Previous studies in China have indicated a high rate of concealment regarding sexual behavior and STIs among patients.¹⁸ Particularly, when clinical presentations primarily involve neuropsychiatric symptoms rather than genital lesions, such concealment can lead to misdiagnosis and underdiagnosis.¹⁹ Thus, even in the absence of suspicious medical or personal histories, considering the possibility of neurosyphilis is essential for middle-aged males presenting with neuropsychiatric symptoms in emergency settings. Only one patient in this cohort was co-infected with HIV (8.3%), whereas literature has reported co-infection rates of up to 40%.²⁰ The relatively low rate of neurosyphilis-HIV co-infection reported in this study might be attributed to other specialized HIV clinics in the region, thereby reducing the HIV prevalence in the emergency department of the comprehensive hospital.

The misdiagnosis rate of neurosyphilis in China exceeds 50.0%.²¹ Within this cohort, the misdiagnosis rate was 91.7%. Patients typically presented with worsening of certain neuropsychiatric symptoms, leading emergency physicians to misdiagnose them with primary neuropsychiatric disorders. Given that neurosyphilis can manifest years or decades after syphilis infection, it is more commonly observed in middle-aged or older individuals.²² Alzheimer's disease typically occurs in the elderly, particularly those aged 65 and above,²³ thus misdiagnosis is possible in the absence of lumbar puncture. Early diagnosis and treatment are crucial for neurosyphilis patients, as delayed treatment often leads to irreversible neurological damage.²⁴ Previous studies have suggested incorporating syphilis serological testing into routine evaluations of psychiatric patients.²⁵ We recommend that laboratory examinations, including RPR and TPPA, be routinely performed in emergency settings when there is a suspicion of neurosyphilis to facilitate timely diagnosis and treatment.

In clinical examination, particular attention is warranted for the Argyll Robertson's pupil. Previous studies have reported a positivity rate for Argyll Robertson's pupil exceeding 20% in patients with general paresis of the insane,²⁶ which also reached 25% in our cohort. Cases of positive Babinski sign and palmomental reflex were also noted in this cohort. Given the extensive spinal cord involvement attributable to neurosyphilis, presenting symptoms can vary, hence lacking pathognomonic symptoms.²⁷ Additionally, while MMSE and MoCA scores hold clinical significance, their utilization in emergency settings remains low. Prior research indicates an average MMSE score of 17.8 in neurosyphilis patients, indicative of moderate dementia.²⁸ Completing MMSE and MoCA scores during treatment aids in cognitive function monitoring, facilitating treatment adjustments based on score variations.

The diagnosis of neurosyphilis primarily relies on serological and CSF laboratory examinations. In our cohort, only four cases (33.3%) exhibited CSF RPR titers $\geq 1:8$. Previous studies also highlighted the elevated false-negative rate of CSF RPR in neurosyphilis patients.²⁹ Due to prolonged infection duration, syphilis antibody titers in blood and cerebrospinal fluid may be low or undetectable in RPR testing.²⁷ Furthermore, the prozone effect in the RPR assay also partially explains the phenomenon of high false-negative rates. The prozone effect, or hook effect, occurs when excessively high antibody concentrations in a sample result in false-negative or diminished reactions in serological assays, including RPR.³⁰

Neuroimaging findings in neurosyphilis vary with disease stage and are generally not pathognomonic.³¹ Nevertheless, studies also suggest that neuroimaging aids in patient management and follow-up.³² Prior studies summarized neurosyphilis cerebral parenchymal lesions as brain atrophy with ventricular dilatation, cortical hypointensity on SWI, multifocal hypoperfusion on brain SPECT, T2-weighted imaging white matter hyperintensities, and bilateral mesiotemporal lobe involvement with atrophy and T2 hyperintensities.^{33,34} The imaging abnormalities observed in our cohort align with these features, explaining most clinical presentations, including irritability, forgetfulness, headaches, emotional lability, impaired memory, and seizures.³²

Only 33.3% of patients in our cohort received standardized treatment under guidelines, and the cure rate remained limited, with irreversible neurological damage and refractory positive RPR titers. Standardized treatment in emergency settings remains uncommon without dermatology guidance, emphasizing the necessity of dermatological intervention in emergencies.

The resurgence of neurosyphilis can be attributed to several factors, particularly the inadequacy of penicillin alone in preventing late complications. A systematic review revealed that alternative treatments, such as ceftriaxone and doxycycline, demonstrated cure rates comparable to those of penicillin, highlighting the necessity for diverse treatment strategies.³⁵ Furthermore, a study evaluating an enhanced regimen that combined doxycycline and ceftriaxone with standard penicillin therapy found a significantly higher serological cure rate (100% vs 68% for standard therapy) and no complications during follow-up. This evidence underscores the importance of exploring and implementing more effective treatment options to address the growing challenge of neurosyphilis.³⁶ Moreover, the rising incidence of syphilis among men who have sex with men (MSM) further compounds the issue. Behavioral factors, including increased rates of unprotected sex, contribute to the transmission and persistence of syphilis.³⁷ The co-infection of HIV and syphilis has been shown to accelerate the progression of syphilis to neurosyphilis.³⁸

Limitations of this study include the difficulty in follow-up for emergency patients and incomplete examinations due to the retrospective nature of the research. The relatively small sample size of 12 patients may affect the generalizability of our findings, as variability in clinical symptoms among patients could influence diagnosis and treatment strategies. Furthermore, the study primarily focuses on the emergency stage of neurosyphilis, without a detailed discussion of long-term prognosis, which is essential for assessing the durability of treatment effects. This cohort requires further validation from larger prospective analyses to enrich our understanding of the diagnosis and treatment of neurosyphilis. Additionally, we summarized and analyzed findings from existing literature in this field to complement our study. One study indicated that among 187 patients with rapidly progressive dementia, neurosyphilis accounted for 17.9%.³⁹ Another investigation involving 149 neurosyphilis patients revealed that 14.09% presented with ischemic stroke as the primary symptom, with a misdiagnosis rate reaching 80.95%.⁴⁰ Among these patients, 17 were not suspected of neurosyphilis during their initial emergency visit. While our study emphasizes memory impairment and cognitive deficits as primary symptoms, the literature highlights ischemic stroke as a significant manifestation with a high misdiagnosis rate. Memory impairment is often misdiagnosed as dementia, whereas ischemic stroke is frequently attributed to cardiovascular diseases. These findings further highlight the variability in clinical presentation of neurosyphilis and its potential to result in misdiagnosis.

Given the characteristics of neurosyphilis patients, emergency physicians must maintain a high level of suspicion and conduct necessary serological screening. The diagnosis of neurosyphilis typically requires multiple CSF evaluations,⁴¹ and lumbar puncture during follow-up is essential. Other literature also highlights the challenges of follow-up for neurosyphilis patients presenting to the emergency department.¹⁰ Upon confirming a diagnosis of syphilis, it is advisable to establish a multidisciplinary team comprising neurology, rehabilitation, and infectious disease specialists to ensure comprehensive follow-up care and psychological support for the patient.

Conclusion

This study underscores the challenges in diagnosing and managing neurosyphilis among emergency department patients, particularly middle-aged males presenting with acute neuropsychiatric symptoms. Delayed diagnosis was common, possibly leading to irreversible neurological damage. The study highlights the importance of considering neurosyphilis in patients with neuropsychiatric symptoms, even in the absence of suspicious medical histories. Clinical manifestations, laboratory examinations, and neuroimaging features are crucial in diagnosing and managing neurosyphilis in emergency department patients.

Abbreviations

CSF, cerebrospinal fluid; PLWH, people living with HIV; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; RPR, serum rapid plasma reagin; TPPA, Treponema pallidum particle agglutination assay; TRUST, toluidine red unheated serum test.

Ethics Statement

This retrospective study was conducted following approval from the Institutional Review Board (IRB) of Peking Union Medical Hospital (ethics number: S-K653) under the ethical standards outlined in the Declaration of Helsinki.

Patient Consent

All patient data were anonymized and maintained with strict confidentiality throughout the study to protect privacy.

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.

Disclosure

We declare that we have no conflicts of interest.

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