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ORIGINAL RESEARCH

Diagnosing Tabes Dorsalis in HIV-Negative Patients: Clinical Features, Neuroimaging, and Laboratory Insights in the Modern Antibiotic Era

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Background: Tabes dorsalis is a late manifestation of neurosyphilis, characterized by progressive ataxia, lightning pains, loss of proprioception, and urinary incontinence. The absence of a definitive diagnostic standard and the non-specific clinical manifestations have led to a significant rate of misdiagnoses.

Methods: Hospitalized patients with tabes dorsalis at Peking Union Medical College Hospital between January 2010 and December 2023 were reviewed.

Results: A total of 13 patients were included, with 10 males and 3 females. The median age was 50 years (range, 34–64). The most frequent initial symptoms were limb numbness (30.8%) and lightning pains (30.8%). Eleven patients (84.6%) received misdiagnoses prior to the final diagnosis. The most frequently observed physical sign was positive Romberg's sign (84.6%). Notably, Argyll Robertson pupil was presented in 7 subjects (53.8%). Serological tests revealed positive rapid plasma regain (RPR) and *Treponema pallidum* particle agglutination (TPPA) for all patients. All CSF samples were TPPA-reactive. Intramedullary hyperintensity on T2-weighted imaging of spinal MRI was found in 5 patients (38.5%). All patients received anti-syphilitic treatment, with effective treatment recorded in five cases.

Conclusion: This study underscores the importance of neurological symptoms and signs in diagnosing tabes dorsalis. Individuals with progressive ataxia and positive Romberg's sign should be closely monitored for potential neurosyphilis. Integrating clinical features, laboratory tests, and neuroimaging could reduce misdiagnosis and expedite the initiation of anti-syphilitic therapy.

Keywords: tabes dorsalis, neurosyphilis, ataxia, cerebrospinal fluid

Introduction

Neurosyphilis occurs when *Treponema pallidum* infects the central nervous system (CNS). As the "great imitator", it can manifest a wide range of symptoms depending on the site of involvement in CNS. Neurosyphilis is divided into early and late stages. The early stage includes asymptomatic meningitis, symptomatic meningitis, and meningovascular syphilis, while the late stage includes general paresis and tabes dorsalis.[1,2]

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Tabes dorsalis is a gradually advancing form of parenchymal neurosyphilis that commonly affects the posterior column and dorsal root of the spinal cord. It is characterized by symptoms such as coordination impairment, lightning pains, sensory disturbances, and urinary incontinence.[3] Given the similarities in clinical presentations of diseases affecting the spinal cord, it is crucial to differentiate tabes dorsalis from other conditions causing nonsyphilitic myelopathy. This includes disorders of vascular, nutritional, metabolic, immune-mediated, and toxic myelopathies.

There was a 32% increase in syphilis cases from 2020 to 2021 in the United States.[4] In China, between 2007 and 2017, the incidence of syphilis showed a notable increase from 15.9/100,000 to 34.5/100,000.[5] Although the rate of syphilis is increasing, the true incidence of neurosyphilis, especially tabes dorsalis, is difficult to determine in the modern antibiotic era for several reasons.[6] The overall increase in syphilis rates may not directly translate to a proportional rise in specific manifestations like neurosyphilis.[7] Advances in antibiotics might have changed the natural course of syphilis and its complications.[8,9] Furthermore, underreporting, misdiagnosis, and the complexity of neurological symptoms could contribute to this challenge.

In the present study, the clinical data of hospitalized HIV-negative tabes dorsalis patients are reviewed, and their clinical, radiographic, and laboratory characteristics are analyzed. The aim of the study is to enhance clinical awareness of this disease and improve early diagnosis and intervention.

Methods

This study retrospectively collected patients who hospitalized for tabes dorsalis from January 2010 to December 2023 at Peking Union Medical College Hospital (PUMCH, Beijing, China). Data of the patients were retrieved through the Electronic Medical Record Analytical Database (PUMCH-EMERALD). Ethics approval for this study was obtained from the Medical Ethics Committee of Peking Union Medical College Hospital (Approval Identifier: S-K653). This study conformed to the principles of the Helsinki Declaration and ethical requirements involving human subjects. Informed consent was not required because of the retrospective design and anonymization of the study.

Based on the European[10] and US[11] guidelines of neurosyphilis, the inclusion criteria were as follows: (1) Clinical manifestations of neurological symptoms, characterized by ataxic gait, positive Romberg's sign, impaired deep and proprioceptive sensation, lightning pains in legs, Argyll Robertson pupils and Charcot joints; (2) Positive results for the serum rapid plasma regain (RPR) and *Treponema pallidum* particle agglutination (TPPA) tests; (3) Positive RPR in cerebrospinal fluid (CSF), or positive TPPA and fluorescent treponemal antibody absorption (FTA-ABS) with increased white blood cells (WBC $\geq 5\times10^6$/L), or positive TPPA and FTA-ABS with protein content >450 mg/L in CSF (Figure 1). The exclusion criteria were as follows: (1) the presence of other known causes inducing these abnormalities; (2) people living with HIV.

Clinical data of all included patients including demographic information, past medical and personal history, symptoms, disease course, previous diagnosis and physical examinations were systemically reviewed. Serological and CSF laboratory test results and neuroimage presentations by spinal, cranial, or knee MRI were analyzed. The MRI results were independently analyzed by two neuroimaging experts from Peking Union Medical College Hospital. Lumbar puncture was performed to collect CSF, with informed consent obtained from all patients for the procedure. Their treatment schedule and follow-up RPR titers were collected. An over fourfold decrease in serum RPR titer within one year after discharge, or both the patient and the clinician reporting improvement of neurological function, would indicate successful treatment.[11,12]

Results

Demographic Information and Previous History

A total of 13 patients with tabes dorsalis were included according to the selection criteria. The median age was 50 years (range, 34–64) and 76.9% (n = 10) of the patients were male. Eleven patients (84.6%) were married. Five patients (38.5%) admitted high-risk sex life, three of whom reported a history of unprotected sexual intercourse more than 10 years ago. Besides, two patients (15.4%, 2/13) mentioned drug abuse, and one (7.7%, 1/13) reported a history of blood transfusion. The occupations of these patients included office clerks (15.4%, 2/13), drivers (15.4%, 2/13), farmers (15.4%, 2/13), civil servant (7.7%, 1/13), dance instructor (7.7%, 1/13), unemployed individuals (15.4%, 2/13), and those unwilling to disclose their occupation (23.1%, 3/13). For infectious comorbidity, two patients were infected with HBV (15.4%), one patient with HCV (7.7%), and one patient with HSV (7.7%).

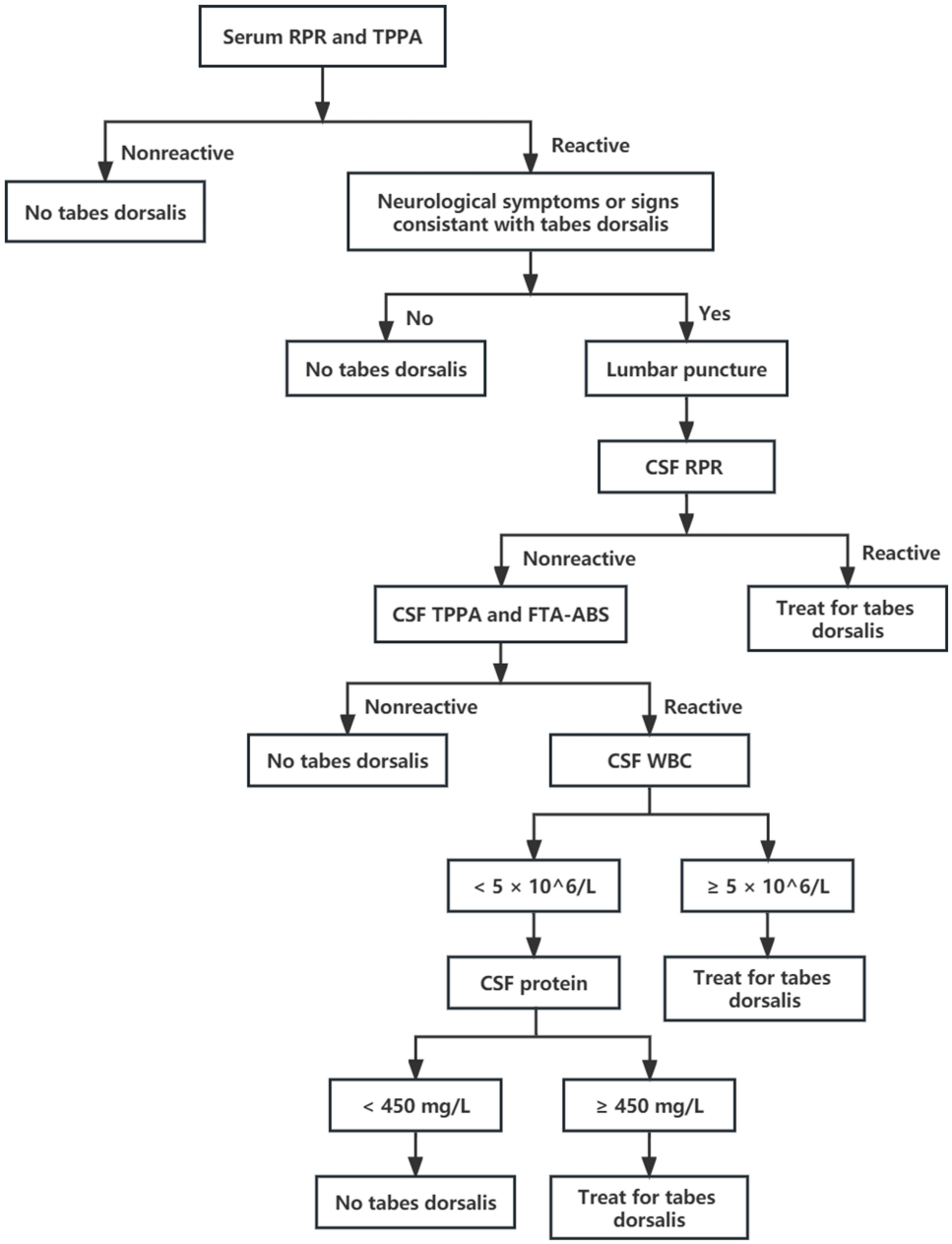

Figure 1 Flowchart for the diagnosis of tabes dorsalis.

Clinical Symptoms and Previous Medical Experience

The initial and overall clinical symptoms of the included patients were diverse (Table 1). The most frequent initial symptoms were limb numbness (30.8%, 4/13) and lightning pains in legs and trunk (30.8%, 4/13). Loss of body balance and coordination with difficulty walking (15.4%, 2/13) was also commonly observed as an early symptom. For overall symptoms at any stage, 10 patients experienced urinary or fecal incontinence (76.9%), and 8 patients reported limb numbness (61.5%). Other prominent manifestations included insomnia (53.8%, 7/13), sensory ataxia (53.8%, 7/13), stabbing pain spreading rapidly in limbs or back (46.2%, 6/13), limb weakness (38.5%, 5/13), and weight loss (30.8%, 4/13).

The median time from symptom onset to hospitalization was 36 months (range, 6–144). A total of four patients (30.8%) reported a prior syphilis infection and two of them received penicillin-based therapy before. Eleven patients (84.6%) were misdiagnosed as other diseased before the final diagnosis. The common misdiagnoses included subacute

Table 1 Initial and Overall Symptoms of Tabes Dorsalis

	Initial Symptoms	Overall Symptoms
Limb numbness	4 (30.8%)	8 (61.5%)
Lightning pains in legs and trunk	4 (30.8%)	6 (46.2%)
Loss of body balance with difficulty walking	2 (15.4%)	7 (53.8%)
Limb weakness	1 (7.7%)	5 (38.5%)
Dizziness	1 (7.7%)	2 (15.4%)
Diplopia	1 (7.7%)	1 (7.7%)
Headache	1 (7.7%)	1 (7.7%)
Memory decline	1 (7.7%)	1 (7.7%)
Urinary or fecal incontinence	0	10 (76.9%)
Insomnia	0	7 (53.8%)
Weight loss	0	4 (30.8%)
Visual impairment	0	3 (23.1%)
Joint swelling	0	2 (15.4%)
Nausea or vomiting	0	2 (15.4%)
Dysarthria	0	2 (15.4%)
Emotional disturbances	0	2 (15.4%)
Chest tightness	0	2 (15.4%)
Hearing loss	0	2 (15.4%)
Rash	0	2 (15.4%)
Personality change	0	1 (7.7%)
Dysphagia	0	1 (7.7%)

combined degeneration (23.1%, 3/13), psychiatric disorders (15.4%, 2/13), joint diseases (15.4%, 2/13), and peripheral neuropathies (15.4%, 2/13).

Physical Examination

The frequently observed physical signs were positive Romberg's sign (84.6%, 11/13), abnormal heel-knee-shin test (69.2%, 9/13), loss of or decreased deep tendon reflexes in the lower extremities (61.5%, 8/13), Argyll Robertson pupil (53.8%, 7/13), and wide-based gait (53.8%, 7/13). Impaired vibratory, position, and pinprick sensations, muscle weakness, hypertonia, and abnormal abdominal reflex were also common signs in this cohort.

Laboratory Tests of Serum and CSF

All patients had positive serum TPPA results. Serum RPR was positive in all included patients (6 RPR titers ≤1:16 and 7 RPR titers ≥1:32). In CSF, RPR was positive in 10 patients (76.9%), with RPR titers ≤1:4 in 4 samples and RPR titers ≥1:8 in 6 samples. Additionally, TPPA and FTA-ABS tests were performed in all CSF samples, and all reported reactivity.

CSF WBC counts of included patients ranged from 0 to 190×10^6/L. Seven patients (53.8%) had CSF pleocytosis. The levels of CSF protein varied from 370 to 1550 mg/L. Twelve patients (92.3%) had elevated CSF protein levels and 7 patients (53.8%) have both pleocytosis and elevated protein levels in CSF.

Neuroimaging Alterations by MRI

All 13 included patients underwent spinal MRI, and 12 of them also had cranial MRI. Abnormal spinal signals were found in 5 patients (38.5%). The most common characteristic of the spinal anomaly was intramedullary hyperintensity on T2-weighted imaging (Figure 2A–F). The cranial MRI revealed abnormal intracranial manifestations in three patients, suggesting general paresis in two cases and syphilitic meningoencephalitis in one case (Figure 3A–F). Four patients underwent spinal contrast-enhanced MRI, and five patients had cranial contrast-enhanced MRI. However, no abnormal

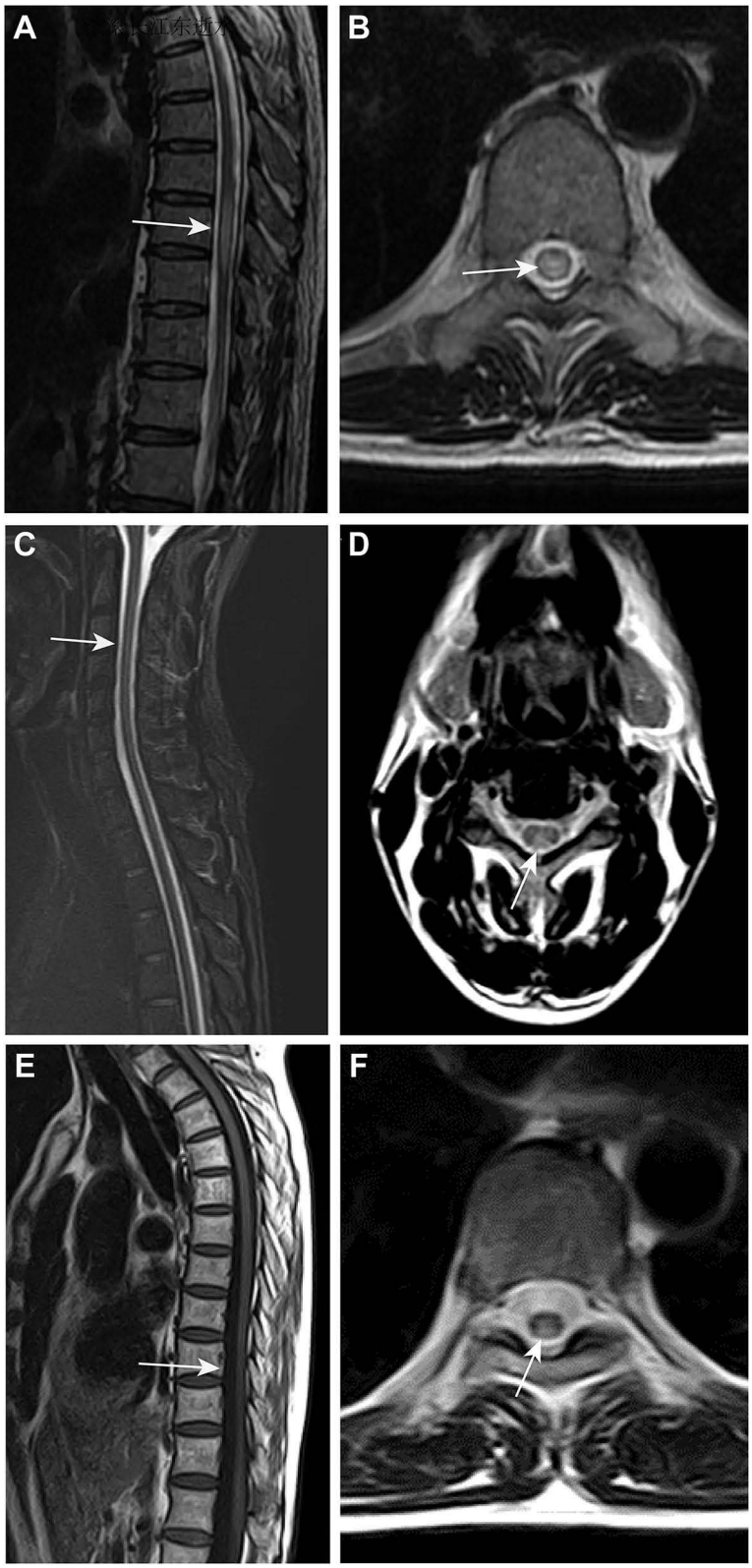

Figure 2 Neuroimaging alterations of tabes dorsalis on spine MRI. (**A** and **B**) In a 56-year-old male patient, the sagittal section (**A**) of T2-weighted image showed intramedullary hyperintensity from T8 to T10 (arrow). The axial section (**B**) of T2-weighted image at the T9 level showed the lesion affecting nearly the entire cross-section of the spinal cord without associated expansion (arrow). (**C** and **D**) In a 34-year-old man patient, the sagittal section (**C**) of T2-weighted image showed intramedullary hyperintensity in the cervical and upper thoracic spine (arrow). The axial T2-weighted image (**D**) at the T2/3 level showed the lesions mainly affecting the dorsal columns (arrow). (**E** and **F**) In a 58-year-old female patient, the sagittal section (**E**) of T1-weighted image showed spinal cord atrophy at the lower thoracic level (arrow). The axial T2-weighted image (**F**) at the T8 level showed intramedullary hyperintensity in the dorsal spinal cord (arrow).

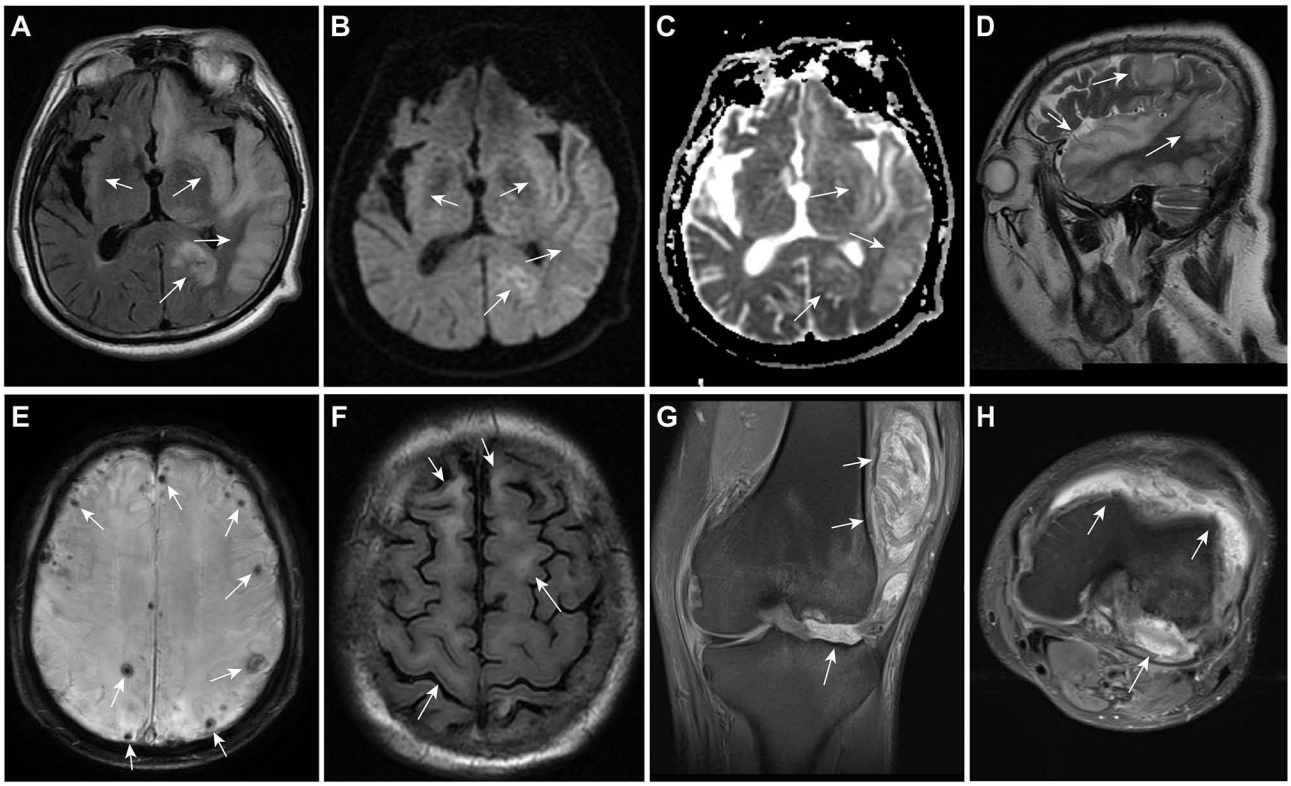

Figure 3 (**A**–**D**) In a 48-year-old male patient with syphilitic meningoencephalitis, the axial FLAIR-weighted image (**A**) and the sagittal T2-weighted image (**D**) showed diffuse hyperintensity and swelling in the bilateral cerebral cortex and subcortical areas, more pronounced on the left side (arrows). The corresponding areas on the axial DWI sequence (**B**) showed slightly increased signal intensity, while the ADC map (**C**) showed increased signal intensity (arrows). (**E** and **F**) In a 60-year-old male patient with general paresis, the SWI sequence (**E**) showed multiple microhemorrhages beneath the cortical surface (arrows), and the FLAIR image (**F**) showed multifocal white matter abnormal signals and brain atrophy (arrows). (**G** and **H**) In a 43-year-old male patient, the coronal (**G**) and axial (**H**) sections of the left knee on MRI revealed articular destruction, with irregularity of articular surface and intra-articular effusion (arrows).

enhancement was observed on the contrast-enhanced MRI. Additionally, MRI imaging of the knee showed articular destruction in two subjects (Figure 3G–H).

Complications

Concomitant findings associated with tabes dorsalis in this cohort were Charcot arthropathy (15.4%, 2/13), general paresis (15.4%, 2/13), cardiovascular syphilis (7.7%, 1/13), and syphilitic meningoencephalitis (7.7%, 1/13). In addition, the complication of ocular syphilis was observed in seven subjects (53.8%), and otologic syphilis was present in two subjects (15.4%).

Treatment and Outcome

All patients received anti-syphilitic treatment during their hospitalization. Four of them received intravenous ceftriaxone (2 g daily) for 2 weeks, and one was treated with doxycycline orally for one month. For patients without history of penicillin anaphylaxis, 6 subjects received intravenous penicillin 4 million units every 4 hours for 2 weeks and 2.4 million units of benzathine penicillin intramuscularly every week for three weeks. Seven patients (53.8%) were given corticosteroids to prevent Jarisch–Herxheimer reaction. One patient presented the Jarisch–Herxheimer reaction after receiving penicillin without corticosteroids. No other adverse events were reported.

Post-treatment serum tests were performed in 11 patients. Among these, two subjects (18.2%) showed a more than four-fold decrease in their serum RPR titers. In contrast, five patients (45.5%) did not exhibit a decrease in RPR titers. For clinical symptoms, limb numbness and weakness were alleviated in four patients, lightning pains decreased in three patients, loss of body balance with difficulty walking was relieved in four patients, and urinary function improved in two

Table 2 MRI Findings, Complications, and Treatment Outcomes in Tabes Dorsalis Patients

	Cases	Percentage of Cases
MRI findings		
Spinal MRI		
Normal	8	61.5%
Intramedullary hyperintensity on T2WI	5	38.5%
Cranial MRI		
Normal	9	75.0%
Abnormal signal	3	25.0%
Brain atrophy	1	8.3%
Complications		
Ocular syphilis	7	53.8%
Otologic syphilis	2	15.4%
Charcot arthropathy	2	15.4%
General paresis	2	15.4%
Cardiovascular syphilis	1	7.7%
Syphilitic meningoencephalitis	1	7.7%
Treatment outcomes		
Effective treatment	5	41.7%
Partial response	5	41.7%
Limited improvement	2	16.7%

patients. The effectiveness of treatment was evaluated in 12 subjects. Among them, five cases of tabes dorsalis (41.7%) demonstrated effective anti-syphilitic treatment outcomes. Another five patients (41.7%) showed a partial response to the treatment, while the remaining two patients (16.7%) reported limited improvement (Table 2).

Discussion

Historical Context

Tabes dorsalis was the most prevalent form of neurosyphilis in the pre-antibiotic era. In the modern era, a shift in the clinical patterns of neurosyphilis was observed, characterized by a decrease in the incidence of tabes dorsalis.[13] However, the findings of this study suggest that tabes dorsalis is not rarely reported and deserves continued clinical vigilance. In the post-COVID-19 era, syphilis is anticipated to resurface as a major public health issue. Many countries have experienced significant increases in syphilis cases post-lockdown, surpassing pre-pandemic levels.[4,14,15] Therefore, it is crucial for clinicians to enhance their understanding of neurosyphilis, particularly tabes dorsalis, which is a life-threatening infection of the nervous system.

Clinical Characteristics

Syphilis is more common among mid-age males, particularly in men who have sex with men.[16] The sex ratio was 10:3 (male:female), and the median age of our patients with tabes dorsalis was 50 years, consistent with previous studies.[13,17] Both age and gender should be considered in the process of making a differential diagnosis. The investigation of occupation revealed the diverse backgrounds of patients with tabes dorsalis, with a noteworthy portion being either employed in low-skilled jobs or experiencing unemployment. Regarding sexual life and infectious comorbidity, only 38.5% of patients disclosed a high-risk sex history and merely 15.4% of patients reported a history of infectious disease. However, neurosyphilis should not be overlooked even in the claimed absence of any relevant history, and sex education is recommended to be widely promoted in the society.

The most common initial symptoms were limb numbness and lightning pains, highlighting the diverse neurological manifestations associated with tabes dorsalis. Romberg's sign, a key component of the neurological examination assessing proprioception and coordination, was the most frequently observed physical sign, detected in 84.6% of patients.

This high incidence emphasizes the impact of tabes dorsalis on sensory and motor functions. Argyll Robertson pupil is a hallmark sign of tabes dorsalis and is identified in up to 60% of patients.[1,18–20] In our cohort, 53.8% of patients exhibited this sign, similar with the incidence reported in previous studies.[18,21]

Tabes dorsalis typically manifested between 3 and 47 years after the primary infection, with an average onset occurring around 21 years later.[21] However, most of the patients with tabes dorsalis were not aware of the prior syphilis infection and misdiagnoses happened frequently since tabes dorsalis mimics other causes of myelopathy. In our study, the median duration from symptom onset to hospitalization was 3 years, ranging from 0.5 to 12 years. The misdiagnosis rate was 84.6%, and the remaining 15.4% of patients did not receive any specific or meaningful diagnosis before hospitalization. The lack of awareness regarding neurosyphilis and inadequate screening for syphilis prolonged the time required to establish a confirmed diagnosis.

Diagnosis

Serological tests play a crucial role in confirming the diagnosis, with all patients exhibiting positive TPPA and RPR results. Previous research has revealed that a serum RPR titer ≥1:32 helps predict the likelihood of neurosyphilis, especially in HIV-negative subjects.[22] However, in this study, 46.2% of patients had a serum RPR titer of ≤1:16. Having a low serum RPR titer may not exclude the possibility of neurosyphilis due to declining titers over time in late neurosyphilis.[3] The consistent reactivity of CSF samples to TPPA and FTA-ABS further supported the involvement of neurosyphilis in these cases. Lumbar puncture should be recommended for a patient displaying neurological, ocular, or otologic symptoms associated with serologic evidence of syphilis.

Pleocytosis and elevated protein levels in CSF may not always be present in tabes dorsalis. In this study, CSF protein levels were elevated in most subjects, whereas increased WBC counts in CSF were observed in only about half of the patients. As tabes dorsalis represents the late stage of neurosyphilis, the inflammatory response tends to be less pronounced compared to the early stage.[6,23] Therefore, in the presence of a normal CSF routine test, late-stage neurosyphilis, especially tabes dorsalis, could not be ruled out.

Currently, there is no universally accepted "gold standard" for the diagnosis of neurosyphilis.[24,25] Various guidelines offer different opinions regarding lumbar puncture in patients with syphilis and the utility of CSF laboratory tests.[10,11,26] Notably, the serum RPR test is only 50 to 75% sensitive in late symptomatic neurosyphilis and the CSF RPR has an even higher false-negative rate.[3] Consequently, effective biomarkers are urgently needed for the diagnosis of late neurosyphilis, especially tabes dorsalis, to improve both sensitivity and specificity. By analyzing 223 CSF samples using large-scale proteomic profiling and machine learning models, Li et al identified semaphorin family member 7A (SEMA7A), serpin family A member 3 (SERPINA3), and inter-alpha-trypsin inhibitor family member 4 (ITIH4) as key biomarkers for neurosyphilis.[27] To avoid lumbar puncture, Xie et al suggested that serum ubiquitin C-terminal hydrolase-L1 (UCH-L1), glial fibrillary acidic protein (GFAP), and neurofilament light chain (NF-L) could serve as promising biomarker candidates for the diagnosis of neurosyphilis in HIV-negative patients.[28]

Neuroimaging Alterations

Neuroimaging findings, specifically intramedullary hyperintensity on T2-weighted spinal MRI, were identified in 38.5% of patients, indicating focal inflammation of spinal cord. Given that 61.5% of patients showed normality of spinal MRI, it is suggested that tabes dorsalis may not always be associated with spinal MRI abnormalities, consistent with previous studies reporting MRI abnormalities in tabes dorsalis.[13,17,21] In a study involving six patients with tabes dorsalis, spinal MRI revealed abnormalities in 33% of the patients.[29] Tabes dorsalis primarily involves chronic and insidious degenerative changes rather than acute inflammation.[21] Consequently, the degeneration of the posterior roots and columns of the spinal cord may not present significant or detectable changes on spinal MRI.

However, the integration of spinal and cranial MRI, along with consideration of joint involvement, contributes to a more holistic understanding of the disease presentation.[30] Charcot arthropathy is an unusual but recognized complication of tabes dorsalis reported in previous studies.[3,31–33] The cranial MRI results further illuminate the broader neurological implications of tabes dorsalis. General paresis, characterized by progressive cognitive and motor dysfunction,[3] and syphilitic meningoencephalitis, involving inflammation of the brain and meninges,[34] underscore the severity and diversity of neurological complications in untreated tabes dorsalis patients.

Management

The management of tabes dorsalis, a late-stage parenchymatous form of neurosyphilis, continues to pose challenges. In our cohort, 41.7% of patients were effectively treated with penicillin or ceftriaxone, consistent with the previous study.[13] Drawing from historical experience, it is suggested that while penicillin may not necessarily improve late syndromes of neurosyphilis, it often serves to halt their progression. The use of penicillin in the context of tabes dorsalis is more focused on preventing further deterioration rather than achieving complete resolution of established neurological symptoms.[3,35] This underlines the importance of early detection and treatment in neurosyphilis to prevent the advancement of the disease to its late stages.

Limitations and Prospects

This study has several limitations that must be considered when interpreting the results. First, the study focused exclusively on hospitalized patients, which may introduce selection biases by excluding outpatients with tabes dorsalis. Hospitalized patients often represent more severe cases or those with complications, and the findings may not be representative of the broader population managed in outpatient settings. Second, the retrospective nature of this study introduces inherent biases and limitations in data collection. Retrospective studies rely on existing records, which may be incomplete or inaccurately documented. Additionally, the retrospective design limits the ability to control for all potential confounding factors, which can influence the study's outcomes. Third, since the CSF-VDRL test is not available in our center, we use the CSF-RPR as a substitute. However, the CSF-RPR can sometimes be nonreactive even when the CSF-VDRL would be reactive, making it a less reliable test for diagnosing neurosyphilis. Finally, this study only reviewed patients from a single center with a relatively small sample size. This geographic and institutional limitation may impact the generalizability of the findings. Differences in patient demographics, healthcare practices, and resource availability between centers can influence the outcomes and applicability of the results to other settings.

Future research on tabes dorsalis should aim to address several key gaps in the current understanding and management of the disease. First, long-term, prospective studies are needed to better understand the natural history and progression of tabes dorsalis. These studies could help identify early markers of the disease, track the progression of symptoms, and evaluate the long-term outcomes of different treatment strategies. Second, accurate and timely diagnosis of tabes dorsalis remains a challenge. Research should focus on developing and validating new diagnostic tools that can detect the disease earlier and more reliably. Third, it is crucial to investigate optimal antibiotic regimens, including the duration and combination of antibiotics, to ensure effective eradication of the pathogen. Additionally, developing comprehensive rehabilitation programs that address the physical, cognitive, and emotional aspects of recovery for patients with tabes dorsalis is essential.

Conclusion

In this study, a significant misdiagnosis rate for tabes dorsalis patients was noted, with most patients not correctly treated before the final diagnosis was made. In our cohort, limb numbness and lightning pains were the most frequent initial symptoms, while Romberg's sign and Argyll Robertson pupil were the most common physical signs, providing important clues for early diagnosis. Lumbar puncture is recommended when there is serological evidence of syphilis along with clinical symptoms indicative of tabes dorsalis. To reduce misdiagnosis and improve treatment outcomes for tabes dorsalis, a comprehensive diagnostic approach that integrates clinical features, laboratory tests, and neuroimaging is essential. This strategy facilitates the prompt initiation of anti-syphilitic therapy and prevents late-stage complications. Additionally, policymakers should ensure the availability of advanced diagnostic tools and support continuous medical education for clinicians to enhance the management of neurosyphilis.

Data Sharing Statement

All inquiries can be directed to the corresponding authors.

Ethics Statement

Ethics approval for this study was obtained from the Medical Ethics Committee of Peking Union Medical College Hospital (Approval Identifier: S-K653). This study conformed to the principles of the Helsinki Declaration and ethical requirements involving human subjects. Informed consent was not required because of the retrospective design and anonymization of the study.

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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

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