Neurosyphilis presenting as status epilepticus and hemiplegia diagnosed by metagenomic next-generation sequencing: A case report

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Abstract. The current study aimed to present a diagnostically challenging case of neurosyphilis manifesting with atypical neurological symptoms, emphasizing the importance of clinical vigilance and advanced diagnostics in avoiding misdiagnosis and inappropriate intervention. In the present study, a case of neurosyphilis, initially misdiagnosed and treated as acute cerebral infarction, is reported. Diagnostic analyses included serial brain magnetic resonance imaging (MRI), continuous electroencephalography (EEG) monitoring and metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid (CSF) for pathogen identification. The results revealed that the patient presented with status epilepticus and hemiplegia. Follow-up MRI after transfer revealed extensive patchy cortical and subcortical white matter abnormalities in the right cerebral hemisphere. Notably, a thalamic signal abnormality observed on pre-thrombolysis diffusion-weighted imaging had notably diminished. EEG demonstrated periodic lateralized epileptiform discharges (PLEDs). CSF mNGS definitively identified 883 specific sequences of *Treponema pallidum*. Despite targeted anti-syphilitic and antiepileptic therapy, the patient's consciousness failed to improve, with persistent PLEDs on EEG. The patient was later discharged against medical advice due to pulmonary infection and hypotension and was subsequently confirmed deceased. In conclusion, the current case illustrates the markedly diverse and misleading presentations of neurosyphilis, which can mimic other acute neurological conditions. It underscores the need for maintaining a high index of suspicion and utilizing comprehensive diagnostic tools, including mNGS, to ensure accurate diagnosis and prevent the consequences of missed diagnosis or incorrect treatment.

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Introduction

Neurosyphilis is a severe complication caused by the invasion of the central nervous system (CNS) by *Treponema pallidum*, which can affect the brain parenchyma, spinal cord and peripheral nerves. Due to its complex and diverse clinical manifestations that can mimic various neurological disorders, it has been termed the 'great imitator' in the medical field (1). This disease can occur during either the early or late stages of syphilis infection (2). Global syphilis incidence has risen 60% since 1990. Populations of men who have sex with men have a 15- to 20-fold higher rate, with nearly one-half co-infected with HIV. Neurosyphilis, once affecting one-third of syphilis patients, now predominantly occurs in untreated HIV-infected individuals, with 3-5% of US cases developing complications and higher risks in white individuals (2- to 3-fold vs. black individuals) and males (2-fold vs. females) (3). The current diagnosis of neurosyphilis primarily relies on a comprehensive assessment including clinical presentation, serological tests, cerebrospinal fluid (CSF) analysis and neuroimaging. However, the absence of a definitive gold standard for diagnosis still poses notable challenges for its early detection (3). The application of metagenomic next-generation sequencing (mNGS) has provided new diagnostic avenues for CNS infections caused by rare pathogens that are difficult to identify using traditional methods. The present study retrospectively analyzed the clinical data of a patient admitted to Hebei General Hospital who presented with status epilepticus (SE) and hemiplegia as the initial symptoms and was ultimately diagnosed with neurosyphilis confirmed by CSF mNGS. By reviewing the current case and relevant literature, the present study aimed to enhance clinicians' understanding and improve the diagnostic and therapeutic capabilities regarding this disease.

Case report

A 56-year-old female presented to Hebei General Hospital (Shijiazhuang, China) in June 2025 with a 1-year history of intermittent headache and dizziness. The patient had developed progressive cognitive decline over the preceding 6 months, characterized by memory impairment and an episode of topographic disorientation. Brain magnetic resonance imaging (MRI) revealed chronic ischemic cerebral changes and cerebral atrophy (Fig. 1). The patient was treated with medications comprising of Danzhen Toutong Capsules (2 g three times a day), Pentoxifylline Sustained-Release Tablets (0.4 g twice a day) and Xinnaoning Capsules (1.35 g three times a day) to improve cerebral circulation and memory

In August 2025, the patient was noted by family to be lethargic. On the way to the hospital, the patient developed a loss of consciousness accompanied by generalized tonic-clonic seizures, featuring upward gaze deviation and unresponsiveness to verbal stimuli. Intramuscular diazepam was administered, and the convulsions in the limbs ceased subsequently; however, consciousness did not fully recover. The patient could open their eyes but lacked consciousness and was unable to communicate. Furthermore, the patient's family noted reduced movement in the left limb, which was confirmed by clinicians. Brain diffusion-weighted imaging (DWI) revealed right thalamic and fronto-temporo-parietal hyperintensities (Fig. 2). Based on the clinical presentation, a diagnosis of cerebral infarction was considered, and recombinant human TNK tissue-type plasminogen activator was administered as a single intravenous bolus of 12.5 mg for thrombolytic therapy. However, the patient failed to recover consciousness following this treatment, and developed intermittent convulsions in the left limb. Consequently, the patient was transferred to the Department of Neurology, Hebei General Hospital (Shijiazhuang, China) for further management 3 days after admission. The patient had no personal or family history of epilepsy and denied any history of sexual activity that could result in exposure to infection or intravenous drug use.

The physical examination on admission revealed stable vital signs. No notable rash was observed on physical examination. During neurological examination, the patient could open eyes but lacked consciousness. The patient's bilateral pupils were round and equal in size, with prompt light reflex, and bilateral frontal wrinkles and nasolabial folds were symmetrical. Neurological examination was limited by poor cooperation; however, reduced spontaneous movement of the left limbs and bilateral Babinski signs and absence of neck stiffness were observed.

The patient was started on antiepileptic therapy with sodium valproate and levetiracetam. The initial dosage of levetiracetam was 500 mg twice daily; however, as the patient continued to exhibit involuntary twitching movements in the left limb, the dose was increased to 1,000 mg twice daily after 3 days. The dosage of sodium valproate was 1 mg/kg/h. While this regimen prevented the recurrence of generalized tonic-clonic seizures, the patients' mental status remained persistently altered without notable improvement.

Laboratory investigations revealed marked inflammatory markers, including leukocytosis [white blood cells (WBCs), $15.24x10^9$ cells/l; reference range, $3.5\text{-}9.5x10^9$ cells/l] with neutrophilic predominance (90.90%; reference range, 40-75%;) and elevated C-reactive protein (CRP, 57.35 mg/l; reference range, 0-6 mg/l), serum amyloid A (SAA, 452.07 mg/l; reference range, 0-10 mg/l) and D-dimer level was elevated at 0.85 mg/l fibrinogen equivalent units (FEU; reference range, 0-0.55 mg/l FEU). Serological testing was positive for syphilis, with a reactive anti-*Treponema pallidum* antibody, a positive Treponema pallidum particle agglutination test (TPPA) and a positive rapid plasma reagin (RPR) at a titer of 1:32. No notable abnormalities were detected in liver or kidney function, electrolytes, blood glucose, thyroid function, myocardial enzymes or HIV antigen/antibody testing. Echocardiography and lower extremity deep venous ultrasound revealed no marked abnormalities. Brain MRI demonstrated abnormal signals in the right cerebral cortex and subcortical white matter involving the frontal, parietal, temporal and occipital lobes, as well as the insula and thalamus, alongside cerebral atrophy. Multiple intracranial arterial stenoses were observed (Fig. 3). Comparison with the pre-thrombolysis DWI revealed notable resolution of the thalamic signal abnormality (Fig. 4). Contrast-enhanced brain MRI revealed swelling and abnormal signal intensity involving the right frontal, parietal, temporal, occipital and insular lobes. Abnormal parenchymal enhancement was noted in the right caudate nucleus region of the basal ganglia. Additionally, leptomeningeal enhancement was observed in the right frontal, temporal and insular regions (Fig. 5). A video electroencephalogram (vEEG) obtained on admission demonstrated diffuse background slowing, characterized by abundant medium-to-high amplitude polymorphic Δ/θ waves across all leads, and a right frontotemporal focus exhibiting periodic lateralized epileptiform discharges (PLEDs) (Fig. 6). Lumbar puncture revealed an opening pressure of 170 mmH_2O, and the CSF was colorless and clear. Analysis showed a lymphocytic pleocytosis (WBC count, $123x10^6$ cells/l; 57% lymphocytes), elevated total protein (85.15 mg/dl), decreased glucose (2.40 mmol/l) and slightly decreased chloride (119.4 mmol/l) (reference values: Opening pressure, 80-180 mmH_2O; WBC count, $0\text{-}8x10^6$ cells/l; protein, 15-45 mg/dl; glucose, 2.5-4.5 mmol/l; and chloride, 120-130 mmol/l). A comprehensive autoimmune encephalitis antibody panel and a concentrated CSF smear for acid-fast bacilli returned negative results. mNGS of the CSF detected 883 sequence reads of *Treponema pallidum*, using the Nucleic Acid Extraction or Purification Kit (catalogue no. VM020; Vision Medicals (https://www.visionmedicals.com/) for DNA/RNA preparation, with sample quality/integrity verified by Qubit fluorometer. Sequencing was performed as single-end 50 bp with single-end barcoded sequencing, using the Sequencing Reaction Universal Kit (combined probe anchor polymerization sequencing method; specification/model: 940-000522-00, G99 SM App-D FCL SE100, 1 test/box; Wuhan MGI Tech Co., Ltd.). The final library loading concentration was calculated as C(nM)=[C(ng/μl)]/[fragment length (bp) $x660x10^{-6}$], with DNA concentration measured by Qubit fluorometer, yielding a final concentration of 118.94 nM, and data were analyzed using the pathogen NGS digital management platform MARS 3.0 (version 3.0; Vision Medicals). In this CSF mNGS assay, by using pathogen capture-based high-throughput sequencing with a

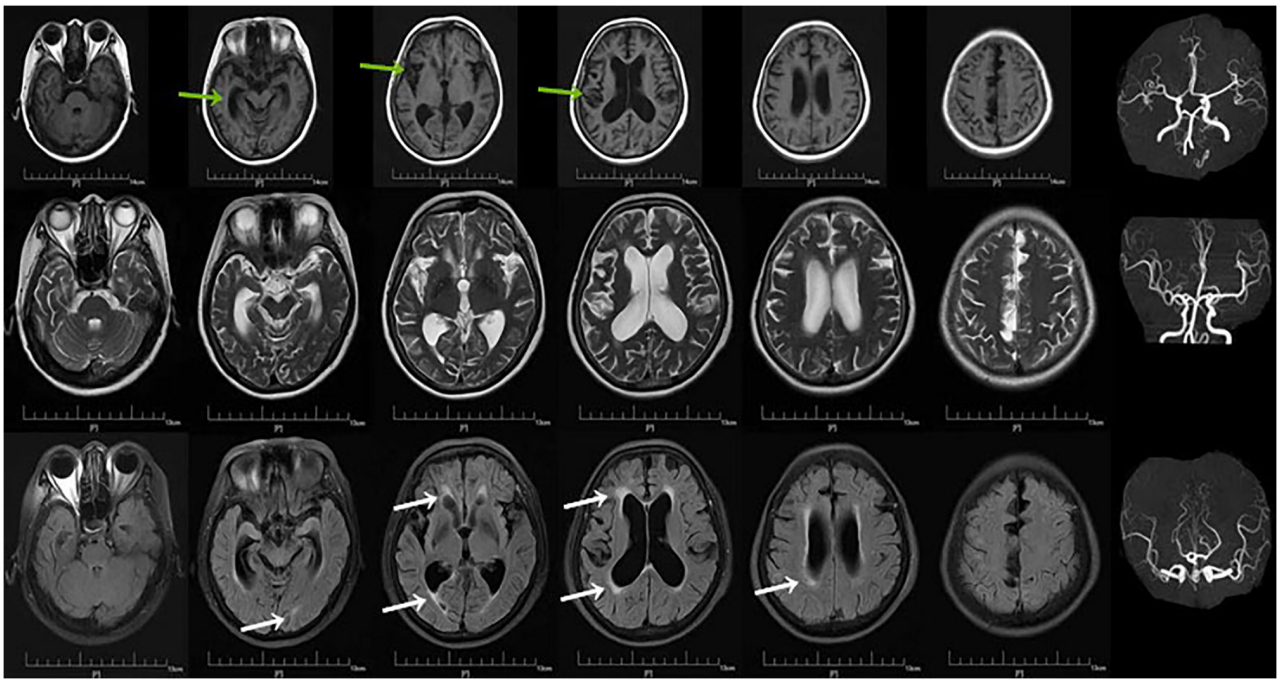

Figure 1. Brain magnetic resonance imaging performed in the outpatient setting in June 2025. Fluid-attenuated inversion recovery sequence demonstrated periventricular white matter hyperintensity (white arrow), while T1-weighted imaging revealed cerebral atrophy (green arrow).

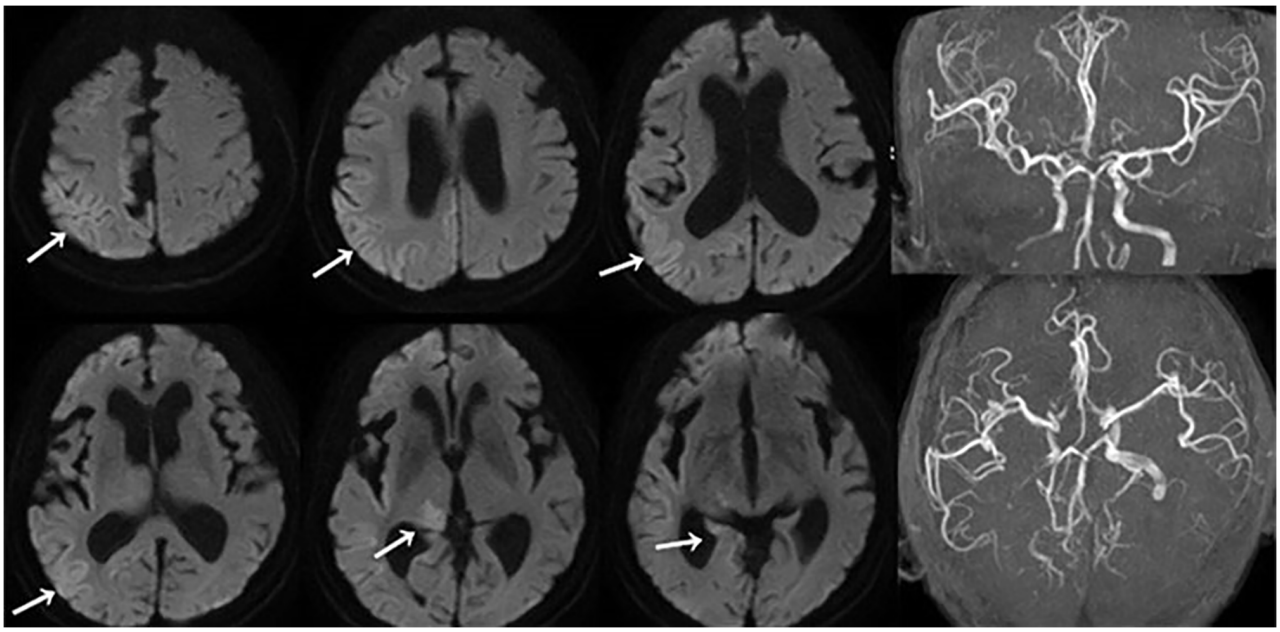

Figure 2. Brain magnetic resonance imaging performed in another hospital in August 2025, 3 days prior to admission to Hebei General Hospital. Brain diffusion-weighted imaging demonstrates acute changes in the right thalamus and fronto-temporo-parietal cortex (white arrow).

robust database and full-process quality control, *Treponema pallidum* was identified with 883 specific reads and a genus-level abundance of 61.46%, far exceeding background microbial counts. Given the sterile nature of the CSF, this result meets the criteria for pathogenic positivity. Through stringent measures, including environmental controls, negative controls, molecular barcodes, bioinformatics filtering and manual review, contamination from environmental, operational or skin commensal sources was thoroughly excluded across the entire workflow, from specimen handling to bioinformatics and clinical interpretation. This positive result thus holds substantial clinical reference value.

Other potential etiologies for seizures and imaging abnormalities were systematically excluded, such as CNS infections (CSF NGS detected no other bacteria or viruses), autoimmune encephalitis (negative comprehensive antibody panels), acute ischemic stroke (no clinical improvement after thrombolysis and marked DWI lesion resolution), as well as

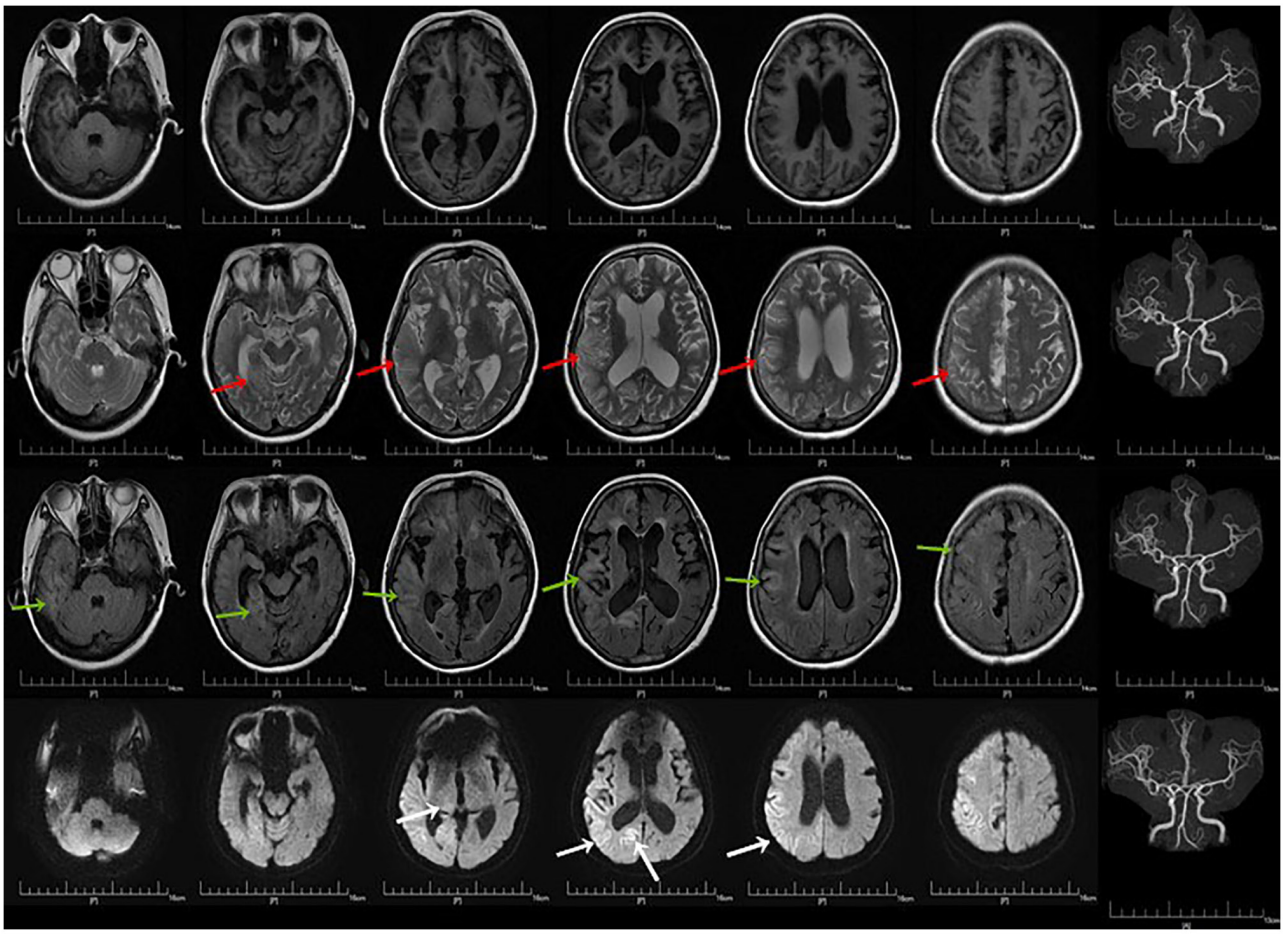

Figure 3. Brain magnetic resonance imaging performed in August 2025, at 1 day post-admission. Fluid-attenuated inversion recovery sequence (green arrow) and T2-weighted imaging (red arrow) demonstrated hyperintensity in the right cerebral cortex and subcortical white matter involving the frontal, parietal, temporal and occipital lobes, as well as the insula and thalamus. DWI (white arrow) demonstrated acute changes in the fronto-temporo-parietal cortex. The DWI hyperintensity in the right thalamus shown in Fig. 2 had diminished or was no longer clearly visible on this DWI examination. DWI, diffusion-weighted imaging.

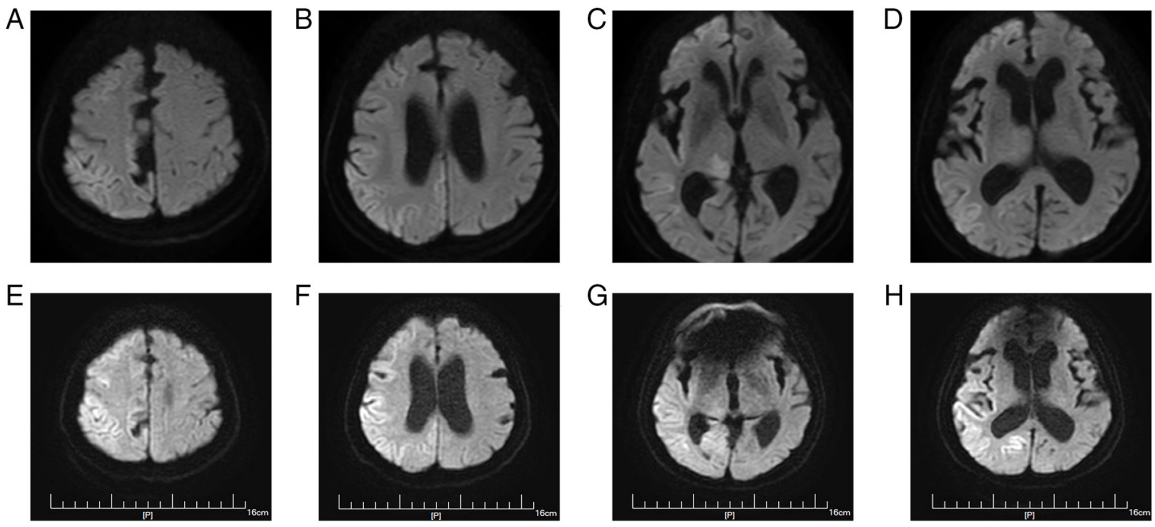

Figure 4. Brain magnetic resonance imaging performed in August 2025, 3 days prior to admission to Hebei General Hospital. (A-D) DWI performed at symptom onset demonstrates (C) hyperintensity in the right thalamus. (E-H) Follow-up DWI (3 days later, at 1 day post-admission) showed (G) reduced right thalamic hyperintensity and (H) new right occipital lobe signal abnormality.

metabolic, neoplastic and primary epileptic causes (normal blood tests, unremarkable contrast-enhanced MRI and negative personal/family history). Accordingly, the diagnosis of neurosyphilis was established.

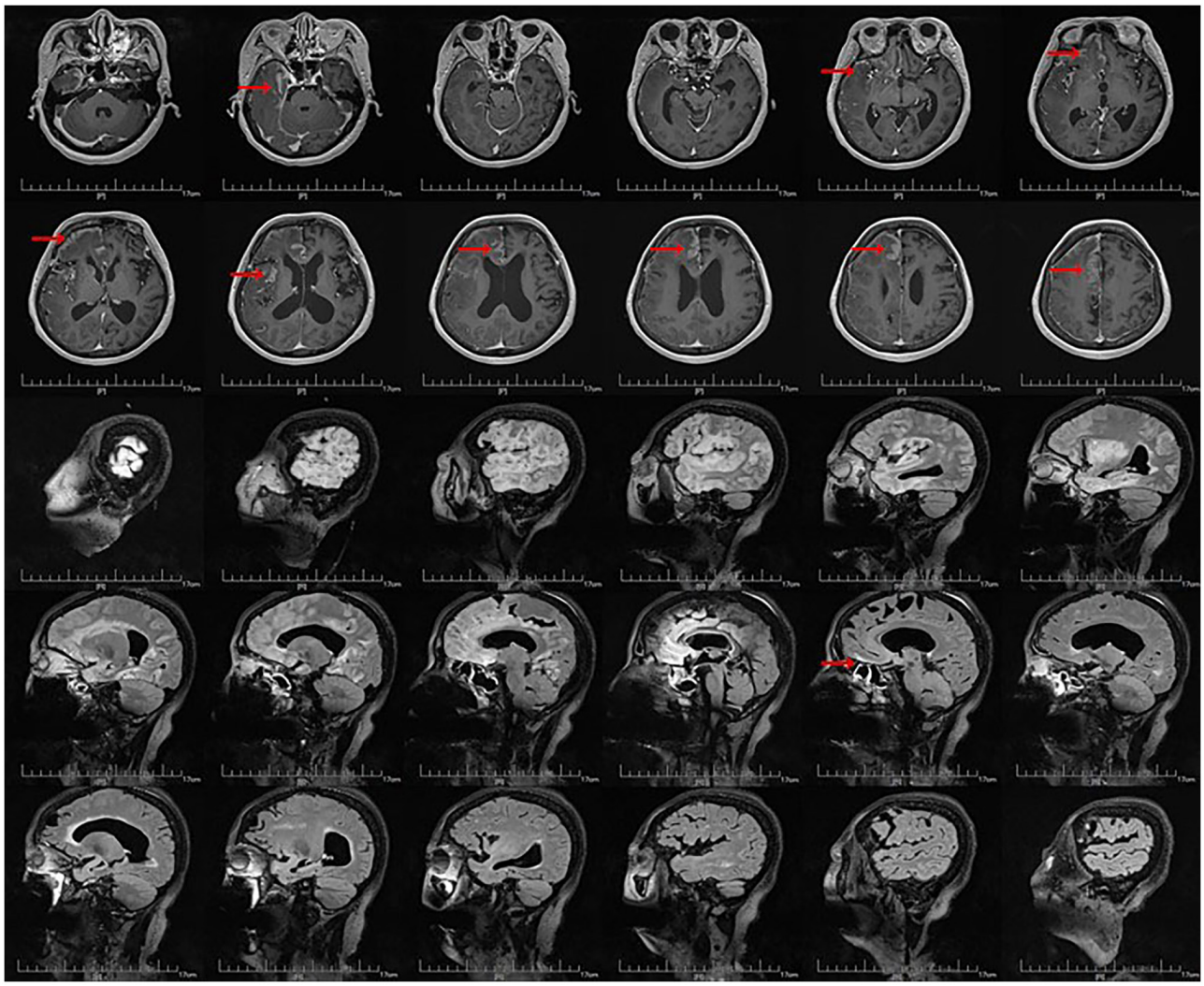

Figure 5. Brain magnetic resonance imaging performed in August 2025, at 5 days post-admission. Contrast-enhanced brain magnetic resonance imaging. Right frontal, temporal and insular lobes showed cortical and leptomeningeal enhancement (red arrow).

The patient initially received ceftriaxone sodium 2 g once daily from 1 day after admission owing to suspected CNS infection. Following confirmation of the diagnosis, the antibiotic regimen was switched to intravenous penicillin sodium ($3.2x10^6$ U every 4 h) 3 days after admission, with intramuscular dexamethasone 5 mg administered on the same day. Oral methylprednisolone (6 tablets) was also prescribed on day 4 and 5 of hospitalization. Penicillin therapy was continued for 6 days, when the patient was discharged against medical advice. On hospitalization day 4 the patient developed new-onset involuntary twitching of the chin and left limbs, prompting the addition of phenobarbital (0.1 g every 8 h) to the antiepileptic regimen. A repeat vEEG (8 days after the initial vEEG) revealed persistent PLEDs with wider spatial distribution, although the degree of background slowing had slightly improved (Fig. 6).

During hospitalization, the patient developed a secondary pulmonary infection. On hospitalization day 9, the patient experienced hemodynamic and respiratory instability with hypotension and hypoxemia, necessitating dopamine infusion for blood pressure support. Given the critical clinical status, endotracheal intubation and transfer to the neurological intensive care unit were recommended. However, the patient's family declined further intensive care and opted for discharge against medical advice. Post-discharge follow-up revealed that the patient succumbed to the disease in September 2025.

Discussion

Neurosyphilis is defined as an infection of the CNS caused by the spirochete *Treponema pallidum* (4). Following entry through mucosal surfaces or cutaneous barriers, the pathogen disseminates hematogenously, with sexual contact and vertical transmission serving as the primary modes of spread. Pathogenetically, *Treponema pallidum* has been shown to evade host immune surveillance through mechanisms that include the induction of microglial apoptosis and inhibition of microglial migration (5). Neurosyphilis may develop at any stage following initial infection. Early CNS involvement is characterized by CSF invasion, with viable organisms detectable in the CSF of ~25% of untreated individuals during early syphilis (6).

Syphilis has become a public health concern worldwide. Over the past two decades, there has been a resurgence of

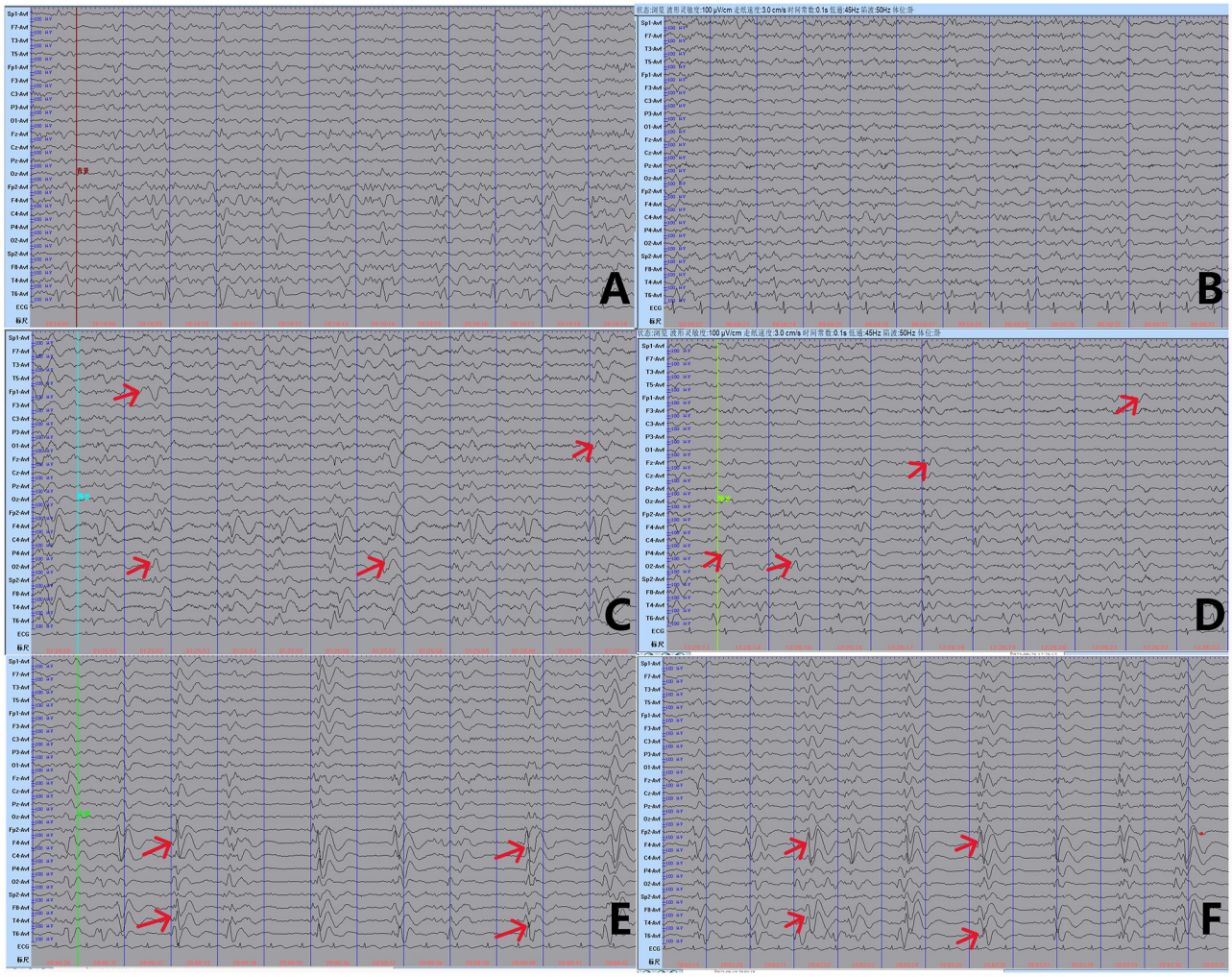

Figure 6. Video electroencephalography findings. (A) Diffuse background slowing (August 2025). (B) Diffuse background slowing (8 days later). (C) Medium- to high-amplitude polymorphic Δ/θ waves, all leads (August 2025; red arrow). (D) Medium- to high-amplitude polymorphic Δ/θ waves, all leads (8 days later; red arrow). (E) Right frontotemporal PLEDs (August 2025; red arrow). (F) Right fronto-central-temporal PLEDs with occasional ipsilateral spread (8 days later). PLEDs, periodic lateralized epileptiform discharges (red arrow).

syphilis epidemics in high-income countries (7). In China, officially reported syphilis cases in 2008 had tripled compared with 2004, and had increased by 10-fold over the preceding decade (8). The 2019 Global Burden of Disease Study reported ~50 million global prevalent cases of syphilis, representing a 60% increase since 1990 (9). Furthermore, the World Health Organization estimated ~7 million new cases in 2020, indicating that the disease remains a persistent global public health challenge (10).

Treponema pallidum can invade multiple compartments of the CNS, including the meninges, brain parenchyma and vasculature. The inability of the CNS to mount an effective, localized immune response against the spirochete results in a broad and often non-specific clinical spectrum. In the post-antibiotic era, widespread antibiotic use has substantially altered this disease's presentation. While classic manifestations such as memory impairment, optic neuropathy, personality changes and meningitis remain typical, their lack of specificity necessitates differentiation from a wide range of neurological and psychiatric disorders. Conversely, atypical neurological presentations, including cranial nerve palsies and seizures, have become increasingly common (11). Seizures in neurosyphilis can occur at multiple stages of the disease, including the meningovascular, general paresis, gummatous and early asymptomatic stages. A previous study reported that the incidence of seizures in the late stage of general paresis could be as high as 60% (12). Conversely, Sinha *et al* (13) demonstrated that seizures are more frequently observed during the meningovascular stage. The pathogenesis of seizures in neurosyphilis is multifactorial, primarily involving the following mechanisms: i) Meningeal and cerebrovascular inflammation, where meningeal inflammation from *Treponema pallidum* lowers seizure threshold via cortical irritation and epileptogenic foci, and endarteritis obliterans of small-to-medium arteries causes ischemia/infarction, triggering seizures; and ii) direct neural injury and chronic parenchymal changes, where direct parenchymal invasion with neuronal loss, gliosis and neuroinflammation also contributes to epileptogenesis (14-17).

SE associated with neurosyphilis is exceedingly rare, and its presentation as the initial manifestation is even more uncommon (14,18). In the current case, the patient presented with SE as the initial symptom. EEG monitoring during

admission revealed generalized slow waves across all leads and PLEDs. PLEDs are an EEG phenomenon characterized by high-voltage, stereotyped, periodic transient discharges localized to one cerebral hemisphere. Previous research indicates that acute stroke, brain tumors and CNS infections are the most common etiologies of PLEDs, followed by traumatic brain injury and alcohol withdrawal. They can also occur in less common conditions such as posterior reversible encephalopathy syndrome, familial hemiplegic migraine and cerebral amyloid angiopathy (19). Fever and metabolic imbalances can act as potential precipitating factors (20).

PLEDs have been identified in multiple studies as a notable feature of neurosyphilis (14,21,22). The majority of PLEDs appear within the first 4 days following seizure onset or SE initiation, and some research suggests that PLEDs can be considered a later manifestation of SE itself (23). PLEDs confined to one hemisphere with a tendency to spread to the contralateral side are associated with recent frequent seizures, as observed within the 10-day period prior to and including the day of PLED recording, or the occurrence of SE (24,25). Follow-up studies have shown that PLEDs can resolve following control of the infection with standard penicillin therapy (13,14,25).

In the present case, quantitative analysis of the initial EEG revealed α%, 8.71; β%, 10.3; θ%, 27.02; δ%, 53.96; and (θ% + δ%)/(α% + β%), 4.26. Subsequent quantitative analysis of a follow-up EEG showed α%, 10.19; β%, 14.45; θ%, 22.78; δ%, 52.56; and (θ% + δ%)/(α% + β%), 3.058. After 7 days of penicillin treatment, the repeat EEG showed improvement in slow-wave activity compared with the previous recording; however, PLEDs were still present.

The clinical manifestations of neurosyphilis are complex and diverse, resulting in non-specific neuroimaging findings. MRI has been established as a crucial tool in aiding the diagnosis of neurosyphilis, particularly when CSF findings are atypical, as it can provide important supplementary information. The imaging presentation of neurosyphilis exhibits dynamic changes across different disease stages, commonly including cerebral infarction, white matter lesions, meningitis, gummas and cerebral atrophy (13,26). A previous study by Sinha *et al* (13) indicated that the rate of abnormal brain MRI findings in patients with neurosyphilis exhibiting seizures is as high as 86%, with diffuse cerebral atrophy, medial temporal lobe abnormalities, and meningeal enhancement being particularly frequent. Several cases reported in the literature describe neurosyphilis with imaging features involving bilateral medial temporal lobes, resembling limbic encephalitis (27,28). In the present case, initial DWI showed right thalamic and fronto-temporo-parietal hyperintensities; repeat DWI at 3 days revealed reduced thalamic signal extent and intensity. Previous literature reports indicate that imaging findings in neurosyphilis can show notable improvement following appropriate anti-syphilitic treatment (14,29). However, the current case was initially diagnosed as acute cerebral infarction; consequently, the initial management consisted only of thrombolysis and medications to improve circulation, without anti-syphilitic treatment.

The aforementioned imaging changes may be attributed to two potential explanations: i) The initial thalamic DWI abnormality could be related to the seizure activity itself: During seizures, increased metabolic demand with relative hypoperfusion can cause cytotoxic edema (DWI hyperintensity). After sedation and antiepileptic therapy, which reduce cerebral metabolic rate, the thalamic DWI signal partially resolved. It has been reported that seizure-related peri-ictal DWI abnormalities often resolve completely after the episode is controlled, typically involving structures such as gray matter, subcortical white matter or the hippocampus (30-32). In a prospective study of 206 patients with SE, Bosque Varela *et al* (33) found that peri-ictal MRI abnormalities were reversible within 1 week in 59% of cases, with the frontal lobes, thalamus and hippocampus being the most commonly affected structures. Previous reports have shown that seizure-related MRI abnormalities can resolve within days-to-weeks after a single seizure (34,35).; and ii) the short-term dynamic changes observed in thalamic DWI signal abnormalities may also be attributed to the natural disease progression of neurosyphilis itself. It has been reported that radiological alterations can gradually reverse after several weeks-to-months of appropriate antisyphilitic therapy. A case of neurosyphilis presenting with transient global amnesia-like attacks had bilateral limbic system involvement (basal ganglia and thalamus) on MRI, with marked reduction of the abnormalities 1 month after treatment (36). A case of cerebral syphilitic gumma completely resolved on MRI after 14 days of penicillin, supporting the reversibility of neurosyphilitic lesions (37). However, in the current case, the diagnosis had not been confirmed prior to the repeat MRI, and the patient had not received standard anti-syphilitic treatment. This finding supports the reversibility of seizure-related cytotoxic edema rather than a therapeutic effect of anti-syphilitic therapy.

The diagnosis of neurosyphilis relies on a combination of clinical presentation, serological testing and CSF analysis. Serological evaluation typically integrates specific *Treponema pallidum* assays (such as TPPA or TPHA) with non-treponemal tests (such as RPR or VDRL). The former exhibit high specificity, but remain positive lifelong, which limits their utility for monitoring therapeutic response. By contrast, non-treponemal tests allow quantitative assessment of treatment efficacy through antibody titers, which are generally elevated at diagnosis and decline following therapy. Serological cure is conventionally defined as a 4-fold decrease in titer within 3-6 months after treatment completion. CSF examination is crucial for diagnosis, with classic findings including levels of protein >0.45 g/l and WBC count >5 cells/μl (7). A positive CSF non-treponemal test (CSF-VDRL/RPR) is diagnostic for neurosyphilis; however, its sensitivity is limited (CSF-VDRL, 67-72%; and CSF-RPR, 51-82%), meaning that a negative result does not exclude the diagnosis (7,38,39). CSF treponemal tests exhibit high sensitivity but lower specificity (40). According to diagnostic criteria, the presence of neurological symptoms with a positive CSF-VDRL confirms the diagnosis. If CSF-VDRL is negative but neurological symptoms are present alongside positive serology and abnormal CSF routine parameters, further evaluation with tests such as CSF-FTA-ABS is warranted (41).

mNGS of CSF, an efficient and broad-spectrum pathogen detection technology, provides important auxiliary value in diagnosing neurosyphilis. This technique enables unbiased detection of *Treponema pallidum* DNA in CSF, proving particularly useful for differentiating cases with atypical presentations or negative conventional tests. Furthermore, it can provide information

on pathogen subtype and drug resistance, informing precise treatment and efficacy evaluation (42,43). CSF mNGS for neurosyphilis has suboptimal sensitivity; negative results cannot rule out the disease, mainly due to low *Treponema pallidum* burden and its biological properties. Specificity is relatively high, but detected DNA cannot distinguish active from prior infection; thus, serological correlation is required. Furthermore, the lack of standardized protocols across the workflow and high costs preclude its use as a first-line test. Therefore, mNGS should serve as an adjunct to conventional serological and CSF examinations, not as a standalone diagnostic tool (44).

The patient in the present case report was a middle-aged woman who presented with SE as the initial manifestation. Initial brain DWI revealed right thalamic and fronto-temporo-parietal hyperintensities. A repeat DWI performed 3 days later showed marked resolution of the thalamic signal. Serological tests for syphilis were positive, vEEG showed PLEDs and CSF mNGS was positive for *Treponema pallidum*. Although the patient was promptly treated with penicillin G for syphilis, the patient was discharged automatically due to complications, including pulmonary infection and unstable blood pressure. The patient subsequently succumbed to the disease in September 2025, which precluded any post-treatment follow-up. Review of the medical record indicated that a follow-up vEEG after initiating penicillin G showed a reduction in slow waves compared with previous recordings, indirectly suggesting a positive response to the anti-syphilitic treatment. The family reported that the patient had experienced intermittent headaches and dizziness over the past year, which could potentially be attributed to transient meningitis caused by the initial invasion of the CNS by *Treponema pallidum*. The cognitive decline observed over the past 6 months, characterized by poor memory, initially led to a diagnosis of cerebral atrophy. Integrating the clinical picture and imaging findings, the neurosyphilis subtype was considered to be parenchymatous neurosyphilis (general paresis).

Several limitations of the current study should be acknowledged. First, this is a single case report, and caution is needed when generalizing the findings to the broader neurosyphilis population. Second, CSF-VDRL was not routinely performed in Hebei General Hospital because the reagent was unavailable during the study period. Third, the patient passed away shortly after discharge, which precluded long-term follow-up to assess treatment response and functional outcomes.

Despite the aforementioned limitations, the present case offers several novel insights. First, SE as the initial manifestation of neurosyphilis is rarely documented, and concurrent acute-phase PLEDs and serial DWI changes have been even less frequently reported. Second, the rapid resolution of thalamic DWI hyperintensity within 3 days before anti-syphilitic treatment strongly supports seizure-related cytotoxic edema as the predominant mechanism, rather than syphilitic vasculitis. Third, this case further corroborates the adjunctive diagnostic value of CSF mNGS in atypical neurosyphilis, particularly when CSF-VDRL is unavailable.

In summary, the major contributors to the poor outcome were delayed diagnosis (months after symptom onset), refractory SE, extensive brain parenchymal damage on MRI, pulmonary infection, inadequate anti-syphilitic therapy and refusal of intensive care. Earlier screening at the outpatient stage and prompt treatment at the time of cognitive decline would likely have yielded a favorable prognosis. In clinical practice, a high index of suspicion for syphilis is warranted when young and middle-aged adults present with new-onset seizures, stroke-like episodes, sudden cognitive decline, unexplained psychiatric symptoms or meningitis-like symptoms such as headache. A thorough history, detailed physical examination, and integration of neuroimaging, syphilis serology and advanced tests such as CSF mNGS are essential for early diagnosis, enabling the initiation of standardized treatment and long-term follow-up.

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Availability of data and materials

The raw sequencing data generated in the present study have been deposited in the NCBI Sequence Read Archive (SRA) under BioProject accession number PRJNA1512120 and SRA accession number SRR40155268. These data are publicly available at https://www.ncbi.nlm.nih.gov/sra/SRR40155268.

Authors' contributions

HC was responsible for drafting the manuscript. SD handled revisions and polishing. YZ checked and verified the EEG data. RD provided feedback on the discussion section and reviewed the accuracy of terminology throughout the entire text. YZ and RD reviewed and verified all the raw data. RD and LL were responsible for collecting the patient's cerebrospinal fluid genetic testing data and assisted in checking and verifying the original data, including images. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study has been approved by the Ethics Committee of Hebei General Hospital (approval no. 2026-LW-180).

Patient consent for publication

The patient was comatose upon admission and remained unconscious until her death. Consequently, informed consent was obtained from the patient's son, who signed the written informed consent form authorizing the publication of this study, provided that the patient's identity and personal information would be fully anonymized and protected.

Competing interests

The authors declare that they have no competing interests.

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