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Clinical Insights into Neurosyphilis Patients with Leptomeningeal Enhancement of Spinal Cord

Wenjing Zhang[1,2,*], Xiaoyang Ma[1,2,*], Kaiyu Qin[1,2], Cheng Kou[1,2], Canglin Song[1,2], Dongmei Xu[1,2]

[1]National Center for Infectious Disease, Beijing Ditan Hospital Capital Medical University, Beijing, People's Republic of China; [2]Department of Neurology, Beijing Ditan Hospital Capital Medical University, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Dongmei Xu, Department of Neurology, Beijing Ditan Hospital Capital Medical University, No. 8. Jingshun East Street, Chaoyang District, Beijing, 100015, People's Republic of China, Email xdmlb@163.com

Background and Objectives: This study aims to report the clinical, biological, and imaging features of cross-sectional study of neurosyphilis patients with leptomeningeal enhancement of spinal cord. Here, 51 neurosyphilis patients with leptomeningeal enhancement of spinal cord positivity are described, offering a promise in terms of early diagnosis, thereby enabling timely detection and treatment.

Methods: We retrospectively included all neurosyphilis patients enrolled in this study from December 2019 to January 2024. We identified 51 included patients with leptomeningeal enhancement of spinal cord positivity. Their neuroimaging, socio-demographical, clinical status, presentations, and laboratory manifestations were reported retrospectively.

Results: Magnetic resonance imaging showed lumbar or conus medullaris and cauda equina radial enhancement in 72.7%, leptomeningeal enhancement of cervical spine in 65.9%, and thoracic involvement in 55.3%. Twenty of 51 neurosyphilis patients completed the follow-up. Among the 20 patients, the lesioned region in half of patients was decreased or disappeared after therapy. The predominant phenotype was tabes dorsalis. Median age at onset was 51 years, and 72.5% were male. Urinary incontinence was found in 33.3% of patients, and memory deterioration in 39.2%. The most frequent physical sign was Argyll Robertson pupil (45.1%). The levels of white blood cells (25/28, 89.3%) and protein concentration (23/28, 82.9%) of cerebrospinal fluid were reduced in more patients after therapy.

Conclusion: In this study, we first concurrently investigated the clinical course and the biological and imaging features of leptomeningeal enhancement of spinal cord. Leptomeningeal enhancement of spinal cord is common with neurosyphilis. Our findings can be useful for raising clinical awareness to select patients with symptoms of myelopathy in whom MRI images should be investigated.

Keywords: neurosyphilis, leptomeningeal enhancement of spinal cord, cerebrospinal fluid, spine MRI

Introduction

Syphilis is a bacterial infection typically spread through sexual contact and caused by *Treponema pallidum*.[1] Syphilis has been re-emerging in recent years worldwide.[2] In China, rates of syphilis have increased from 31 cases per 100,000 population in 2014 to 38 cases per 100,000 population in 2019, with an average annual growth of 4.41%.[3] *Treponema pallidum* invades the nervous system within days after initial infection. The neurosyphilis clinical course could be categorized into early (1 to 2 years after primary infection) or late.[4] Typically, early neurosyphilis is asymptomatic, evidenced only by a cellular reaction in the cerebrospinal fluid (CSF) or manifested as symptomatic meningitis with headache and cranial-nerve palsies, and occurring within weeks or a few years after the infection.[5] Meningovascular neurosyphilis is displayed as stroke, occurring 1 to 10 years after the primary infection, and is usually interposed between early and late neurosyphilis. Later forms of neurosyphilis, which develop decades after primary infection, can present as tabes dorsalis, general paresis (GP), and syphilitic spinal cord gumma.[6]

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However, oligosymptomatic or atypical forms of neurosyphilis have become more frequent.[7] Leptomeningeal enhancement of spinal cord (LESC) is a rare manifestation of neurosyphilis. Based on our previous experience, we believe that the prevalence of LESC in neurosyphilis might have been underestimated, as it seemed more frequent at diagnosis using contrast enhanced magnetic resonance imaging (MRI) of the spine. Therefore, we report 51 cases of LESC in neurosyphilis patients, to describe their clinical, biological, and imaging features, and to assess the clinical course.

Materials and Methods

Participants

We conducted a retrospective review of patient records at Department of Neurology, Beijing Ditan Hospital from December 2019 to January 2024 for our study. This study was approved by the Ethics Review Board of Beijing Ditan Hospital, Capital Medical University in Beijing China (approval no.: DTQH201607). Written informed consent was obtained from the recruited patients or their family members.

Diagnostic Criteria

The diagnostic criteria for neurosyphilis complied with the guidelines of the United State Center for Disease Control (CDC)[8] and the European Guidelines.[9] The criteria included positive serologies and at any stage conforming to 1 of 2 conditions in the CSF: (1) positive toluidine red unheated serum test (TRUST) or rapid plasma regain (RPR) titer; (2) positive *T. pallidum* particle agglutination (TPPA) or fluorescent treponemal antibody absorption (FTA-ABS), with white blood cells (WBC) >5/μL or protein concentration above 45 mg/dL with other known causes.[10] Patients with a prior history of any disease that could impair the immune system, including immunosuppressive therapy and human immunodeficiency virus (HIV) infection, were excluded.

Statistical Analyses

Statistical analyses were carried out by SPSS Statistics 25.0 (IBM Corporation, New York, USA). Statistical significance was defined as a two-sided $P < 0.05$. Continuous variables were presented as median (minimum–maximum), and categorical variables as frequencies and percentages. The levels of WBC and protein in CSF were compared between baseline group and after therapy group, and compared by two-tailed *t* test.

Results

Spinal Cord MRI Features of Neurosyphilis Patients with LESC

In our study, 131 patients presented symptoms of myelopathy, and MRI examinations were performed after the confirmation of neurosyphilis. A total of 51 LESC-positive syphilis patients were enrolled in our study. The disease duration was 33 (2–168) months. The flowchart for screening neurosyphilis patients with LESC is shown in Figure 1. Among 51 patients, a total of 41 included patients underwent the examination of cervical spine enhanced MRI scan (Supplementary Table 1). Of 27 patients (65.9%, 27/41), sagittal T1-weighted images of the spinal cord showed point-like or linear enhancement in leptomeningeal surface (Figure 2). A total of 38 enrolled patients completed the thoracic spine enhanced MRI examination (Supplementary Table 1). In 21 patients, sagittal T1-weighted image of the spinal cord showed continuous point or linear high signal intensity of LESC (55.3%, 21/38) (Figure 3). A total of 44 patients finished the lumbar spine enhanced MRI test (Supplementary Table 1), and 32 patients were positive for linear reinforcement (67.8%, 32/44) in lumbar region or conus medullaris and cauda equina (Figure 4).

Proportion of Different Clinical Phases of Neurosyphilis Patients with LESC

Among our patients, 6 were early neurosyphilis patients, including 1 (of 51; 2.0%) case of asymptomatic neurosyphilis, and 5 (of 51; 9.8%) cases were syphilitic meningitis. A total of 45 patients were late neurosyphilis patients. Meningovascular forms accounted for 2.0%. A total of 25 of 51 (49.0%) cases were tabes dorsalis, 23 of 51 (45.2%) cases were GP, and 2 of 51 (4.0%) cases were syphilitic spinal cord gumma (Figure 5). Three patients presented one or

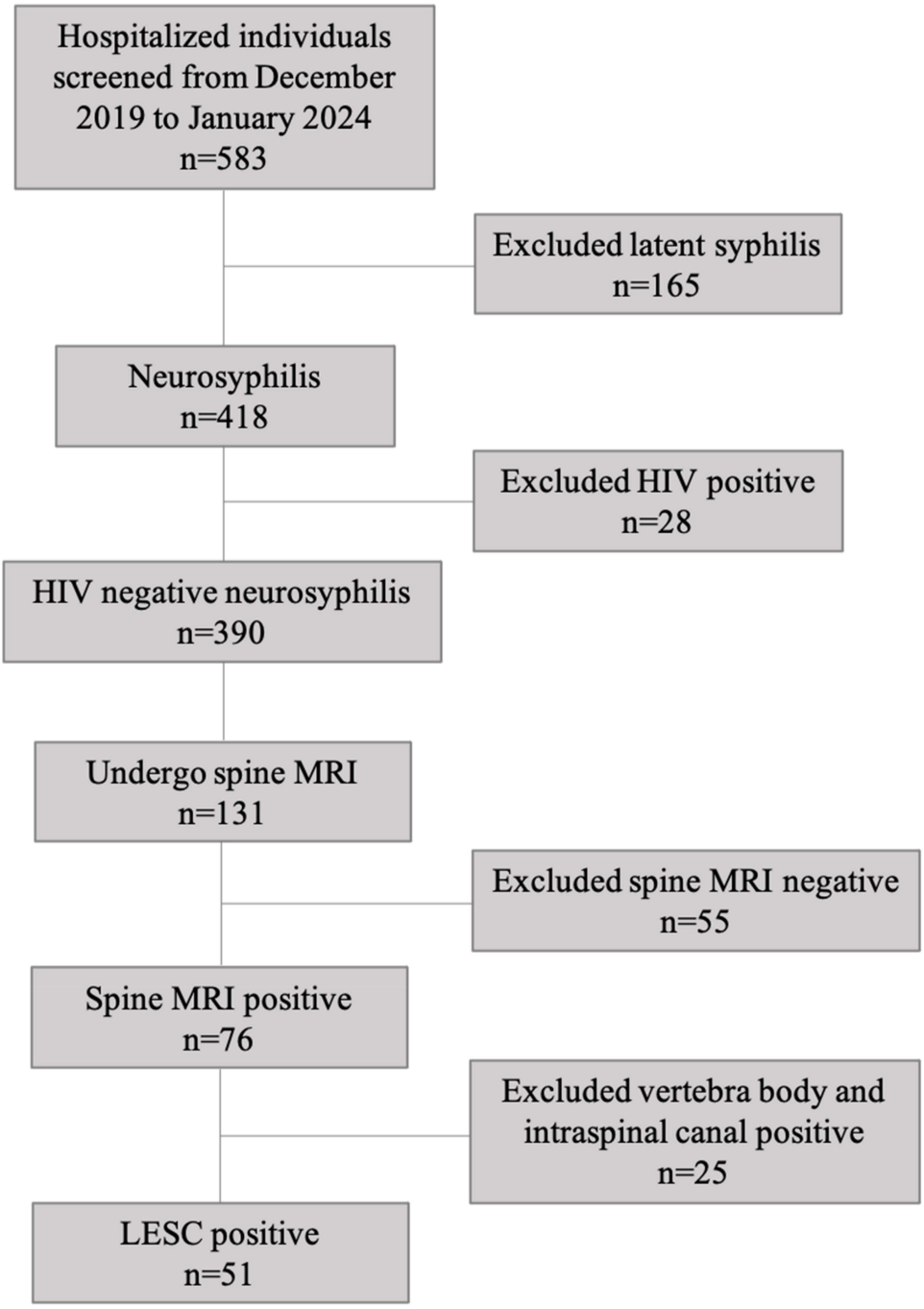

Figure 1 Flowchart for screening patients with LESC.
Abbreviations: HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; LESC, leptomeningeal enhancement of spinal cord.

overlapped with other neurosyphilis stage: One of 51 patients presented tabes dorsalis complicated with syphilitic spinal cord gumma. One patient presented meningovascular neurosyphilis accompanied with tabes dorsalis and GP. One patient displayed tabes dorsalis combined with GP (Table 1).

Detailed Clinical Forms of Neurosyphilis Patients with LESC

The distribution of patients by sex, age, age of onset, and disease duration is described (Table 2). Of the 51 neurosyphilis patients with LESC, 37 of 51 (72.5%) patients were male. Patients' age ranged from 21 to 74 years old, and the median

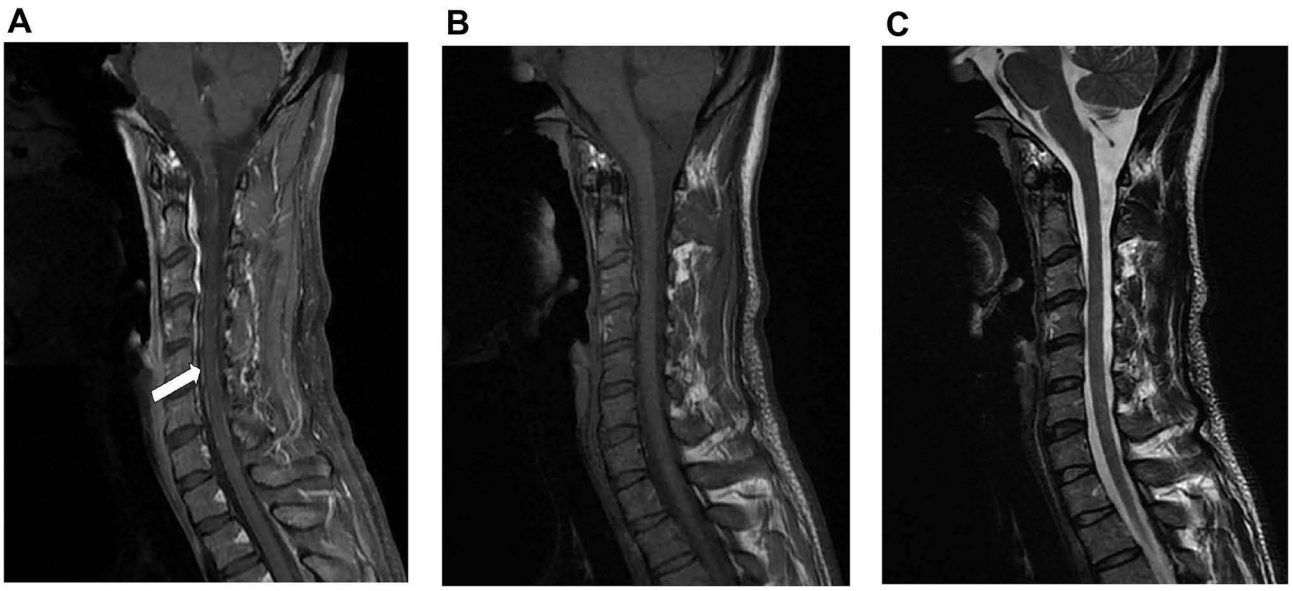

Figure 2 Cervical spine MRI scan of neurosyphilis patients with LESC showed linear enhancement of leptomeningeal surface lesions in T1 hyperintensity. (**A**) Sagittal T1-postgadolinium images reveal leptomeningeal enhancement (arrow). (**B**) T1-weighted sagittal image. (**C**) T2-weighted sagittal image.

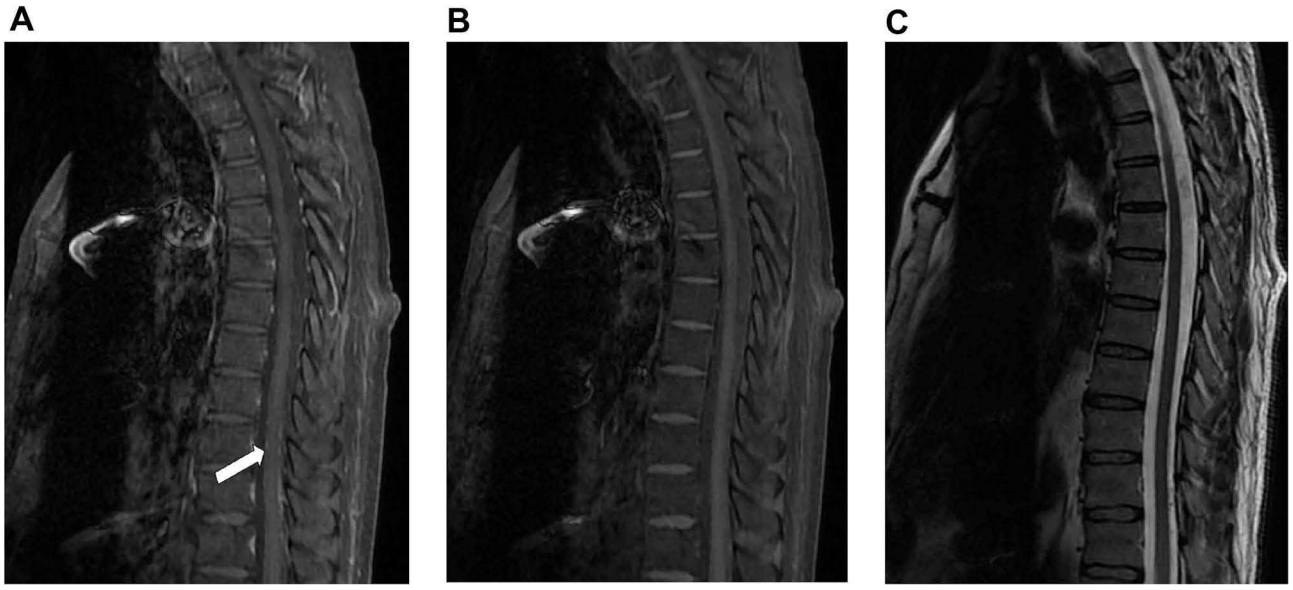

Figure 3 Thoracic spine MRI scan of neurosyphilis patients with LESC showed point enhancement of leptomeningeal surface lesions in T1 hyperintensity. (**A**) Sagittal T1-postgadolinium images reveal leptomeningeal enhancement (arrow). (**B**) T1-weighted sagittal image. (**C**) T2-weighted sagittal image.

symptom onset age was 51 years old. Median age of onset was 47 years old, and disease duration was 33 months. Among them, the most predominant clinical syndrome of myelopathy was urinary incontinence (17/51, 33.3%). Memory deterioration was reported in 20 cases (20/51, 39.2%). Other disease manifestations included loss of balance (16/51, 31.4%), numbness (13/51, 25.5%), sense of foot cotton (11/51, 21.6%), and prickling pain (11/51, 21.6%). Less common (<3%) clinical manifestations included dizziness, visual field defect, and deafness. The most common physical sign among the 51 patients was Argyll Robertson pupil (23/51, 45.1%). Other signs included hyporeflexia (22/51, 43.1%), impaired deep sensation (21/51, 41.2%), and cognitive decline (19/51, 37.3%). Less common (<5%) signs involved nystagmus and meningismus.

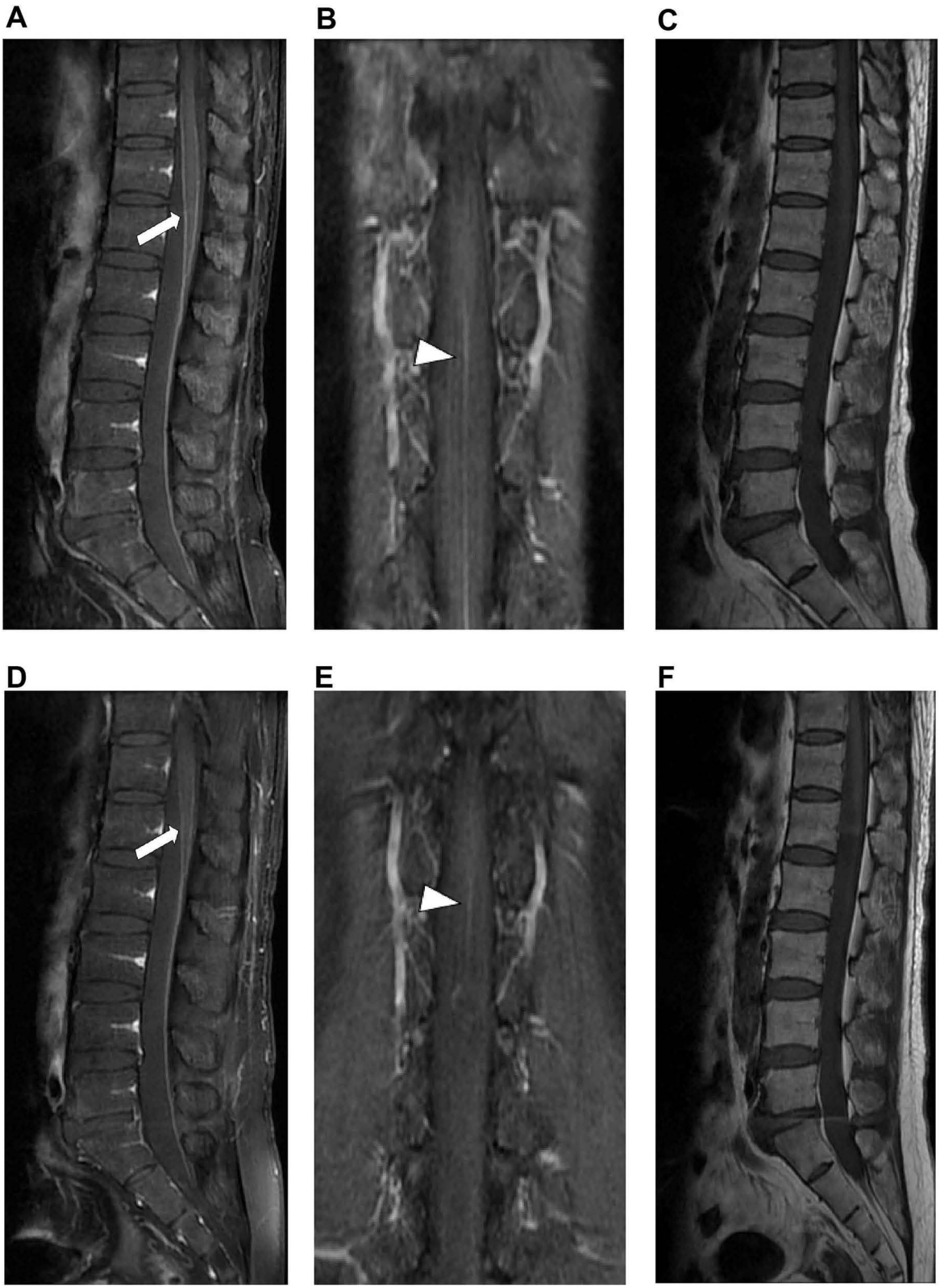

Figure 4 Lumbar spine MRI scan of neurosyphilis patients with LESC showed linear reinforcement in the lumbar region, conus medullaris, and cauda equina. (**A, D**) Sagittal T1-postgadolinium images reveal leptomeningeal enhancement (arrow). (**B, E**) Coronary T1-postgadolinium images reveal leptomeningeal enhancement (arrowhead). (**C, F**) T1-weighted sagittal image. (**D**–**F**) One year later, linear enhancement of the lumbar region had been decreased (arrow and arrowhead).

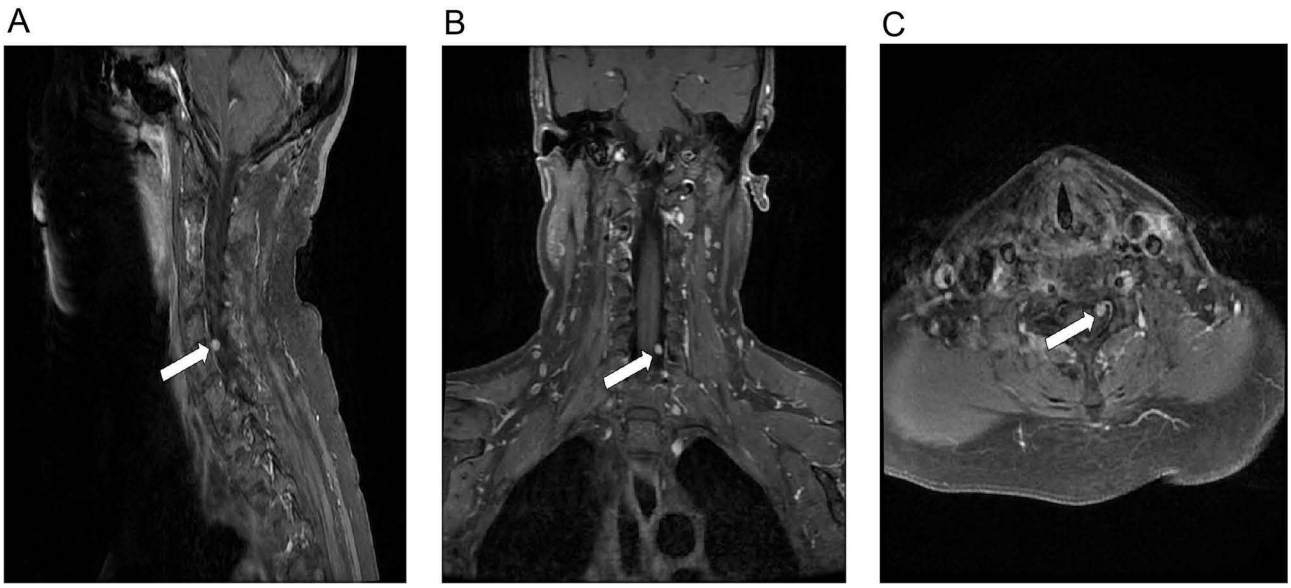

Figure 5 Cervical spine MRI scan of syphilitic spinal cord gumma in T1 hyperintensity. (**A**) Sagittal T1-postgadolinium images reveal nodular leptomeningeal enhancement (arrow). (**B**) Coronary T1-postgadolinium (arrow). (**C**) Axial T1-postgadolinium image (arrow).

CSF Findings of Neurosyphilis Patients with LESC

All 51 patients enrolled had positive serum and CSF TPPA. Analysis of the serum and CSF at baseline has been summarized in Supplementary Table 2. Twenty-six serum samples (54.2%, 26/48) ≤1:16 and 22 serum samples (45.8%, 22/48) ≥1:32 are described as below. Nineteen CSF samples (41.3%, 19/46) were TRUST-negative, and 27 CSF samples (58.7%, 27/46) were TRUST-reactive, with titers ≤1:16. Thirty-four patients (79.1%, 34/43) had CSF pleocytosis, and 37 patients (80.4%, 37/46) had elevated CSF protein content. Both CSF pleocytosis and elevated CSF protein levels were found in 27 patients tested.

Repeat analysis after therapy in the serum and CSF is shown in Supplementary Table 2. Thirty-two serum samples (84.2%, 32/38) ≤1:16 and 6 serum samples (15.8%, 6/38) ≥1:32 were recorded as below. Nine CSF samples (25.7%, 9/35) were TRUST-negative, and 26 CSF samples (74.3%, 26/35) were TRUST-reactive, with titers ≤1:16. CSF analysis revealed pleocytosis in 14 patients (40.0%, 14/35), and 13 patients (37.1%, 13/35) had elevated CSF protein level. Nine patients had both CSF pleocytosis and increased CSF protein level.

Table 1 Proportion of Clinical Phases of Neurosyphilis Patients with LESC

Clinical Phases	Patients (%)
Early	
Asymptomatic early neurosyphilis	1 (2.0%)
Syphilitic meningitis	5 (9.8%)
Early or late	
Meningovascular neurosyphilis	1 (2.0%)
Late	
Tabes dorsalis	25 (49.0%)
GP	23 (45.1%)
Syphilitic spinal cord gumma	2 (3.9%)
LESC in neurosyphilis	51 (100.0%)

Note: Data were presented as number (percentage).
Abbreviations: LESC, leptomeningeal enhancement of spinal cord; GP, general paresis.

Table 2 Detailed Clinical Presentation and Signs of 51 Cases of Neurosyphilis with LESC

Demographic Information	Patients (%)	Median (Range)
Male [*n* (%)]	37 (72.5%)	
Female [*n* (%)]	14 (27.5%)	
Age [years, median (minimum–maximum)]		51 (21–74)
Age of onset [years, median (minimum–maximum)]		47 (26–72)
Disease duration [months, median (minimum–maximum)]		33 (2–168)
Symptoms		
Symptoms of myelopathy		
Lighting pain	10 (19.6%)	
Prickling pain	11 (21.6%)	
Girdle sensation	3 (5.9%)	
Numbness	13 (25.5%)	
Lumbago	2 (3.9%)	
Urinary incontinence	17 (33.3%)	
Sense of foot cotton	11 (21.6%)	
Loss of balance	16 (31.4%)	
Non symptoms of myelopathy		
Psychological and behavior disorders	12 (23.5%)	
Memory deterioration	20 (39.2%)	
Seizure	5 (9.8%)	
Weakness of limb	5 (9.8%)	
Bradykinesia	5 (9.8%)	
Trembling hands	3 (5.9%)	
Dizziness	1 (2.0%)	
Fever	2 (3.9%)	
Headache	4 (7.8%)	
Sleep disturbances	8 (15.7%)	
Slurred speech	5 (9.8%)	
Hypopsia	10 (19.6%)	
Double vision	5 (9.8%)	
Visual field defect	1 (2.0%)	
Deafness	1 (2.0%)	
Tinnitus	2 (3.9%)	
Signs		
Cognitive decline	19 (37.3%)	
Aphasia	3 (5.9%)	
Argyll Robertson pupil	23 (45.1%)	
Nystagmus	1 (2.0%)	
Weakness of limb	5 (9.8%)	
Rigidity	4 (7.8%)	
Tremor	6 (11.8%)	
Candy sign	5 (9.8%)	
Hyporeflexia	22 (43.1%)	
Ataxia	10 (19.6%)	
Sensory level	11 (21.6%)	
Impaired superficial sensation	8 (15.7%)	
Impaired deep sensation	21 (41.2%)	
Positive Babinski sign	5 (9.8%)	
Positive Romberg sign	14 (27.5%)	
Meningismus	1 (2.0%)	

Note: Data were presented as number (percentage).
Abbreviation: LESC, leptomeningeal enhancement of spinal cord.

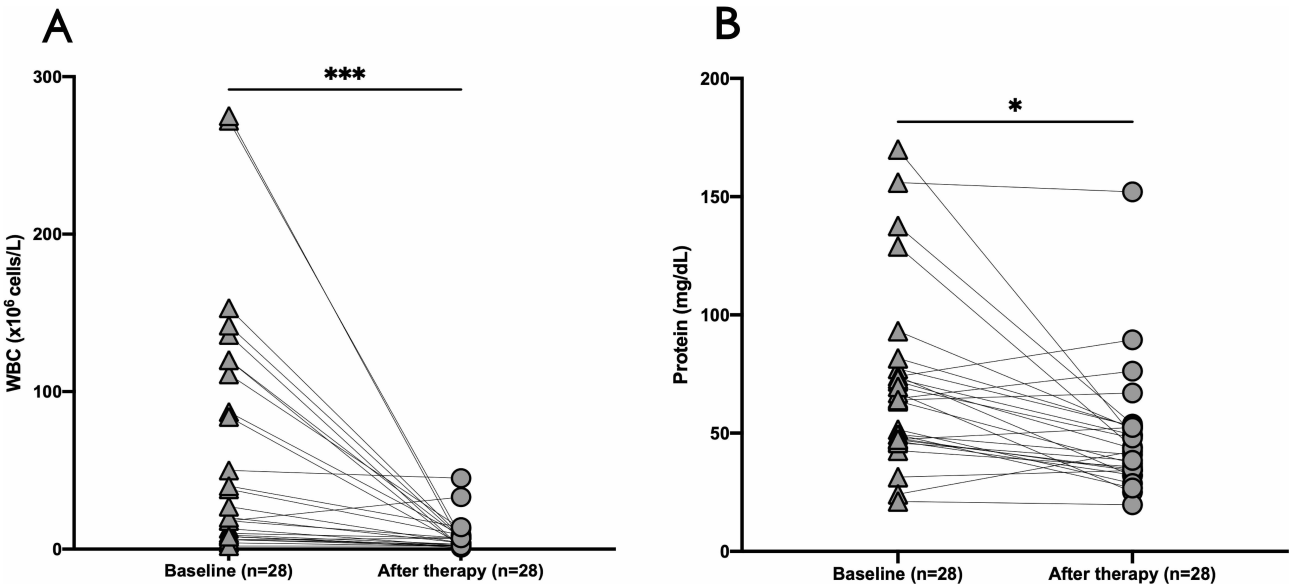

Figure 6 The levels of WBC and protein in the CSF at baseline versus after therapy in neurosyphilis with LESC. The WBC level in the CSF of 28 patients was measured at baseline and after therapy (**A**). The protein level in the CSF of 28 patients was quantified at baseline and after therapy (**B**). **P*<0.05, ****P*<0.001 for baseline group versus after therapy group. Student's *t*-test was used to compare baseline group versus after therapy group (*n*=28).
Abbreviations: WBC, white blood cell; CSF, cerebrospinal fluid; LESC, leptomeningeal enhancement of spinal cord.

The concentrations of WBC and protein in the CSF were quantified in 28 patients both at baseline and after therapy (Figure 6). The level of WBC was decreased in more patients with LESC (25/28, 89.3%) after therapy. The CSF protein concentration was reduced in 23 patients with LESC (23/28, 82.9%) compared with baseline. Compared with the baseline group, the after therapy group had significantly decreased levels of WBC ($P < 0.001$) and CSF protein ($P < 0.05$).

Treatment Response and Outcome

All patients underwent intravenous injections of penicillin G at a dosage of 24,000,000 U daily, for 10–14 days. Next, intramuscular injections of benzathine benzylpenicillin G were managed at a dosage of 2,400,000 U weekly for three times. Median follow-up duration for the 20 patients was 6.5 months (range 4–23). Ten patients were in remission after therapy at last follow-up (Figure 5), 4 had remained unchanged, and 6 had progressive disease despite treatment.

Discussion

MRI Findings of Neurosyphilis with LESC

MRI findings in LESC have been infrequently reported. In these patients, spinal cord enhanced MRI scan might be used to assess the areas of spinal cord involvement, and seriousness of neurological impairments in patients with LESC. In this study, 51 neurosyphilis patients presented symptoms of myelopathy, and were found LESC-positive after MRI examinations were performed. This group of patients showed a median duration of the disease of 33 months. Spinal cord MRI mainly showed abnormal spotted and linear enhancement in leptomeningeal after postcontrast T1-weighted images, involving a range of spinal cord areas such as cervical, thoracic, lumbar, and sacral, and cauda equina (Figures 2–4). The structure of blood–spinal cord barrier (BCB) lay between the intraspinal blood vessels and CNS parenchyma, and it was sealed tightly by endothelial cells of the blood vessels.[11] Some researchers reported that impaired BCB function had also been proposed to relate to psychiatric disorders.[12] The mechanism of LESC was still unclear. Accordingly, we speculated that the *Treponema pallidum* might invade the nervous system, prompting the immune responses to the CNS parenchyma, and further destroying the BCB.

In our study, lumbar spine enhanced MRI test of 32 patients (72.7%, 32/44) showed a higher positive rate than that of cervical and thoracic spine enhanced MRI examination (Figure 4). Some studies reported that the dorsal surface of the posterior longitudinal ligament of lumbar spine was covered by a thin dorsal outer layer of the anterior and lateral

peridural membrane and with a thin dorsal layer.[13] We speculated that it was relatively easy to be invaded compared with cervical and thoracic spine.

Among 51 patients, 20 cases completed follow-up of between 4 months and 2 years. MRI revealed that enhancement of spinal cord in the lesioned region was decreased or disappeared in 10 of 20 (10/20, 50%) cases after therapy (Figure 4). Our patients received a recommended treatment option for neurosyphilis through the CDC treatment guidelines.[14] We found that some patients were more likely to have treatment failure compared with others. In our study, 4 of 20 (4/20, 20%) had remained unchanged, and 6 (6/20, 30%) had progressive disease despite treatment. However, some studies reported that the doses did not attain effective treponemicidal levels of penicillin in CSF.[15] Future studies in time and dosage of penicillin for patients with LESC should offer additional treatment appropriate to cure it.

However, the lack of characteristic clinical and imaging findings leads to difficulty in distinguishing LESC from other conditions. In the future, biopsy for diagnosis can be considered to test this hypothesis. The spinal cord parenchyma and the central canal was formed by astroglia, the ependymal cells,[11] and the expression of glial fibrillary acidic protein (GFAP) was rich at the edges of the piamater and spinal meninges. Overall, the role of LESC may involve astroglia, and future studies in immunohistopathology of GFAP should provide new insights into disease mechanisms.

Frequency of LESC in Neurosyphilis Patients

Inadequately treated and untreated neurosyphilis patients could develop neurological infections in approximately 25–40% of cases.[8,16] In symptomatic neurosyphilis, LESC has become a rare manifestation. Our study identified 51 patients with LESC represented by clinical, biological, and radiologic data, which was poorly reported until now. Tabes dorsalis, a late neurological complication of neurosyphilis,[17] was defined as a degradation of the nerves in the dorsal columns of the spinal cord,[18] occurring in 25 of our patients (25/51, 49.0%) (Table 1). Tabes dorsalis occurred 15–30 years after the primary infection, and patients presented with ataxic gait, urinary incontinence, loss of position sense, and pain and thermal sensation.[17] GP was present in 23 of our patients (23/51, 45.1%). GP accounted for 25.6%–38.9% of neurosyphilis,[19,20] and was usually accompanied with tabes dorsalis. One asymptomatic participant was described in our cohort. Patients with asymptomatic neurosyphilis and CSF abnormalities had a rate of 30%–70% risk of future neurological features compared with 5% if CSF was normal.[21] However, there were no direct evidences regarding the various stages, and the clinical periods of neurosyphilis could overlap. Our finding emphasized the importance of early diagnosis and treatment.[22]

Clinical Course of LESC in Neurosyphilis Patients

The clinical significance of LESC has been barely reported. Our result showed that 37 (37/51, 72.5%) patients were male, in agreement with male predominance in neurosyphilis.[23,24] The median age of onset was 51 years old in our project, older than the 45 years old reported in previous studies in neurosyphilis.[25] The differences of the results might be because the clinical phases of LESC patients recruited in this study were late stage with tabes dorsalis (49.0%) and GP (45.1%). Among the logical symptoms associated with LESC, urinary incontinence (17/51, 33.3%) was probably the most likely to be related to LESC (Table 2). Other clinical syndromes of myelopathy include loss of balance, numbness, prickling pain, sense of foot cotton, and lighting pain. We speculated that LESC was also a rare cause of myelopathic syndromes in general, but different from tabes dorsalis. Because of the non-specific syndromes, spine contrast-enhanced magnetic resonance scan for neurosyphilis was required in all patients with unclear myelopathy. Apart from urinary incontinence, we found other clinical presentation, memory deterioration, which was not described in the previous studies. A relatively lower incidence of dizziness, visual field defect, and deafness was also recorded in our study as shown in Table 2.

Neurological examination findings were valuable for assessing neurological involvements. Argyll Robertson's pupil, which fails to react to the influence of light,[26] but promptly constricts when concentrating on a near object, was originally associated with tabes dorsalis and was also seen in GP.[18] Previous studies found that the incidence of Argyll Robertson's pupil was 20%–31%.[24] In this study, 23 patients (23/51, 45.1%) exhibited this sign, higher than in previous studies. We speculated that participants enrolled in this study were mostly tabes dorsalis (49.0%) and GP (45.1%). Twenty-two (22/51, 43.1%) patients had hyporeflexia, which accounted for the most common physical signs among the 51 patients, except for Argyll Robertson's pupil. Reflexes prompted pathology along a specific nerve course to a part of the spinal

cord.[27] In brief, those with underlying LESC required much more intensive attention. LESC should be followed carefully, and spine contrast enhanced MRI scan and retreatment may be considered.

Serological and CSF Analysis of Neurosyphilis with LESC

No single laboratory tools could determine a diagnosis of neurosyphilis in most clinical stages.[21] Current recommendations relied on laboratory tests such as serological and CSF examinations to diagnose neurosyphilis.[24] Previous studies showed that high serum TRUST titer cutoff of >1:32 was confirmed as an independent risk factor for predicting neurosyphilis.[28] In our study, 22 serum samples (45.8%, 22/48) were ≥1:32 at baseline. The differences of the results might be because enrolled participants received treatment previously.

Baseline CSF examinations are reported in Supplementary Table 2. CSF pleocytosis, a WBC count >5 μL was defined as being highly sensitive but not specific to neurosyphilis.[21] Increased CSF protein concentration, a cutoff of >45 mg/dL[29] was nonspecific and the least defining CSF parameter. In our project, 34 patients (79.1%, 34/43) had CSF pleocytosis, and 37 patients (80.4%, 37/46) had elevated CSF protein content. We speculated that the mechanism of LESC might be involved in the role of immune responses to the central nervous system (CNS) invasion.[30]

CSF pleocytosis (25/28, 89.3%) and CSF protein concentrations (23/28, 82.9%) were decreased in patients with LESC (Supplementary Table 2 and Figure 6), and 15 of 35 (42.9%) had a normal CSF data after therapy. We noticed that the CSF parameters did decline but failed to recover the syndromes and spine contrast enhanced MRI imaging of LESC. Indeed, 42.9% of patients had a normal CSF examination, with MRI imaging abnormal. We speculated that the disappearance of LESC might be delayed beyond immune responses to CNS and neurological syndromes. However, the specific patterns still need to be further summarized. Further studies are needed to assess the role of LESC in neurosyphilis.

Limitations

This investigation had limitations. First, lumbar puncture was delayed in some patients because of severe psychiatric and behavioral symptoms. Additionally, the cross-sectional project hampered causal interpretation of our findings, thus further longitudinal studies with large samples are needed. Finally, during the epidemic of COVID-19, Beijing Ditan Hospital Capital Medical University served as the designated hospital, and the number of neurosyphilis patients was decreased. In the future, we will focus on the role of association and mechanism between neuroinflammation induced by astroglia activation to find the biomarker for early diagnosis of LESC.

Data Sharing Statement

The data are available from the first author upon reasonable request.

Ethics Approval and Consent to Participate

The procedures for this respective study were conducted in accordance with the Declaration of Helsinki on ethical principles for medical research involving human subjects. This study protocol was approved by the Ethical Review Board of Beijing Ditan Hospital, Capital Medical University.

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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 no competing interests.

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