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ORIGINAL RESEARCH

Clinical and Laboratory Characteristics, Neuroimaging Alternations and Treatment Response of 25 HIV-Negative General Paresis Patients

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Purpose: General paresis is a common type of neurosyphilis featuring progressive cognitive deterioration. The lack of a golden standard of diagnosis and its nonspecific clinical manifestations resulted in a high rate of misdiagnoses. This study aims to investigate the clinical, laboratory and radiological presentations of general paresis and enrich its knowledge for timely diagnoses.

Patients and methods: The study collected hospitalized patients admitted for general paresis from September 2002 to November 2022. Their socio-demographical and medical status, clinical presentations, cognitive assessments, laboratory and radiographical manifestations and treatment information were collected retrospectively.

Results: A total of 20 males and 5 females were included. Patients' ages ranged from 30 to 66 years (average 50.3 years). The average and median time for diagnosing general paresis was 14.1 months and 10.0 months respectively. The most frequent initial symptom is memory deterioration (68.0%). Impaired calculative ability and memory deterioration were the most frequent cognitive anomalies, as found in 50% and 45.4% of subjects during examination. The mean and median scores of MoCA was 16.7 and 17 respectively. Serological tests revealed positive TPPA for all patients and a median RPR titer at 1:64 positive. All CSF samples with TPPA and FTA-ABS results reported positivity. The MRI manifestations of general paresis include patchy or speckled hyperintensities (70.8%) and cerebral atrophy (45.8%). The most common lesioned sites in MRI were the ventricular and paraventricular area (50.0%) and temporal lobes (45.8%). For treatment, penicillin-based anti-syphilitic plans were adopted in 17 patients (68.0%).

Conclusion: The clinical features and radiological alternations of general paresis patients often exhibited diverse and nonspecific alternations. However, some specific clinical manifestations and auxiliary examinations can provide meaningful clues for the identification and differential diagnosis of this disease.

Keywords: neurosyphilis, general paresis, syphilis, neuropsychiatric symptoms

Introduction

Syphilis is a chronic and systemic disease caused by Treponema pallidum (TP) infection, primarily acquired via sexual behavior. Neurosyphilis can occur at any stage of syphilis when TP seeds in the central nervous system (CNS). As "the great imitator", neurosyphilis can cause diverse nonspecific neuropsychiatric alternations depending on the site of CNS involvement,[1] presenting serious challenges in its clinical diagnosis.

General paresis is a parenchymal neurosyphilis type characterized by progressive cognitive deterioration with or without affective behavioral disorders.[2] General paresis is recognized as a "treatable" dementia with the appropriate and timely treatment of antibiotics, so early diagnoses are very crucial. However, general paresis presents various nonspecific

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symptoms and is often misdiagnosed as other neuropsychiatric diseases, such as schizophrenia, mood disorders and Alzheimer's disease (AD).[3,4]

With the rising incidence of syphilis,[5–7] general paresis as an unrare type of neurosyphilis deserves more scientific investigations and clinical vigilance. This study aims to review the clinical data of hospitalized general paresis patients and to analyze their demographic, clinical, laboratory and radiographical characteristics, as well as treatment responses, in the hopes of raising better awareness and improving early diagnosis.

Method

Study Subject

The study retrospectively collected patients in Peking Union Medical College Hospital (PUMCH) who are hospitalized for general paresis from September 2002 to November 2022. All patients whose discharge diagnosis included "neurosyphilis" or "general paresis" were searched and examined in the internal medical record system. Based on previous studies on general paresis[3,8] and the diagnosis guideline of neurosyphilis,[9,10] the included subjects should meet the following criteria: (1) Clinical manifestations of neurological or psychiatric symptoms, mainly characterized by cognitive impairment, mental abnormalities, impaired social function and affective disorders; (2) Positive serological result of the Treponema pallidum particle agglutination (TPPA) and rapid plasma regain (RPR) tests (3) Positive RPR results in cerebrospinal fluid (CSF), or positive TPPA with pleocytosis (white cell counts in CSF $\geq 5 \times 10^6$/L) or positive TPPA with protein content> 450 mg/L (4) Exclusion of other known causes for these abnormalities. Study subjects were excluded if they were HIV-positive.

Study methods

For included subjects, information on their demographical profiles, medical and sexual history, clinical symptoms, disease course and previous medical experience were collected. Findings from physical examinations, cognitive assessments (general evaluation, Montreal Cognitive Assessment (MoCA)), serum and CSF laboratory tests and cranial MRI were analyzed. Their treatment plan and follow-up RPR evaluation were summarized. For effectiveness, patients were assessed as effectively treated if, within one year after the discharge, follow-up serum RPR titers exhibited an over fourfold decrease (or entirely negative),[2,11] or if both the doctor and the patient saw a clear improvement in clinical symptoms.

Results

Personal Profile and Previous History

Overall, 70 confirmed neurosyphilis inpatients were found from the medical record system, among which 25 of them satisfied the criteria of general paresis and were included as study subjects, constituting 35.7% of overall neurosyphilis inpatients.

The sex distribution was 20 males versus 5 females. Patients' ages ranged from 30 to 66 years, and the average and median ages were 50.3 years and 50.0 years, respectively. For sexual contact and suspicious histories, 11 patients admitted a promiscuous or high-risk sex life (44.0%), including with sex workers. Two patients mentioned long travel histories for work (8.0%), two mentioned drug abuse and one claimed a previous blood transfusion (8.0%). Seven patients denied any suspicious personal records (28.0%). An investigation of occupation revealed that the general paresis inpatients comprised office clerks (5/25, 20.0%), drivers (3/25, 12.0%), semi-skilled workers (3/25, 12.0%), unemployed (3/25, 12.0%), businessman (1/25, 4.0%), peasant (1/25, 4.0%), and teacher (1/25, 4.0%). The remaining eight subjects have irregular types of jobs or prefer not to disclose (32.0%). An assessment of infectious comorbidities revealed that three patients are infected with HBV (12.0%), and two patients with HCV (8.0%).

Clinical Symptoms, Disease Course and Previous Medical Experience

The most frequent initial symptom is memory deterioration, as manifested in the onset of 17 general paresis inpatients (68.0%) (Table 1). Personality change (24.0%, 6/25), emotional disturbances (20.0%, 5/25) and sleep abnormalities

Table 1 Details of Initial and Overall Symptoms of General Paresis

	Initial Symptoms	Symptoms at Any Stage
Memory decline	17 (68.0%)	21 (84.0%)
Personality change	6 (24.0%)	15 (60.0%)
Agitation/aggression and irritability	6 (24.0%)	11 (44.0%)
Sleep-wake circle disturbances	5 (20.0%)	19 (76.0%)
Emotional disturbances	5 (20.0%)	16 (64.0%)
Abnormal behavior	3 (12.0%)	13 (52.0%)
Unsteady gait	2 (8.0%)	5 (20.0%)
Delusions and hallucinations	1 (4.0%)	8 (32.0%)
Dysarthria	1 (4.0%)	6 (24.0%)
Disorientation	1 (4.0%)	4 (16.0%)
Epileptic seizures	1 (4.0%)	4 (24.0%)
Incomprehensible speech or communication difficulty	0	10 (40.0%)
Urinary or fecal incontinence	0	5 (20.0%)

(20.0%, 5/25) were also commonly observed in our cohort as early symptoms. All patients with personality changes presented a shift towards more aggression and irritability (24.0%, 6/25).

For all presented symptoms in any period, 21 subjects experienced different degrees of memory impairment (84.0%), and 19 subjects reported disturbances in sleep-wake cycles (76.0%). Other prominent manifestations included emotional disturbances (64.0%, 16/25), personality change (60.0%, 15/25) and abnormal behavior (52.0%, 13/25). Abnormalities in language function were also commonplace, with 10 subjects having incomprehensible speech or impaired understanding (40.0%) and six with dysarthria (24.0%).

The average and median disease course upon hospitalization was 16.4 and 15.0 months respectively. Before the final diagnosis, the overlooked or misdiagnosed general paresis happened to 88.0% of our subjects (22/25). The most common misdiagnosis was affective disorder (16.0%, 4/25), with three subjects treated as depression and one as mania. Less common misdiagnoses comprise stroke (8.0%, 2/25), schizophrenia spectrum disorders (8.0%, 2/25), Alzheimer's disease (4.0%, 1/25) and other neuropsychiatric conditions. Besides misdiagnosis, six patients of our cohort could not receive any specific or meaningful diagnosis during previous medical consultations (24.0%). The average and median time for diagnosing general paresis was 14.1 months and 10.0 months respectively. Though some patients mentioned resolved rounded genital ulcers upon inquiry, no subjects brought up a prior syphilis infection.

Examination of Physical Signs

The most frequently observed physical signs are pathological neurological reflexes in general paresis subjects (28.0%, 7/25). We observed the presence of both positive palmar grasp reflex and Babinski's sign in 4 out of 25 individuals. Pupillary abnormalities are also frequent findings in this cohort, with five patients (20.0%) manifesting a varying degree of Argyll Robertson's pupil.

Assessment of Cognitive Condition

General Assessment of Cognition

Impaired calculative ability and memory deterioration were the most frequent cognitive anomalies, found in 50% and 45.4% of the assessed subjects (11/22 and 10/22 respectively). Eight patients had trouble conducting normal communications with the examiner (36.4%) due to either slurred speech or impaired comprehension. Temporal or spatial disorientation was also observed in 36.4% of subjects (8/22).

Cognitive Function Test MoCA

MoCA is a widely accepted clinical screening tool for assessing overall cognitive function and detecting dementia.[12] With 30 points overall on MoCA scales, seven patients underwent the MoCA assessment. Their scores averaged at 16.7 and ranged from 5 to 24, with the median score at 17.0. Four subjects are categorized as having severe cognitive impairments and three are considered mildly impaired.

Laboratory Tests of Serum and CSF

Syphilitic Serological Findings

All studied patients revealed positive status in TPPA and RPR tests, except for one patient with negative RPR. Among the positive titers for RPR, results ranged from 1:4 positive to 1:256 weakly positive, with a median titer at 1:64 positive.

Analysis of CSF Abnormalities

CSF RPR titers varied from negative to 1:16 positive, with levels ≥1:8 in 8 patients (32.0%). The TPPA test and FTA-ABS were conducted in the CSF copies of 22 and 20 patients respectively, and all reported reactivity.

The leukocyte counts of patients with general paresis ranged from 0 to 97×10^6/L. Seventeen subjects reached CSF leukocytes greater than 5×10^6/L (68.0%); For CSF protein, its level varied from 310 to 1550 mg in patients and averaged at 804 mg. Twenty-two copies exceeded the normal protein level for cerebrospinal fluid (88.0%), and 16 subjects have both pleocytosis and abnormally elevated protein content in CSF (64.0%).

Cranial MRI

A total of 24 included patients underwent the cranial MRI examination (Table 2 and Figure 1). In 5 patients, the cranial MRI did not reveal any meaningful cerebral irregularities (20.8%). Patchy or speckled hyperintensities were observed in 17 subjects (70.8%). Other common characteristics of brain anomalies were cerebral atrophy (45.8%, 11/24) and dilated ventricles and fissures (29.2%, 7/24). In previous literature, cerebral atrophy was reported to be the cardinal feature in the MRI of general paresis patients. In our study, 6 subjects showed diffuse brain atrophy from MRI scans (25.0%), and 5 showed local cerebral atrophy either in the temporal lobes (12.5%) or the hippocampus (8.3%).

The analysis of the lesioned site in MRI showed that the ventricular and paraventricular area were the most affected structure (50.0%, 12/24), followed by the temporal lobes (45.8%, 11/24), frontal lobes (33.3%, 8/24) and parietal lobes (29.2%, 7/24).

Table 2 Details of MRI Lesion Sites and Characteristics in General Paresis Patients

MRI findings	Cases	Percentage of Cases
Lesion site		
Ventricular and paraventricular area	12	50.0%
Temporal lobe	11	45.8%
Frontal lobe	8	33.3%
Parietal lobe	7	29.2%
Insula	3	12.5%
Hippocampus	3	12.5%
Cerebellum	3	12.5%
Occipital lobe	2	8.3%
Basal ganglia	1	4.2%
Description of lesion characteristics		
Cerebral atrophy	11	45.8%
Patchy hyperintensities (with or without swelling)	9	37.5%
Speckled hyperintensities	8	33.3%
Ventricles or fissure dilation	7	29.2%
Suspected foci of lacunar infarction or anomalies in cerebral small vessels	3	12.5%
Subdural effusion	1	4.2%

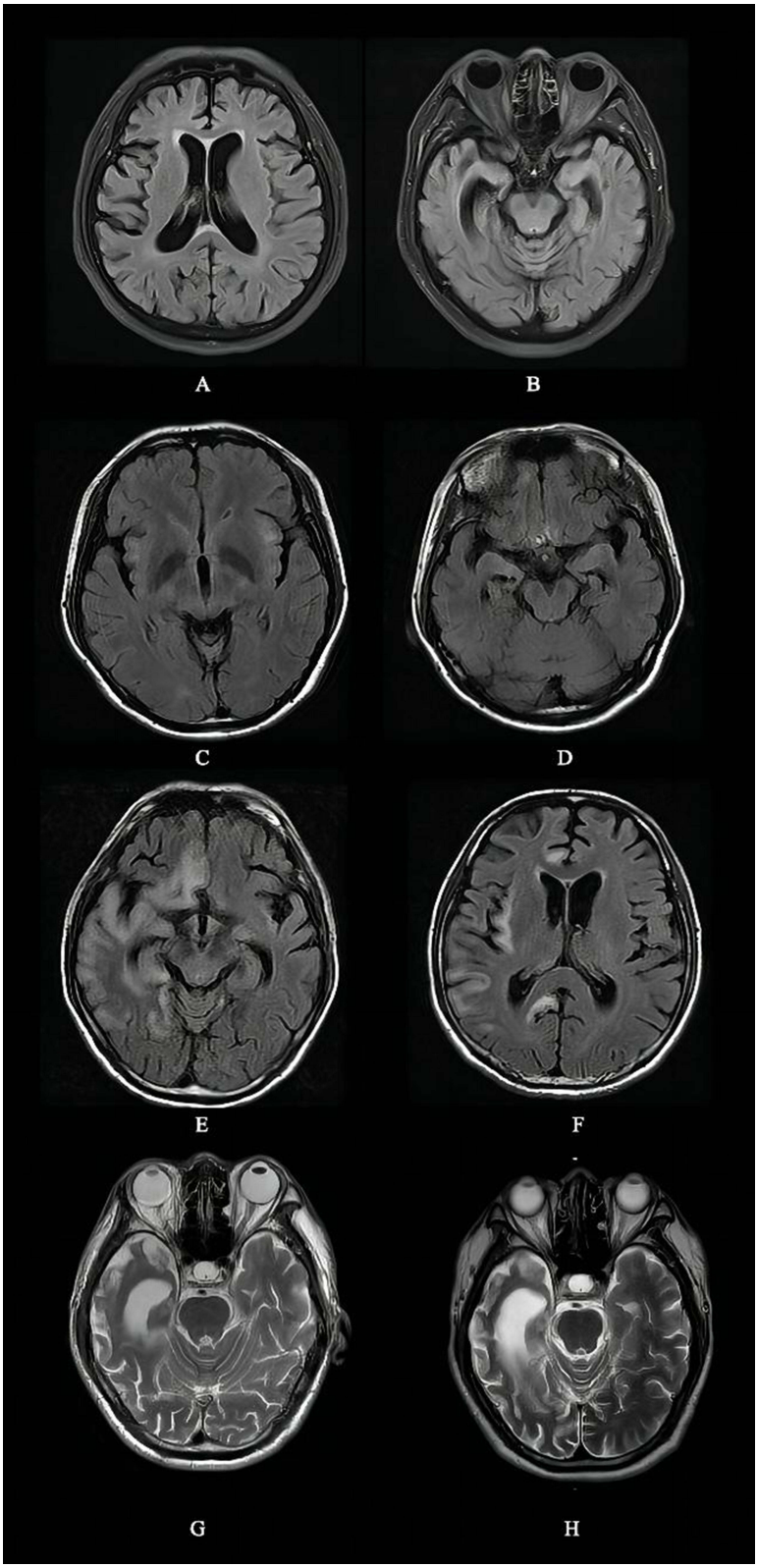

Figure 1 MRI findings of general paresis in T2 and FLAIR. (**A**, **B**) A 61-year-old female patient shows diffuse brain atrophy, dilation of lateral ventricles and widening of the sulcus. (**C**, **D**) A 31-year-old male patient shows symmetrical patchy hyperintensities in frontal lobes and corpus callosum splenium, with mild atrophy in the hippocampus. (**E-H**) A 61-year-old male patient shows (**E**, **F**) diffuse hyperintensities and swelling in the right temporal lobe, parietal lobe and occipital lobe and the right thalamus in 2014. In 2015 post treatment, her previous swollen and lesioned areas in 2014 were significantly atrophied, the right lateral ventricle is dilated, and the abnormal hyperintensities reduced in size as shown in (**G**). The right ventricle was further dilated in 2018 (**H**).

Treatment and Response

During the hospitalization, penicillin-based anti-syphilitic plans were adopted in 17 patients (68.0%). Twelve subjects (48.0%) were treated based on the US CDC guidelines[10] and Chinese STI guidelines[13] regarding syphilis with intravenous aqueous crystalline penicillin 4 million units every 4 hours for 14 days and intramuscular benzathine penicillin 2.4 million units every week for three weeks. Adjuvant corticosteroids were prescribed for 9 patients to prevent Jarisch-Herxheimer reaction (36.0%). Two patients who undertook penicillin-based treatment without corticosteroids manifested the Jarisch-Herxheimer reaction (8%).

Post-treatment syphilitic serum results were collected in 14 patients. Their serum RPR titers after treatment ranged from 1:1 to 1:64. The median titer was 1:8, as compared to 1:64 before treatment. The RPR titer did not decrease in 5 subjects (35.7%), even though 4 of them used sufficient penicillin. The evaluation of treatment effectiveness was available in 19 subjects, and 68.4% of them (13/19) were effectively treated after hospitalization, and four patients revealed poor improvement in general paresis (21.1%), and other two patients showed limited improvement.

Discussion

A previous review on neurosyphilis reported that 10%-20% of neurosyphilis manifests as general paresis,[1] but retrospective studies of neurosyphilis reported 25.6% to 38.9% of neurosyphilis as general paresis,[14–17] consistent with our finding of 35.7%. The severe nature of this parenchymal neurosyphilis might have caused the overrepresentation of general paresis in neurosyphilis statistics in the clinical setting. Neurosyphilis has a significant male preponderance. The sex ratio (male: female) was 4.0 to 8.67 in our result and in previous studies.[3,16,18] The average and median age of general paresis patients were around 50 years in our research, overall consistent with previous literature.[3,16,18] The age of disease onset should be an essential consideration during the differential diagnosis between general paresis and other neurodegenerative disorders. Clinicians should be particularly vigilant for middle-aged patients (especially males) with unexplained neuropsychiatric symptoms such as memory loss and cognitive impairment. Detailed inquiries about patients' sexual behavior and history of infectious disease should be inquired, and neurosyphilis should not be ruled out if the alleged history revealed no relevant risk. As demonstrated in this study, only 45.9% of patients admitted promiscuous or high-risk sex history. Serological tests of TPPA and RPR are always necessary for differential diagnosis of neurosyphilis. The occupations and social status investigation show that the backgrounds of general paresis patients are diverse, but people with low-skilled jobs or unemployment status constitute a substantial population. As syphilis has become an important public health issue, policymakers should encourage better education programs to effectively deliver sexual health knowledge to this population.

Symptoms of general paresis can be further categorized into early and late symptoms.[19] Familiarity with the common initial presentations can help the identification of this insidious disease at a treatable stage. To our knowledge, our study presents the first analysis of the initial symptoms of general paresis patients. The most frequent early symptoms are memory deterioration, emotional abnormalities and personality change (being more aggressive and irritable). More severe symptoms such as abnormal behaviour, delusions and hallucinations, impaired language and urinary or fecal incontinence are also common but usually develop during the later course of the disease. As manifested by these severe symptoms, not only can advanced cognitive functions but also more preliminary modalities, such as motor and excretory control, can deteriorate when general paresis developed into mixed-type neurosyphilis. The spectrum of general paresis symptoms in our study was similar to that in previous studies, but a higher incidence of sleep-wake circle disturbances and a lower incidence of psychiatric irregularities were recorded in our subjects.[3,16,18]

A high misdiagnosis rate of general paresis has been warned repeatedly in previous literature.[3,16,20,21] The misdiagnosis rate was 88.0% in this cohort. The most frequent misdiagnoses are depression, stroke and schizophrenia spectrum disorders. Depression and other mood disorders were also the most frequent misdiagnosis in previous studies of general paresis,[3,15] highlighting the importance of syphilis curricula among psychiatrists. Psychiatric disorders can arise secondarily from general paresis. Wang et al advocated syphilitic serological testing as a routine evaluation for patients with psychiatric disorders.[22] Our cohort's average delay from disease onset to treatment exceeds a year. With delayed or missed diagnoses, general paresis can rapidly progress to irreversible functional loss.

Physical examination also offered meaningful signs for assessing general paresis and neurological involvements. The palmar grasp reflex is a primitive reflex indicative of cortical disinhibition and frontal lobe impairment, usually in accordance with abnormal emotions and psychosis.[23] Babinski sign suggests the impairments in the corticospinal tract. The manifestation of pathological reflexes demonstrated the extensive neurological impairments in general paresis beyond cognitive-related cerebral areas and its tendency to progress into mixed-type neurosyphilis. These valuable physical signs were consistent with some clinical symptoms we observed in general paresis patients, such as mood disturbances and unsteady gait. Argyll Robertson's pupil is a classical and indicative sign of later-stage neurosyphilis. In our cohort, 20% of patients exhibited this sign, lower than the incidence of 25%-31% reported in previous literature,[3,18] but this difference is consistent with shorter delays in the general paresis diagnosis in our cohort as compared to previous studies.

In terms of cognitive evaluations, Wang et al found an AD-like mental impairment pattern of decline in memory, language and executive function in general paresis.[24] In our study, the average and median scores of MoCA both fell into the range of mild cognitive impairment This assessment revealed the occurrence of cognitive abnormalities in tested general paresis patients at a rate as high as 100%. Although MMSE is more commonly practiced, MoCA has been advocated as an indispensable clinical measure of cognitive function due to its superiority in the absence of ceiling and floor effects and the sensitive detections of cognitive heterogeneity.[25,26] This tool also deserves due attention in the cognitive evaluation of general paresis patients.

Because of the lack of specificity of neuropsychiatric manifestations, laboratory diagnostic tools such as serological and CSF examinations have been the critical basis for screening and confirming neurosyphilis. The serological RPR test is primarily used for syphilis screenings and treatment evaluation, and the TPPA test is used for the diagnosis. Previous literature showed that high serum RPR titers ≥1:32 predicts a high likelihood of neurosyphilis.[27] In this study, 80% of general paresis subjects were in accordance with this titer range of serum RPR.

MRI findings can be used to evaluate the areas of CNS involvement, severity of neurological impairments and project the prognostic outcomes in general paresis.[28,29] The patchy or speckled hyperintensities in T2 and FLAIR MRI scans were assumed to indicate microglia hypertrophy, gliosis, edema, cytotoxicity, or vascular occlusion,[3] as a result of Nissl-Alzheimer arteritis in general paresis development.[30] Previous literature found that these hyperintensities partially resolve after antibiotic treatment in general paresis patients.[31–33] We also observed this improvement in our subject (Figure 1G). Brain atrophy constitutes another cardinal radiographical feature, with a reported incidence of 56.1% −100%,[3,16,18,29] while the observation was 45.8% among our patients. This abnormality is believed to correlate with neuron loss and irreversible cerebral cortex destruction in neurosyphilis patients.[34]

Previous literature reported similar CNS involvement in radiographical findings, but these studies claimed different opinions over the diagnostic value of MRI in general paresis.[3,16,18,29,35] Increasing evidence points to the medial temporal lobe as a crucial structural involvement in general paresis. Mehrabian et al argued that T2 hyperintensities in the medial temporal lobe necessitate the differential diagnosis of neurosyphilis.[35] The degree of atrophy in this important structure has also been correlated with poor prognostic outcomes in general paresis.[28,36]

This study has several limitations. Only hospitalized patients were included. Excluding general paresis outpatients may have caused selection biases. Also, because of the retrospective nature of this investigation, certain examinations were incomplete in patients. Therefore, the conclusions of this cohort need to be further validated in large prospective analyses.

Conclusion

In this study, the clinical features and radiological alternations of general paresis patients exhibited diverse and nonspecific alternations, but specific clinical manifestations and auxiliary examinations also provided meaningful clues for its identification and differential diagnosis.

The prognosis of general paresis patients is extremely poor if not treated actively. However, most patients were not correctly treated within the first year of the disease. Our cohort also found that some patients did not undergo necessary auxiliary examinations or attend follow-up evaluations. Formal clinical guidelines are desired for the evaluation process of general paresis patients, and more efforts should focus on tracing the follow up of these patients. Through this

research, we hope clinicians can better understand general paresis and maintain sufficient vigilance for its clinical presentations.

Abbreviations

TP, Treponema pallidum; CNS, Central nervous system; AD, Alzheimer's disease; PUMCH, Peking Union Medical College Hospital; TPPA, Treponema pallidum particle agglutination; RPR, Rapid plasma regain; CSF, Cerebrospinal fluid; MoCA, Montreal Cognitive Assessment.

Data Sharing Statement

Because of data availability policy of PUMCH and the private content in the original medical record, the original data of the study is unavailable.

Ethical Approval

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Review Board of Peking Union Medical Hospital (ethics number: S-K653). The committee determined that consent from study participants was not required because of the retrospective nature of this study, along with stringent measures implemented to ensure the privacy and confidentiality.

Author Contributions

Mingjuan Liu conceived and designed the study and drafted the manuscript. Hanlin Zhang acquired the data, analyzed and interpreted the result, and critically revised the manuscript. Mingli Li provided significant input in the study design, data analysis and interpretation. Jun Li contributed to the acquisition of data, analysis and interpretation, and critically revised the manuscript. Meiyi Tong, Jia Zhou, Yining Lan, Mengyin Wu, Yanfeng Li, Ling Leng, and Heyi Zheng also made important contributions to the study design, data acquisition, analysis and interpretation, and critical review of the manuscript. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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