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Clinical and laboratory characteristics in patients suffering from general paresis in the modern era

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ABSTRACT

Background: No gold standard currently exists for the diagnosis of general paresis (GP), thus often resulting in unnecessarily delayed therapeutic decision.
Methods: A retrospective chart review was performed for 85 inpatients with GP in Zhongshan Hospital, Medical College of Xiamen University, and the characteristics of their clinical profiles, serum and cerebrospinal fluid (CSF) examinations, neuroimaging examination, and electroencephalogram (EEG) data were analyzed.
Results: Among the 85 GP patients, the clinical symptoms that were frequently observed upon admission included a variety of psychiatric–behavioral symptoms and varying degrees of cognitive impairment. All of the patients had positive serum *Treponema pallidum* particle agglutination (TPPA) assays, 96.47% of the patients had positive CSF TPPA assays, and 41.18% of the patients had both CSF pleocytosis and elevated CSF protein levels. Focal atrophy in one cerebral region or in multiple regions was evident in neuroimages. The EEG data primarily showed slightly abnormal EEG activity.
Conclusion: These results demonstrate the complexity of the clinical characteristics of GP and highlight the importance of early diagnosis.

1. Introduction

According to the National Sexually Transmitted Disease Surveillance System and the Sentinel Site Network of China (Chinese Center for Disease Control and Prevention, http://www.chinacdc.cn), 437,686 cases of syphilis occurred in 2013, representing an increase of 6.73% over the same period in 2012. If left untreated, 30% of syphilis patients may develop cardiovascular disease and neurosyphilis (NS) [1]. Syphilitic infection of the central nervous system can occur early or late in the course of the disease [2]. In accordance with the clinical characteristics, NS can be divided into the following types: asymptomatic NS, syphilitic meningitis, meningovascular NS, and parenchymal NS (including general paresis (GP) and tabes dorsalis) [1].

GP, a clinical type of NS, can occur at any stage of syphilis and has a peak incidence in 10–20 years after syphilitic infection [3]. The clinical spectrum of GP is very broad and may include cognitive impairment, a delusional or apathetic state, dysarthria, myoclonus, intention tremor, seizures, hyperreflexia, and Argyll Robertson pupils [4]. Argyll Robertson and hyperreflexia are commonly observed in cases of GP [5]. These variable, nonspecific presentations cannot only create diagnostic problems but also result in poor therapeutic decision. The lack of a gold standard for GP diagnosis often delays diagnosis and causes serious consequences [6].

The clinical and laboratory characteristics of GP require urgent investigation in the modern era. The purpose of the present study was to review the medical records of patients with GP and to analyze the characteristics of their clinical profiles, cerebrospinal fluid (CSF) examinations, neuroimaging examinations, and electroencephalogram (EEG) data in the hopes of improving the early diagnosis of GP.

2. Methods

2.1. Participants

A retrospective review of patient records (excluding return visit patients) between June 2005 and June 2014 in Zhongshan Hospital,

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Medical College of Xiamen University was performed. A total of 261 hospitalized patients were identified as having NS. HIV screening was performed using an enzyme-linked immunosorbent assay with HIV1 + 2 antigens/antibodies (Beijing Wantai Biological Pharmacy Enterprise Co. Ltd., China) and HIV-positive patients were excluded from this study. The ethics committees of the Medical College of Xiamen University approved this study. Because some patients were physically unable to answer our questions, certain information was obtained from their relatives at admission.

2.2. Diagnostic criteria

The diagnosis of syphilis was established with European Guidelines [7]. The diagnostic criteria for NS complied not only with the Centers for Disease Control guidelines [8] but also with European Guidelines [7]. Therefore, the criteria for a diagnosis of NS in our study included positive serological test results and one or more of the following: positive CSF rapid plasma reagin (RPR), positive CSF *Treponema pallidum* particle agglutination (TPPA) assays, increased CSF protein (>500 mg/L) or white blood cells (WBCs) ($>10 \times 10^6$ cells/L), or an otherwise unexplained neurological manifestation consistent with NS [9,10]. The criteria for excluding NS were similar to those used in our previous study [11]: (1) patients seronegative for TPPA or (2) patients seropositive for TPPA but negative for CSF RPR and CSF TPPA, without CSF pleocytosis and elevated CSF protein and without any characteristic symptoms or signs of NS. GP was diagnosed based on the clinical evaluations, serological tests, and CSF examinations [12].

2.3. Syphilitic serologic tests

The syphilitic serologic tests for each sample were performed using RPR (InTec, Xiamen, China) and TPPA assays (Fujirebio, Tokyo, Japan) according to the manufacturers' instructions and as previously reported [13,14].

2.4. Examination of CSF protein and WBCs

Approximately 2 mL of CSF samples was collected in plain sterile tubes and analyzed within 1 h to measure the protein content using a Roche–Hitachi Modular P800 analyzer (Roche Diagnostics, F. Hoffmann-La Roche Ltd., Basel, Switzerland), and the CSF WBC count was obtained using an automatic blood cell XE5000 analyzer (Sysmex International Reagents Co., Ltd., Japan) [15].

2.5. Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), computed tomography (CT) Scan, and EEG assessment

Within 7 days of the assessment, a multislice MRI of the brain was performed on the patients [3]. In brief, the images were acquired using a 3.0 T super-conducting magnet (Siemens Company, Germany), and the imaging sequences included a coronal T1-weighted spin echo and an axial T2-weighted spin echo. MRA imaging was performed after the administration of 20 cm^3 of IV Gd-DTPA at an injection rate of 5 cm^3 per second by first utilizing a 3D spoiled gradient echo sequence. CT scan was performed using a 16-slice MSCT scanner with a 0.42-s rotation time (Siemens Company, Germany). EEG data were recorded using a 19-channel MR-compatible EEG system (Nicolet Biomedical, USA).

3. Results

3.1. Clinical data

Between June 2005 and June 2014, 261 hospitalized patients were diagnosed with NS in Zhongshan Hospital, Medical College of Xiamen University. Based on clinical evaluations, serological tests, and CSF examinations, 85 patients were diagnosed with GP. The GP patients included 71 males and 14 females, with an overall median age of 52 years (range: 35–79 years). None of the 85 GP patients had a history of psychiatric disorders or substance abuse (except alcohol) or a family history of psychiatric disorders among their first-degree relatives.

3.2. Original diagnosis of GP

Among the 85 GP patients, 31 patients had a history of syphilis. They were diagnosed with syphilis in the outpatient department, and the diagnoses were confirmed by lumbar puncture and clinical evaluations during their hospital stays. For these 31 patients, GP was an obvious diagnosis upon hospitalization. However, another 54 patients (46 males, 8 females) were first treated in the neurology department, and none of them were initially suspected as having GP. The original diagnoses were dementia (13 patients), schizophrenia (12 patients), hypertensive arteriosclerotic intracerebral ischemic stroke (9 patients), epilepsy (7 patients), memory disorder (4 patients), Parkinson's disease (4 patients), or Alzheimer's disease (2 patients); the other three patients were initially diagnosed with viral encephalitis, depression, and transient ischemic attack, respectively (Table 1). These 54 patients were diagnosed with GP during follow-up treatment. The rate of clinical misdiagnosis was 63.53%.

3.3. Presentation of symptoms and signs of GP

The most frequent clinical symptoms of GP patients presented at admission included a wide variety of psychiatric–behavioral symptoms, including emotional problems (41.18%, 35/85), personality changes (30.59%, 26/85), delusions (9.41%, 8/85), hallucinations (5.88%, 5/85), and abnormal behaviors (36.47%, 31/85).

The other most frequent and important clinical symptom of GP patients was cognitive impairment. Forty-eight patients (56.47%) displayed varying degrees of intelligence and memory decline. Epileptic seizures (18.82%, 16/85), dysarthria (14.12%, 12/85), fecal and urinary incontinence (11.76%, 10/85) and sleep–wake cycle disruption (11.76%, 10/85) were also common symptoms. Symptoms such as unsteady gait and tremors were observed in some cases (Table 2).

Many patients displayed more than one clinical sign, resulting in overlap of the primary indicators of GP among the patients. The most common sign was amnesia, which appeared in 62 of the 85 patients (72.94%). Amnesia indicated a severe degree of memory decline and was in accordance with the patient's cognitive impairment. The other common signs included cerebellar ataxia (31.76%, 27/85) and muscle weakness (27.06%, 23/85). Less common (<10%) clinical signs included paresthesias, optic atrophy, Argyll Robertson pupils, hyperreflexia, and facial paralysis. Although Argyll Robertson pupils, which are small, asymmetric, irregular, and poorly responsive to direct light with maintained appropriate constriction on accommodation, are an important and typical sign of GP, but the incidence of this sign in the present study was only 3.53% (3/85) (Table 3).

Table 1
Original diagnoses of 54 GP patients.

Original diagnosis	Cases	% of cases
Dementia	13	24.07
Schizophrenia	12	22.22
Hypertensive arteriosclerotic Intracerebral ischemic stroke	9	16.67
Epilepsy	7	12.96
Memory disorder	4	7.41
Parkinsonism	4	7.41
Alzheimer's disease	2	3.70
Transient ischemic attack	1	1.85
Viral encephalitis	1	1.85
Depression	1	1.85
Total	54	100