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Neuroimaging of six neurosyphilis cases mimicking viral encephalitis

Tao Xiang [1], Guoliang Li *, Lan Xiao, Si Chen, Hao Zeng, Bo Yan, Yingfang Liang

Department of Neurology, Xiangya Hospital, Central South University, 87 Xiangya Road, Changsha, Hunan 410008, China

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ABSTRACT

Background: Neurosyphilis is known as "the great imitator" due to its wide range of clinical symptoms and abnormalities upon magnetic resonance imaging (MRI). Typical findings of both neurosyphilis and viral encephalitis include unilateral or bilateral MR hyperintensities in mesiotemporal lobes upon T2-weighted imaging or fluid attenuation inversion recovery (FLAIR) imaging. Accordingly, patients with neurosyphilis are frequently misdiagnosed with viral encephalitis, which prevents them from receiving appropriate treatment and often results in greater neurologic damage.

Methods: Clinical characteristics and MRI changes of 6 neurosyphilis patients admitted to our hospital between March 2012 and November 2012 were retrospectively reviewed.

Results: All 6 cases were tested positive for assays measuring *Treponema pallidum* hemagglutination (TPHA), rapid plasma reagin (RPR), and antibodies against syphilis in the serum and cerebrospinal fluid (CSF). Likewise, all patients were negative for antibodies against viral pathogens. T2-weighted or FLAIR MRI of the brains in all cases revealed either unilateral or bilateral hyperintensities in the mesiotemporal lobes, including the hippocampi. Electroencephalography showed relevant, localized slow or spiked waves. Patient prognoses were good in the 4 cases that received early anti-syphilis treatment, but the 2 cases that received delayed treatment due to misdiagnoses did not see substantial symptomatic improvements.

Conclusions: Neurosyphilis should be considered when there is mesiotemporal involvement upon MRI. Early treatment for syphilis is critical for positive outcomes.

1. Introduction

Neurosyphilis is an infectious disease caused by invasion of the central nervous system by *Treponema pallidum*. It is categorized as asymptomatic neurosyphilis, acute syphilitic meningitis, cerebrovascular neurosyphilis, or encephalitis and general paresis [1]. Findings of neurosyphilis upon MRI are varied and commonly present as cerebrovascular disease-like changes, brain atrophy, and nonspecific white matter lesions in the temporal lobes [2]. This study retrospectively reviewed 6 cases of neurosyphilis with mesiotemporal lesions that mimicked viral encephalitis.

2. Subjects and methods

Clinical and laboratory data were retrospectively reviewed from 6 neurosyphilis cases with mesiotemporal lesions that were admitted to our hospital from March 2012 to November 2012. Cerebrospinal fluid (CSF) rapid plasma reagin (RPR) tests were used to diagnose neurosyphilis, given that the specificity (99.3%) and sensitivity (75%) of RPR are similar to the specificity (99%) and sensitivity (70.8%) of Venereal Disease Research Laboratory (VDRL) tests [3], but they are easier and less expensive to perform. *T. pallidum* hemagglutination (TPHA) tests were chosen over fluorescent treponemal antibody absorption (FTA-abs) tests because TPHA tests are simpler and less expensive to perform [4]. CSF measurements included white blood cell (WBC) counts, percentage of monocytes, protein levels, glucose levels, chloride levels, and syphilis antibody detection. Characteristics of brain MRI, and electroencephalography were also reviewed. All patients were treated for syphilis and followed up at 4 months.

3. Diagnostic criteria

Diagnosis of symptomatic neurosyphilis is based on 3 major criteria [1,2,5,6]: (1) clinical symptoms or signs consistent with neurosyphilis in the absence of other known causes of these abnormalities, (2) CSF protein >0.45 g/L or leukocyte counts >5 cells/mm^3, and (3) serology that tests positive for CSF markers of neurosyphilis (RPR, TPHA).

4. Results

Table 1 shows the clinical manifestations of all 6 cases. Table 2 shows the results of CSF analyses. Electroencephalography showed localized

* Corresponding author. Tel.: +86 13808423674; fax: +86 731 89753241.
E-mail addresses: 327987649@qq.com (T. Xiang), tvtvtv06@163.com (G. Li).
[1] Tel.: +86 15200900764.

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Table 1
Clinical data of neurosyphilis in all cases.

Case	Sex	Age (years)	Form of onset	Duration	Clinical symptoms	Clinical signs
1	M	43	Acute	5 days	Fever, irritability, seizures, nonsense	Stiff neck, Kernig (+), tendon hyperreflexia
2	M	30	Acute	7 days	Seizures, confusion	Stiff neck, sleepiness, Argyll-Robertson pupil of right side
3	M	45	Subacute	2 months	Headache	No positive sign
4	M	53	Subacute	3 months	Personality change, cognitive deficits	Tedon hyperreflexia
5	M	39	Chronic	2 years	Seizures, dementia, cognitive deficits	Pupillary reflexes slow, ataxic gait
6	M	46	Chronic	4 years	Personality change, seizures, weakness of left limbs, urinary incontinence	Hemiparalysis of left limbs

Table 2
Laboratory data of CSF test in six cases.

Case	Pressure (mm H2O)	Pro (mg/dl)	Cell (cells/mm^3)	Sugar (mmol/l)	Chlorine (mmol/l)	Syphilis antibodies	RPR	TPHA
1	250↑	49↑	23↑	2.6	123	+	+	+
2	220↑	71↑	9↑	2.9	127	+	+	+
3	190↑	48↑	16↑	3.2	129	+	+	+
4	140	77↑	25↑	3.5	131	+	+	+
5	130	55↑	4	4.78↑	125	+	+	+
6	110	65↑	18↑	3.5	120	+	+	+

slow or spiked waves that indicated brain lesions in all cases. All patients showed abnormal MR hyperintensities in the hippocampi (either unilaterally or bilaterally). Patients 1 and 3 showed abnormal bilateral hyperintensities in the temporal lobes on T2-weighted or FLAIR imaging. Patients 2, 4, and 6 showed hippocampal atrophy, and Patient 4 had extensive brain atrophy (Fig. 1). All patients were administered intravenous doses of penicillin G (range 18–24 MU/day) every 4 to 8 h. Upon follow-up at 4 months, clinical symptoms in all patients had been relieved to some degree.

5. Discussion

This study examined the clinical features of 6 patients who presented with either bilateral or unilateral MRI hyperintensities in

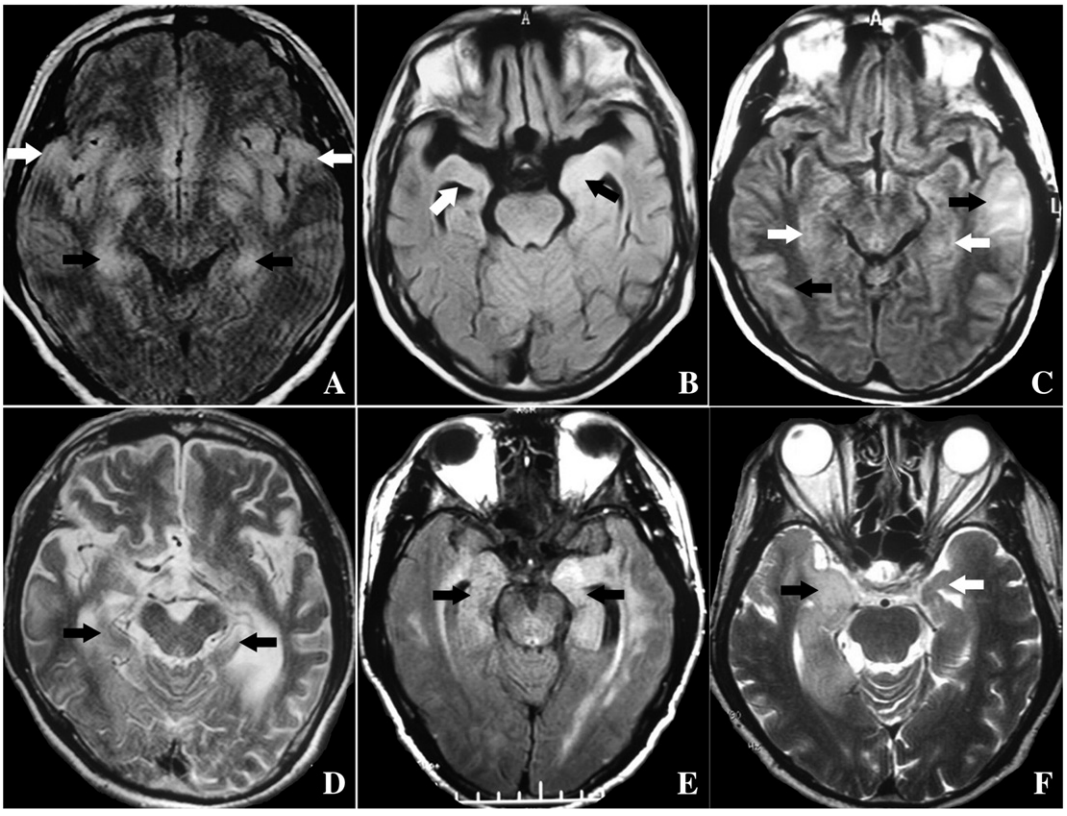

Fig. 1. (A) Axial FLAIR image of Patient 1 showing bilateral hyperintensities in the mesiotemporal lobes (*white arrows*), including the hippocampi (*black arrows*). (B) Axial FLAIR image of Patient 2 showing a hyperintensity in the left hippocampus (*black arrow*) and atrophy in the right hippocampus (*white arrow*). (C) Axial FLAIR image of Patient 3 showing bilateral hyperintensities in the hippocampi (*white arrows*) and temporal lobes (*black arrows*). (D) Axial T2-weighted image of Patient 4 showing bilateral hyperintensities in the hippocampi, brain atrophy, and bilateral hippocampal atrophy (*black arrows*). (E) Axial FLAIR image of Patient 5 showing bilateral hyperintensities in the hippocampi (*black arrows*). (F) Axial T2-weighted image of Patient 6 showing a hyperintensity in the right hippocampus (*black arrow*) and atrophy of the left hippocampus (*white arrow*).

the mesiotemporal lobes, including the hippocampi. Bilateral or asymmetrical mesiotemporal hyperintensities upon T2-weighted or FLAIR imaging is typically considered to indicate "virtually pathognomonic" viral encephalitis [7]. The pathophysiological mechanisms of this change are thought to be due to the proliferation of *T. pallidum*, which readily occludes small blood vessels and creates anaerobic conditions that lead to collapse of vessel walls and further reductions in cerebral blood flow to the temporal lobe and limbic system (hippocampus, basal ganglia, and thalamus) [8,9]. The etiology of MRI signal changes in the mesiotemporal lobes is still not well understood. Signal changes may be caused by the combination of edema and gliosis, or related to increased permeability of the blood–brain barrier and meningeal inflammatory reactions in small vessels leading to vasogenic and cytotoxic edema [7,10].

Additional imaging features may help to differentiate the rare presentation of neurosyphilis from the more common presentation of viral encephalitis. Neurosyphilis typically presents with atrophy of the mesiotemporal lobes rather than the global atrophy caused by cortical and subcortical edema associated with viral encephalitis [1]. Atrophy is related to the indolent nature of neurosyphilis, which is very different from the rapid and intense onset of viral encephalitis [11]. In addition, gyral enhancement, signs of hemorrhage, and areas of restricted diffusion are frequently described in viral encephalitis, but typically absent in neurosyphilis [12]. Imaging of viral encephalitis often shows clear boundaries between lesions and the outer edge of the lenticular nucleus. These delineations have been described as "knife" signs and may represent an important distinguishing feature [13,14].

Onset of neurosyphilis is generally subacute or chronic and is characterized by a slow progression and long course [7]. Four cases in our study were subacute or chronic. Neurosyphilis is considered to be a treatable disease, with early diagnosis and treatment being critical to favorable prognosis. However, lesions from neurosyphilis can be irreversible in late stages of the disease, and atrophy of the mesiotemporal lobes, including the hippocampi, is considered to be indicative of poor prognosis [9]. In our study, Patients 5 and 6 were originally misdiagnosed with viral encephalitis for up to 2 years before receiving anti-syphilis treatment as a part of the study. Symptoms of these 2 cases showed no obvious improvement after treatment for syphilis. The remaining 4 patients received anti-syphilis treatment in a timely manner and their symptoms did improve to varying degrees upon follow-up.

In summary, this study demonstrates that clinical and imaging features of neurosyphilis can mimic those of viral encephalitis. Although syphilis is not routinely tested for in patients, neurosyphilis should be considered in addition to viral encephalitis when MRI reveals changes in the mesiotemporal lobes. Prompt clinical testing for syphilis in these patients using conventional methods (syphilis antibodies, RPR, TPHA in the serum and CSF) is beneficial for early diagnosis and treatment of the disease.

Conflicts of interest

The authors have no conflicting interests to declare.

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