Neurosyphilis with oral-facial-lingual dyskinesia: A case report

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Abstract. The present study describes the case of a 52-year-old male patient who presented with subacute onset dysarthria and oral-facial-lingual dyskinesia, with normal blood glucose and acanthocyte levels, and no history of drug use. The patient tested negative for autoimmune encephalitis-related antibodies and paraneoplastic-related antibodies. The level of cerebrospinal fluid (CSF) protein was slightly elevated, and the *Treponema pallidum* hemagglutination assay and rapid plasma reagin test were positive in both serum and CSF samples. After 1 month of treatment with doxycycline, the patient's oral-facial-lingual dyskinesia was significantly improved, suggesting the diagnosis of neurosyphilis.

Introduction

Patients with neurosyphilis often present with a wide range of neurological symptoms. For this reason, neurosyphilis is commonly referred to as the great imitator. In rare cases, neurosyphilis can be the primary manifestation of dyskinesia; the most common dyskinesia is Parkinson's syndrome, with others existing such as dystonia, ataxia, myoclonus and chorea (1). Orofacial dyskinesia caused by neurosyphilis and characterized by continuous, slow, and regular rhythmic contraction of masticatory muscles is referred to as the 'Candy sign' (2). Although the disease is generally rarely reported in literature, neurosyphilis with oral-facial-lingual dyskinesia is even rarer, leaving clinicians with insufficient knowledge about it and the potential for misdiagnosis. The present study reports a case of neurosyphilis with oral-facial-lingual dyskinesia as the main symptom, therefore raising awareness of the disease and reducing the risk of misdiagnosis

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Case report

A 52-year-old male patient was admitted to the Department of Neurology of the Xiangya Hospital of Central South University (Changsha, China) in May 2020 due to dysarthria for 2 months and severe involuntary oral-facial-lingual movements for one month. At 2 months prior to admission, the patient developed dysarthria without other symptoms such as dysphagia, a choking cough due to drinking water, dizziness, headaches, nausea, vomiting, limb hemiplegia, or numbness. The patient was diagnosed with acute cerebral infarction in the First Hospital of Changsha (Changsha, China) and was prescribed aspirin enteric-coated tablets 100 mg and atorvastatin calcium 20 mg once a night for 1 month. However, these treatments failed to improve his dysarthria. Unfortunately, 1 month later, the dysarthria worsened and the patient experienced persistent orofacial and lingual involuntary movements, as well as pain in both sides of the lower jaw. Occasionally, a choking cough occurred when drinking water. The patient refused to undergo polysomnography procedure, but clinical observation suggested the recurrence of dyskinesias only during wakefulness, but not any stage of sleep. There was a prior history of hypertension and a history of 'penicillin' allergy. The patient had no history of tremors, jerks, intravenous drug abuse, toxin exposure, or head injury. None of the family members had a known history of tremors, Parkinsonism, memory disturbance, psychiatric disorders, and venereal diseases. A physical examination performed on admission revealed a heart rate of 86 beats/min (normal range, 60-100 beats/min) and a blood pressure of 142/86 mmHg (normal range, 90-120/60-80 mmHg). Moreover, the patient was conscious, alert, and had dysarthria. There was no neck rigidity associated with meningitis, and all the cranial nerves were normal on examination. The patient had a light and accommodation reflex. Examination of the motor system revealed involuntary movements in the form of frequent opening and closing of the mouth, continuous perioral movement (chewing movements), and protrusion of the tongue. All the deep tendon reflexes were well stimulated and the plantar showed flexor responses on both sides. No cerebellar or sensory deficits were found and his gait was grossly normal.

Table I. Laboratory findings.

Types	Value	Laboratory range
Blood		
RPR	1:16 positive	Negative
TPHA	Positive	Negative
CSF		
RPR	1:4 positive	Negative
TPHA	Positive	Negative
WBC (x10^6cells/l)	6	≤10
Protein (g/l)	1.01	0.15-0.45

RPR, rapid plasma reagin; TPHA, trepomema pallidum hemagglutination assay; CSF, cerebrospinal fluid; WBC, white blood cell count; 1:16, the serum RPR tests at the titer level; 1:4, the CSF RPR tests at the titer level.

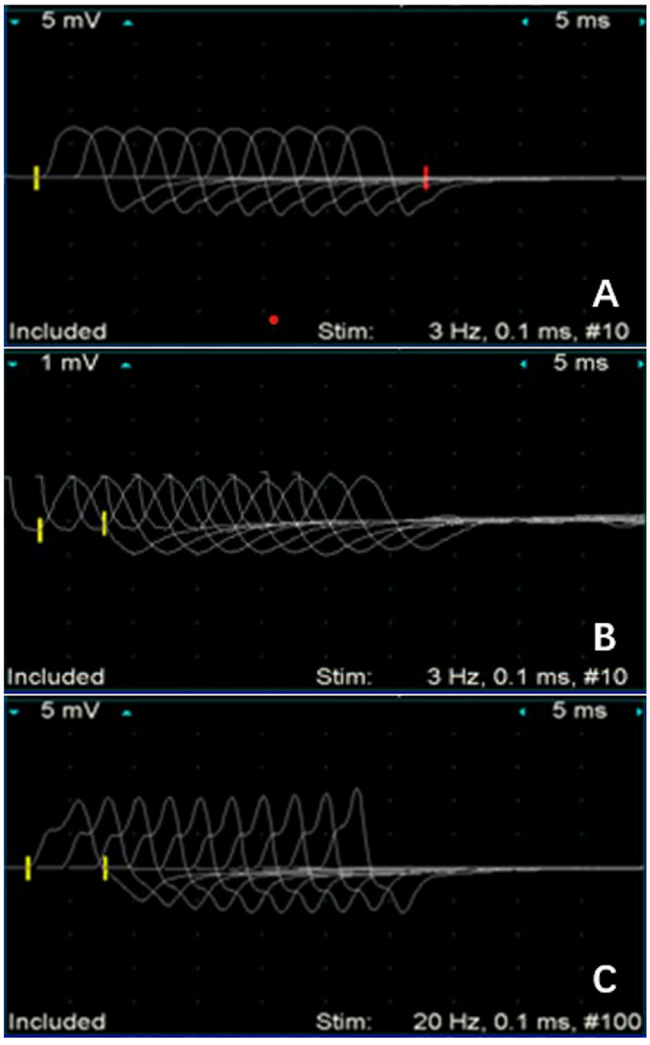

Figure 1. Repeated nerve stimulation was normal. The left (A) ulnar nerve and (B) facial nerve did not show significant amplitude reduction after repeated low-frequency electrical stimulation. (C) The amplitude of left ulnar nerve did not increase significantly after repeated high-frequency electrical stimulation.

Laboratory test results. Erythrocyte sedimentation rate of 35 mm/h (normal range, 0-10 mm/h), fasting blood glucose of 5.1 mmol/l (normal range, 3.9-6.1 mmol/l), glycosylated hemoglobin of 5.0% (normal range, 4.0-6.0%), and tumor markers were normal. Acanthocytes, HIV, hepatitis B, and hepatitis C were negative. The serum paraneoplastic anti-Hu, anti-Yo, anti-Ri, anti-Ma2/Ta, anti-CV2/CRMP5, anti-Amphiphysin antibodies, NMDAR, LGl1, GABABR, CASPR2 antibodies in the blood and CSF were negative using the indirect immunofluorescence method of cell-based assay (CBA). The patient had a positive rapid plasma reagin (RPR) test with a serum titer of 1:16 and a positive *Treponema pallidum* hemagglutination assay (TPHA). Moreover, lumbar puncture pressure was 150 mmH20 (80-180 mmH20), the total number of cells in the CSF was 6(≤10x10^6 cells/l), protein concentration was 1.01 g/l (0.15-0.45 g/l), the patient had a positive RPR with a CSF titer of 1:4 and the CSF a positive TPHA (Table I). The findings of electromyogram (EMG) (Fig. 1) and brain MRI scanning showed no abnormalities and enhancement signs such as brain atrophy and lacunar lesions in the bilateral basal ganglia. The Fazekas score in the deep brain and near the ventricle was 3 (3), indicating increased white matter content in the brain (Fig. 2).

Treatment and follow-up. According to CDC 2015 Guideline for the Diagnosis and Treatment of Syphilis (4), doxycycline is an effective alternative for early and late latent syphilis in cases where penicillin cannot be used. Because the patient had a history of 'penicillin' allergy, intravenous doxycycline (100 mg, Bid) was administered for 15 days. It was standard clinical treatment. During the follow-up visit in August 2022, orofacial and lingual dyskinesia were significantly improved, but his dysarthria was not improved and mild cognitive decline was observed.

Discussion

The present study describes the case of a 52-year-old male patient who presented with subacute onset dysarthria and oral-facial-lingual dyskinesia. The patient had normal blood glucose and echinocytocytes, with no history of drug abuse. Moreover, autoimmune encephalitis-related antibodies and paraneoplastic-related antibodies were negative. Based on these results, the possibility of echinocytosis, anti-NMDA autoimmune encephalitis, and drug-related movement disorders, among others were excluded. The TPHA and RPR test results for serum were all positive. In addition, the lumbar puncture pressure was 150 mmH_20, the protein concentration was 1.01 g/l, while TPHA and RPR tests for CSF were positive. Based on the 2020 German Guideline on the Diagnosis and Treatment of neurosyphilis (5), a diagnosis of neurosyphilis (meningeal vascular syphilis) was made. The patient showed a significant improvement in oral-facial-lingual dyskinesia after treatment with doxycycline, which further supported the diagnosis of neurosyphilis. Several oral and facial movement disorders present with multiple symptoms, such as Neuroacanthocytosis, Meige syndrome, anti-NMDA autoimmune encephalitis, frontotemporal dementia, Huntington's disease, neurodegeneration of cerebral iron deposition, cerebrovascular disease, levodopa-induced dyskinesia in Parkinson's disease, antipsychotic-induced tardive dyskinesia, among others. However, orofacial dyskinesia caused by neurosyphilis has been rarely reported.

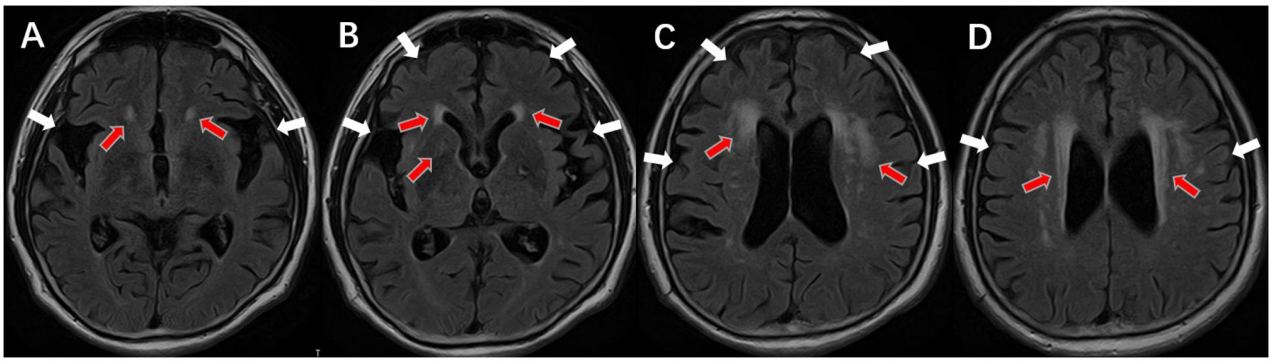

Figure 2. Brain T2-weighted fluid-attenuated inversion recovery revealed bilateral frontal and temporal lobes brain atrophy (shown by the white arrow) and lacunar lesions in the bilateral basal ganglia, and the Fazekas score in the deep brain and near the ventricle was 3, indicating a high white matter content in the brain (shown by the red arrow). (A-D) represent different levels of brain MRI.

Neurosyphilis is a chronic infectious disease caused by Treponema pallidum which infects the central nervous system. It can also involve the brain, meninges, spinal cord, or blood vessels leading to diverse pathological and clinical manifestations. For this reason, it is known as a great imitator. Orofacial dyskinesia caused by neurosyphilis is known as the 'Candy sign' (2). Some scholars even believe that the candy sign can be regarded as a specific symptom of neurosyphilis (6). Lenka *et al* (7) reported that penicillin treatment improved the symptoms of neurosyphilis, which presented only with the candy sign and abnormal vocalization. Martinelli *et al* (6) reported that, in addition to the candy sign, neurosyphilis was accompanied with mental disorders and memory loss. Notably, anti-syphilis treatment significantly improved the orofacial movement disorder but did not ameliorate cognitive disorder. Moreover, the penicillin effectively treated neurosyphilis with cognitive impairment, accompanied with the candy sign (8). In another study, it was found that neurosyphilis was also characterized by Argyll Robertson pupil, frequent paroxysmal oral-automatism seizures, periodic lateralized discharges (PLEDs) with triphasic waves, behavioral changes, and memory decline (9). Administration of penicillin significantly decreased the severity of PLED, seizures, behavioral changes, and memory decline. However, it did not improve rhythmic orofacial involuntary movements and Argyll Robertson pupil, which indicated an irreversible characteristic of late-stage neurosyphilis syndromes. In the present case, the patient presented with tongue dyskinesia and dysarthria in addition to candy sign. Administration of the anti-syphilis treatment resulted in a significant reduction in the oral-facial-lingual dyskinesia, although it did not improve the dysarthria. Considering that neurosyphilis with oral-facial-lingual dyskinesia is rare in clinical practice, it is likely to be misdiagnosed.

Movement disorders in patients with neurosyphilis can result from ischemic lesions in various areas such as the midbrain (red nucleus, substantia nigra), cerebellum, and basal ganglia. Moreover, the presentations of clinical movement disorders in these cases are generally similar to those seen in cases with ischemic lesions in the same locations due to other causes (10). Based on these findings, we hypothesized that the candy sign may be caused by the following factors. i) Vascular occlusion in arteritis leading to ischemic necrosis in the basal ganglia region and decreased number of neurons in the substantia nigra striatum; ii) dysfunction of transmitter transmission or metabolism in cortico-basal ganglia pathway. Among these factors, ischemic necrosis in the basal ganglia region caused by arteritis vascular occlusion may be the main mechanism underlying the occurrence of the candy sign.

Neurosyphilis, known for its elusive nature, manifests with a wide array of complex and diverse clinical symptoms. It can potentially affect any region of the nervous system without presenting distinct features, thereby resulting in a considerable rate of misdiagnosis during the initial stages. Therefore, if a patient presents with orofacial dyskinesia, a comprehensive analysis of their medical history, clinical symptoms, and imaging data should be made, while considering the risk of neurosyphilis. Fortunately, neurosyphilis is curable; thus, once diagnosed, regular anti-syphilis treatment should be administered to improve patient's prognosis.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL and HZ contributed to the conceptualization and design of the study, the collection of clinical information and the

drafting of the manuscript. BL and DO obtained MR images and analyzed patient data. GL was responsible for formulating the patient's treatment plan. YL and GL contributed to critical revisions of the intellectual content and confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The patient provided their written informed consent to participate in this study. Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in the article.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of any accompanying images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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