



Clinical Reasoning: The “Great Imitator”

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SECTION 1

A 69-year-old man presented with 1 week’s history of sweating, confusion, drowsiness, and vomiting. He complained of “burning fumes” olfactory hallucinations. He had hiccups and his wife had witnessed limb jerking. He had a history of paroxysmal atrial fibrillation, hypertension, hyperlipidemia, and type 2 diabetes mellitus.

On examination, he was afebrile but confused. He looked unwell and flushed. His speech was slow and

perseverant. There was visible right-sided lower lip and jaw twitching. He displayed impaired recall and executive processing on cognitive assessment. He had episodic impaired responsiveness with right hand stereotyped movements.

Questions for consideration:

1. What investigations would you order at this point?
2. Which diagnosis could account for this presentation?

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SECTION 2

Initial blood tests showed renal impairment with creatinine of 170 mg/dL. The leukocyte count, C-reactive protein, and blood sugars were all within normal range. Urine dipstick, chest X-ray, and ECG had normal results. CT head showed subtle hypoattenuation in the right temporal lobe.

The working diagnosis was a subacute encephalitis with temporal-onset seizures. There were features

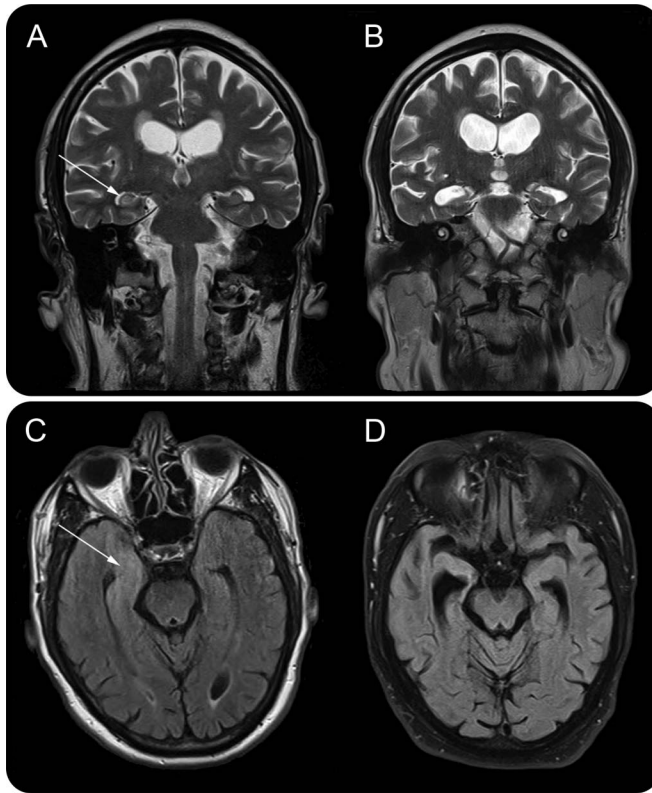
such as the hiccups and the facial jerks that could suggest extratemporal involvement. However, focal motor seizures and hiccups can arise from the temporal lobe.

Questions for consideration:

1. What is the most likely diagnosis?
2. What treatment would you administer?
3. Would you order any further tests?

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Figure MRI pretreatment and post-treatment



Coronal T2-weighted (A, B) and axial fluid-attenuated inversion recovery (C, D) images of the patient pretreatment (A, C) and post-treatment (B, D) for neurosyphilis. Pretreatment, swelling, and edematous signal change were seen in the right amygdala and hippocampus (arrows) mimicking a viral encephalitis. The follow-up imaging 6 months post-treatment shows atrophy of the right medial temporal structures.

SECTION 3

IV acyclovir treatment was commenced for a presumed diagnosis of herpes simplex encephalitis. Levetiracetam was administered for the focal seizures. CSF analysis showed 90 leukocytes/mm³ (90% lymphocytes), erythrocytes <1/mm³, protein 0.90 g/L, and normal glucose. CSF oligoclonal bands were positive and cytology was negative for malignant cells. MRI brain scan showed right-sided signal change in the medial temporal lobe on T2 and fluid-attenuated inversion recovery sequences (figure, A and C). CSF viral PCR was negative for varicella zoster, herpes simplex virus (HSV) 1 and 2, and enteroviruses.

Questions for consideration:

1. What action would you take at this point?
2. Are there any other diagnoses that you are thinking of?

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SECTION 4

A screen for immune-mediated encephalitis including antineuronal antibodies, testicular ultrasound, and CT body were negative. EEG showed almost continuous right-sided polymorphic delta waves and no periodic lateralized discharges (PLEDs) or epileptiform discharges but by this point the clinical twitching and automatisms had ceased. A repeat CSF was traumatic and showed 51 leukocytes/mm³ (80% lymphocytes), 2,870 erythrocytes/mm³, and protein 1.12 g/L. Repeat viral PCR panel was negative.

The most likely diagnosis was thought to be PCR-negative HSV encephalitis, although we also considered mimic processes that could give rise to this presentation such as inflammation or neoplasia.

Questions for consideration:

1. What would you do now with regards to treatment and further management of this patient?
2. Are there any other tests that would be helpful?

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SECTION 5

A course of IV acyclovir was continued for 21 days, despite 2 negative CSF HSV PCR results. A 3T intracranial magnetic resonance angiography had normal results. Further history from the patient's wife alluding to risk factors

for sexually transmitted infections was volunteered.

Question for consideration:

1. Are there any other investigations that you would now request?

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SECTION 6

Venereal Disease Research Laboratory (VDRL) serology was positive with a positive rapid plasma reagin (RPR) and positive immunoglobulin M enzyme immunoassay, suggestive of recent treponemal infection. CSF VDRL was also positive with positive RPR titer and treponemal

partial agglutination assay. HIV testing was negative.

Questions for consideration:

1. What further questions would you ask?
2. Would you ask for the involvement of any other teams?
3. What treatment would you now institute?

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SECTION 7

The patient admitted to a rash over his palms and soles a few weeks prior but denied a primary chancre. He was treated with high-dose IV benzylpenicillin after consultation with the infectious diseases team. The case was reported to the public health authorities. Full sexual health screening was carried out including

hepatitis B and C, gonorrhea, and chlamydia testing. Repeat HIV testing was negative.

Questions for consideration:

1. What follow-up should the patient be offered?
2. What tests should be performed to ensure successful treatment?

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SECTION 8

Following treatment, the patient showed signs of cognitive recovery at 6 months. Follow-up imaging showed resolution of the signal change with asymmetrical atrophy of the right medial temporal lobe (figure, B and D). Serum and CSF serology was persistently positive at similar titers.

DISCUSSION Syphilis is a sexually transmitted bacterial infection caused by *Treponema pallidum*. The incidence is increasing, with 2,978 new cases of primary, secondary, or early latent syphilis diagnosed in the United Kingdom in 2012, compared to 2,005 in 2003.^{1,2}

Neurosyphilis has been historically described as 2 distinct entities: tabes dorsalis and general paresis, presenting several years after the onset of primary symptoms.³ However, early latent forms of the disease are recognized and syphilis can present with neurologic manifestations at any point during the course of the disease. Within hours to days of inoculation, there is bacterial spread to other body tissues and within hours bacteria can be isolated within the nervous system.⁴ After early neurologic invasion, the majority of patients will clear the infection. Approximately 13%–20% will develop latent asymptomatic neurosyphilis and can then develop early meningeal syphilis, neurovascular syphilis, tabes dorsalis, or general paresis.

Partially treated syphilis secondary to widespread penicillin use has led to previously unrecognized neurologic presentations. Atypical presentations are thought to account for up to 13% of neurosyphilis cases in one large cohort.⁵

There are several reported cases of neurosyphilis mimicking HSV encephalitis.⁶ There are further reports of similar radiologic findings but with a more chronic history resembling an immune encephalitis.⁷ The clinical presentations unified by these radiologic findings are therefore diverse. CSF findings of lymphocytosis and elevated protein are often unhelpful in narrowing down the differential. All the reported HSV mimic cases are in HIV-negative patients and all but one were in men. The disease duration is usually short and the prognosis is good with treatment. However, limited long-term follow-up data suggest that neurocognitive problems may ensue.

The etiology of this temporal lobe–dominant presentation of neurosyphilis is unclear. In all patients reported, the imaging abnormalities resolved with treatment, usually with subsequent atrophy. The most prevalent form of neurosyphilis is meningovascular and therefore the cause of the T2-weighted signal change is thought to be edema and gliosis. Changes in meningeal and cerebral capillaries can cause increased permeability of the blood–brain barrier and vasogenic edema. Cytotoxic edema may also follow from meningeal inflammation and small vessel involvement with parenchymal hypoxia. There may also be contributory interstitial

edema from arachnoid villi obstruction secondary to fibrin deposits and leukocytes. Infection-induced small vessel changes can lead to gliosis. It has been argued that the imaging changes do not obey vascular territories and usually syphilitic arteritis predominantly affects medium to large vessels.⁸ The inflammatory changes are thought to cause irreversible atrophic changes, despite treatment. Diffuse cerebral dysfunction and cerebral association connections between the temporal lobes and other parts of cortex may occur and contribute to atrophy.⁹

The diagnosis of syphilis is made through the use of nontreponemal (VDRL, RPR) and treponemal confirmatory tests (immunofluorescence immunoassays). If there is clinical suspicion for neurosyphilis, CSF examination is warranted. CSF VDRL is highly specific, but insensitive. CSF fluorescent treponemal antibody absorption test is highly sensitive, and should be used in combination with CSF cell count, protein, and blood serology. Following confirmation of neurosyphilis, treatment is with 14 days of high-dose IV penicillin or 3 weekly doses of IM benzathine penicillin G. There is the possibility of developing the Jarisch-Herxheimer reaction, which occurs on treatment initiation, and is believed to be caused by endotoxin release as large numbers of bacteria are killed by antibiotic therapy. This is characterized by malaise, pyrexia, tachycardia, hyperventilation, and hypotension. Testing for other sexually transmitted infections, including HIV, and contact tracing should be performed, as well as screening for multi-system complications of syphilis.⁶

If the initial CSF examination demonstrates a pleocytosis, CSF analysis should be repeated every 6 months until the cell count is normal. Retreatment may be necessary if there are persistent changes in the protein or cell count. RPR titers can correlate with disease activity, and a fourfold reduction in titer is used to provide supportive evidence of successful treatment.⁶

Sir William Osler once said “he who knows syphilis, knows medicine,” alluding to the heterogeneity of clinical presentations associated with the disease.¹⁰ The historical tabes dorsalis and general paresis are now rare and alternative presentations of neurosyphilis are more common.⁵ Early symptomatic neurosyphilis is also rare but presentation as a clinicoradiologic mimic of herpes encephalitis is being increasingly reported. This highlights the importance of including neurosyphilis in the differential diagnosis of an uncharacterized limbic encephalitis, along with paraneoplastic encephalitis and acute disseminated encephalomyelitis. The “encephalitic” findings of MRI temporal lobe signal change and EEG PLEDs are non-specific and alternative causes should be sought if the CSF PCR is negative. This is particularly important as some of the other conditions are amenable to treatment and can carry a favorable prognosis.

This case provides a teaching and learning resource and highlights the ongoing importance of remembering

syphilis in the differential diagnosis of neurologic and psychiatric presentations within our practice.

AUTHOR CONTRIBUTIONS

Nazia Karsan was responsible for writing the manuscript, including the literature review. Robert Barker provided an expert neuroradiology opinion on the imaging and provided the MRI pictures. John O'Dwyer was the consultant in charge of the case and proofread and edited the manuscript before submission.

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N. Karsan and R. Barker report no disclosures relevant to the manuscript. J. O'Dwyer has received speaker honoraria from UCB Pharma and consultancy fees from Eisai. Go to Neurology.org for full disclosures.

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