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Syphilitic meningitis presenting with multiple cranial neuropathies

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SUMMARY

Syphilis is increasingly prevalent in the community. The protean manifestations of neurosyphilis make the recognition, diagnosis and early initiation of treatment challenging. We report a case of early syphilitic meningitis presenting with multiple cranial neuropathies. Cerebrospinal fluid (CSF) examination was inflammatory with predominant lymphocytosis. The patient was diagnosed with neurosyphilis based on serum as well as CSF testing. Intravenous benzylpenicillin treatment resulted in rapid improvement of neurological symptoms. Neurosyphilis should be considered in immunocompetent patients presenting with multiple cranial neuropathies, or isolated cranial neuropathies without vascular risk factors.

BACKGROUND

Syphilis is a common sexually transmitted infection (STI) caused by the spirochete bacterium *Treponema pallidum*. Syphilis is endemic in low/middle-income countries and incidence is increasing in developed countries over the past 20 years.^{1 2} Incidence is highest among individuals residing in endemic areas, men who have sex with men, sex workers and intravenous drug users.² Concurrent human immunodeficiency virus (HIV) infection and other STIs are common. Clinical manifestations can be varied, making clinical recognition and diagnosis challenging. When detected, syphilis is effectively treated with penicillin with no known cases of documented resistance.² We report a case of neurosyphilis presenting as multiple cranial neuropathies in an HIV-negative individual.

CASE PRESENTATION

A 37-year-old woman presented with a 2-week history of progressive neurological complaints. Symptoms started with a sensation of disequilibrium and unsteadiness on her feet, and subsequently difficulty closing both eyes, right lip numbness, sequential bilateral hearing impairment (right, followed by left) and slurred speech. She denied limb weakness or numbness, headache, neck stiffness, photophobia, nausea, vomiting or visual changes. She also denied fever, rash, lymph node swelling or night sweats. She did note 10 kg weight loss in the few months prior to presentation in the context of recently diagnosed type 2 diabetes mellitus. She had since commenced metformin, gliclazide and dulaglutide which improved the diabetic control. Other comorbidities included morbid obesity (weight 96 kg, body mass index 40 kg/m²), asthma and eczema. She

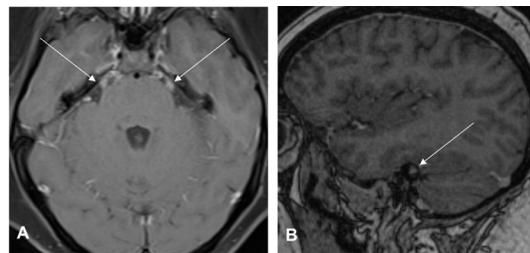


Figure 1 Postcontrast enhancement of cranial nerves V, VII, VIII. A. Bilateral trigeminal nerves exiting pons, T1 Fast Spin Echo; B. facial and vestibulocochlear nerve at the geniculate ganglion, T1 Gradient Recall Echo.

had not been taking steroids or immunosuppressant medication. She was born and raised in a subtropical region in Australia and denied significant travel history. She had been engaging in unprotected sex but denied intravenous drug use.

On the examination, there were bilateral cranial neuropathies involving trigeminal (V), abducens (VI), facial (VII), vestibulocochlear (VIII) and hypoglossal (XII) nerves. Lateral gaze was restricted bilaterally and there was bilateral upper and lower facial weakness with impaired eyebrow raise, eye closure and inability to smile. Weber's test lateralised to the left ear and Rinne's test demonstrated air conduction greater than bone bilaterally. Tongue was weak but midline on protrusion. Sensation was decreased to light touch and pinprick in V2 distribution on the right side. The remainder of the neurological examination was unremarkable. There was no palpable lymphadenopathy or splenomegaly.

INVESTIGATIONS

Initial laboratory tests were consistent with mild inflammation; elevated C reactive protein of 12 mg/L (<10 mg/L), erythrocyte sedimentation rate 21 mm/hour (<12 mm/hour) and thrombocytosis of $447 \times 10^9/L$ ($150\text{--}400 \times 10^9/L$). The remainder of the full blood examination, renal function, electrolytes and liver function tests were unremarkable. Serum beta human chorionic gonadotropin was <1.2 IU/L and haemoglobin A1c was 8.7% (72 mmol/mol). Cerebrospinal fluid (CSF) examination demonstrated normal opening pressure of 13.5 cm H₂O (10–25 cm H₂O), elevated protein of 1.28 g/L (<0.45 g/L) with normoglycaemia (CSF 3.8 mmol/L, serum 5.4 mmol/L) and lymphocyte predominant (76%) leucocytosis of $0.441 \times 10^9/L$ (< $0.005 \times 10^9/L$). Magnetic resonance imaging (MRI) scan of the brain with gadolinium demonstrated enhancement



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Table 1 Serological and antimicrobial testing

	Serum		CSF	
Syphilis	TPPA	Positive	TPPA	Positive
	CMIA	Positive	VDRL	Positive (1:8)
	RPR	1:32	Syphilis PCR	Negative
Other	ACE	53 nM/mL/m (20-70)	ACE	2 U/L (\leq 2 U/L)
	ANA	1: 160, speckled	Cryptococcal Antigen and PCR	Negative
	ENA	Negative	Ziehl-Neelsen stain (acid-fast bacilli)	Negative
	ANCA (MPO, PR3)	<1 IU/mL	Herpes simplex virus 1/2 PCR	Negative
	Rheumatoid Factor	<15 IU/mL	Enterovirus PCR	Negative
	CCP	<1 U/mL	Human Herpesvirus 6 PCR	Negative
	Cryoglobulins	Negative	Cytomegalovirus PCR	Negative
	HIV	Non-reactive	Varicella zoster virus PCR	Negative
	Hepatitis B Surface Ab		Human parechovirus PCR	Negative
	Hepatitis B Surface Ag	Negative	Gram stain, bacterial culture	Negative
	Hepatitis B Core Ab	Negative	Flow cytometry	Polyclonal B cell population
	Hepatitis C Core Ab	Negative	Cytology	Negative for Malignancy
	GQ1b	Negative		

Ab, antibody; Ag, antigen; ANA, antinuclear antibody; ANCA, antineutrophilic cytoplasmic antibody; CCP, anticitrullinated peptide antibody; CMIA, chemiluminescent microagglutination immunoassay; CSF, cerebrospinal fluid; MPO, myeloperoxidase; NR, normal range; PR3, proteinase 3; RPR, rapid plasma reagin; TPPA, treponema pallidum particle agglutination assay; VDRL, venereal disease research laboratory test.

of the trigeminal nerve at the pons, as well as facial and vestibulochoclear nerves at the geniculate ganglion (figure 1A,B). There was no evidence of recent infarct or leptomeningeal enhancement. Contrast-enhanced MRI of the spine was unremarkable. Computed tomography (CT) scans of the neck, chest, abdomen and pelvis were negative for malignancy or lymphadenopathy. Serum *T. pallidum* particle agglutination assay (TPPA) and chemiluminescent microparticle immunoassay (CMIA) IgG and IgM were positive, with a rapid plasma reagin (RPR) titre of 1:32, consistent with active syphilis infection. Further CSF analysis showed positive TPPA, venereal disease research laboratory test (VDRL) titre of 1:8 and negative *T. pallidum* PCR. Workup for other infectious, autoimmune and neoplastic disorders was negative (table 1).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of multiple cranial neuropathies is broad. In this case, based on the clinical presentation of cranial neuropathy and ataxia, our initial working diagnosis was Miller-Fisher syndrome. This was rapidly revised to infectious (fungal, viral or atypical bacterial, eg, syphilis, tuberculosis, borreliosis) autoimmune (sarcoid, behcet, systemic lupus erythematosus (SLE)) or malignancy (leptomeningeal carcinomatosis, lymphoma) when the CSF results were obtained. Further discussion on differential diagnoses for meningitis associated with cranial neuropathies can be found in table 2. Neurosyphilis was confirmed based on positive treponemal and non-treponemal tests on serum and CSF. Potential differentials of sarcoid, SLE, viral, fungal and atypical bacterial infections as well as malignancy were excluded or rendered less likely based on imaging, serology, PCR and pathology tests as outlined in table 1. Meningitic and meningovascular forms of syphilis were both considered. Despite the absence of leptomeningeal enhancement on MRI brain scan, given the widespread bilateral cranial neuropathies, lack of clinical seizures, marked CSF pleocytosis and radiological absence of stroke, early syphilitic meningitis was considered more likely.

TREATMENT

On further history, she denied a primary syphilitic chancre. During screening for concurrent STIs, *Chlamydia trachomatis* was detected on first-pass urine PCR.

Our patient was diagnosed with early syphilitic meningitis with multiple cranial neuropathies and commenced on intravenous benzylpenicillin 1.8 g 4 hourly according to local therapeutic guidelines (Electronic Therapeutic Guidelines, Australia) for a 15-day course. Given her comorbidities of poorly controlled diabetes and morbid obesity, a decision was made in consultation with the infectious diseases team not to treat prophylactically with steroid medication. Initiation of antibiotic treatment was closely monitored in the inpatient setting and she did not develop Jarisch Herxheimer reaction. Her cranial neuropathies improved dramatically by the eighth day of treatment. Concurrent chlamydia infection was treated with a 7-day course of 100 mg doxycycline two times per day.

OUTCOME AND FOLLOW-UP

The patient was discharged home to complete her course of antibiotic therapy. She is scheduled for outpatient review with the local infectious diseases team for serological monitoring of RPR titre and consideration of repeat CSF examination to confirm adequacy of neurosyphilis treatment.

DISCUSSION

Symptomatic early neurosyphilis is a rare complication of syphilis infection, occurring in 1.8% of primary infections, as compared with the more frequently encountered late symptomatic neurosyphilis, which occurred in 10%–20% of infections in the preantibiotic era.³ It is estimated that 50% of primary syphilis infections are associated with central nervous system invasion and abnormal CSF examination,² but the majority of these remain asymptomatic. Early neurosyphilis can be asymptomatic, meningeal or meningovascular. Asymptomatic neurosyphilis is defined as CSF abnormalities (elevated protein, pleocytosis, positive VDRL) without neurological signs or symptoms, in a patient

Table 2 Differential diagnoses for meningitis associated with cranial neuropathy

Diagnosis	Clinical features	Confirmatory tests	
Infectious	Viral	Acute meningitis	CSF Viral PCR
	▶ Varicella zoster virus		
	▶ Enterovirus		
	▶ Herpes simplex virus		
Fungal	Subacute/chronic meningitis	CSF India Ink Stain, Gram Stain, Periodic Acid Schiff Stain	
	Sinusitis, pulmonary involvement (±multiorgan)	CSF Fungal Culture	
	Focal neurological deficits (CNS abscess, granuloma, cryptococcoma)	CSF Cryptococcal antigen	
	hydrocephalus		
Mycobacterial	Subacute/chronic meningitis	CSF Acid Fast Bacilli	
	Pulmonary involvement	CSF TB PCR	
	Systemic symptoms (night sweats, loss of weight, lymphadenopathy)	CSF TB culture	
	Hydrocephalus		
Spirochete	Subacute/chronic meningitis	Serum TPPA, RPR.	
	Tabes dorsalis	CSF TPPA, VDRL.	
	Neuropsychiatric	CSF <i>Treponema pallidum</i> PCR.	
	Fever, genital ulcers, lymphadenopathy	Serum and CSF Borrelia-specific IgM, IgG	
▶ <i>Treponema pallidum</i>	Multiorgan involvement		
	Fever, rash, myalgia		
	Carditis		
	Polyradiculitis		
Autoimmune	Sarcoidosis	Subacute/chronic meningitis	Nil-specific CSF test
		Anterior uveitis	Raised CSF ACE supportive.
		Pulmonary (interstitial lung disease, hilar lymphadenopathy)	Non-necrotising granuloma on biopsy
	±multisystem involvement		
	Hypercalcaemia		
	Behcet's disease	Subacute/chronic meningitis	Nil specific.
	Neurological symptoms associated with systemic flare	Skin pathology test supportive.	
	Recurrent oral and genital ulceration		
	Pan uveitis, skin lesions, arthropathy		
	Systemic lupus erythematosus	Subacute/chronic meningitis	ANA, dsDNA, anti-Sm, C3, C4 levels
	Malar rash, photosensitivity		
	psychosis, seizures		
	arthritis, serositis (pericarditis, pleuritis)		
	Interstitial lung disease		
	Antiphospholipid syndrome lupus nephritis		
Malignant	Leptomeningeal carcinomatosis	Subacute/chronic meningitis	Malignant cells on CSF cytology.
		Evidence of systemic malignancy	
	Breast, lung, gastrointestinal and melanoma more common		
	Lymphoma	Subacute/chronic meningitis	Lymphoma cells on CSF flow cytometry.
	Higher risk with high grade lymphomas, more extensive extranodal disease		
	Lymphadenopathy, hepatosplenomegaly		

ANA, antinuclear antibody; CNS, central nervous system; CSF, cerebrospinal fluid; dsDNA, anti double stranded DNA antibodies; RPR, rapid plasma reagin; TB, Tuberculosis; TPPA, treponema pallidum particle agglutination assay; VDRL, venereal disease research laboratory test.

with a primary syphilis infection. Meningeal forms present with meningism, significant CSF pleocytosis (10–400/mm³) and uncommonly cranial nerve palsies, while meningovascular forms present with the above plus stroke, seizures, myelopathy and a lesser degree of CSF pleocytosis (5–100/mm³).³ Diagnosis of syphilis requires two-stage testing with positive non-treponemal (RPR, VDRL) as well as treponemal tests (CMIA, TPPA). Either of the above can be used for initial screening, and if positive, the other is used as a confirmatory test.² On CSF, non-treponemal tests such as VDRL have a higher specificity than treponemal tests due to passive transfer of antibodies across the blood–brain barrier and thus VDRL is the diagnostic test of choice for neurosyphilis. Imaging findings include leptomeningeal and cranial nerve enhancement in the early meningeal form, as well as white matter lesions and cerebral infarction in the meningovascular form.⁴

In the past 90 years, there have been 12 cases in the literature of syphilis presenting with multiple cranial neuropathies.^{5–15} Of these, 10 cases were diagnosed with early syphilitic meningitis, one with early meningovascular syphilis and one with late latent syphilis. A further three cases in the non-English literature are reviewed by Piura *et al.*¹² Of the 12 cases, the seventh and eighth nerves were more commonly involved (12/12 and 11/12, respectively), the fifth nerve was involved in three cases, and the sixth in two. Ten of these patients presented without a history of a primary chancre while four had preceding rash and lymphadenopathy. Four of the patients were HIV coinfecting, six were HIV-negative and two had unknown status. Of the patients that were HIV-unknown or negative, three presented without any risk factors for syphilis.

This case was unique due to multiple cranial nerve involvement. This is the most extensive cranial neuropathy to be

reported to date with syphilitic infections, with most previously reported cases involving between one to three cranial nerves. Interestingly, our patient presented without any risk factors for syphilis, likely reflecting the increasing prevalence in the community. This combined with the lack of meningeal symptoms and the broad range of differentials for multiple cranial neuropathies made the diagnosis more challenging. Serological tests for syphilis, followed by CSF studies if serology returns positive, should be considered in all patients presenting with multiple cranial neuropathies, as well as in patients presenting with isolated cranial neuropathies without vascular risk factors.

Learning points

- ▶ Syphilis should be considered in all patients with cranial neuropathies and cerebrospinal fluid (CSF) pleocytosis, as early recognition and treatment can lead to dramatic clinical improvement.
- ▶ In this context, syphilis screening should be performed even in the absence of traditional risk factors or history of primary chancre, given the concerning increase in syphilis incidence over the past two decades.
- ▶ Subacute-chronic meningitis can occur without typical symptoms of headache, photophobia and neck stiffness, and CSF examination remains an important diagnostic tool in patients with unexplained cranial neuropathies.

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