Syphilitic meningitis presenting with multiple cranial neuropathies

Melissa Chu,1 Shejil Kumar,1 Jonathan Sturm2

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.3 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, glimepiride 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 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 (150–400 $\times 10^9$/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...
of the trigeminal nerve at the pons, as well as facial and vestibulocochlear 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 \textit{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 \textit{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, tuberculous, borreliosis) autoimmune (sarcoid, bechet, 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 meningo-vascular 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, \textit{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 comorbidies 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. \(^1\) 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 meningo-vascular. Asymptomatic neurosyphilis is defined as CSF abnormalities (elevated protein, pleocytosis, positive VDRL) without neurological signs or symptoms, in a patient

### Table 1 Serological and antimicrobial testing

| Serum                 | CSF                  |
|-----------------------|----------------------|
| **Syphilis**          |                      |
| TPPA Positive         | TPPA Positive        |
| CMIA Positive         | VDRL Positive        |
| RPR 1:32              | Syphilis PCR Negative|
| **Other**             |                      |
| ACE 53 nM/mL/m (20-70) | ACE 2 U/L (≤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/L            | Human Herpesvirus 6 PCR Negative |
| Cryoglobulin Negative | Cytomegalovirus PCR Negative |
| HIV Non-reactive      | Varicella zoster virus PCR Negative |
| Hepatitis B Surface Ab Negative | Human paracoxivirus PCR Negative |
| Hepatitis B Surface Ig Negative | Gram stain, bacterial culture Negative |
| Hepatitis B Core Ab Negative | Flow cytometry Negative |
| Hepatitis C Core Ab Negative | Cytology Negative |
| GQ1b Negative         | Polyclonal B cell population 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.
with a primary syphilis infection. Meningeal forms present with meningism, significant CSF pleocytosis (10–400/mm³) and uncommonly cranial nerve palsies, while meningo-vascular forms present with the above plus stroke, seizures, myelopathy and a lesser degree of CSF pleocytosis (5–100/mm³). 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. 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.

In the past 90 years, there have been 12 cases in the literature of syphilis presenting with multiple cranial neuropathies. Of these, 10 cases were diagnosed with early syphilitic meningitis, one with early meningo-vascular 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 coinfected, 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.

Table 2 Differential diagnoses for meningitis associated with cranial neuropathy

| Diagnosis         | Clinical features                                                                 | Confirmatory tests                                      |
|-------------------|----------------------------------------------------------------------------------|--------------------------------------------------------|
| Infectious        |                                                                                  |                                                        |
| Viral             |                                                                                  |                                                        |
| Varicella zoster virus | Acute meningitis                                                               | CSF-Viral PCR                                          |
| Enterovirus       |                                                                                  |                                                        |
| Herpes simplex virus | Subacute/chronic meningitis                                                       |                                                        |
| Fungal            |                                                                                  |                                                        |
| Cryptococcus neoformans and Cryptococcus gatti | Sinusitis, pulmonary involvement (multorgan)                                      | CSF India Ink Stain, Gram Stain, Periodic Acid Schiff Stain |
| Histoplasma Capsulatum | Focal neurological deficits (CNS abscess, granuloma, cryptoctococcoma)              | CSF Fungal Culture                                      |
| Coccidioides immitis | Hydrocephalus                                                                     | CSF Cryptococcal antigen                                |
| Blastomyces dermatitidis |                                                                                  |                                                        |
| Mycobacterial     |                                                                                  |                                                        |
| Mycobacterium tuberculosis | Subacute/chronic meningitis                                                       | CSF Acid Fast Bacilli                                   |
| Spirochete        |                                                                                  |                                                        |
| Treponema pallidum | Subacute/chronic meningitis                                                       | CSF TB PCR                                             |
| Borrelia burgdorferi | Neuropsychiatric                                                                 |                                                        |
| Autoimmune        |                                                                                  |                                                        |
| Sarcoaidosis      | Subacute/chronic meningitis                                                       | Nil-specific CSF test                                  |
| Behcet’s disease  | Subacute/chronic meningitis                                                       | Raised CSF ACE supportive, Non-necrotising granuloma on biopsy |
| Systemic lupus erythematous | Subacute/chronic meningitis                                                       | Nil specific. Skin pathergy test supportive.            |
| Malignant         |                                                                                  |                                                        |
| Leptomeningeal carcinomatosis | Subacute/chronic meningitis                                                       | Malignant cells on CSF cytology.                       |
| Lymphoma          | Subacute/chronic meningitis                                                       | Lymphoma cells on CSF flow cytometry.                  |

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.
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.

**Contributors** MC and SK assessed, investigated and managed the patient under the supervision of JS. MC and SK acquired and synthesised the data and drafted the manuscript. JS assisted in drafting the work and revising it critically. MC, SK and JS approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** None declared.

**Patient consent for publication** Obtained.

---

**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.

---

**References**

1. Koijma N, Klausner JD. An update on the global epidemiology of syphilis. *Curr Epidemiol Rep* 2018;5:24–38.
2. Ghanem KG, Ram S, Rice PA. The modern epidemic of syphilis. *N Engl J Med* 2020;382:845–54.
3. Ropper AH. Neurosyphilis. *N Engl J Med* 2019;381:1358–63.
4. Czarnowska-Cubała M, Wighlus M, Cubala WJ, et al. MR findings in neurosyphilis—a literature review with a focus on a practical approach to neuroimaging. *Psychiatr Danub* 2013;25 Suppl 2:S153–7.
5. Casolla B, Ristori G, Romano A, et al. Subacute multiracial neuropathy revealing an early case of meningeal syphilis. *Neuro Sci* 2015;36:1033–4.
6. Ting C-H, Wang C-W, Lee J-T, et al. Bilateral facial nerve palsy as the sole initial symptom of syphilis: a case report. *CEM* 2015;17:576–81.
7. Alqahtani S. Acute cranial neuropathies heralding neurosyphilis in human immunodeficiency virus-infected patient. *Am J Case Rep* 2014;15:411–5.
8. Smith MM, Anderson JC. Neurosyphilis as a cause of facial and vestibulocochlear nerve dysfunction: MR imaging features. *AJNR Am J Neuroradiol* 2000;21:1673–5.
9. Davis LE, Sperny S. Bell’s palsy and secondary syphilis: CSF spirochetes detected by immunofluorescence. *Ann Neurol* 1978;4:378–80.
10. Komamara H, Nakamura T, Kobayashi J, et al. Early neurosyphilis presenting with multiple cranial nerve palsy: A case report of management by combined penicillin-corticosteroid treatment. *J Infect Chemother* 2019;25:362–4.
11. Maeda T, Yoshizawa S, Hirayama T, et al. Neurosyphilis mimicking Ramsay Hunt syndrome. *J Nippon Med Sch* 2015;82:254–6.
12. Piura Y, Mina Y, Azenstein O, et al. Neurosyphilis presenting as cranial nerve palsy, an entity which is easy to miss. *BMJ Case Rep* 2019;12:e226509.
13. Young AS, Carroll AS, Welgampola MS, et al. Acute unilateral peripheral vestibulopathy in neurosyphilis. *J Neurol Sci* 2017;378:55–8.
14. Hong JH, Lee HY, Lim MK, et al. Meningovascular and spinal form of neurosyphilis presenting as multiple cranial nerve palsy, cerebral infarction and meningomyelitis in a human immunodeficiency virus Negative-Patient: MR imaging features. *J Korean Soc Magn Reson Med* 2014;18:263.
15. Nunes da Silva MJ, Oliveira V, Sousa AE, et al. [Headaches, otalgia and peripheral facial palsy as a form of presentation of neurosyphilis]. *Rev Neurol* 2000;31:544–6.