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Neurosyphilis presenting with behaviour change and temporal and frontal lobe MRI abnormalities

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Abstract

General paresis is the result of a chronic, slowly progressive meningoencephalitis secondary to central nervous system infection by *Treponema pallidum* and its onset is insidious with predominant cognitive deficits and neuropsychiatric manifestations. We report a case of a patient who presented with behavioural change and was found to have MRI signal abnormalities in the medial temporal lobe. A viral or autoimmune aetiology was initially pursued prior to the diagnosis of neurosyphilis. The patient's clinical status and MRI findings improved following a 14-day course of intravenous benzylpenicillin therapy. Neurosyphilis is an easy-to-screen and treatable disease that should be considered in the differential diagnosis in patients presenting with MRI signal abnormalities in the temporal lobes or limbic structures. Early recognition and initiation of treatment may limit cognitive complications and morbidity.

Keywords: Neurosyphilis, magnetic resonance imaging, limbic encephalitis

CASE REPORT

A previously healthy, 50-year-old male presented with a 3-month history of progressive behavioural change which encompassed insomnia, incoherent speech, and delusions of grandiosity accompanied by outbursts of physical aggression. There was no history of malnutrition, seizures or fever. The patient was part of a polygynous marriage but had no other known history of extra-marital relationships, alcoholism or recreational drug use. The patient was afebrile and vital signs were normal. He was inattentive and disoriented, rambling incoherently in mixed languages and had visual hallucinations. Neurological examination was unremarkable with preserved tone, power, reflexes, coordination and sensation. The patient's cranial nerve functions were intact and there was no meningism. The patient was initially diagnosed with first-onset psychosis and treated with antipsychotics.

The patient's inflammatory markers, metabolic screen (thyroid function tests, liver function tests, renal function and electrolytes, vitamin B12 and folate) and toxicology screen returned as normal. Computed Tomography of the brain showed no acute intracranial abnormalities. A human immunodeficiency virus (HIV) screen returned negative, but the patient's serum syphilis total antibody and Treponema Pallidum Particle Agglutination (TPPA) assay were reactive, with a positive rapid plasma reagin titre of 1:16. Electroencephalography did not identify the presence of epileptiform abnormalities. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was subsequently performed (Figure 1) which demonstrated T2-weighted hyperintensities involving bilateral temporal and limbic structures (Figure 1A-C) as well as the left parasagittal frontal lobe (Figure 1D). No abnormal leptomeningeal enhancement or restricted diffusion was seen.

Cerebrospinal fluid (CSF) analysis through lumbar puncture identified raised CSF protein of 0.57 g/L [0.15-0.40g/L] without evidence of pleocytosis or hypoglycorrhachia. CSF cultures were negative. A multiplex (FilmArray) CSF polymerase chain reaction (PCR) panel returned negative for pathogens including human herpesvirus 6 (HHV6) and herpes simplex virus (HSV) 1 and 2. An additional monoplex CSF HSV PCR also returned negative. An extensive assay of onconeural and neuronal cell-surface antibodies associated with limbic encephalitis including N-methyl-d-aspartate receptor (NMDAR), leucine-rich glioma inactivated 1 (LGI1), contactin-associated protein-

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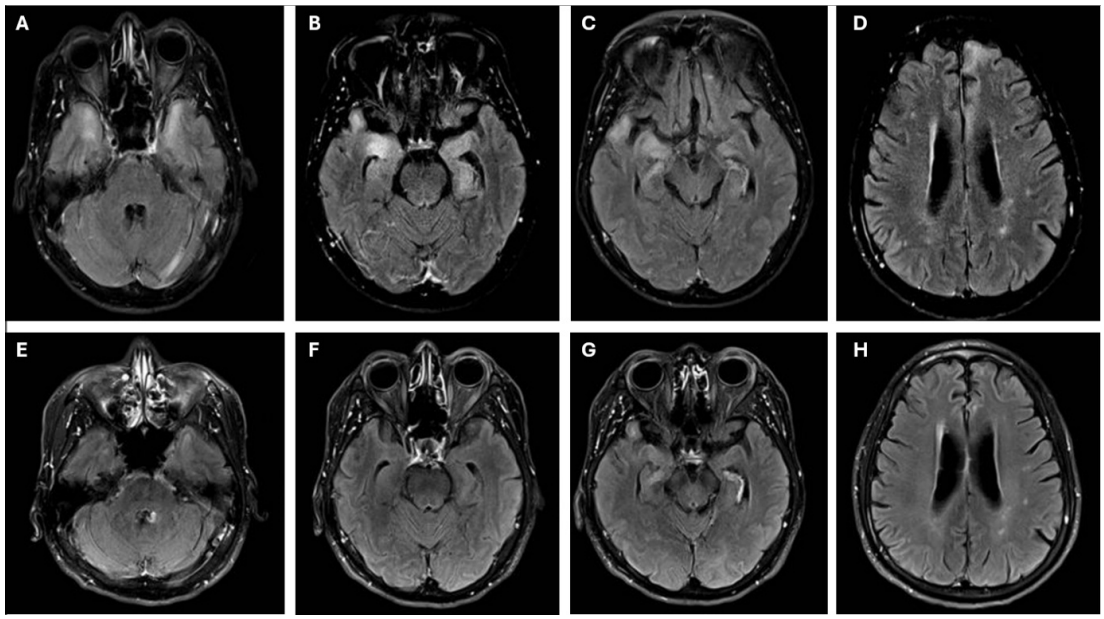

Figure 1. Pre- (A-D) and post-treatment (E-H) contrast enhanced T2-weighted axial MRI slices demonstrating T2 hyperintensities involving the bilateral temporal lobes and limbic structures (A-C), as well as the left parasagittal frontal lobe (D) which improved following a 14-day course of IV benzylpenicillin therapy.

like 2 (CASPR2), γ-aminobutyric acid B receptor (GABABr), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), Hu, Ma2, amphiphysin and collapsin response mediator protein 5 (CRMP5) eventually returned negative. The patient's CSF venereal disease research laboratory (VDRL) test returned positive with a 1:32 titre. The patient was thus diagnosed with general paresis secondary to parenchymatous neurosyphilis.

Clinical course

The patient was initially treated with intravenous (IV) ceftriaxone and acyclovir for presumed infective encephalitis which was stopped after CSF cultures and viral PCR returned negative. The patient was planned for a course of IV methylprednisolone as empiric therapy for autoimmune encephalitis when CSF VDRL results returned positive. The patient completed a 14-day course of IV benzylpenicillin dosed at 18 million units per day. Repeat MRI at 3 months post-treatment (Figure 1E-H) showed improvement in T2-weighted hyperintensities, with the patient returning to his cognitive and behavioural baseline.

DISCUSSION

Syphilis is a sexually transmitted infection caused by the Gram-negative spirochete bacterium *Treponema pallidum*. The incidence of syphilis is approximately 5.1 per 100,000 population.[1] Neurosyphilis is the result of central nervous system invasion by *Treponema pallidum*, which may occur in up to 30% of patients with early syphilis.[2] A common manifestation of early neurosyphilis, typically within the first year of infection, is syphilitic meningitis which generally presents with features of meningism. Early asymptomatic neurosyphilis has been reported in some 25-35% of people infected with syphilis whereby CSF abnormalities (pleocytosis or elevated CSF protein) are detected in the absence of any neurological signs or symptoms.[2,3] Patients with asymptomatic neurosyphilis are at increased risk of developing late neurological complications compared to patients with syphilis who have a normal CSF examination.[4] Clinical manifestations of late neurosyphilis, typically occurring 5-25 years after infection, include meningovascular or parenchymal syphilis, the latter of which comprises general paresis and/or tabes dorsalis. General paresis is the result of a chronic, slowly progressive meningoencephalitis and its onset is insidious with predominant cognitive deficits and neuropsychiatric manifestations. Parenchymatous neurosyphilis has been reported to cause MRI signal changes in the medial temporal lobe with cases meeting clinical and neuroimaging criteria for possible autoimmune limbic encephalitis.[5,6]

Table 1: Differential diagnosis of MRI findings of T2 weighted signal abnormalities in the temporal lobes or limbic structures.[9,10]

Disease	Distinctive clinical features	Diagnostic tests
Herpes simplex encephalitis	Fever Haemorrhagic lesions on MRI	HSV DNA in CSF on viral PCR
HHV-6 encephalitis	Most common in immunosuppressed patients	HHV-6 DNA in CSF on viral PCR
HIV	Risk factors include unprotected sexual intercourse, having multiple sexual partners, sexual workers	HIV serology
Neurosyphilis	Risk factors include unprotected sexual intercourse, having multiple sexual partners, sexual workers	CSF treponemal antibody tests
Whipple's disease	Polyarthralgia, diarrhoea, oculomasticatory myorhythmia	*Trophyrema whippeli* DNA in CSF
Post-ictal changes	History of seizure	Electroencephalogram
Glioma	Contrast enhancement	Tissue biopsy
Paraneoplastic autoimmune limbic encephalitis	Associated cancers: small cell lung cancer (Hu, amphiphysin, CRMP5, GABA-Br, AMPAR), testicular cancer (Ma2), thymomas (AMPAR CRMP5),	Serum or CSF antibody assay
Non-paraneoplastic autoimmune limbic encephalitis	Anti CASPR2 encephalitis – Morvan syndrome (neuromyotonia, dysautonomia, insomnia, encephalopathy)	Serum or CSF antibody assay (LGI1, CASPR2, NMDAR)
	Anti-LGI1 encephalitis – hyponatraemia, faciobrachial dystonic seizures	
	Anti-NMDAR encephalitis – hallucinations, seizures, movement disorders and dysautonomia	

The differential diagnosis of MRI signal abnormalities in the medial temporal lobes is discussed in Table 1 and encompass both infective and non-infective aetiologies. For patients presenting with such neuroimaging abnormalities, a recommended first line workup should include lumbar puncture with multiplex viral PCR, serum HIV screen, serum syphilis TPPA and CSF VDRL thereafter if the serum TPPA result returns positive. Further testing for onconeural or neuronal surface antibodies or tissue biopsy may be considered if the initial workup returns negative.

Current best practice for diagnosing neurosyphilis relies on a combination of clinical history, physical examination findings, serum antibody tests, CSF analysis and neuroimaging. Treponemal tests, like syphilis TPPA, detect syphilis-specific antibodies. Once an individual has been infected with syphilis, these tests will usually remain positive for life. CSF assays for patients with neurosyphilis may reveal a lymphocytic pleocytosis and/or raised CSF protein; these findings are not specific, with normal CSF protein being identified in up to 47% of patients with neurosyphilis.[2] The CSF VDRL is regarded as the gold standard non-treponemal test to establish a diagnosis of neurosyphilis, with a sensitivity of 27-98.3% and a specificity of 74-100%.[2,7] CSF treponemal antibodies such as the CSF fluorescent treponemal antibody and TPPA have a sensitivity that ranges from 42-100% due to high intrathecal production; however, the specificity of CSF treponemal antibodies is relatively lower at 12.8-100% due to possible spillover from the systemic circulation.[2]

Treatment of neurosyphilis is with IV penicillin G administered as 3 to 4 million units every 4 hours for 10-14 days. Alternatives for penicillin-allergic patients include IV ceftriaxone 2 grams per day for 10-14 days or oral doxycycline 100mg twice a day for 1 month.[8]

Neurosyphilis is an easy-to-screen and treatable disease that should be considered in the differential

diagnosis in patients presenting with MRI signal abnormalities in the temporal lobes or limbic structures. Early recognition and initiation of treatment may limit cognitive complications and morbidity.

DISCLOSURE

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