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REVIEW

Neurosyphilis in disguise

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Abstract

Purpose Neurosyphilis can mimic different diseases, not only in its clinical presentation but also on imaging. *Treponema pallidum* is also known as the "great imitator." Having an ultimate diagnosis of neurosyphilis is quite critical as this can affect management drastically. Herein, we discuss the case of a 69-year-old female who was treated for neurosyphilis, while having an atypical imaging finding of anterior temporal lobe enhancement that simulated an infection with herpes simplex virus (HSV); we also review the available literature on different imaging findings in both the early and late stages of the disease.
Methods We performed a literature search using the new PubMed in June 2021. The terms "neurosyphilis", "MRI", and "neuroimaging" were used either alone or in combination with "early neurosyphilis" or "late neurosyphilis". Data on neurosyphilis and imaging findings was mainly derived from review articles, cohort studies, case series, and individual reports.
Conclusion Neurosyphilis can present with an extensive variation and different patterns on the MRI, and clinicians must be aware of the wide variety in radiological presentations. Anterior temporal lobe involvement is a rare presentation and requires evaluating for neurosyphilis to prevent a missed diagnosis and treatment.

Keywords Anterior Temporal Lobe · Mesisal Temporal Lobe · MRI · Neurosyphilis · Syphilis

Introduction

Few disorders are restricted or limited to involve the anterior temporal lobes; this is mostly seen due to herpes simplex virus (HSV) encephalitis, mesial temporal sclerosis, post ictal edema, Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CARASIL), and its autosomal dominant form (CADASIL) and gliomas [1]. We conducted this literature review aiming to understand the magnetic resonance imaging (MRI) findings of neurosyphilis as many patients reported in the literature have been misdiagnosed, received the wrong treatment, and faced a relapse of the disease due to the atypical and odd presentation on the MRI. We present a case where neurosyphilis involved the anterior temporal lobes on MRI. A high level of suspicion is absolutely needed to rule out syphilis, and we hope that neurologists and radiologists take it into consideration when facing an anterior temporal lobe involvement.

Our case presentation

A 69-year-old female presented with untreated syphilis infection that was diagnosed almost 20 years prior to her presentation. She was brought in with progressive decline in memory and confusion over 1 month. According to the family, the patient was not able to recall the name of her children or do her daily activities. On initial examination, she was alert but not oriented to herself, family members, location, nor time; she had perseveration while answering questions, and she was able to only mimic commands. The rest of her examination was otherwise unremarkable. Head computed tomography (CTH) was unremarkable. MRI of the brain with and without contrast showed anterior temporal lobes, insular cortex and pons T2, and fluid-attenuated recovery (FLAIR) hyperintensities that were all enhancing (Fig. 1). Syphilis serology was positive and reactive for IgG/IgM. Rapid plasma reagin (RPR) was nonreactive. Treponema pallidum hemagglutination (TPHA) test was positive, and HIV was negative. Cerebrospinal fluid (CSF) studies showed protein of 94.6 mg/

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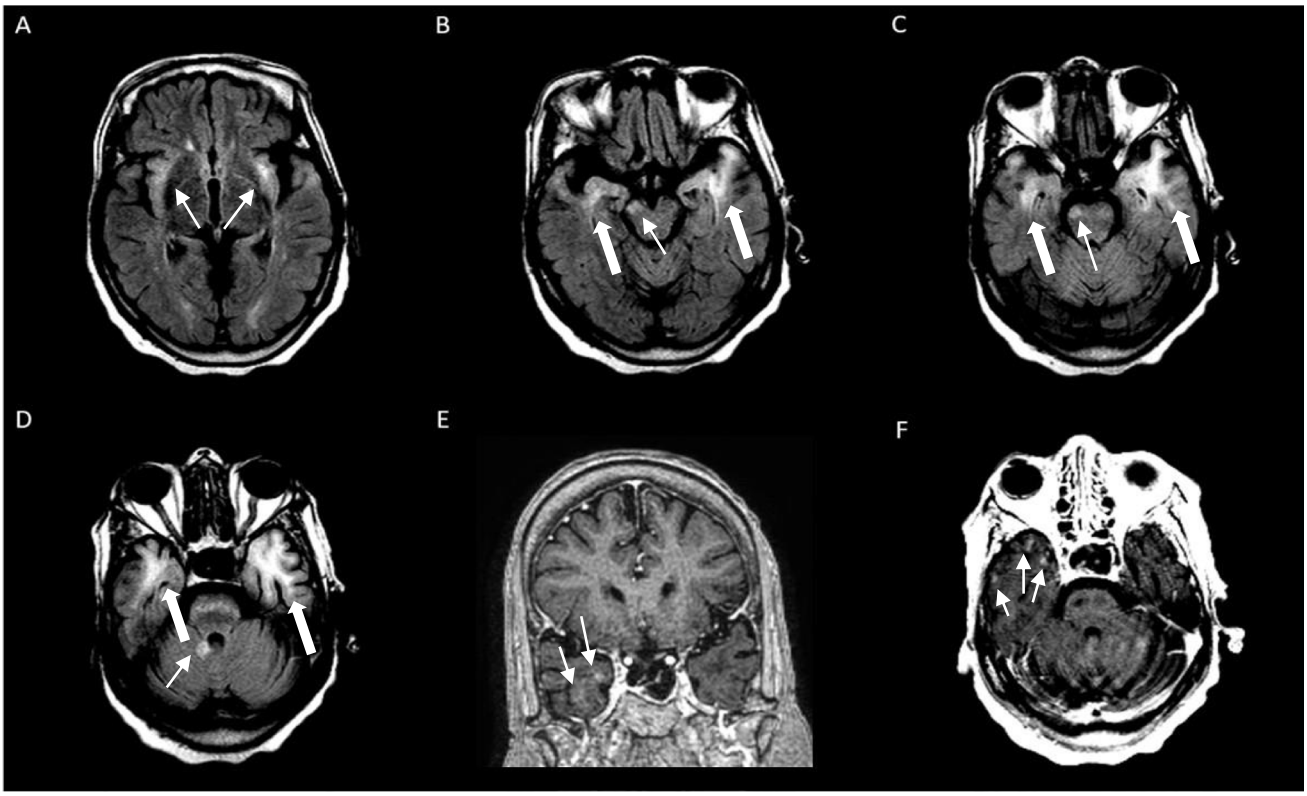

Fig. 1 Axial T2-FLAIR-weighted sequence without contrast showing bilateral insular (**A**), bilateral anterior temporal lobes (**B**, **C**, **D**—thick white arrows), right cerebral peduncle of the midbrain (**B**), anterior pons (**C**), and right superior cerebellar peduncle hyperintensities (**D**). Coronal T1-weighted with contrast (**E**) showing punctate foci of enhancement involving the right anterior temporal lobe that also show up on axial T1-weighted with contrast (**F**)

dL, WBC of 15 cells/mm^3 with lymphocytic predominance, and RBC of 35 cu/mm; Venereal Disease Research Laboratory (VDRL) test in the CSF was negative. Viral studies in the CSF, including cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes simplex virus-1 (HSV1), herpes simplex virus-2 (HSV2), and autoimmune encephalitis panel were all negative. Given the positive syphilis serology, negative VDRL in the CSF, elevated protein and lymphocytic predominance, and the clinical presentation, a presumptive diagnosis of neurosyphilis was made. Benzathine penicillin G 24 million units was given for the total of 14 days with improvement in her mental status on follow-up at 1 and 2 months (Fig. 2).

Discussion

Neurosyphilis can present at any stage of the disease [2]. It is categorized into early and late stages. Early neurosyphilis can present as meningeal, parenchymal, meningovascular disease, or can be merely asymptomatic. Late neurosyphilis can also present years after the initial infection, which manifests as tabes dorsalis and general paresis [3]. Our patient was peculiar given the fact she was diagnosed with late neurosyphilis with parenchymal involvement mainly in the anterior temporal lobe, unlike other reported cases where mesial temporal enhancement was the culprit. Despite the negative VDRL-CSF, a large proportion of neurosyphilis patients have false-negative VDRL-CSF as it has a low sensitivity [4]. Many patients have a combination of the several forms of neurosyphilis (outlined below). We have reviewed the literature and analyzed the different presentations of neurosyphilis (early and late) that appears on the MRI. Awareness of this condition, recognizing its characteristic MRI findings and having it on the list of differential diagnosis is of utmost importance for clinicians (Table 1).

Asymptomatic neurosyphilis

Asymptomatic neurosyphilis is defined as the presence of CSF abnormalities consistent with neurosyphilis in an asymptomatic patient without any neurological signs of the disease that also has positive serological markers [4]. It can present as an incidental finding in a completely asymptomatic patient, with a reactive CSF-VDRL. Roughly, in 75% of neurosyphilis patients, we can also expect to find a normal brain MRI or a nonspecific cerebral atrophy that might reflect a quiescent and long-standing disease [3].

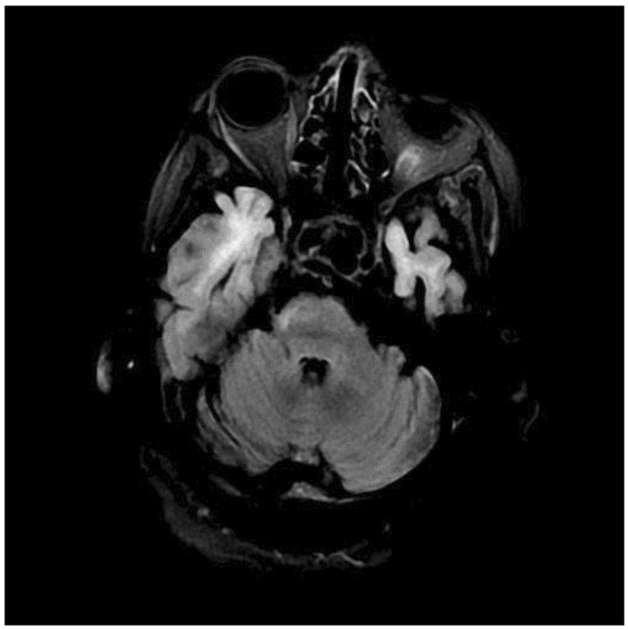

Fig. 2 Two months after receiving treatment, the previously described T2/FLAIR hyperintensity in the cerebellum is no longer visualized. It is also showing a stable anterior temporal lobe hyperintensities

Early symptomatic neurosyphilis

Acute syphilitic meningitis

a. Leptomeningeal enhancement

Acute syphilitic meningitis involves a diffuse inflammation of the meninges that leads to meningeal irritation. Patients usually present with headache, neck stiffness, confusion, and cranial nerve involvement. Leptomeningeal involvement can also be quite extensive to produce a thick exudate that can be seen on gross examination, reflected as a leptomeningeal enhancement on MRI [5].

b. Cranial nerve involvement

Cranial nerve disease can also be evident as exudates and inflammation extending from leptomeninges to cranial nerves. It has been reported that cranial nerve involvement can manifest as a diffuse and an asymmetric enhancement of the involved cranial nerve, either isolated nerves or in combination. Cranial nerve involvement included the 7th and 8th quite often [6, 7]. Another case showed a unilateral optic tract lesion surrounded by a rim of enhancement in a patient presenting with an isolated right homonymous hemianopsia [8]. Involvement of the optic [9], trochlear [10], oculomotor and trigeminal [11, 12, 18], and vagus nerves [13] has also been reported.

c. Syphilitic gumma

Syphilis can also cause a granulomatous inflammation forming central nervous system (CNS) gummas; those are frequently seen and often misdiagnosed as intracranial malignancies [5]. Signs and symptoms are often secondary to space occupation and can occur anywhere in the brain or spinal cord. Reported cases often present as T1 hypointense and T2 hyperintense lesions with adjacent edema [5]. Sometimes, however, they will present as a T1 isointensity and a T2 isointensity or hypointensity. The majority of these lesions are found on brain convexities. Other locations include pituitary gland and cerebellopontine angle [14]. They can also present as a ring enhancing lesion [15, 16], nodularity with a dural tail associated with thickening and enhancement of surrounding meninges [17, 18].

d. Acute syphilitic meningomyelitis

Neurosyphilis can involve the spinal cord as either tabes dorsalis or syphilitic myelitis. Syphilitic meningomyelitis is described as progressively worsening paraplegia with variable sensory and sphincter disturbances and loss of superficial abdominal reflexes [19]. T2 hyperintense lesions confined to the central and superficial parts of the spinal cord that extends over multiple levels and associated with enhancement is commonly described, having the characteristic "candle guttering appearance" or the "flip-flop sign" indicating syphilitic myelitis [20, 21].

In contrast to tabes dorsalis, dorsal column is usually affected rather than centrally with a similar T2 hyperintensity [22, 23]. Given the rarity of syphilitic myelitis and the fact that it presents with no specific clinical nor imaging findings, we must consider its possibility in a long segment abnormality, as it is potentially treatable.

e. Parenchymal lesions

Parenchymatous neurosyphilis can be seen in both early and late stages of the disease, where leptomeningeal involvement due to *Treponema pallidum* can directly extend to the parenchyma [24]. FLAIR and T2 mesiotemporal hyperintensities are a well-described pattern [25–30]; they can be bilateral and asymmetric. Thalamic involvement has also been reported [31]. Bilateral mesial and anterior temporal T2 hyperintensity are considered to be "virtually pathognomonic" for HSV encephalitis [25]. Although neurosyphilis is known to involve the more commonly reported and characteristic mesial temporal lobes and hippocampi involvement, a very few cases—including our own—have mentioned the possibility of an anterior lobe involvement [32]. The exact cause behind temporal lobe hyperintensity is unclear but might be related to edema and gliosis resulting from the inflammation [25].

Neurosyphilis has a more indolent course than HSV, and therefore, imaging will be significant for cerebral atrophy with larger temporal horns [33, 34]. This is unlikely the case in HSV as the infection is more fulminant, and hence, findings will be secondary to mass effect and signs of hemorrhage. Clear boundaries between lesions on the outer edge of lenticular nuclei, often called "knife signs," are also more suggestive for viral than bacterial encephalitis [27].

Table 1 Clinical and radiological characteristics of Neurosyphilis throughout the literature

Author	Year	Study type	Age (years old)	Gender	Clinical presentation	Onset of initial infection	Test used for diagnosis	MRI finding
Frohman and Wolansky	1996	Case report	42	Female	Progressive vision loss		RPR 1:32, serum FTA-Abs-positive	Right optic nerve enhancement
Smith and Anderson	2000	Case report	51	Female	Headache, bilateral facial weakness, and bilateral hearing loss		CSF with high protein, lymphocytic pleocytosis, VDRL-CSF +	T1 enhancement of bilateral 8th CN
Bash et al	2001	Case report	50	Male	Memory loss and confusion		RPR 1:64, TPHA, CSF-VDRL, and FTA-ABS-positive	Unilateral mesial temporal lobe FLAIR and T2-hyperintensity without enhancement
Pollock et al	2007	Case report	61	Male	Left-sided hemiparesis		N/A	Ring enhancing multiple gummatous lesions
Hadrane et al	2007	Case report	41	Male	Right 8th and left 7th nerve palsies		VDRL and TPHA in the CSF	Syphilitic gummas and cranial nerve enhancement
Fargen et al	2009	Case report and literature review	All age groups (95.4% were > 18 years old)	86 were males and 49 were females	Headache and seizures being most common		RPR: 1:32, CSF-VDRL-negative	T1-hypointense on and T2hyperintense with adjacent edema on non-contrast-enhanced MRI. All cases revealed contrast enhancement
Ghanem	2010	Literature review	N/A	N/A	N/A	N/A	N/A	Generalized cerebral atrophy and T2 hyperintensities
Pandey et al	2011	Case report	39	Male	Paresthesia in the lower limbs and vision loss	20 years prior to presentation	Positive CSF-TPHA and VDRL but normal CSF	Normal brain MRI, spinal cord MRI showing T2 intramedullary hyperintensity without enhancement and cord atrophy
Klein and Ridley	2014	Case report	41	Male	Left vocal fold paresis and velopharyngeal incompetence		CSF with high protein, VDRL-positive	MRI was not done but patient had vagal neuropathy on examination
Author	Year	Study type	Age (years old)	Gender	Clinical presentation	Onset of initial infection	Test used for diagnosis	MRI finding

Table 1 (continued)

Author	Year	Study type	Age (years old)	Gender	Clinical presentation	Onset of initial infection	Test used for diagnosis	MRI finding
Pesaresi et al	2015	Case series and literature review	38–43	N/A	General paresis on the insane presenting as personality changes, memory impairment, and/or aphasia		TPHA serum and CSF, CSF pleocytosis, and protein	SWI cortical hypointensity
Siu	2017	Case report and literature review	41	Male	Numbness in his upper and lower limbs		CSF-VDRL-positive	MRI spine showing T2 focal enhancement without spinal cord atrophy
Wu and Wu	2019	Case series and literature review	4 patients, age range of 30–69	2 males and 2 females	N/A		N/A	MRI with T2 hyperintensity associated with enhancement in cervical and thoracic spinal cord and cauda equina
Elmouden et al	2019	Case series and literature review	12 patients, age range of 33–57	(92% males) and one female	N/A	Median of 20 years	N/A	All cases with hyperintense T2 in the spinal cord, syringomyelia in one case and spinal atrophy in two cases
Komamura et al	2019		51	Male	Right peripheral facial nerve palsy	N/A	RPR 1:16, serum TPHA positive, CSF with positive TPHA and FTA-ABS	Hyperintense lesions in the medial side of the right trigeminal nerve on contrast-enhanced T1-weighted imaging
Piura et al	2019	Case report	34	Male	Ipsilateral hearing impairment and facial weakness	N/A	High protein, lymphocytic pleocytosis, CSF and serology-positive TPPA	T1 enhancement of 7th and 8th CN
Santana et al	2020	Pictorial essay	N/A	N/A	N/A		N/A	T1 anterior temporal lobe enhancement
Feitoza et al	2020	Case report	26	Male	Acute onset right hemiparesis, diplopia and fever	N/A	VDRL in serum and CSF were positive	Left hemipontine infarction
Thibodeau et al	2021	Case report	37	Female	Decline in mental status	4 months prior to her presentation	RPR 1:32,	T2/FLAIR cerebral gummatous lesions

Table 1 (continued)

Author	Year	Study type	Age (years old)	Gender	Clinical presentation	Onset of initial infection	Test used for diagnosis	MRI finding
Our case	2021	Case report and review	69	Female	Progressive dementia, aphasia, and confusion	20 years ago	Positive serum RRP and TPHA. VDRL negative	Bilateral anterior temporal lobe enhancement on T2 and FLAIR

CSF, cerebrospinal fluid; *FLAIR*, fluid-attenuated inversion recovery; *FTA-ABS*, Fluorescent Treponemal Antibody Absorption Test; *MRI*, magnetic resonance imaging; *N/A*, not available; *RPR*, rapid plasma regain; *TPHA*, indirect hemagglutination assay; *VDRL*, Venereal Disease Research Laboratory

Meningovascular syphilis

Meningovascular neurosyphilis mainly presents with a prodrome of symptoms that can include headaches, dizziness, insomnia, or even emotional liability that can last weeks to months. This "subacute encephalitis" is usually followed by a vascular event secondary to endarteritis anywhere in the CNS [35]. Changes on MRI, such as parenchymal enhancement, stroke, white matter changes, are mainly secondary to endarteritis and vasculitis [4]. Syphilis can cause vasculitis via direct invasion of vascular wall, immune complex deposition, or through secondary cryoglobulinemia leading to vascular wall thickening with contrast enhancement [36]. ICH and subarachnoid hemorrhages have also been reported [3].

Peng et al. studied 14 patients; the most common imaging finding reported was a mesial temporal lobe cortical atrophy, and 43% (6 patients) had multiple cerebral infarcts associated with vascular stenoses, including the anterior cerebral artery and the middle cerebral artery (MCA) [37]. Another study also redemonstrated cerebral infarctions as being the second most common imaging finding of neurosyphilis; with the MCA being the main culprit vessel, basilar artery abnormalities were also well-reported in literature [38–41]. Angiographic intra- and extracranial stenoses were also reported, presenting as segmental constriction or occlusions which can be concentric, asymmetric, and with a beaded appearance [42, 43].

Pesaresi et al. described 3 patients with neurosyphilis; MRI-SWI sequences were studied closely, showing a bizarre hypointensity mainly in frontotemporal lobes. The hypointensities were extending over the whole cortical thickness from cortical/subcortical junction prior to giving antibiotics. However, after treatment, those lesions were significantly lesser in size. This was thought to be secondary to iron deposition in brain tissue, in the walls of cortical vessels, and in the cytoplasm of microglial cells. Those cells show an activated state in neurosyphilis and assume a bipolar form perpendicular to the dural surface across cortical layers [44].

Late syphilis

Parenchymal involvement in the chronic disease is very rarely seen in the antibiotic era but if it was present, then it can be as either general paresis or tabes dorsalis [37, 45].

General paresis

Patients with general paresis present with irritability, forgetfulness, personality changes, and headaches that can evolve into seizures, delirium, depression, psychosis, and Argyll-Robertson pupils which is mainly thought to be secondary

to the extensively damaged parenchyma in cortical regions of the brain [4]. The average time from the infection to onset of general paresis (also called general paresis of the insane) is between 15 and 20 years [46].

Cortical atrophy was the most common feature of general paresis on MRI, usually with a wide varying degree of atrophy and hyperintensity of frontal, temporoparietal lobes, hippocampus, and corpus callosum on the T2 and FLAIR and is considered to be the etiology of dementia in affected patients [5]; this oftentimes can be misdiagnosed as Alzheimer's disease as they would present with a similar progressive cognitive decline with atrophy on imaging [47].

Mesial temporal atrophy has been recognized as a typical feature of this condition and usually associated with a poor prognosis. This is usually associated with other findings such as small vessel disease, infarctions, and edema; this could be the result of small vessel arteritis and resulting ischemia. Those were mainly reported as multiple, discrete lesions that were ranging between 2 and 8 mm in size [37], sometimes, not only atrophied but also hyperintensity of frontal, temporoparietal lobes. Hippocampal and corpus callosum on the T2 and FLAIR have experienced improvement after initiating antibiotic treatment [3, 37]. Given the onset of the initial infection, our patient with her clinical presentation of progressive decline dementia, would mostly fit under this category.

Tabes dorsalis

Tabes dorsalis, similar to general paresis, is the neurological manifestation of a previous infection with syphilis after an average latency period of 20–25 years [45, 46]. Affecting the posterior columns of the spinal cord and dorsal roots, this disease commonly presents as ataxia and neuropathic pain and less commonly as paresthesia and Romberg was the first to describe this classic manifestation. On imaging, it has been well-described as T2 hyperintense intramedullary lesions with T1 contrast enhancement. Cord atrophy also has been described in literature and this carries a worse prognosis [21]. Tabes dorsalis can also mimic subacute combined degeneration of the spinal cord, fulfilling *T. pallidum*'s well-known moto "the great masquerader" [22].

Conclusion

Many questions persist on how to diagnose neurosyphilis with imaging and with neurosyphilis incidence being on the rise, we hope that this review raises awareness and highlights the utmost importance of syphilis mimicry of other disease processes, considering the potential therapeutic implications and the quite different treatment pathways and the prevention of ongoing neurological damage. This unusual finding and remarkable similarity of both imaging findings plus the clinical presentation makes it worth listing neurosyphilis next to many disease processes including HSV on the differential list.

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Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

Ethics approval No institutional approval required for Case Reports.

Consent to participate The subject included has given consent to participate.

Consent for publication The subject included has given consent and agreed to the publication of the manuscript.

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