Neurosyphilis in MRI: a pictorial review to remember the old faces of the great mimicker

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Learning objectives

To review neurosyphilis clinical-pathological main aspects according to the different subsets of clinical presentation and highlighting typical and atypical neurosyphilis imaging findings correlating to the possible differential diagnosis.
Background

Syphilis is a systemic sexually transmitted disease caused by the spirochete *Treponema pallidum*. Around 5.6 million new cases of syphilis in patients aged 15-49 years worldwide in 2012, with a global incidence rate of 1.5 cases per 1000 females and 1.5 cases per 1000 males. Left untreated, syphilis can progress through four stages: primary syphilis, secondary syphilis, latent syphilis, and tertiary syphilis (1).

Invasion of the central nervous system by spirochetes may occur in up to 40% of untreated patients. Neurosyphilis is classified as asymptomatic neurosyphilis, interstitial neurosyphilis (syphilitic meningitis or meningovasculitis), parenchymatous neurosyphilis (general paresis or tabes dorsalis), and cerebral syphilitic gumma. Manifestations of patients with neurosyphilis are diverse and have no specificity in clinic (1,2).

Besides being a well known disease, neurosyphilis is also known as the "great imitator", considering the different possibilities of central nervous system impairment, such as isolated cranial nerve involvement, tumoral-like variants, spinal, bone and meningovascular subsets. These presentations can mimic several disorders like intra- and extra-axial neoplasm, multiple sclerosis and autoimmune encephalitis, and should be always considered as a differential diagnosis (3-5).
Findings and procedure details

We have conducted a pictorial essay of typical and atypical imaging features of neurosyphilis.

We also divided didactically them according to its pattern of structures involved, as well as its main differential diagnosis (Fig. 1 on page 9).

• Cranial nerves involvement (optic neuropathy; multiple cranial nerves; otosyphilis);
• Tumor-like lesions (intra- and extra-axial, including lesions with and without gadolinium enhancement);
• Spinal cord abnormalities;
• Bone impairment;
• Meningovascular subset.
• Miscellaneous

1) CRANIAL NERVES INVOLVEMENT

According to the literature, acute syphilitic basilar meningitis can be characterized primarily by the presence of cranial nerve involvement, most commonly the 8th (42%), 7th (41%), 2nd (27%), and 3rd (24%) cranial nerves. Involvement of the seventh and eighth cranial nerves results in symptoms of facial paralysis, sensorineural hearing loss, and vertigo. A high index of suspicion and knowledge of the Magnetic resonance imaging (MRI) features is necessary to diagnose this highly treatable cause of progressive hearing loss and facial paralysis [2,6] (Fig. 2 on page 9).

In syphilis, optic neuritis is rare and there is nothing characteristic about its appearance to distinguish it from non-syphilitic involvement of similar distribution. The optic nerve involvement may be unilateral or bilateral and manifest as perineuritis, anterior or retrobulbar optic neuritis or papilledema. Usually, optic perineuritis is asymptomatic, in optic neuritis however, there is usually rapid visual failure [7]. (Fig. 3 on page 10, Fig. 4 on page 11)

2) SPINAL CORD ABNORMALITIES

Jean-Alfred Fournier in 1875 hypothesized that there may be a syphilitic origin for tabes dorsalis, which is characterized by general paresis, optic atrophy, myelitis. Of people infected with Treponema pallidum, 3-5% develop neurosyphilis; 5% of those individuals develop tabes dorsalis, a form of late tertiary syphilis, 10-20 years later. It is
a progressive degenerative process involving demyelination and inflammatory changes of the spinal cord. The dorsal root ganglion, nucleus fasciculus, posterior column tract, and lumbosacral roots are more susceptible to demyelination [8].

Imaging findings show edema and spinal cord enlargement in acute setting, that evolver to atrophy and residual intramedullary hyperintensity on T2WI without any enhancement on gadolinium, suggestive of focal myelitis. In advanced cases, anterior horn cells may also be involved [9]. (Fig. 5 on page 12)

As differential diagnosis, other infectious diseases that affect the dorsolateral medullary column can be considered, such as HIV, manifesting as vacuolar myelopathy and HTLV-1 spinal cord involvement. Non-infectious diseases that show similar spinal cord findings to syphilis are multiple sclerosis and adrenomyeloneuropathy. (Fig. 6 on page 13)

3) TUMOR-LIKE LESIONS

Cerebral syphilitic gumma, was first described by Botalli in 1563, and it is a rare manifestation typically of tertiary syphilis, with formation of circumscribed masses of granulation tissue, due to an excessive response of the cell-mediated immune system to T. pallidum [9, 10].

Gummas are uncommon and usually develops from the dura and pia mater over the cerebral convexity or at the base of the brain. Single or multiple masses attached to the dura mater can invade brain parenchyma, with development of symptoms similar to those of other tumors arising from brain parenchyma, often accompanied by a seizure, other differential diagnosis that should be considered are toxoplasmosis, lymphoma, bacterial and fungal infections, all of them more common in HIV-positive patients [10, 11].

On CT images, they appear as peripherally located lesions that are isoattenuating relative to the cortex. On MRI, they are low or isointense relative to gray matter on T1-weighted images (T1WI), hyperintense on T2-weighted images (T2WI) with post-contrast enhancement [12]. Another feature described in the literature is the adjacent area of the mass showing high intensity on T1WI and a low intensity on T2-weighted images [13]. (Fig. 7 on page 14)

Advanced sequences are not always useful, specially when facing rim enhancement lesions. Diffusion-weighted images can show high signal intensity in the central portion of the lesion, indicating the possibility of brain abscess, whereas MR spectroscopy can show higher peaks of choline compounds, indicating the possibility of tumor rather than abscess [12, 13]. (Fig. 8 on page 15)
Spirochetes are rarely identified from tissue samples, therefore, under clinical suspicion of cerebral gumma, serologic tests and polymerase chain reaction (PCR) for *T. pallidum* can be useful for definitive diagnosis [10].

Although in many times it is not possible to distinguish brain gumma from other lesions solely based on the imaging aspects, case reports suggest that, from an empirical perspective, a high-dose penicillin therapy accompanied with MRI findings of a decrease in mass size, would be useful for the diagnosis and treatment of brain gumma, specially in cases where neurosyphilis could be diagnosed based on the CSF examination, thereby avoiding unnecessary surgeries [10]. (Fig. 9 on page 16)

4) BONE INVOLVEMENT

Skeletal system involvement usually occurs at a late or tertiary stage of the disease and the diagnosis of syphilitic osteitis is usually suspected because of the presence of either mucocutaneous findings or generalized lymphadenopathy [14].

Skull base involvement can be shown at conventional radiographs and CT scans as round osteolytic areas with demineralization or sclerosis of the outer table and diploe, with irregular moth-eaten morphology, characteristic of calvarial syphilitic involvement. New bone formation can also be seen sometimes, typically along the periphery of the lesion [14].

MRI demonstrates marrow space involvement and periosteal process, allowing a better assessment of the degree of intracranial extension than CT. It may also show the focal enhancing calvarial lesions and adjacent enhancing soft tissue abnormality in the scalp [14].

Another known form of bone involvement is the luetic osteitis of the temporal bone, a rare but important cause of deafness. A typical permeative, moth-eaten appearance lesion of the temporal bone, with resorption of the otic capsule and involvement of the ossicular chain, being highly specific for this form of the disease [15]. Its occurrence has been increasing with the rising prevalence of acquired immunodeficiency syndrome. Computed tomography (CT) imaging features of the petrous temporal bones shows extensive, bilateral lucent areas in the otic capsule, particularly around the cochlea but also involving the vestibule and semicircular canals. As additional findings, enhancement of the cochlea and of the vestibulocochlear nerves can also be seen as the result of spreading of the inflammatory process via the endolymphatic or perilymphatic fluids [15]. (Fig. 10 on page 17, Fig. 11 on page 18)
Importantly, these cases present ossicular involvement and sparing of the fissula ante fenestram. Some diseases can be considered as differential diagnosis, such as osteopetrosis, osteogenesis imperfecta, paget’s disease and fibrous dyplasia [14].

5) MENINGOVASCULAR

Meningovascular syphilis is a distinct form of neurosyphilis characterized by a combination of chronic syphilitic meningitis and arteritis, leading to a meningoencephalopathic syndrome with superimposed cerebrovascular or myelovascular events. It results in injury to the blood vessels of the leptomeninges, brain, and spinal cord, leading to infarctions, with histopathological findings similar to autoimmune arteritis, such as lupus erythematosus or polyarteritis nodoseouz [16].

Clinically it manifests as an acute stroke syndrome or, more commonly, as a subacute illness. Symptoms include headache, vertigo, seizures, transient hemiplegia, insomnia, and psychological disturbances, and may appear from months to years after the primary infection [12, 16].

Two types of arteritis have been described: Heubner arteritis, the most common form, affecting medium and large arteries, and Nissl-Alzheimer arteritis, affecting small arterial vessels. Both types resulting in vessel occlusion and secondary ischemia. There are no specific radiological findings for meningovascular syphilis. MRI usually shows multiple areas of brain or spinal cord infarction, meningeal thickening and abnormal enhancement. Angiography often reveals varying degrees of segmental, concentric steno-occlusive arteriopathy [17]. (Fig. 12 on page 19)

Although there are no specific findings, it is important to place meningovascular syphilis upon the differential diagnosis when facing cases of young adults presenting with multiple brain and spinal ischemic lesions, specially when history of prior sexually-transmitted diseases, high-risk sexual behavior, and symptoms such as progressive headaches, memory disturbances, or behavioral abnormalities are present [17]. (Fig. 13 on page 20)

6) MISCELANEOUS

A) NEUROSYPHILIS X MULTIPLE SCLEROSIS

Optic neuritis is the most common multiple sclerosis presentation as a clinically isolated syndrome. Optic nerve involvement in syphilis is often a later stage manifestation of the
disease, however, it can occur earlier in immunocompromised patients. The involvement of other cranial nerves is an important clue for distinguishing syphilis from multiple sclerosis in the case of optic neuritis [18].

Spinal cord involvement in *tabes dorsalis* can also mimic multiple sclerosis, presenting as long-segment hyperintensity on T2WI of the lateral columns, occasionally with gadolinium enhancement, usually evolving to atrophy of the lateral columns. Characteristic spinal cord lesions in multiple sclerosis are usually focal, ovoid and do not extend longer than three vertebral bodies segments in length. Atypical clinical presentation and imaging features that do not fit the classic pattern should raise suspicion for other conditions, such as infectious diseases and syphilis [18]. (Fig. 14 on page 21)

**B) NEUROSYPHILIS X DEMENTIA**

Although rare, neurosyphilis can present itself as a cause of dementia characterized by a rapidly progressive course and psychiatric symptoms. Diagnosis of neurosyphilis should be suspected in the presence of rapidly progressive dementia associated with neuropsychiatric symptoms, such as personality changes, amnesia, delusions, hallucinations and delirium. While there is no specific imaging pattern for neurosyphilis, MRI can be helpful excluding other diagnoses with similar clinical presentation, such as sporadic Creutzfeldt-Jakob disease and inflammatory/autoimmune, malignancy-related or toxic-metabolic conditions. Focal or diffuse brain atrophy as well as infarcts and white matter changes are usually described [19]. (Fig. 15 on page 22, Fig. 16 on page 23, Fig. 17 on page 24)

**C) NEUROSYPHILIS X ENCEPHALITIS (INFECTIOUS AND NON-INFECTIOUS/ AUTO-IMMUNE)**

Bilateral mesiotemporal T2WI hyperintensity on MRI is characteristic of herpes virus encephalitis and auto-immune limbic encephalitis, however are not specific to them. A similar imaging pattern can be found in patients with neurosyphilis, as described in a few case reports. The literature shows that the temporal lobe involvement can be unilateral or bilateral, and frontal lobe lesions can also be found. Another feature that may be present is leptomeningeal enhancement [20, 21, 22]. (Fig. 18 on page 25, Fig. 19 on page 26)
Fig. 1: Differential diagnosis of neurosyphilis

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Fig. 2: Multiple cranial nerve involvement. Female, 25 years-old, bilateral hearing impairing, diplopia and facial hypoesthesia. Enlargement and abnormal enhancement of the 3rd nerves (yellow arrows), 5th nerves (red arrows) and cochlear and internal auditory canal - 7th/8th nerves (blue arrows).

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**Fig. 3:** Isolated optic neuritis. Male, HIV positive, 4 days of visual disturbances. Palmar and plantar hyperemic lesions typical of the secondary syphilis (yellow circles). Cerebral spinal fluid distension of bilateral 1st nerve myelin sheath and subtle enhancement of the optic papilla (red arrows).

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Fig. 4: Male patient, 42 years old, bilateral progressive visual loss. VDRL +. Bilateral anormal T2 sign and enhancement of optic nerve (right > left).

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Fig. 5: Extensive myelitis secondary to syphilis infection. Intramedullary hyperintensity on T2WI, marked gadolinium enhancement, suggestive of myelitis. Patient has evolved to severe spinal cord atrophy.

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Fig. 6: Differential diagnosis for spinal cord atrophy secondary to syphilis. Image A showing diffuse spinal cord atrophy in the context of vacuolar mielitis. Image B demonstrate spinal atrophy, predominantly in the posterolateral segments (similar to syphilitic involvement - red arrows) in a patient with adrenomyeloneuropathy.

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Fig. 7: Male, 38 years old. Extra-axial Gumma. Multiple extra-axial lesions adjacent to frontal lobes with marked hipointensity on T2WI (red arrows), dural and lesional post contrast enhancement (yellow arrows) and extensive vasogenic edema (blue arrows), some of them showing restricted diffusion central areas (green arrow).

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**Fig. 8:** Female, 43 years old, seizures. Intra-axial gumma. Isolated intra-axial lesion on superior temporal gyrus with peripheral hipointensity on T2WI and FLAIR (red arrows), rim enhancement (yellow arrow). Diffusion-weighted images can show high signal intensity in the central portion of the lesion with low ADC (blue arrow). MR spectroscopy is not specific.

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Fig. 9: Male, 21 years old. HIV + not treated. Bilateral deafness, visual disturbance and headache. Frontal opercular extra-axial lesion (yellow arrow), associated to adjacent vasogenic edema (red arrow). Bilateral internal auditive canal and cochlear enhancement (left > right) - blue arrow. Cystic bilateral parotid lesions - Benign lymphoepithelial lesions (green arrow).

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**Fig. 10:** Luetic osteitis of the temporal bone. Unenhanced computed tomography, axial view: images at the level of the cochlea, showing a permeative, 'moth-eaten' pattern of demineralisation involving the left otic capsule (red arrows).

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**Fig. 11:** Otosyphilis. Female, 25 year old, HIV positive, bilateral earing loss more severe on the right. Bilateral cochlear abnormal signal on FLAIR and T2, associated to post contrast right basal turn enhancement and left auditory internal canal (yellow arrows).

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Fig. 12: Meningovascular syphilis (arteritis). Heubner arteritis. Wall thickening and abnormal enhancement of the basilar artery and left internal carotid artery (red arrows)

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**Fig. 13:** Meningovascular syphilis. Contrast-enhanced FLAIR axial view shows hyperintense cerebrospinal fluid filling the convexity sulci, as well as abnormal left frontoparietal pachymeningeal thickening and enhancement (red arrows)

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**Fig. 14:** Neurosyphilis x multiple sclerosis. 35 years old male patient, progressive cognitive impairment. Multiple hyperintense on FLAIR periventricular and juxtacortical lesions mimicking demyelinating lesions (red arrow). There is abnormal linear perivascular space enhancement associated.

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**Fig. 15:** Brain atrophy. Male, 48 years-old, presenting with dementia and psychiatric symptoms for 2 weeks. Axial T1WI and T2WI show signs of bilateral temporal atrophy. The coronal T1WI shows signs of right hippocampal atrophy, with loss of it's internal architecture (red arrow).

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Fig. 16: Brain atrophy. Male, 52 years-old, presenting with amnestic and behavioral troubles. Coronal T1WI and T2WI, axial FLAIR and T2WI displays brain atrophy, mostly on temporal lobe (left > right). Brain spect shows bitemporal hipoperfusion (left-right)

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**Fig. 17:** Meningovascular syphilis and brain atrophy. Extensive leptomeningitis, associated to abnormal areas of T2 hiperintensity in medium cerebelar peduncle and periatrial region.

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**Fig. 18:** Temporal encephalitis. MR images show bilateral mesiotemporal hyperintensity on FLAIR (left). Contrast-enhanced T1WI axila view shows bilateral mesiotemporal foci of enhancement as well as leptomeningeal thickening (red arrows).

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Fig. 19: Syphilitic encephalitis mimicking autoimmune encephalitis, 45 years old male patient behavioural disturbance and fever, VDRL +. MR images display symmetrical bilateral white matter hypersignal in FLAIR. No foci of diffusion restriction or abnormal parenchymal enhancement. There is abnormal cochlear enhancement on the right.

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Conclusion

Syphilis is a treatable and curable re-emergent disease. It is important that radiologists recognize it as a "great imitator" differential diagnosis, considering the many available possibilities of neurosyphilis clinical presentation as well as its non-specific imaging findings, in order to provide early diagnose and treatment.
References


