MR FINDINGS IN NEUROSYPHILIS – A LITERATURE REVIEW WITH A FOCUS ON A PRACTICAL APPROACH TO NEUROIMAGING

Monika Czarnowska-Cuba, Mariusz S. Wiglusz, Wiesław Jerzy Cuba, Katarzyna Jakuszkowiak-Wojten, Jerzy Landowski & Krzysztof Krysta

1First Department of Radiology, Medical University of Gdańsk, Poland
2Department of Psychiatry, Medical University of Gdańsk, Poland
3Department of Psychiatry and Psychotherapy, Medical University of Silesia, Katowice, Poland

SUMMARY

Background: Syphilis is a sexually transmitted disease caused by Treponema pallium. The invasion of the central nervous system is observed in 5-10% of untreated patients and may occur at any stage of the disease. The diagnosis of the early stage of syphilitic infection is complex as many patients present either nonspecific symptoms or are asymptomatic. The identification of the most common radiologic characteristics of neurosyphilis is important in the proper diagnosis of the infection.

Method: The paper reviews the MR findings in neurosyphilis presented in the literature with the emphasis on common traits, patterns and factors in MR neuroimaging in neurosyphilis.

Results: Twelve papers were selected as suitable for analysis. Psychiatric symptomatology was the most common clinical manifestations of neurosyphilis. As MRI findings in neurosyphilis were not highly specific it proved being the most sensitive technique in detecting the changes in cerebral vasculitis commonly presenting with focal areas of high signal intensity in any distribution with areas of infarction and hemorrhage observed at times. In neurosyphilis medium and small vessels are usually involved. Parenchymal and meningeal enhancement was usually demonstrated. The most frequently involved arteries are middle cerebral artery and branches of the basilar artery. However, normal findings were also common.

Conclusions: The most common MR diagnostic features are medium contrast enhancement, atrophy, white matter lesions, cerebral infarction, oedema. Radiologists, neurologists, and psychiatrists should take neurosyphilis into consideration when facing the differential diagnosis in central vascular disorders.

Key words: syphilis - magnetic resonance – neuroimaging – neuroinfection - diagnostics

INTRODUCTION

Syphilis is a sexually transmitted disease caused by Treponema pallium. Current reports on the number of patients with neurosyphilis have increased with the advent of the human immunodeficiency virus (HIV) epidemic. The invasion of the central nervous system is observed in 5-10% of untreated patients and may occur at any stage of the disease. The diagnosis of the early stage of syphilitic infection is complex as many patients present either nonspecific symptoms or are asymptomatic. The identification of the most common radiologic characteristics of neurosyphilis is important in the proper diagnosis of the infection (Suarez et al. 1996, Rozwens et al. 2003).

The aim of the paper is to review the MRI (Magnetic Resonance Imaging) findings in neurosyphilis presented in the literature.

EPIDEMIOLOGY, PATHOLOGY AND CLINICAL MANIFESTATION

Multiple bacteria, viruses, fungi, and protozoa have been reported as causes of central nervous system (CNS) vasculitis, particularly in immunocompromised hosts. Syphilis and tuberculosis have re-emerged as prominent causes of CNS vasculitis because of the HIV epidemic. The neuroinfection can cause vasculitis by direct invasion of the vessel wall, immune complex deposition, or through secondary cryoglobulineaemia (Scolding 2009).

Vasculitis may be classified by the histology of the lesion or by the size of the vessel involved (Scolding 2009). The categorization by vessel size into large, medium, and small vessels according to the Chapel Hill nomenclature (Jennette et al. 1994) and American College of Rheumatology classification (Hunder et al. 1990) seem to be the most useful for neuroimaging purposes (Küker 2007). The current modified Chapel Hill classification indicates that the vessels predominantly involved in large vessel cerebral vasculitis include internal carotid artery, intracranial vertebral artery, basilar artery, M1 and A1 segments of middle and anterior cerebral arteries and P1 segment of the posterior cerebral artery. Middle-sized vessels are similar in size to those distal to the bifurcation of the middle cerebral artery. Small-sized vessel vasculitis involves vessels beyond the resolution of digital subtraction cerebral angiography (DSA) (Küker 2007).

Vasculitis associated with infections can affect vessels of all three sizes. In neurosyphilis usually medium and small vessels are involved. The most
frequently involved arteries are the middle cerebral artery and branches of the basilar artery (Holland et al. 1986). The clinical manifestations of primary vasculitis of the CNS are limited to the nervous system and may include headaches, encephalopathy, stroke, coma, cranial neuropathies, and myelopathy (Mumtaz et al. 2005). In addition, systemic symptoms, such as fever, malaise, rash, myalgias, arthritis, arthralgias, are usually absent (Okuda & Vollmer 2005). At this time, psychiatric symptomatology is the most common clinical manifestation of neurosyphilis (Mitsonis et al. 2008, Cubala & Czarnowska-Cubala 2008).

Neurosyphilis may be categorized as early and late. Early neurosyphilis affects primarily the meninges and cerebrospinal fluid and occurs within weeks or a few years of the infection. The meningovascular form is characterized by mild, non-supportive, chronic inflammation of the leptomeninges and involvement of the small blood vessels of the meninges, brain and spinal cord leading to infarcts and transitory or permanent ischemic incidents (Kent & Romanelli, 2008). Late stage neurosyphilis primarily affects the CNS parenchyma and is observed several years to decades after the initial infection (Marra 2004). Psychotic symptoms and cognitive impairment may present as the consequence of the extensively damaged parenchyma in cortical regions of the brain, known as general paresis, the encephalitic form of neurosyphilis, which typically presents as progressive cognitive decline beginning 10–20 years after the point of infection. The clinical features of the general paresis include cognitive impairment, delusions, apathy, seizures, dysarthria, myoclonus, intention tremors, hyperreflexia, and Argyll-Robertson pupils (Kent & Romanelli, 2008, Luo et al. 2008, Rozwens et al. 2003). Variable degrees of cerebral recovery process after receiving antisyphilitic therapy has been reported (Luo et al. 2008, Lee et al. 2009, Tso et al. 2008, Kararizou et al. 2006).

MRI FINDINGS IN NEUROSYPHILIS

MRI is the most sensitive technique in detecting changes in cerebral vasculitis involving large, medium, and small vessels. Its sensitivity approaches 100%. However, its specificity is considerably lower. Thus, a normal MRI examination result does not exclude vasculitis (Kraemer & Berlit 2009, Harris et al. 1994, Calabrese et al. 1997, Aivv et al. 2006).

Neurovasculitis in MR images usually presents with focal areas of high signal intensity. Those may be observed at any distribution, including subcortical white matter, deep white matter, or gray matter with areas of infarction and hemorrhage. Parenchymal and meningeal contrast minimum enhancement can also be demonstrated. Also, multiple areas of infarction in different vascular regions and of different ages are suggestive of cerebral vasculitis (Küker 2007). More advanced MRI procedures, including perfusion, spectroscopy, and diffusion weighted imaging (DWI), are also of vital usefulness in imaging the cerebral vasculitis. The magnetic resonance perfusion demonstrates the microscopic flow of blood through brain tissue. It provides measures of cerebral blood flow, cerebral blood volume, and the mean transit time of a unit of blood through a unit of tissue (Gomes 2010). MRI may directly demonstrate vessel wall inflammation, probably with high diagnostic accuracy.

The imaging signs of cerebral vasculitis may be divided in to:
- cerebral perfusion deficits;
- ischemic brain lesions;
- intracerebral or subarachnoid hemorrhage:
- vascular stenoses unlikely to be atherosclerotic;
- direct imaging signs of cerebral vasculitis (vessel wall thickening with contrast enhancement (Küker 2007).

The most frequently reported signs are the ischemic changes in vascul-MR (Spitzer et al. 2005). MRI is a very sensitive method for the investigation of cerebral ischemia. Multiple infarcts of different ages seem to be suggestive of cerebral vasculitis, particularly when the lesions are located in various vascular territories and do not have atypical embolic pattern (Küker 2007).

ADDITIONAL INFORMATION ON INDIVIDUAL STUDIES

As many as two-thirds of patients with neurosyphilis are reported to have a normal MRI, or a nonspecific mild-to-moderate cerebral atrophy (Conde-Sendin et al. 2004, Santos et al. 2005, Denays et al. 1999). However, literature reports indicate some specificity of the findings in neurosyphilis. Our literature search retrieved 90 cases of neurosyphilis MRI findings (Table 1). These reports significantly varied in the terminology and methodology applied. Nevertheless, the relevant data was gathered from the reports (Table 2).

Common findings include hypointensity on T1, hyperintensity on T2, medium contrast enhancement, perilesional oedema, meningeal enhancement/dural tail, T1 isointense lesion, T2 isointense lesion, T2 hypointense lesion, cerebral infarction, arteritis, nonspecific white matter lesions involving the frontotemporal lobes, hippocampus and periventricular area, atrophy, gummata, extraxial enhancement, high signal changes in the bilateral mesial temporal lobes including both hippocamps and amygdalas in T2-images and FLAIR and DWI sequence, ventricular dilatation. Normal neuroimaging findings are also common (Fadil et al. 2006, Fragen et al. 2009, Peng et al. 2008, Yu et al. 2010, Yao et al. 2012, Primavera et al. 1998, LoVecchio 1995, Heald et al. 1996, Suarez et al. 1996, Brightbill et al. 1995, Bash et al. 2001, Jeong et al. 2009). The most prominent diagnostic phenomenon associated with neurosyphilis are, atrophy, white matter lesions, cerebral
Table 1. Incidence of MR findings in neurosyphilis

<table>
<thead>
<tr>
<th>No.</th>
<th>Normal atrophy</th>
<th>cerebral infarction</th>
<th>white matter lesion</th>
<th>gummas</th>
<th>contrast enhancement</th>
<th>T1 hypointensity</th>
<th>T1 isointensity</th>
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CONCLUSION

Psychiatric symptomatology is now the most common clinical manifestations of neurosyphilis (Cubala & Czarnowska-Cubala 2008, Mitsonis et al. 2008, Rozwens et al. 2003).

Although MRI findings in neurosyphilis are not highly specific, the identification of the most common radiologic appearances of neurosyphilis is essential in the process of the differential diagnosis. Tuberculosis, cytomegalovirus, syphilis, malaria, Varicella zoster virus, human immunodeficiency virus (HIV), borrelial burgdorferi, hepatitis B virus and hepatitis C virus infections, several fungal and rickettsial infections have also been associated with cerebral infectious vasculitis. MRI is the most sensitive technique in detecting the changes in cerebral vasculitis commonly presenting with focal areas of high signal intensity in any distribution with areas of infarction and hemorrhage observed at times. Parenchymal and meningeal enhancement is usually demonstrated. Multiple areas of infarction in different vascular territories and of different ages in a young patient are said to be suggestive of cerebral vasculitis (Küker 2007). In neurosyphilis medium and small vessels are usually involved. The most frequently involved arteries are middle cerebral artery and branches of the basilar artery (Holland et al. 1986). Our review indicates the most common diagnostic features are medium contrast enhancement, atrophy, white matter lesions, cerebral infarction, and oedema. However, normal findings are also common. The major central nervous system abnormalities mimicked by the neurosyphilis in MRI imaging are herpes simplex encephalitis, mesial temporal sclerosis, leukoaraiosis, normal pressure hydrocephalus, and glioblastoma multiiforme (Fadil et al. 2006).

MR is also a powerful tools to follow-up after antibiotic therapy. Correlation between the clinical symptoms, laboratory studies and radiological findings seems vital in the proper diagnosis of neurosyphilis infection along with treatment monitoring and follow-up.
### Table 2. Classification of CNS vasculitis

<table>
<thead>
<tr>
<th>Primary angiitis of the central nervous system</th>
<th>Infectious vasculitis</th>
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<tbody>
<tr>
<td></td>
<td>– Varicella zoster virus</td>
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<td></td>
<td>– Human immunodeficiency virus</td>
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<td>– Syphilis</td>
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<td>– Fungal infections</td>
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<td>– Other bacterial infections</td>
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<tr>
<th>Necrotizing vasculitis</th>
<th>Vasculitis associated with collagen vascular disorders</th>
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<tbody>
<tr>
<td>– Wegner’s granulomatosis</td>
<td>– Systemic lupus erythematosus</td>
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<td>– Churg–Strauss syndrome</td>
<td>– Sjogren syndrome</td>
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<tr>
<td>– Polyarteritis nodosa</td>
<td>– Rheumatoid arteritis</td>
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<td>– Polyaeritis nodosa</td>
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<th>Giant cell arteritis</th>
<th>Hypersensitivity vasculitis</th>
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<tr>
<td>– Giant cell arteritis</td>
<td>– Drug-induced</td>
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<tr>
<td>– Takayasu’s arteritis</td>
<td>– Toxin-induced</td>
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<tr>
<th>Vasculitis associated with systemic disorders</th>
<th>Miscellaneous</th>
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<tbody>
<tr>
<td>– Sarcoidosis</td>
<td>– Vasculitis associated with neoplasia</td>
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<tr>
<td>– Behçet’s disease</td>
<td>– Kawasaki’s disease</td>
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</table>

Radiologists, neurologists, and psychiatrists should take neurosyphilis into consideration facing the differential diagnosis in central vascular disorders (Peng et al. 2008, Rozwens et al. 2003).

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**Conflict of interest:** None to declare.

**References**


Correspondence:
Wiesław Jerzy Cubala MD., Ph.D.
Department of Psychiatry, Medical University of Gdańsk
Dębinki 7 St. build. 25, 80-952 Gdańsk, Poland
E-mail: cubala@gumed.edu.pl