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

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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 vascuclar disorders.*

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

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INTRODUCTION

Syphilis is a sexually transmitted disease caused by Treponema pallium. Current reports on the number of patients with nurosyphilis 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 cryoglobulineamia (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, Cubała & Czarnowska-Cubała 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, Aviv 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, particulularly 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, gummas, extraaxial 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

	MR findings							
No.	Normal	atrophy	cerebral infarction	white matter lesion	gummas	contrast enhancement	T1 hypointensity	T1 isointensity
1.				50%		50%		
2.	31%	37%	23%	20%	6%	6%		
3.	33%	66%		50%				
4.			100%					
5.		100%						
6.		100%						
7.					100%			
8.						100%	61%	38%
9.	7%	50%	43%	50%				
10.								
11.								
12.								

No.	T2 hypointensity	T2 hyperintensity	mesio-temporal hyperintensity	oedema	arteritis	ventricular enlargement	meningitis	author
1.			50%			50%		Fadil et al. 2006
2.								Brightbill et al. 1995
3.			33%			17%		Yu et al. 2010
4.								Primavera et al.1998
5.								LoVecchio et al. 1995
6.								Heald et al. 1996
7.								Suarez et al. 1996
8.	13%	67%		52%			35%	Fragen et al. 2009
9.					29%			Peng et al. 2008
10.			100%			100%		Bash et al. 2001
11.			100%					Jeong et al. 2009
12.		100%		100%				Yao et al. 2012

infarction, medium contrast enhancement, oedema (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, Brightbill et al. 1995, Bash et al. 2001, Jeong et al. 2009).

CONCLUSION

Psychiatric symptomatology is now the most common clinical manifestations of neurosyphilis (Cubała & Czarnowska-Cubała 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), borrelia 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 multiforme (Fadil et al. 2006).

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

Table 2. Classification of CNS vasculitis

Primary angiitis of the central nervous system
Infectious vasculitis
– Varicella zoster virus
– Human immunodeficiency virus
– Syphilis
– Fungal infections
– Other bacterial infections
Necrotizing vasculitis
– Wegner's granulomatosis
– Churg–Strauss syndrome
– Polyarteritis nodosa
Vasculitis associated with collagen vascular disorders
– Systemic lupus erythematosus
– Sjogren syndrome
– Rheumatoid arteritis
– Polyarteritis nodosa
Giant cell arteritis
– Giant cell arteritis
– Takayasu's arteritis
Hypersensitivity vasculitis
– Drug-induced
– Toxin-induced
Vasculitis associated with systemic disorders
– Sarcoidosis
– Behcet's disease
Miscellaneous
– Vasculitis associated with neoplasia
– Kawasaki's disease

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

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References

1. *Aviv RI, Benseler SM, Silverman ED, Tyrrell PN, Deveber G, Tsang LM, Armstrong D: MR imaging and angiography of primary CNS vasculitis of childhood. AJNR Am J Neuroradiol 2006; 27:192-9.*
2. *Bash S, Hathout GM, Cohen S: Mesiotemporal T2-Weighted Hyperintensity: Neurosyphilis Mimicking Herpes Encephalitis. AJNR Am J Neuroradiol 2001; 22:314-6.*
3. *Brightbill TC, Ihmeidan IH, Donovan Post MJ, Berger JR, Katz DA: Neurosyphilis in HIV-Positive and HIV-Negative Patients: Neuroimaging Findings. AJNR Am J Neuroradiol 1995; 16:703-11.*
4. *Calabrese LH, Duna GF, Lie JT: Vasculitis in the central nervous system. Arthritis Rheum 1997; 40:1189-1201.*
5. *Conde-Sendin MA, Amela-Peris R, Aladro-Benito Y, Maroto AA: Current clinical spectrum of neurosyphilis in immunocompetent patients. Eur Neurol 2004; 52:29-35.*
6. *Cubała WJ, Czarnowska-Cubała M: Neurosyphilis presenting with depressive symptomatology: is it unusual? Acta Neuropsychiatr 2008; 20:110.*
7. *Denays R, Collier A, Rubinstein M, Atsama P: A 51 yearold woman with disorientation and amnesia case report. Lancet 1999; 354:1786.*
8. *Fadil H, Gonzalez-Toledo E, Kelley BJ, Kelley RE: Neuroimaging findings in neurosyphilis. J Neuroimaging 2006; 16:286-9.*
9. *Fragen KM, Alvernia JE, Lin CS, Melgar M: Cerebral syphilic gummata: a case presentation and analysis of 156 reported cases. Neurosurgery 2009; 64:568-75.*
10. *Gomes LJ: The role of imaging in the diagnosis of central nervous system vasculitis. Curr Allergy Asthma Rep 2010; 10:163-70.*
11. *Harris KG, Tran DD, Sickels WJ, Cornell SH, Yuh WT: Diagnosing intracranial vasculitis: the roles of MR and angiography. AJNR Am J Neuroradiol 1994; 15:317-30.*
12. *Heald A, Connolly S, Hudgson P: Neurosyphilis presenting as complex partial status epilepticus. Eur Neurol 1996; 36:111-2.*
13. *Holland BA, Perrett LV, Mills CM: Meningovascular syphilis: CT and MR findings. Radiology 1986; 158:439-2.*
14. *Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, Edworthy SM, Fauci AS, Leavitt RY, Lie JT: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990; 33:1122-8.*
15. *Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, Hagen EC, Hoffman GS, Hunder GG, Kallenberg CG: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum 1994; 37:187-92.*
16. *Jeong YM, Hwang HY,Kim HS: MRI of Neurosyphilis Presenting as Mesiotemporal Abnormalities: a Case Report. Korean J Radiol 2009; 10:310-2.*
17. *Kararizou E, Mitsonis C, Dimopoulos N, Gkiatas K, Markou I, Kalfakis N: Psychosis or simply a new manifestation of neurosyphilis? J Int Med Res 2006; 34:335-7.*
18. *Kent ME, Romanelli F: Reexamining syphilis: an update on epidemiology, clinical manifestations, and management. Ann Pharmacother 2008; 42:226-36.*
19. *Kraemer M, Berlit P: Systemic, secondary and infectious causes for cerebral vasculitis: clinical experience with 16 new European cases. Rheumatol Int 2010; 30:1471-6.*
20. *Küker W: Cerebral vasculitis: imaging signs revisited. Neuroradiology 2007; 49:471-9.*
21. *Lee CH, Lin WC, Lu CH, Liu JW: Initially unrecognized dementia in a young man with neurosyphilis. Neurologist 2009; 15:95-7.*
22. *LoVecchio F: Neurosyphilis presenting as refractory status epilepticus. Am J Emerg Med 1995; 13:6854.*
23. *Luo W, Ouyang Z, Xu H, Chen J, Ding M, Zhang B: The clinical analysis of general paresis with 5 cases. J Neuropsychiatry Clin Neurosci 2008; 20:490-3.*
24. *Marra CM: Neurosyphilis. Curr Neurol Neurosci Rep 2004; 4:435-40.*

25. *Mitsonis CH, Kararizou E, Dimopoulos N, Triantafyllou N, Kapaki E, Mitropoulos P, Sfagos K, Vassilopoulos D: Incidence and clinical presentation of neurosyphilis: a retrospective study of 81 cases. Int J Neurosci 2008; 118:1251-7.*
26. *Mumtaz S, Fowler MR, Gonzales-Toledo E, Kelley RE: Central Nervous System Vasculitis. Pathogenesis, Immunology, and Clinical Management In: Alireza M, Steven AJ, editors. Current Clinical Neurology. Inflammatory Disorders of the Nervous System. Totowa: Humana Press, 2005; 257-68.*
27. *Okuda DT, Vollmer TL: Primary Angiitis of the Central Nervous System. In: Filippi M, De Stefano N, Dousset V, McGowan JC, editors. MR Imaging in White Matter Diseases of the Brain and Spinal Cord. Medical Radiology Diagnostic Imaging. Berlin-Heidelberg: Springer, 2005; 293-310.*
28. *Peng F, Hu X, Zhong X, Wei Q, Jiang Y, Bao J, Wu A, Pei Z: CT and MR findings in HIV-negative neurosyphilis. Eur J Radiol 2008; 66:1-6.*
29. *Primavera A, Solaro C, Cocito L: De Novo Status Epilepticus as the Presenting Sign of Neurosyphilis. Epilepsia 1998; 39:1367-9.*
30. *Rozwens A, Radziwiłłowicz P, Jakuszkowiak K, Cubała WJ: (Neurosyphilis with its psychopathological implications. Literature review). Psychiatr Pol 2003; 37:477-94. (in Polish)*
31. *Santos AV, Matias S, Saraiva P, Goulao A: Differential diagnosis of mesiotemporal lesions: Case report of neurosyphilis. Neuroradiology 2005; 47:664-7.*
32. *Scolding N: Central nervous system vasculitis. Semin Immunopathol 2009; 31:527-36.*
33. *Spitzer C, Mull M, Rohde V, Kosinski CM: Non-traumatic cortical subarachnoid haemorrhage: diagnostic work-up and aetiological background. Neuroradiology 2005; 47:525-31.*
34. *Suarez JI, Mlakar D, Snodgrass SM: Cerebral syphilitic gumma in an HIV-negative patient presenting as prolonged focal motor status epilepticus. N Engl J Med 1996; 335:1159-60.*
35. *Tso MK, Koo K, Tso GY: Neurosyphilis in a non-HIV patient: more than a psychiatric concern. Mcgill J Med 2008; 11:160-3.*
36. *Yu Y, Wei M, Huang Y, Jiang W, Liu X, Xia F, Li D, Zhao G: Clinical presentation and imaging of general paresis due to neurosyphilis in patients negative for human immunodeficiency virus. J Clin Neurosci 2010; 17:308-10.*
37. *Yao Y, Huang E, Xie B, Cheng Y: Neurosyphilis presenting with psychotic symptoms and status epilepticus. Neurol Sci 2012; 33:99-102.*

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