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PICTORIAL REVIEW

Spectrum of neurovascular complications from central nervous system infections (viral, bacterial and fungal)

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ABSTRACT

In the following pictorial review, common and uncommon neurovascular complications associated with a spectrum of viral, bacterial and fungal infections involving the central nervous system will be illustrated. These complications include cerebral vascular insult, venous thrombosis, vasculitis and aneurysm formation. They can occur as separate entities but are often inter-related. The imaging features of neurovascular complication related to infections can provide clues and aid diagnosis when considering the potential mode of infectious spread and the type of potential infectious organism involved. The radiological appearances vary from common features that are shared by several types of pathogens to typical characteristics of a type of infectious organism.

INTRODUCTION

The spectrum of neurovascular complications associated with central nervous system (CNS) infections can vary from 1–5% in human immunodeficiency virus (HIV) infection[1,2] to as high as 57% in tuberculous meningitis.[3]

A wide variety of infectious pathogens including acquired and opportunistic bacterial, viral, fungal and parasitic pathogens can involve the CNS. The potential mode of infectious spread includes haematogenous, localised, direct inoculation or perineural spread.[4] The arterial and venous neurovascular manifestations of CNS infections encompass cerebral vascular insult, venous thrombosis, aneurysm formation, and vasculitis.[2,5]

Many of these complications are commonly inter-related and can occur simultaneously or sequentially. Early diagnosis can often be challenging and associated with vague or evolving neurological or psychiatric presentation. Imaging findings, can play a pivotal role when combined with the clinical history and laboratory testing in confirming the suspicions of an infectious pathogen. Some imaging features may be non-specific and can shared by different pathogens, while some findings may be distinctive for certain micro-organisms.[6] Diagnosis is key to initiating targeted treatment in order to reduce the significant morbidity and mortality that can be associated with CNS infections.

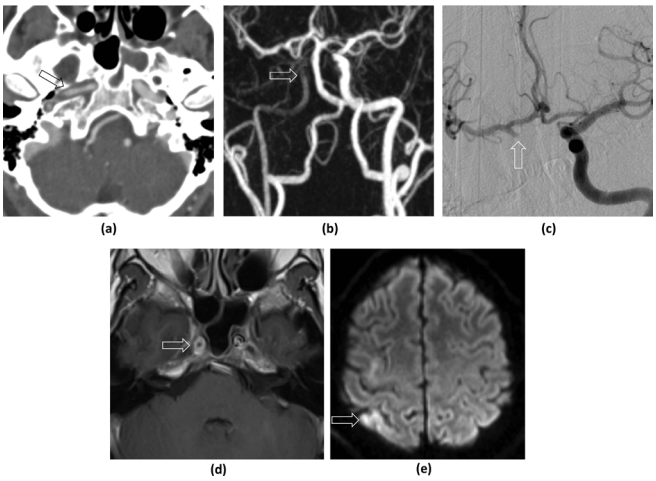
Viral infection

Viral infection-related stroke can occur directly from the inflammatory arterial wall changes of the small intracranial vessels or indirectly from a pro-thrombotic effect.[6] Patients with HIV-associated vasculopathy can clinically manifest as cerebral infarction, aneurysmal formation and vasculitis, which may be directly or indirectly related to HIV infection (Figure 1). The incidence of cerebrovascular events ranges from 1 to 5%, however, in reported autopsies can be as high as 11 to 34%.[1,2] In advanced HIV infection, this is further compounded by CNS opportunistic infections.[2] Figure 2 is a case of cytomegalovirus (CMV) ventriculitis with a focal infarct demonstrated in the left temporal stem. CMV reactivation can have serious complications in an immunocompromised host and are more common in those with advanced HIV or acquired immune deficiency syndrome. A nationwide population-based cohort study of 439 HIV patients suggested that CMV end-organ disease was an independent risk factor for developing ischaemic (adjusted hazard ratio [aHR], 3.14; 95% confidence Interval [CI] 1.49 to 6.62) but not haemorrhagic stroke (aHR, 2.52; 95% CI 0.64 to 9.91).[7]

Atypical infection

Atypical bacterial infection such as *Mycobacterium tuberculosis* involves the CNS in 1% of cases. This occurs predominately in the immunocompromised patient population (*e.g.* HIV), and is associated with a high mortality as well as long

Figure 1.HIV vasculitis resulting in occlusion of the right internal carotid artery and infarct. (a) Contrast axial CT shows reduced calibre of the right ICA which on the time-of-flight MRA (b) is shown to involve the entire ICA with complete occlusion at the anterior genu. (c) DSA intracranial angiogram shows filling of the right hemisphere intracranial arteries from a left carotid injection via the anterior communicating artery due to a short segment occlusion of the right supraclinoid carotid artery. (d) Enhanced MRI demonstrates abnormal enhancement and thickening of the wall of the right ICA. (1e) DWI shows focal infarcts in the right frontoparietal lobe.



term neurological compromise.[8] Cerebrovascular complications are relatively common, especially in the advanced stages of the disease, affecting 15–57% of patients with tuberculous meningitis.[3] Infarcts tend to be multifocal and involve the perforators and terminal cortical branches with the basal ganglia most affected (Figure 3).[9]

Systemic infection

Infectious endocarditis is a common cause of septic emboli to the brain where it can manifest as focal infarcts. Cerebral infarction occurs predominantly at the corticomedullary junction in the middle cerebral artery distribution. Infarction occurs as a consequence of embedded embolic material and occlusion of the intracranial arterial vessels.[6] This can lead to subarachnoid haemorrhage and infarction with haemorrhagic transformation.

Figure 2.CMV ventriculitis resulting in a focal infarct. (a) Coronal FLAIR MRI shows a rim of hyperintense signal lining the ventricular surface. (b) Enhanced axial MRI shows subtle enhancement in the areas of increased FLAIR signal. (c) Axial DWI demonstrates a focal infarct in an area of non-enhancement in the left temporal stem.

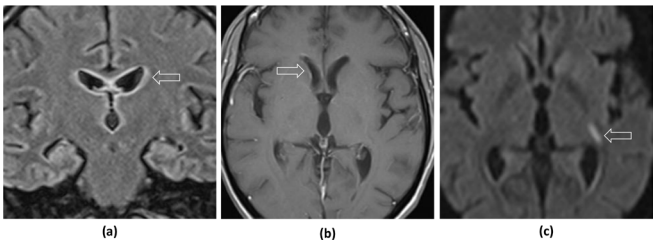


Figure 4 illustrates a patient with infective endocarditis and diffusion weighted images demonstrates restriction in multiple vascular distributions consistent with multiple embolic cerebral infarction.

VENOUS SINUS THROMBOSIS

Cerebral venous sinus thrombosis secondary to infection accounts for less than 10% of aetiologies.[4] The anatomic predilection of cerebrovascular complication is dependent on the mechanism of spread.[10] Thrombosis within an infected vein or sinus is referred to as septic thrombophlebitis, most commonly caused by *Staphylococcus aureus* and streptococcal species.[11] In cases of mastoiditis, it is thought the inflammatory process and spread of infection occurs through coalescent bone erosion with subsequent peri-sinus abscess formation and mural thrombus formation in the sigmoid sinus. Organisms associated with mastoiditis related venous thrombophlebitis include *Proteus mirabilis, Pseudomonas aeruginosa and Bacteroides fragilis* (Figure 5).[11]

The cerebral veins and dural sinuses lack valves and allow bidirectional blood flow depending on pressure gradients, this makes them particularly vulnerable to thrombosis from adjacent sites of infection. In the acute stage of thrombus formation, there is obstruction to venous return resulting in a reduction in cerebral blood flow and perfusion pressure. Infection of the vessel wall with enzymes, neutrophils and pro-inflammatory cytokines results in vessel wall integrity loss and narrowing. This in turn can predispose to stenosis and infarction. Intracranial infection can occur within the thrombus which can act as a growth medium. Findings from an initial non-enhanced CT study may show hyperdense thrombus within a cortical vein or sinus and indirect signs such as venous infarction (Figure 6). Thrombosis on an enhanced CT venogram will manifest as a filling defect within the dural sinus (Figures 5 and 7).[10,11]

VASCULITIS

CNS vasculitis can be categorised by aetiology (primary or secondary), pathology (granulomatous, necrotising or lymphomatous) and size of the vessel (small, medium or large) involved. It is an uncommon cause of haemorrhagic and ischaemic stroke.[12]

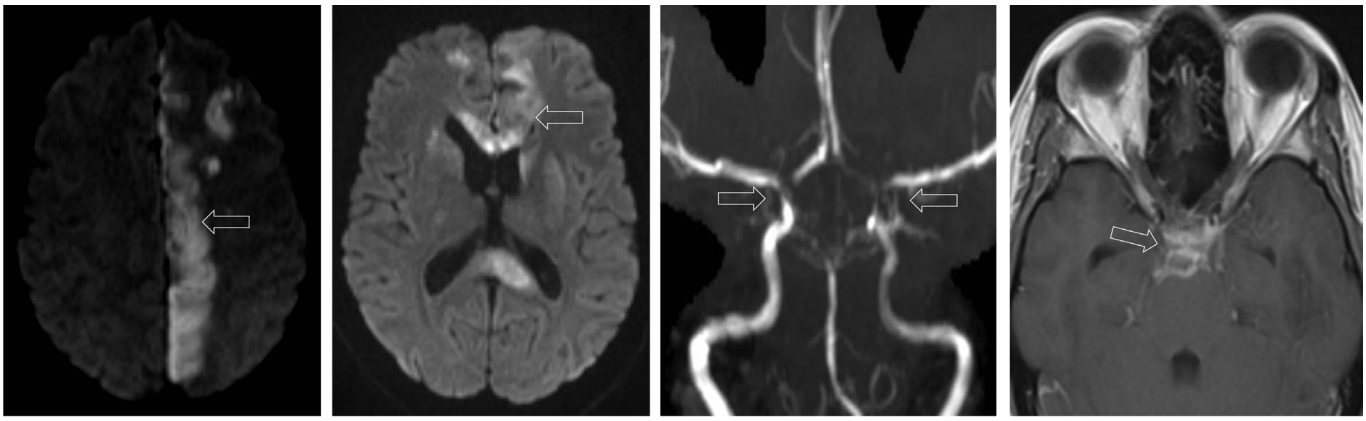
Human immunodeficiency virus

HIV-associated vasculopathy can clinically manifest as cerebral infarction, aneurysmal formation and vasculitis, which may be directly or indirectly be related to HIV infection. This has been attributed to either direct HIV infection or as result of accelerated atherosclerosis due to changes to endothelial homeostasis.[13] Intra and extracranial vessels can be involved. Vascular abnormalities of medium and large size vessels can be assessed with CT angiogram (CTA) or magnetic resonance angiogram (MRA). Intracranial vascular involvement results in segmental stenosis, dilatation, fusiform aneurysm and tapering of vessels (Figure 1).

Tuberculosis

In tuberculosis infection of the CNS, three pathological processes: infiltrative, proliferative and necrotising vascular pathologies are thought to occur in cerebral vessels. The cerebral vessels commonly

Figure 3.Tuberculous meningitis with vasculitis of the ICA resulting in acute infarcts. (a,b) Axial DWI shows extensive ischaemia in the left peri-callosal arterial supply and left and right anterior communicating artery territories. (c) Time-of-flight MRA shows bilateral narrowing of the ICA tips and ICA bifurcations due to vascular inflammation. (d) Enhanced axial MRI demonstrates abnormal basal meningeal thickening and enhancement consistent with tuberculous meningitis.

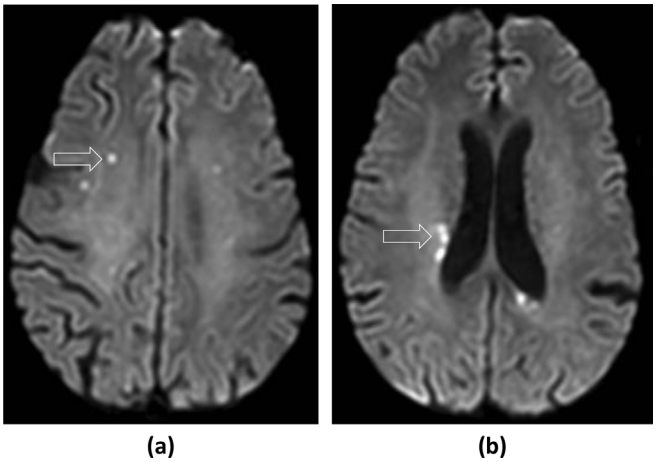


involved are those at the sylvian fissures and basal regions, which are surrounded by inflammatory exudates at these sites. Inflammatory vessel wall infiltration can involve both arteries and veins. Large intracranial arteries are affected in the basal regions resulting in narrowing, vasculitis and vasospasm (Figure 3). This can result in large vessel cerebral infarction as a sequelae.[14]

Varicella zoster virus

Latent reactivation of the varicella zoster virus (VZV) produces herpes zoster. This occurs in individuals with declining cell mediated immunity in the elderly and those that are immunocompromised. Central spread and reactivation of the virus results in VZV vasculopathy. The subsequent neurological complications range from transient ischaemic attacks and stroke (Figure 8) to ruptured aneurysm with subarachnoid haemorrhage. VZV is the only virus in humans with the ability to replicate in cerebral arteries and produce disease.[15]

Figure 4.*Abiotrophia* endocarditis with embolic infarcts. (a,b) DWI shows multifocal acute infarcts in the supratentorial white matter.



Intracranial vascular involvement has been demonstrated in up to 70% of patients with VZV infection, involving the small and large vessels.[16] Common sites of VZV vasculopathy are the terminal internal carotid artery, anterior and middle cerebral arteries (M1 segment). Imaging findings range from stenosis, thickening of vessel walls and enhancement on neuroimaging which has been shown to improve with antiviral treatment. Arteries infected with VZV show disruption of the internal elastic lamina and loss of vessel wall integrity secondary to insufficient medial smooth muscle cells.[17]

Figure 5.Mastoiditis with acute venous sinus thrombosis. (a) Enhanced axial CT shows acute thrombus in the right sigmoid sinus and opacification of the right mastoid air cells secondary to acute mastoiditis (b).

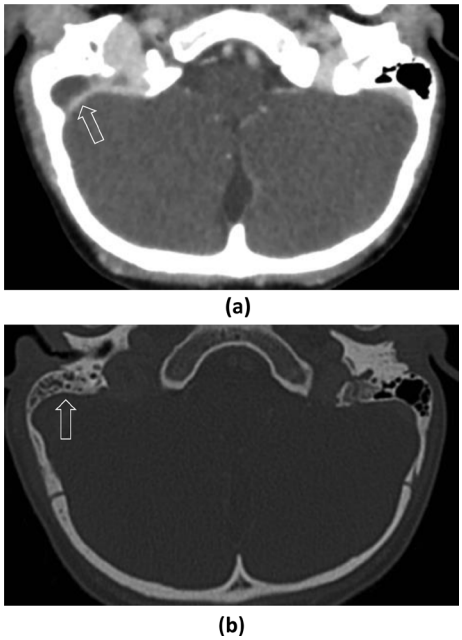
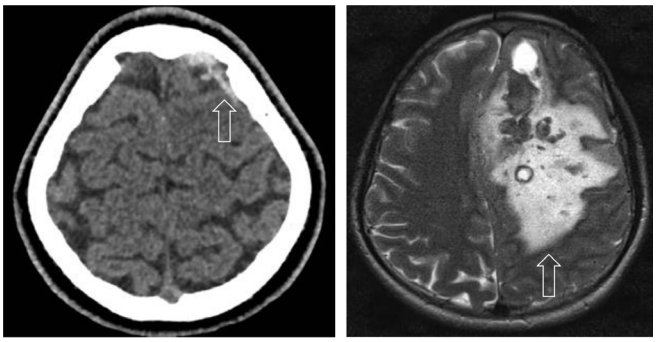


Figure 6.Cortical vein thrombosis from a *Pseudomonas* neck ulcer. (a) Unenhanced axial CT shows an acute cortical vein thrombus overlying the left frontal lobe. (b) Axial T2 MRI demonstrates extensive haemorrhagic transformation within an area of venous infarction in the left cerebral hemisphere with contralateral midline shift.



ANEURYSM FORMATION

Bacterial and fungal related infectious endocarditis are a potential cause of septic emboli and formation of neurovascular mycotic aneurysms. Both of these infections are different in their histopathologic features and imaging appearances. The incidence of mycotic aneurysm constitutes 1 to 3% of all causes of intracranial aneurysm with bacterial causes far more common than fungal. Cerebral infarction, and subarachnoid haemorrhage are serious neurological complications of mycotic aneurysms.[18 19]

Bacterial

In bacterial infective endocarditis, intracranial mycotic aneurysms are detected in up to 8% of cases. Common organisms causing intracranial mycotic aneurysms include *Streptococcus viridans* and *Staphylococcus aureus*.[20] Bacterial mycotic aneurysms are characterised by multiple small, saccular intracranial aneurysms affecting the distal segment of vessels. Vessel invasion occurs from within vessels and causes occlusion of the vasa vasorum (Figure 9).[19]

Figure 7.Tuberculous empyema with transverse sinus thrombosis. (a) Coronal CT venogram demonstrates a large left parietotemporal epidural collection (white arrow) with reduced enhancement in the left sigmoid sinus in comparison to the right (black arrow). (b) Coronal enhanced MRI performed post drainage shows a small residual epidural collection with avid enhancement and thickening of the adjacent dura extending to, and involving, the left sigmoid sinus.

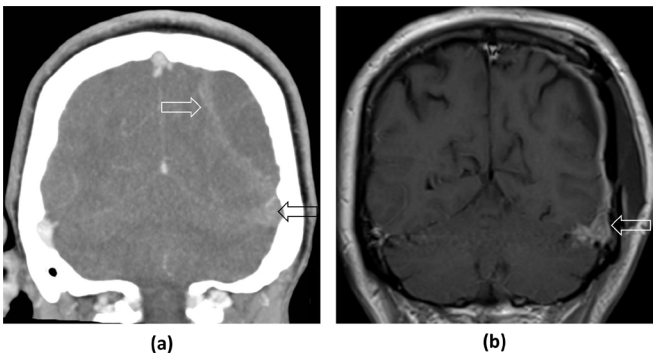
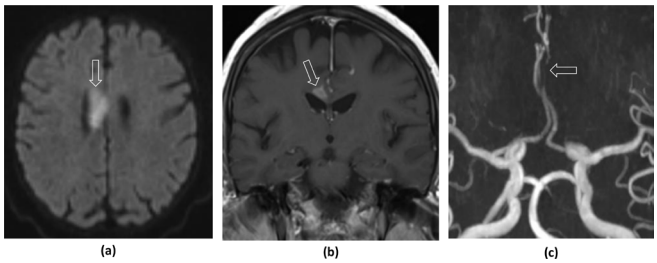


Figure 8.Patient with varicella zoster encephalitis and right anterior cerebral artery territory infarct. (a) DWI shows true restricted diffusion in the right aspect of the body of the corpus callosum in keeping with an acute right ACA territory infarct. (b) Coronal enhanced MRI shows focal pathological enhancement in this area with an MRA (c) demonstrating focal stenosis of the right A2 segment.



Fungal

Fungal infection of the central nervous system is rare. It usually presents as an opportunistic infection in an immunosuppressed host. Aspergillus is the most common cause of mycotic fungal aneurysm and intracranial spread, and usually occurs as a result of haematogenous spread or direct extension from the sinuses (Figure 10). Angio-invasive Aspergillus can result in fusiform aneurysm formation characterised by invasion of proximal vascular segments starting at the adventitia. Fungal aneurysms are also longer and larger than bacterial mycotic aneurysms.[19] The angio-invasive nature of Aspergillus is explained by the production of elastase enzyme which digests elastin in the blood vessel wall generating an inflammatory vascular reaction.[21] As a consequence, vasculitis and embolisation of hyphal lesions and *in-situ* thrombosis can occur.[19]

CONCLUSION

The cerebrovascular complications of central nervous system infections range from common to rare clinical manifestations that are dependent on the location of infection, type of

Figure 9.A patient with a *Streptococcus sanguis* infectious pseudoaneurysm. (a) Unenhanced axial CT shows a right parenchymal frontoparietal haemorrhage. (b) CT angiogram demonstrates pooling of contrast posteriorly in keeping with active haemorrhage. (c) Coronal DSA angiography demonstrates a 4 mm wide necked pseudoaneurysm arising from a superior parietal branch of the right middle cerebral artery.

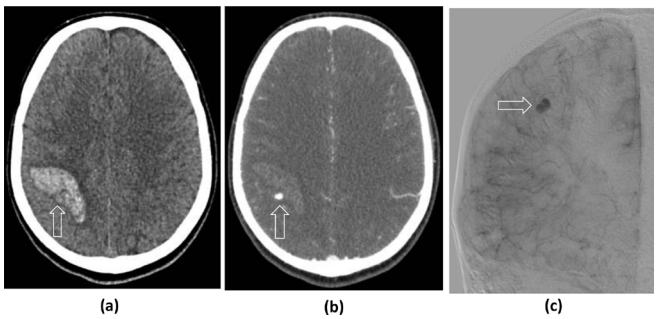
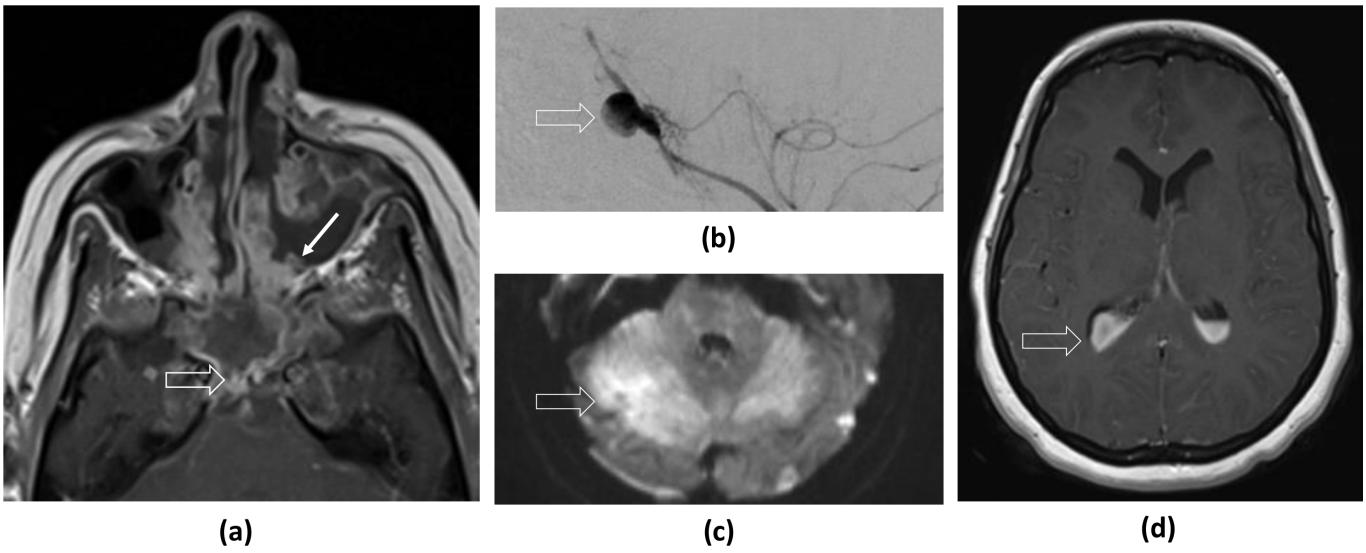


Figure 10.A patient with invasive fungal *Aspergillosis* resulting in a mycotic basilar aneurysm and posterior circulation infarcts. (a) Enhanced axial MRI shows extensive enhancing sino-nasal disease affecting the ethmoid, left maxillary sinus (solid arrow) and sphenoid air sinus. Enhancing soft tissue extends through the clivus into the posterior fossa where there is enhancement around the basilar artery (hollow arrow). (b) Lateral view DSA angiogram shows a dissecting mycotic basilar artery aneurysm with occlusion of the distal basilar artery. (c) DWI shows bilateral cerebellar infarcts with an enhanced MRI (d) demonstrating ventricular haemorrhage.



causative organism and mechanism of vascular involvement. It is imperative to recognise CNS infections in the aetiology of stroke, venous sinus thrombosis, vasculitis and intracranial aneurysm on imaging, particularly as this may have a significant impact on the clinical management and outcome for the patient.

REFERENCES

1. Greist A. Prothrombotic states in HIV disease and stroke complications. *Seminars in Cerebrovascular Diseases and Stroke* 2002; **2**: 159–69. doi: https://doi.org/10.1053/scds.2002.124061
2. Benjamin LA, Bryer A, Emsley HCA, Khoo S, Solomon T, Connor MD. HIV infection and stroke: current perspectives and future directions. *Lancet Neurol* 2012; **11**: 878–90. doi: https://doi.org/10.1016/S1474-4422(12)70205-3
3. Misra UK, Kalita J, Maurya PK. Stroke in tuberculous meningitis. *J Neurol Sci* 2011; **303**(1-2): 22–30. doi: https://doi.org/10.1016/j.jns.2010.12.015
4. Guenifi W, Boukhrissa H, Gasmi A, Rais M, Ouyahia A, Hachani A, et al. Cerebral venous thrombosis during tuberculous meningoencephalitis. *J Mal Vasc* 2016; **41**: 210–4. doi: https://doi.org/10.1016/j.jmv.2016.03.002
5. Del Brutto OH. Chapter 43 - Infections and stroke. In: Fisher M, ed. *Handbook of Clinical Neurology. Elsevier*; 2008. pp. 851–72.
6. Swinburne NC, Bansal AG, Aggarwal A, Doshi AH. Neuroimaging in central nervous system infections. *Curr Neurol Neurosci Rep* 2017; **17**: 49. doi: https://doi.org/10.1007/s11910-017-0756-8
7. Yen Y-F, Jen I, Chen M, Chuang P-H, Liu Y-L, Sharp GB, et al. Association of cytomegalovirus end-organ disease with stroke in people living with HIV/AIDS: a nationwide population-based cohort study. *PLoS One* 2016; **11**: e0151684. doi: https://doi.org/10.1371/journal.pone.0151684
8. Cherian A, Thomas SV. Central nervous system tuberculosis. *Afr Health Sci* 2011; **11**: 116–27.
9. M-LS T, Viswanathan S, Rahmat K, Nor HM, Kadir KAA, Goh KJ, et al. Cerebral infarction pattern in tuberculous meningitis. *Sci Rep* 2016; **6**: srep38802.
10. Shen X, Morón FE, Gao B. Imaging of cerebral venous complications in patients with infections. *Radiology of Infectious Diseases* 2017; **4**: 131–5. doi: https://doi.org/10.1016/j.jrid.2017.08.002
11. Seven H, Ozbal AE, Turgut S. Management of otogenic lateral sinus thrombosis. *Am J Otolaryngol* 2004; **25**: 329–33. doi: https://doi.org/10.1016/j.amjoto.2004.04.005
12. Navalkele D, Martin-Schild S. Central nervous system vasculitis. *Neuroinflammation* 2018; 493–503.
13. Pagiola IC, Paiva ALC, de Aguiar GB, de Oliveira ACP, Conti MLM, Gagliardi RJ, et al. Cerebral aneurysms associated with human immunodeficiency virus in adults: literature review and new perspectives. *Rev Assoc Med Bras* 2016; **62**: 85–9. doi: https://doi.org/10.1590/1806-9282.62.01.85
14. Lammie GA, Hewlett RH, Schoeman JF, Donald PR. Tuberculous cerebrovascular disease: a review. *J Infect* 2009; **59**: 156–66. doi: https://doi.org/10.1016/j.jinf.2009.07.012
15. Amlie-Lefond C, Gilden D. Varicella zoster virus: a common cause of stroke in children and adults. *J Stroke Cerebrovasc Dis* 2016; **25**: 1561–9. doi: https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.03.052
16. Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, et al. The varicella zoster virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology* 2008; **70**: 853–60. doi: https://doi.org/10.1212/01.wnl.0000304747.38502.e8

17. Nagel MA, Forghani B, Mahalingam R, Wellish MC, Cohrs RJ, Russman AN, et al. The value of detecting anti-VZV IgG antibody in CSF to diagnose VZV vasculopathy. *Neurology* 2007; **68**: 1069–73. doi: https://doi.org/10.1212/01.wnl.0000258549.13334.16
18. Frazee J. *Inflammatory aneurysms*. New York: McGraw Hill; 1996.
19. Ho CL, Deruytter MJ. CNS aspergillosis with mycotic aneurysm, cerebral granuloma and infarction. *Acta Neurochir* 2004; **146**: 851–6. doi: https://doi.org/10.1007/s00701-004-0292-6
20. Topcuoglu MA, Kursun O, Buonanno FS, Singhal AB. Abstract WP335: intracranial mycotic aneurysms in infective endocarditis: incidence, predictors and outcome. *Stroke* 2017; **48**: AWP335.
21. Blanco JL, Hontecillas R, Bouza E, Blanco I, Pelaez T, Muñoz P, et al. Correlation between the elastase activity index and invasiveness of clinical isolates of Aspergillus fumigatus. *J Clin Microbiol* 2002; **40**: 1811–3. doi: https://doi.org/10.1128/JCM.40.5.1811-1813.2002