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Section 1 Infectious Conditions

Chapter 1

Neurosyphilis and Strokes

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Treponema pallidum

Treponema pallidum subsp. *pallidum* spirochetes are slender, tightly coiled, unicellular, helical bacteria, 6–15 nm in length, and 0.2 μm in diameter (LaFond and Lukehart, 2006). The genome is a single, circular chromosome of about 240,000 base pairs, which places it in the lowest range for all bacteria. In addition, unlike most other pathogenic bacteria, the genome lacks apparent transposable elements. These observations may explain why *T. pallidum* has remained sensitive to penicillin for more than 60 years and is so difficult to cultivate. *T. pallidum* has not been successfully cultured in vitro although the spirochete will infect experimental animals such as mice, rabbits, and monkeys, but mice do not develop clinical disease. The width of *T. pallidum* is so narrow that the spirochetes are not visualized by light microscopic examination of fixed cerebrospinal fluid (CSF) sediment or brain tissues using Gram or hematoxylin and eosin stains. However, spirochetes may be detected by dark field microscopy or by light microscopy when Warthin–Starry silver stain or immunohistochemistry stains are used. The intact spirochete has been found to have few surface proteins that elicit an immune response. The typical antibody develops when the spirochete is partially damaged, exposing the foreign antigens. This is one reason why the development of syphilis vaccines has been so difficult.

In nature, the only hosts for *T. pallidum* are humans. The organism is transmitted from person to person, mainly through vaginal or rectal sexual intercourse, when the spirochete penetrates intact mucosal membranes. However, occasional transmission has followed kissing, oral sex, close contact with an infected primary lesion, infected fresh blood transfusion, accidental inoculation, or by spread across the placenta from an infected mother to her fetus (congenital syphilis). The number of spirochetes required to infect a human is unknown but rabbits can be infected with a small number of organisms.

History and Epidemiology of Neurosyphilis

The origin of syphilis remains unknown. However, by the sixteenth century it had rapidly spread throughout Europe, reportedly causing high morbidity and mortality. Current epidemiology and historical evidence argues that syphilis was endemic in the New World and came to Europe when Columbus returned (Farhi and Dupin, 2010). Unfortunately, in past centuries little is known about what syphilis did to the central nervous system (CNS) and the types of vascular disease it may have caused. By the twentieth century, but before the advent of penicillin, it was estimated that approximately 10 percent of adults living in New York, Paris, or Berlin had a positive Wasserman blood test (nontreponemal antibody test similar to the rapid plasma reagin [RPR] or Venereal Disease Research Laboratory [VDRL] assay). In spite of the high prevalence of syphilis, relatively few patients developed severe disease. In one study of 473 patients with untreated early syphilis, two-thirds never developed clinical symptoms and only 9.5 percent developed neurosyphilis (Moore, 1941). A separate study estimated that only 6.5 percent of infected individuals subsequently developed symptomatic neurosyphilis, with 2.3 percent developing meningovascular syphilis (Clark and Danbolt, 1955).

With the discovery of penicillin, the prevalence of syphilis in the United States rapidly fell from about 400 cases/100,000 population in the 1940s, to less than 100 cases/100,000 in the late 1950s, and to less than 30 cases/100,000 by 1990 (Peterman *et al.*, 2005). However, the prevalence of primary and secondary syphilis rose again in early 2000, particularly in young men. In San Francisco, the incidence of neurosyphilis has risen sixfold since 2000 and occurred primarily in men who had sex with men (MSM) (San Francisco Department of Public Health, 2005). The current incidence of syphilis in the United States is 14.9 cases per 100,000 with the highest incidence in 20–24-year-olds (Shockman *et al.*, 2014). Large metropolitan cities have higher incidences than small cities. Syphilis is a reportable disease in every state. Worldwide, syphilis remains a serious disease with an estimated 12 million new cases occurring each year (Hook and Peeling, 2004).

Pathogenesis of Early Neurosyphilis

Neurosyphilis begins with invasion of the CNS by spirochetes during the period of spirochete dissemination from the primary lesion (called "secondary syphilis"). The term "early neurosyphilis" refers to meningitis associated with secondary syphilis, asymptomatic neurosyphilis, and meningovascular syphilis and lasts up to two decades (Merritt *et al.*, 1946; Simon, 1985). Late neurosyphilis involves general paresis and tabes dorsalis, develops from spirochete invasion of the brain or spinal cord parenchyma, and typically develops decades after the initial infection (Marra, 2004; Simon, 1985).

Secondary syphilis begins 2–12 weeks (mean 6 weeks) after the primary infection (Marra, 2004, 2015). In 40 percent of these patients, there is dissemination to the CNS. CSF findings include a mononuclear cell pleocytosis, slightly elevated protein, normal glucose, reactive CSF-VDRL test, and the

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identification of spirochetes by animal inoculation, polymerase chain reaction (PCR), or histologic staining (Davis and Sperry, 1978; Lukehart *et al.*, 1988; Merritt and Moore, 1935; Noordhoek *et al.*, 1991).

While most patients with secondary syphilis do not develop signs of meningitis, occasionally patients develop aseptic meningitis with headaches, nausea, stiff neck, and low-grade fever (Merritt and Moore, 1935). A few patients will also develop unilateral or bilateral cranial nerve palsies, especially peripheral facial palsy, deafness and/or vertigo, diplopia, or difficulty in swallowing or protruding the tongue (Alpers, 1954). A few patients with secondary syphilis also develop strokes (Merritt and Moore, 1935).

In most patients with CNS involvement during secondary syphilis, the spirochetes disappear from the CSF and the meningitis spontaneously terminates within 3 months. In some patients, however, the CNS infection persists and a stage of asymptomatic neurosyphilis begins. A 2004 neurosyphilis study found that a serum RPR titer of greater than or equal to 1:32 is highly associated with neurosyphilis regardless of the syphilis stage or concurrent HIV infections (Marra *et al.*, 2004b). Five to ten years later, growth of spirochetes in the meninges may result in meningovascular syphilis (i.e. tertiary syphilis) (Simon, 1985). The incidence of developing tertiary syphilis is unclear but the Oslo study in the preantibiotic era reported that 6.5 percent of cases developed tertiary syphilis (Gjestland, 1955).

Meningovascular Syphilis

The incidence of strokes from meningovascular syphilis in the prepenicillin era has been estimated to range from 2.3 to 20 percent of all neurosyphilis cases (Clark and Danbolt, 1955; Kierland *et al.*, 1942; Merritt *et al.*, 1946; Moore, 1941). In the post-antibiotic era, the reported incidence of strokes from meningovascular syphilis ranges from 7 to 23 percent of all patients with neurosyphilis (Aho *et al.*, 1969; Burke and Schaberg, 1985; Danielsen *et al.*, 2004; Hooshmand *et al.*, 1972; Hotson, 1981; Nordenbo and Sorensen, 1981; Perdrup *et al.*, 1981; Timmermans and Carr, 2004). Some of these reports gave data only on meningovascular syphilis and did not distinguish between those patients with strokes and those with only cranial nerve palsies.

The incidence of strokes in meningovascular syphilis varies by study and method of diagnosis. Kelly *et al.*, in study of 218 consecutive patients with a transient ischemic attack (TIA) or stroke, reported only 0.4 percent were from meningovascular syphilis (Kelley *et al.*, 1989). Lu *et al.* determined that 4 percent of their 149 patients with meningovascular syphilis without an HIV infection had a stroke (Liu *et al.*, 2012). Cordato *et al.* examined 893 patients with a stroke and diagnosed 37 (4 percent) with meningovascular syphilis (Cordato *et al.*, 2013). Thus, syphilis accounts for only a small proportion of strokes. The pathology of meningovascular syphilis has two major components. The cause of most cerebrovascular disease is syphilitic endarteritis, usually involving medium-to-large meningeal arteries, called Heubner's endarteritis (Gray and Alonso, 2002). These arteries have concentric collagenous thickening of the intima (endarteritis obliterans) and corresponding thinning of the media. The elastic lamina remains intact, but there may be splitting. Lymphocytes and plasma cells infiltrate the thickened adventitia and penetrate the media. The vasa vasorum is cuffed by inflammatory cells. Lumen constriction occurs from endothelial proliferation and thickening, which can be sufficient to produce ischemic lesions of the brain and spinal cord. The middle cerebral artery is the most commonly involved vessel leading to a stroke, but occasionally the anterior cerebral, posterior cerebral, or basilar artery branches are involved (Merritt *et al.*, 1946). The pathology of the cerebral infarction does not differ from that of other ischemic strokes.

The meninges primarily along the base of the brain have a diffuse or localized chronic inflammation, and some arteries within the meninges are affected by Heubner's endarteritis (Gray and Alonso, 2002). Lymphocytes and some plasma cells combine with fibrous tissue to form perivascular infiltrates around blood vessels along the brainstem in the thickened meninges. The periarteritis may produce cranial nerve palsies and occasionally brainstem ischemic strokes from thrombosis of small penetrating arteries from the vertebral or basilar artery (Brightbill *et al.*, 1995; Johns *et al.*, 1987; Tyler *et al.*, 1994; Umashankar *et al.*, 2004).

The clinical features of brain ischemia from meningovascular syphilis differ from those usually seen in other causes of ischemic strokes. The patient's age at stroke onset is often younger than the typical patient age seen in the more common causes of ischemic strokes. Ninety percent of neurosyphilis strokes are in patients between 30 and 50 years of age (Merritt *et al.*, 1946). The stroke incidence is higher in men than women. However, a more recent study from China found the mean age of their 28 cases was 57 years. A surprising number, who initially were not diagnosed as having meningovascular syphilis, had evidence of recurrent strokes, and often had the typical other risk factors for strokes (Liu *et al.*, 2012).

Up to 25 percent of patients develop a prodrome of headaches, dizziness, and/or emotional disturbances days to weeks prior to the stroke (Merritt *et al.*, 1946). Signs and symptoms of cerebral vascular syphilis vary by site of the infarction. Overall, about 80 percent develop a hemiparesis, 30 percent aphasia, 15 percent hemihypesthesia, 7 percent hemianopia, and 15 percent seizures (Merritt *et al.*, 1946; Alpers, 1954; Perdrup *et al.*, 1981). Because the patient may have coexistent chronic basilar meningitis, about 10 percent will also have cranial nerve palsies, and 30 percent will have abnormal pupils. Of note, 25 percent of patients with strokes will have their symptoms evolve over several days instead of the typical sudden onset (Merritt *et al.*, 1946). Because *T. pallidum* can simultaneously infect the meninges and brain parenchyma, some patients also may have cognitive decline or dementia from general paresis.

Brain CT or MRI of patients with meningovascular syphilis and strokes typically show abnormalities consistent with ischemic lesions, which occasionally may be multiple

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(Holland *et al.*, 1986; Brightbill *et al.*, 1995). Conventional angiography or magnetic resonance angiography may show evidence of arteritis with concentric narrowing of large vessels and often focal narrowing and occasionally dilatations of smaller arteries (Vatz *et al.*, 1974; Peters *et al.*, 1993; Gallego *et al.*, 1994; Brightbill *et al.*, 1995; Gaa *et al.*, 2004; Flint *et al.*, 2005; Peng *et al.*, 2008). The findings are not specific and are compatible with other types of CNS vasculitis and with vasoconstriction unrelated to vasculitis. In a few patients with a stroke and CSF evidence of meningovascular syphilis, arterial imaging may show another cause for the stroke, such as atherosclerosis. At other times, atherosclerosis may be present along with arteritis (Landi *et al.*, 1990). MRI with gadolinium often shows enhancement and thickening of the meninges around the cisterns and brainstem and, occasionally, over the cerebral cortex (Brightbill *et al.*, 1995; Good and Jager, 2000). Nontreponemal extracranial vascular disease may also be present (Aldrich *et al.*, 1983).

The CSF should be abnormal. The opening pressure in a lumbar puncture may be normal to slightly elevated. The CSF typically has a mononuclear cell pleocytosis of 10 to several hundred cells per microliter, normal glucose levels, and protein levels ranging from normal to 250 mg/dL. Oligoclonal bands and elevated CSF immunoglobulin G (IgG) levels are often present (Vartdal *et al.*, 1982). In meningovascular syphilis, the ability to isolate spirochetes by animal inoculation of CSF is very difficult in contrast to secondary syphilis, in which spirochetes can be isolated in up to 30 percent of cases (Lukehart *et al.*, 1988). Likewise, the PCR assays for *T. pallidum* in CSF exist in research laboratories but are not sensitive enough for routine detection of *T. pallidum* in serum or CSF (Wong *et al.*, 2015). Unfortunately, there is no single specific and sensitive test for neurosyphilis, particularly in the setting of marked immunosuppression such as HIV (Marra, 2015).

Syphilitic Myelitis and Spinal Cord Stroke

Syphilis of the spinal cord is a clinical rarity and usually accompanies other forms of cerebral syphilitic involvement. In the classic preantibiotic series at Boston City Hospital, only 31 (1 percent) of the 2,263 patients with syphilis had non-tabetic spinal cord damage (Merritt *et al.*, 1946). Only one-third of those with spinal cord disease had spinal vascular syphilis. Patients could present with an insidious onset or suddenly develop an acute transverse myelitis syndrome. The principal symptoms include paraparesis or paraplegia, urinary and fecal incontinence, and sensory abnormalities with paresthesias, pain, or sensory loss in the lower back and legs. Available pathology shows that the patients had a chronic spinal meningitis with some larger vessels showing typical Heubner's endarteritis. The thoracic spinal cord is the most commonly affected, and patients may present like an acute transverse myelitis. Spinal syphilis is only rarely seen today (Fisher and Poser, 1977; Harrigan *et al.*, 1984; Lowenstein *et al.*, 1987; Silber, 1989). The MRI typically shows short segment, high signal intensity in the thoracic cord on T2-weighted images and abnormal enhancement, predominately in the superficial parts of the spinal cord, on gadolinium-enhanced images (Lowenstein *et al.*, 1987; Nabatame *et al.*, 1992).

Involvement of the cervical spinal cord with quadriplegia is extraordinarily rare but has developed following a syphilitic gumma necrosing the cervical cord or from development of a firm fibrous sheath surrounding the cervical cord (syphilitic hypertrophic pachymeningitis) (Merritt *et al.*, 1946; Silber, 1989).

HIV and Neurosyphilis

Considerable evidence shows that immunodeficiency impairs the clearance of *T. pallidum* from the CNS and may accelerate the course of neurosyphilis (Funnye and Akhtar, 2003; Marra, 2004). Individuals with *T. pallidum* are at higher risk of concurrent HIV infection. The dual infection results in a higher HIV load (Buchacz *et al.*, 2004). Accordingly, HIV tests are recommended in every patient with neurosyphilis (Golden *et al.*, 2003). In addition, HIV patients with untreated syphilis have an increased risk (24 percent) of neurosyphilis (Bordon *et al.*, 1995). Thus, a CSF-VDRL test is needed in every HIV patient who develops cerebrovascular disease, especially if the serum fluorescent treponemal antibody absorption assay (FTA-ABS) or RPR test is reactive.

Currently, in the HIV patient both the CSF-VDRL and CSF-FTA-ABS tests appear adequate for diagnosis of meningovascular syphilis, but slightly more false-positive serum RPR tests are encountered. Treating the patient infected with both *T. pallidum* and HIV may be difficult. There is evidence that penicillin treatment for a duration longer than 14 days is required for meningovascular syphilis in the HIV patient (Marra *et al.*, 2004a).

Diagnostic Evaluation for Syphilis in a Patient with Cerebrovascular Disease

Although cerebrovascular disease from neurosyphilis is uncommon in developed countries, there are several risk factors that increase the probability (Table 1.1).

The laboratory tests help to establish the diagnosis. More than 95 percent of patients with early neurosyphilis have a positive serum RPR test with titers ranging from 1:2 to >1:128. The RPR, VDRL, and toluidine red unheated serum test (TRUST) tests are nontreponemal tests and measure IgG and immunoglobulin M (IgM) antibodies to a cardiolipin–lecithin–cholesterol antigen. These tests are generally expressed as a titer, with higher titers reflecting greater disease activity (Marra, 2015). The reactivity of these tests generally reflects the activity of the disease, and titers decline often to zero following effective antibiotic treatment. A reactive serum RPR test must be confirmed with a positive serum FTA-ABS, *T. pallidum* passive particle agglutination (TPPA) test (which measures IgM and IgG reactive to the whole organism) or enzyme immunoassays (EIAs) and chemiluminescent immunoassays (CIAs) that measure antibodies to recombinant *T. pallidum* proteins. These tests ensure that the RPR reactivity is specific for syphilis as other pathogenic treponemes, such as *T. pallidum* subspecies *pertenue*, the organism that causes yaws, may cross-react with the RPR test (Marra, 2015). Most

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Table 1.1 Diagnostic work-up for syphilis in patients with cerebrovascular disease

Risk factors that increase the probability of neurosyphilis	
1.	Patient is 25–60 years old (younger than expected age in most causes of strokes or TIAs)
2.	Patient has a history of syphilis (treated or unknown treatment) or other sexually transmitted diseases
3.	Presence of ophthalmic abnormalities or cranial nerve palsies
4.	Patient is infected with HIV
5.	Patient immigrated to the United States as an adult from a high-syphilis-risk country such as sub-Saharan Africa, south or southeast Asia, Latin America, or the Caribbean
6.	Patient has stroke symptoms progressing over 24 hours
7.	Patient is a young adult with a stroke plus a history of progressive cognitive impairment or prior cranial nerve palsies
8,	Patient has neuroimaging suggestive of arteritis
Recommended laboratory tests*	
Serum:	
	RPR
	FTA-ABS or other treponemal-specific antibody test
CSF:	
	Cell count
	Glucose
	Protein
	IgG level or IgG index
	Oligoclonal bands
	CSF-VDRL
	CSF-FTA-ABS test under specific conditions
Neuroimaging*	
	Magnetic resonance angiography or conventional angiography

* See text for details of interpretation of results

patients who have reactive specific treponemal tests will have reactive tests for the remainder of their lives, regardless of treatment or disease activity (CDC, 2015). A reactive serum RPR or FTA-ABS test confirms that the patient has active syphilis but does not signify that the patient has neurosyphilis.

The diagnosis of neurosyphilis requires a lumbar puncture and CSF examination. The CSF should always have a pleocytosis of 10 to several hundred white blood cells (predominately lymphocytes and plasma cells) per microliter. The CSF glucose is normal. The CSF protein is typically elevated in the range of 60–250 mg/dL and usually contains an elevated IgG index and the presence of several oligoclonal bands (Vartdal *et al.*, 1982). The oligoclonal bands are directed against *T. pallidum* antigens when tested in a research laboratory.

The CSF-VDRL test is highly specific, but is relatively insensitive. The test is reactive only in about 75 percent of patients with syphilis (CDC, 2002). A reactive CSF-VDRL test is diagnostic for neurosyphilis because factors that cause false-positive serum RPR titers are only rarely present in CSF (CDC, 2002).

The difficulty comes when the patient lacks a positive CSF-VDRL test but has clinical, arteriographic, and CSF findings that are suspicious for neurosyphilis. This occasionally develops in patients who have vascular disease from secondary syphilitic meningitis or from meningovascular syphilis (CDC, 2002; Marra, 2004). If the clinical picture and the rest of the CSF are suspicious for meningovascular syphilis, a reactive CSF-FTA-ABS (without blood contamination in the CSF) is usually considered diagnostic (CDC, 2002). Conversely, a negative CSF-FTA-ABS test excludes neurosyphilis (CDC, 2015, 2002; Davis and Schmitt, 1989).

Treatment

Penicillin is the main treatment for neurosyphilis, but penicillin must achieve sustained treponemicidal CSF levels for a prolonged period to cure. The long treatment period is necessary because penicillin kills only during bacterial cell division and *T. pallidum* has a slow replication rate of at least 30 hours. Aqueous crystalline penicillin G (18–24 million units per day) in adults is administered as 3–4 million units intravenously every 4 hours or by continuous infusion for 10–14 days (Janier *et al.*, 2014; CDC, 2015). Following the end of the intravenous treatment, the patient often is given intramuscular benzathine penicillin (2.4 million units) at 1-week intervals for 3 weeks, especially if there is also HIV infection (Jay, 2006). Under some circumstances, procaine penicillin 2.4 million units intramuscularly once daily plus probenecid 500 mg orally four times a day, both for 10–14 days, can be administered (Janier *et al.*, 2014; CDC, 2015). The major adverse effects of penicillin include anaphylaxis, rash, Stevens–Johnson syndrome, drug-induced eosinophilia, hemolytic anemia, thrombocytopenia, neutropenia, seizures, interstitial nephritis, and pseudomembranous enterocolitis. Because each million units of penicillin contain 1.7 meQ of potassium, serum potassium levels should be carefully followed in patients with renal insufficiency (Jay, 2006; Stockman *et al.*, 2014).

If the patient is allergic to penicillin, desensitization to penicillin should be considered (see CDC, 2002, for method). The CDC syphilis treatment guidelines are published about every 4 years, so one should always consult the latest version. Ceftriaxone (in adults, 2 g intravenously or intramuscularly once daily for 14 days) is currently the alternative treatment of

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choice in the few patients who cannot be desensitized to penicillin (CDC, 2015; Marra, 2004). Of note, azithromycin as an alternative antibiotic should seldom be used because macrolide-resistant mutations of *T. pallidum* are being detected (Lukehart *et al.*, 2004).

Stroke Rehabilitation

No studies have been specifically conducted regarding the rehabilitation of patients following strokes related to syphilis. However, individual case reports describe clinical improvement in syphilitic stroke patients with rehabilitation (Umashankar *et al.*, 2004). We recommend that current guidelines for provision of rehabilitation services following a stroke be followed (Bates *et al.*, 2005; Duncan *et al.*, 2005; Winstein *et al.*, 2016). Patients diagnosed with meningovascular or other forms of syphilis following presentation for an acute stroke will typically spend several weeks as hospital inpatients to receive intravenous penicillin therapy. This treatment period provides a natural time frame within which to initiate inpatient rehabilitation, either in an acute neurologic/medical or rehabilitation ward setting.

Follow-Up

Even though the peak infectious period for syphilis transmission occurs many years before a stroke, it is still important to urge the patient to notify all sexual partners (even if the relationship was years ago) to have serum RPR and FTA-ABS tests.

Every patient with neurosyphilis requires clinical and serologic follow-up at 3, 6, and possibly 12 months (CDC, 2002; Golden *et al.*, 2003; Marra et al., 2004a). The first repeat CSF examination is best at 3 months after treatment to decrease patient loss in follow-up. One prospective study found that the median time for normalization of CSF, including the white blood cell count, CSF-VDRL, and serum RPR, was 3–4 months (Marra *et al.*, 2004a). CSF protein resolves slower. If the CSF is normal at 3 months, then further lumbar punctures are not needed. CDC guidelines recommend that if the CSF cell count has not markedly decreased by 6 months or the CSF is not normal after 2 years, retreatment should be considered (CDC, 2002). Other experts recommend retreatment when there is failure of the serum RPR and CSF-VDRL to decline four-fold or to negative by 1 year (Marra, 2004). Remember that syphilitic re-infections do occur, so recurrence may not indicate treatment failure.

What happens to the cerebral arteritis and arterial stenosis following penicillin therapy is unclear, as limited follow-up imaging studies have been performed (Kelley *et al.*, 2003). Because of this, patients should also receive daily aspirin, or another antiplatelet agent, to minimize further strokes.

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Chapter 2

Vasculitis and Strokes Due to Tuberculosis

Sarosh M. Katrak

Tuberculosis (TB) is considered one of the oldest diseases known to humankind. A human skeleton with evidence of spinal TB from a neolithic cemetery was found near Heidelberg in 1904. This is considered to be the first documented record of human TB (Morse, 1961). It is unfortunate that, despite advances in prophylactic and therapeutic measures, this disease still remains a scourge in large parts of the world. According to the WHO Global Tuberculosis report 2014, four regions (South East Asia, West Pacific, Africa, and East Mediterranean) account for 91.6 percent prevalence and 93.7 percent incidence of TB worldwide. Thus, TB is still a major problem in the developing world. To make matters worse, the HIV pandemic has brought about a resurgence of this dreaded disease in many developed countries (Berenguer *et al.*, 1992; Dube *et al.*, 1992) and an explosion of all forms of TB in the developing countries, particularly in Sub-Saharan Africa, some of which are the poorest countries in the world. Fortunately there is a ray of hope, as new cases have declined since 2011 (WHO Global TB Report 2014).

Tuberculous meningitis (TBM) is the commonest form of neurotuberculosis, accounting for 70–80 percent of the cases (Udani *et al.*, 1971). TBM is still a crippling disease with a high degree of morbidity and mortality. One of the most severe complications of TBM is a stroke due to vascular involvement. Baumgarten (1881) is believed to be the first to describe these changes in autopsy specimens. The first clinical description of diffuse arteritis in the indexed literature was in a 25-year-old male patient with TBM and paraplegia from Dakar, Senegal (Collomb *et al.*, 1967). However, in the same year Wadia and Singhal (1967) described the vascular changes in 33 cases of TBM admitted between 1963 and 1965. Since the early 1970s, considerable work has been published from the Indian subcontinent on the clinical, pathologic, and angiographic studies of vasculitis and strokes in TBM. The newer techniques of neuroimaging – computed tomography (CT) scans, magnetic resonance imaging (MRI), and digital subtraction angiography (DSA) – have added to our understanding of this dreaded complication of TBM.

TBM is invariably secondary to a primary involvement of some extracranial organ, very often pulmonary TB (Vashishta and Banerjee, 1999). Our understanding of the pathogenesis of TBM begins with comprehensive and meticulous studies by Rich and McCordock (1933). They showed that there was a subcortical or meningeal focus, later called the "Rich focus," from which the bacillus gained access to the subarachnoid space. Once it gains entry, there are many factors that determine the type of lesions seen in the central nervous system (CNS). The latency between the onset of infection and the institution of therapy, the age of the patient, the immune status of the patient, and the virulence and drug sensitivity of the bacillus are important determinants modifying the pathology and pathogenesis of neurotuberculosis. Gross examination of the brain at autopsy showed that a thick exudate was most frequently present on the basal aspect (Dastur and Lalitha, 1973; Thomas *et al.*, 1997), where the structures are obscured. Coronal slices of the brain reveal thick, organized exudates all around the optic chiasm, extending into the Sylvian fissures, entrapping the middle cerebral artery (MCA) and its branches.

Askanazy (1910) first described the triad of vascular changes in TBM: panarteritis involving all the three coats in a tuberculous process, caseation of the vessel wall, and fibrinoid swelling. Since then, changes involving the vessels in the brain are the most intensively studied aspect and one of the landmark histopathologic features of TBM. Macroscopically, the basal arteries, particularly the MCA and its branches, are maximally involved. Microscopically, the three most commonly described vascular pathologies are infiltrative/inflammation, proliferative, and necrotizing. These may be in pure forms or in combination, with or without thrombosis. The infiltrative process spreads from the adventitia to the intima and involves the basal vessels maximally reflecting the changes seen in the subarachnoid spaces. Most studies show that the adventitia and intima are most affected as the media is relatively resistant to these changes (Lammie *et al.*, 2009). Smooth muscle cell proliferation leads to thickening of the media and occlusion of arteries. This process occurs in tandem with infiltrative processes and is usually seen in chronic and/or partially treated TBM. Fibrinoid necrosis is the modern terminology for what Azkanazy (1910) described as "fibrinoid degeneration." This process involves predominantly the intima or media or both. It is a non-specific injury and similar changes have been described in malignant hypertension, anti neutrophil cytoplasmic antibody-associated vasculitis, and radiation injury (Lammie *et al.*, 2009). Shankar (1989) observed intracytoplasmic vacuolations of the media in blood vessels in TBM and felt that these changes were also non-specific and compared them to those seen in subarachnoid hemorrhages due to vasospasm.

The role of thrombosis in producing infarcts in TBM is controversial. When specifically looked for, some pathologists have described it as rare (Lehrer, 1966; Dalal, 1979), uncommon (Poltera, 1977; Winkleman and Moore, 1940), or reasonably common (Deshpande *et al.*, 1969, Poltera, 1977). However, thrombosis may play an important role in cerebral

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venous sinus thrombosis or spinal artery thrombosis (Dastur and Lalitha, 1973). The role of thrombosis may be best summarised by the statement of Dalal (1979) "... it is extremely uncommon to find an organising thrombus in an appropriate vascular territory that matches the age of the cerebral infarction".

In spite of meticulous histopathologic studies, the pathogenesis of cerebral infarctions is not fully understood. The initial inflammatory reaction may give way to proliferative stenosis of arteries as the basal exudates thicken. Many authors believe that these changes are more due to disease duration rather than treatment of TBM (Winkleman and Moore, 1940; Dastur and Lalitha, 1973). The pathogenesis may be that most infarcts are due to hypoperfusion secondary to a variable combination of intimal proliferation, fibrinoid necrosis, vasospasm, and thrombosis (Dalal, 1979).

In summary, the pathologic data are disparate and often contradictory. Clinically, infarcts occur in more severe or partially treated TBM, a phase of the illness in which intimal proliferation is likely to occur. Angiographic data and the presence of fibrinoid necrosis may point to the potential role of vasospasms in producing infarcts early in the course of the disease. Similarities to other immune-mediated vasculopathies may suggest an immune-mediated mechanism (Lammie *et al.*, 2009).

In spite of the advances in the molecular biology of tuberculosis the immune response within the brain in TBM remains poorly understood. Several cytokines and chemokines have been studied – tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-1 beta (IL-1ß), and matrix metallopeptidase-9 (MMP-9) – and their serum and cerebrospinal fluid (CSF) levels correlated with the severity of the disease, mortality, and also with CSF lactate levels as a marker for ischemic events in the brain. The results have been disparate and sometimes contradictory. Akalin *et al.* (1994), Babu *et al.* (2008), and Patel *et al.* (2002) found a positive correlation between the CSF levels of TNF-α, IL-1ß, IFN-γ, and IL-10, and the severity of the disease. On the other hand, Donald *et al.* (1995) and Mastroianni *et al.* (1997) did not demonstrate any correlation although there was no decline in the levels of IFN-γ, TNF-α, and IL-10 on a follow up of 3–8 months. High levels of IL-8, IFN-γ, TNF-α, and MMP-9 correlated with high levels of CSF lactate, suggesting a role in the pathogenesis of infarcts (Babu *et al.*, 2008 and Thwaites *et al.*, 2004). However, others (Donald *et al.*, 1995 and Lammie *et al.*, 2009) have suggested that they are merely markers indicating vessel involvement rather than the cause of vasculitis. In a recent study from India, Sinha *et al.* (2015) found that the levels of TNF-α in serum and CSF and IL-1ß in serum correlated significantly with the severity of the disease and even predicted mortality in their patients. Paradoxically, there was no correlation of these cytokines with strokes, which not only contributes to the severity of the disease but also to it resulting in mortality. It would be logical to presume that other pathogenetic factors – such as changes in microvascular reactivity to neurochemicals, cytokines, and the state of cell-mediated immunity (CMI) of the patient at that particular time – play an important role in the genesis of these lesions.

In HIV-infected individuals with TBM, the immune response to the tuberculous bacilli is altered; therefore, pathologic features are very different from those seen in patients with relatively normal CMI. The brains of such individuals showed minimal inflammatory response with parenchymal infarcts and vasculitis, not only in the basal ganglia but in the cortical parenchyma as well (Katrak *et al.*, 2000). This lack of inflammation is also reflected in the CSF (Katrak *et al.*, 2000). The exact reason for this extensive vasculopathy was not clear. It is known that polyclonal B-cell activation occurs in HIV-infected patients, with resultant hypergammaglobulinemia and circulating immune complexes (Cotran *et al.*, 1999). However, it remains speculative that such B-cell activation occurred due to mycobacteria in these patients (Katrak *et al.*, 2000). Simmons *et al.* (2005) correlated low CSF levels of IFN-γ with death in HIV-positive patients in Vietnam. However, this finding was not correlated with the incidence of strokes in these patients.

The controversy regarding the pathogenesis of vasculitis, therefore, is far from resolved. Whether morphologic changes, vasospasm, or an immunologic attack of the vessel wall by cytokines play a major role, is undetermined. Factors like host CMI, particularly in HIV-P patients, and the lineage and virulence of *Mycobacterium tuberculosis* further compound the issue and stress the need for systemic pathologic studies of this entity. The truth may lie in a combination of these factors forming a cascade of events.

The clinical features are usually preceded by a prodromal phase of fatigue, malaise, low-grade fever, and loss of appetite. The further temporal evolution depends on the severity of the disease and complications associated with the involvement of basal structures (namely, cranial nerve palsies, paraplegia, strokes, hydrocephalus, and altered consciousness). Traditionally, the severity of the disease is grouped into three stages: mild (stage 1), moderate (stage 2), and severe (stage 3), with a good correlation with the final outcome (Singhal *et al.*, 1975; Streptomycin in Tuberculosis Trial Committee, 1948). Strokes usually occur in patients in stages 2 or 3. Hence, this dreaded complication is associated with a high mortality and morbidity (Katrak *et al.*, 2000; Misra *et al.*, 2011).

Strokes in TBM occur in 13–57 percent of patients, depending on the method of evaluation. Clinically evident focal neurologic deficits occur in 20 percent of cases (Dalal, 1979); however, in a series from Taiwan, the incidence was as high as 47 percent (Lan *et al.*, 2001). CT scans reveal infarctions in 13–35 percent of patients and MRI has a greater sensitivity, up to 57 percent (Shukla *et al.*, 2008 and Kalita *et al.*, 2009).

In one series, 8 percent of strokes in the young were due to tuberculous vasculitis (Dalal and Dalal, 1989). Focal neurologic deficits usually occur acutely and involve the basal ganglia and subcortical structures. Thus, aphasia, apraxia, and agnosia are uncommon. However, when these occur insidiously, they should arouse suspicion of an evolving tuberculoma in the

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appropriate area. Infarcts in the vertebrobasilar territory were reported as uncommon in the earlier literature (Dalal and Dalal, 1989) but in a recent study, 20 percent of strokes occurred in this territory, based on clinical and MRI evaluation (Kalita *et al.*, 2009). Intracerebral or intraventricular hemorrhages are rare (Dalal and Dalal, 1989). Convulsions may present at any stage of TBM, particularly in children. They occurred in 37.5 percent of patients with vascular involvement as compared to only 20 percent of those without strokes in a case study (Thomas *et al.*, 1997). Convulsions may also occur due to associated tuberculomas, hydrocephalus, or tuberculous meningoencephalitis. Clinically, strokes in individuals co-infected with HIV are no different than those in persons without HIV infection, as reported by several case series (Yechoor *et al.*, 1990; Berenguer *et al.*, 1992; Dube *et al.*, 1992; Porkert *et al.*, 1997; Katrak *et al.*, 2000). However, data from India have shown that the mortality is much higher in these patients (Katrak *et al.*, 2000; Kawre *et al.*, 2001).

The diagnosis of TBM is usually established by the demonstration of acid-fast bacilli, by a direct smear or culture in the CSF, brain parenchyma, tuberculomas, or meninges in biopsy or autopsy material. The sensitivity of Ziehl–Neelsen (Z–N) smear can vary between 10 and 60 percent and culture between 25 and 75 percent (Brancusi *et al.*, 2012). The main drawback of cultures is the long delay (2–6 weeks) before results are available. Newer techniques have increased the diagnostic yield with a minimal delay. Chen *et al.* (2012) reported on a modified Z–N stain with a 100 percent sensitivity for both intracellular and extracellular AFB detection. Newer techniques like the polymerase chain reaction (Takahashi *et al.*, 2005) and Gene Xpert (Denkinger *et al.*, 2014) have increased the diagnostic yield with a high degree of sensitivity/specificity. Unfortunately, the equipment is expensive and requires an elaborate infrastructure, quality control, and high maintenance costs, conditions unavailable in many centers, particularly in developing countries where TBM is rampant.

Neuroimaging procedures are not diagnostic for TBM but have become the standard for detecting its complications. CT or MRI of the head may reveal intense basal enhancement after intravenous contrast administration, communicating or obstructive hydrocephalus, cerebral infarcts, tuberculomas, or a combination of two or more of these features (Figure 2.1). Basal enhancement and tuberculomas are direct features of TBM whereas infarcts and hydrocephalus are signs of its complications. CT scanning lacks the sensitivity of MRI, especially for infarcts. Although the incidence of infarcts on CT varies from 13 to 35 percent (Kalita *et al.*, 2009), the technique is readily available in most centers, particularly in developing countries, it is cost effective, and obviates the need for sedation in acutely ill patients and children as the study duration is short. Infarcts are more common in children (Kingsley *et al.* 1987; Andronikou *et al.*, 2006).

MRI, particularly diffusion-weighted imaging, is very sensitive in detecting infarcts at an early stage and in the VB circulation (Shukla *et al.*, 2008; Pienaar *et al.*, 2009). Magnetic resonance angiography (MRA) has superseded DSA as it is not traumatic and can be used for follow-ups of patients.

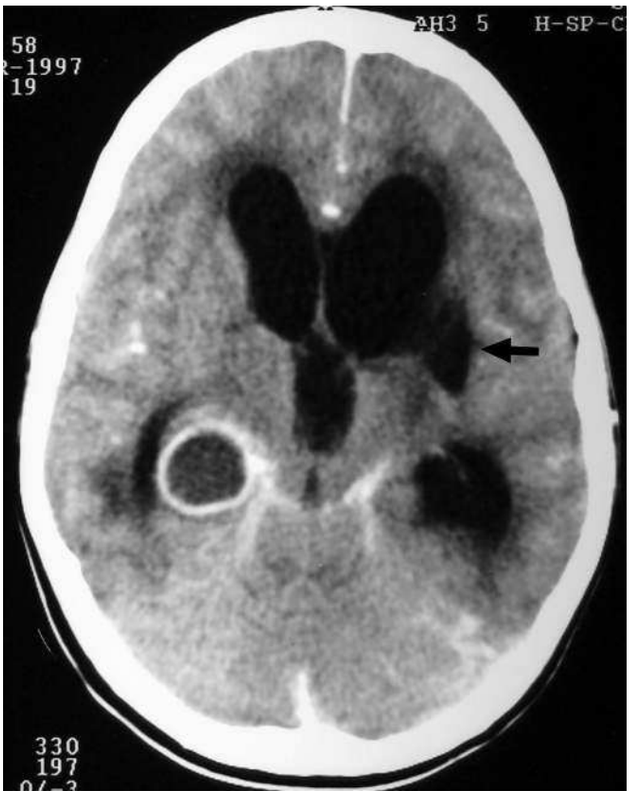

Figure 2.1 Postcontrast axial CT scan showing dense basal exudates around the quadrigeminal cistern, hydrocephalus, right parahippocampal tuberculous abscess, and a left basal ganglia infarct (arrow).

Recently, Kalita *et al.* (2012) detected infarcts in 40 out of 67 patients (59.7 percent) and MRA abnormalities in 50.7 percent of cases. More importantly, over 40 percent of patients with abnormal MRA developed infarcts at 3 months whereas none did with normal MRA images (Kalita *et al.*, 2012). If confirmed by other studies, MRA may have the potential for predicting the chance of an infarction, thereby reducing the mortality and morbidity.

In the Western literature, neuroimaging findings were no different in HIV-infected individuals when compared to non-infected cases (Yechoor *et al.*, 1990; Berenguer *et al.*, 1992; Villora *et al.*, 1995). In contrast to the above findings, we found distinct differences. The basal exudates were sparse and infrequent, tending to occur only after initiation of anti-tuberculous therapy. Ventricular dilatations occurred secondary to atrophy. Granulomatous lesions included tuberculomas as well as toxoplasma granulomas. An interesting observation was that of the occurrence of cortical infarcts in these patients with angiographic evidence of arteritis (Katrak *et al.*, 2000). Similar findings have been described from other centers in India and abroad (Kawre *et al.*, 2001; Sze and Zimmerman, 1988; Andronikou *et al.*, 2006).

The initial data on vascular involvement in TBM were based on cerebral angiography. However, in the modern era, the role of catheter cerebral angiography is limited. It is usually necessary in patients with clinically evident focal neurologic

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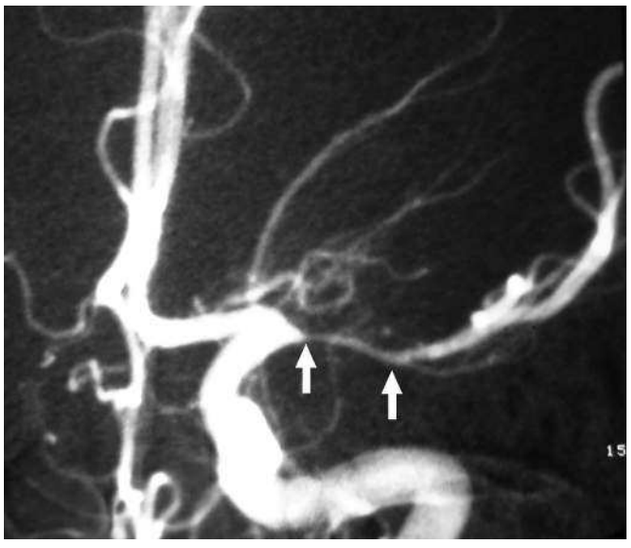

Figure 2.2 Left carotid angiogram of the same patient as in Fig. 2.1 showing organic stenosis or induced vasospasm of the M1 segment of the MCA (between arrows).

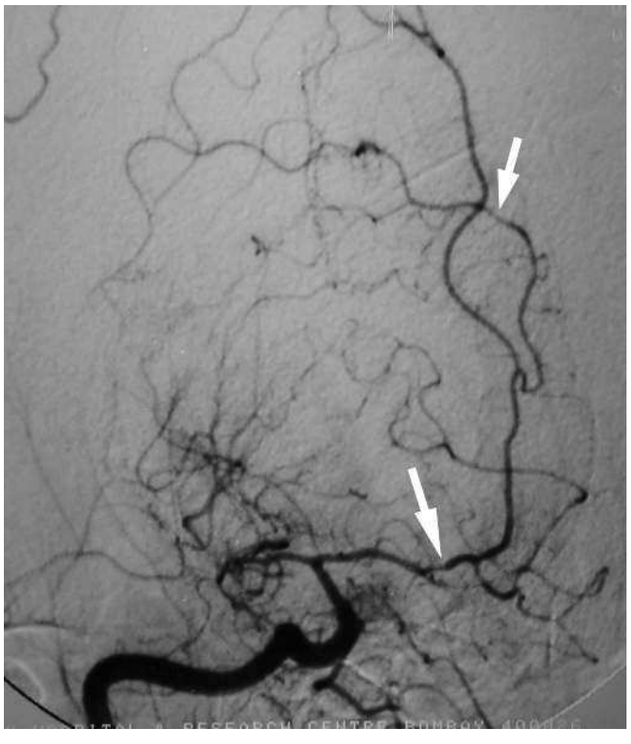

Figure 2.4 Right carotid angiogram, oblique view of a patient with TBM and HIV infection. Total block of the right MCA and areas of segmental narrowing – arteritis – along the right anterior cerebral artery (arrows).

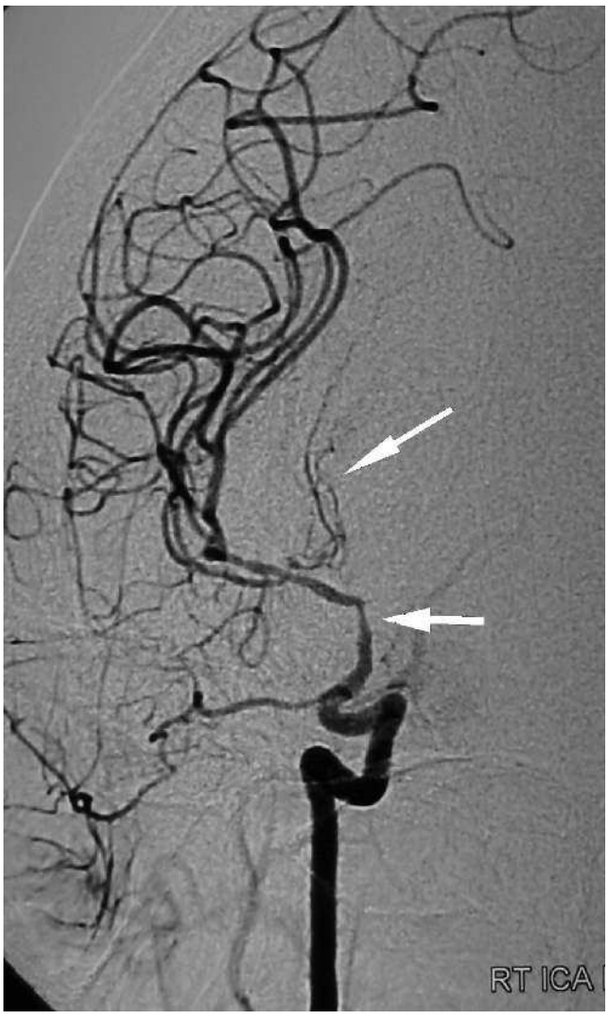

Figure 2.3 Right carotid angiogram showing marked narrowing of the supraclinoid internal carotid artery with segmental narrowing of M1 segments of the MCA (bottom arrow).
Note: only the lateral lenticulostriate perforators are seen (top arrow).

deficits and in those with altered mentation. Lehrer described an angiographic triad of a sweeping pericallosal artery, narrowing of the supraclinoid portion of the internal carotid artery, and narrowed or occluded small or medium-sized intracranial arteries, with scanty collaterals (Lehrer, 1966). This was subsequently confirmed in many studies (Wadia and Singhal, 1967; Dalal, 1979; Rojas-Echeverri *et al.*, 1996; Mishra and Goyal, 1999). The clinico–angiographic correlation is not good. Normal angiograms have been found in patients with clinical or MRI evidence of infarcts in 42–57 percent of cases (Wadia and Singhal, 1967; Dalal, 1979; Rojas-Echeverri *et al.*, 1996). Conversely, a significant reduction in the vascular lumen has been found in patients with no neurologic deficit (Deshpande *et al.*, 1969; Dalal, 1979; Rojas-Echeverri *et al.*, 1996) or neuropathologic changes (Dalal, 1979). Even the mechanism for the angiographic changes is debated. It could be due to organic stenosis of the vessel due to thick basal exudates (Wadia and Singhal, 1967; Dastur *et al.*, 1970; Vashishta and Banerjee, 1999) or to arteritis-induced vasospasms (Dalal, 1979; Yamashima *et al.*, 1985; Rojas-Echeverri *et al.*, 1996); see Figures 2.2 and 2.3.

In our cases of TBM with HIV infection and cerebral infarcts, we had angiographic and pathologic evidence of widespread arteritis (Figure 2.4) (unpublished data). However,

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