Meningo-Vascular Syphilis: Revisiting An Old Adversary

A peculiar pathological presentation within the panorama of neurosyphilis is a phenomenon called meningo-vascular syphilis (MVS) or meningo-vascular neurosyphilis.

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“He who knows syphilis knows medicine”
— Sir William Osler

Syphilis is a debilitating multisystem disease resulting from infection with the spirochete Treponema pallidum. In the United States, it has an incidence of 3.3 to 3.7 per 100,000 people with more than 10,000 cases diagnosed each year (2007 statistics). This figure continues to grow vis-à-vis the global HIV/AIDS epidemic. Since the beginning of the HIV epidemic, the presenting clinical features of syphilis have changed parallel to its rising incidence. Because of its heterogeneous clinical features and the fact that its manifestations mimic other diseases, syphilis still holds the notorious sobriquet of “the Great Masquerader.”

Syphilis is primarily transmitted via sexual contact and can affect virtually every organ. Neurological sequelae of syphilis are well known and can be quite devastating. As intricate as these neurological sequelae are, within the spectrum of the disease, they are collectively referred to as neurosyphilis (NS). NS occurs in about 10 percent of untreated syphillics and typically manifests in secondary and later stages of the disease. It can involve all components of the nervous system, culminating in disorders of the brain, spinal cord, as well as cranial and peripheral nerves. With the advent of antibiotic therapy, the typical clinical presentation of NS has transposed from chronic and delayed forms, which involve central nervous system (CNS) parenchyma, to earlier forms that affect the meninges and CNS blood vessels. A peculiar pathological presentation within the panorama of NS is a phenomenon called meningo-vascular syphilis (MVS) or meningo-vascular neurosyphilis.

MVS is a distinct form of NS characterized by a meningo-encephalopathic syndrome with superimposed cerebrovascular or myelovascular events. It is a combination of chronic syphilitic meningitis and arteritis. Although MVS was perhaps recognized as a disease entity much earlier, it was in 1946 that Merritt, Adams, and Solomon studied the largest MVS series to date and re-emphasized its existence as a unique subset of NS. MVS is a rare yet important condition in the realm of infection-related stroke and cerebrovascular disease. Because the face of syphilis within the dominion of neurology has changed tremendously over the years and as screening tests for syphilis are increasingly becoming routine components of acute stroke laboratory workup (especially in younger patients), the authors felt appropriate to revisit the topic of MVS, with an emphasis on diagnosis and therapy.

The Disease

An unusual cause of stroke, MVS comprises about 10 percent of NS and 3 percent of all syphilis cases. Because of its rarity, exact epidemiological data for MVS are unavailable. The disease most often presents during the first 10 years after the
primary infection, with peak occurrence at four to seven years. Syndromes consistent with MVS have been reported as early as four months after the incipient infection with T. pallidum. Patients with MVS tend to be younger than the typical stroke patient. Seventy-four percent of patients in the series studied by Merritt et al. were under the age 50.

MVS involves an infection-associated inflammatory arteriopathy resulting in injury to the blood vessels of the leptomeninges, brain, and spinal cord, leading to infarctions. The histopathological end result is similar in morphology to autoimmune CNS arteritis. In general, there is diffuse thickening and lymphocytic infiltration of the meninges and the perivascular spaces. Other findings include fibroblastic and collagenous thickening of the intima, thinning of the media, and fibro-inflammatory infiltration of the adventitia of large and medium-sized vessels. The most common form of syphilitic arteritis—known as Heubner arteritis—involves large and medium-sized vessels. Small vessel disease in syphilis is known as Nissl-Alzheimer arteritis. It is characterized by a proliferation of endothelial and adventitial cells. Ultimately, luminal obliteration and rarely aneurysmal ectasia ensue in both types.

MVS usually—but not always—begins as a subacute or chronic encephalopathic syndrome characterized by weeks to months of intermittent headaches, progressive behavioral changes, and movement disorders. This prodromal syndrome occurs in about 25 percent of patients and is a consequence of meningitis caused by inflammation of the leptomeningeal arteries. Along the course of this premonitory interval, there are acute neurological events resulting from cerebral or spinal cord infarctions. Presentations of the cerebral infarcts are non-specific and dependent upon the arterial territory involved. Acute spinal cord infarcts resulting from MVS may clinically present in various forms of myelopathy, including hemiparaplegic syndrome (Brown-Séquard hemiplegia) or transverse myelitis.

**Diagnosis**

The diagnosis of MVS could be as simple as establishing the presence of syphilis in a patient with an acute brain or spinal cord infarct. However, it is necessary to demonstrate evidence of the disease in the CNS by analyzing a cerebrospinal fluid (CSF) sample. Obtaining a complete history is paramount. A young adult presenting with a stroke should raise adequate suspicion to place MVS in the differential diagnosis. In addition to obtaining routine stroke-focused history, an inquiry into prior sexually-transmitted diseases (STD), high-risk sexual behavior, and symptoms such as progressive headaches, memory disturbances, or behavioral alterations is crucial. Figure 1 is an illustration of the clinical and pathological course of MVS.

Brain (MRI diffusion weighted imaging) or spinal cord (sagittal and axial T2 MRI) imaging confirms the presence of an acute infarct, but is not specific to MVS. Angiography often reveals varying degrees of segmental, concentric stenocclusive arteriopathy. These characteristics are nonspecific and by-in-large resemble angiographic findings in CNS arteritis (that is if the disease involves large and medium-sized vessels). The middle cerebral artery is the most commonly affected vessel at a frequency of 66 percent. The basilar artery is the second most commonly affected artery, leading to potentially devastating brainstem and posterior circulation territory infarcts. Multiple arteries are involved in 12 percent of cases. Extracranial arteries, including cervical internal carotid artery, can also be affected. Angiography is most often unremarkable in patients with small vessel MVS. Therefore, this modality has limited utility in diagnosis and confirmation of small vessel MVS.

As previously mentioned, many centers include serum non-treponemal (NT) tests—such as rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL)—in the set of preliminary stroke laboratory examination, especially as a part of a “young stroke” workup. RPR and VDRL are screening serological tests for syphilis and correlate with disease activity. They lack sensitivity in
early and late syphilis and often yield false positives. False-positive reactions are associated with increased age, pregnancy, drug abuse, malignancy, and autoimmune diseases (such as systemic lupus erythematosus), as well as with viral (particularly Epstein-Barr virus and hepatitis virus), protozoal, and mycoplasmal infections. Serum RPR has a sensitivity of 78 percent and a specificity of 85 percent, while VDRL has a sensitivity and a specificity of 86 percent and 85 percent, respectively. If serum RPR or VDRL is positive, then a titer is obtained. An RPR or VDRL titer of 1:8 or greater is suggestive of syphilis (but not necessarily NS).

False positives are usually below these levels. The second step is to perform a confirmatory test. Several such tests are available including fluorescent treponemal antibody absorption (FTA-Abs), Treponema pallidum hemagglutination assays (TPHA and MHA-TP), Treponema pallidum particle agglutination assay (TP-PA), and the Toluidine red unheated serum test (TRUST). The most commonly used confirmatory test is FTA-Abs, which has a very high sensitivity for all stages of the disease.

Once syphilis is confirmed in the stroke patient, it is imperative to treat, regardless of whether or not the disease is the cause of the stroke. However,
treponemal infection of the CNS must be established because the treatment regimen for NS is different than non-CNS syphilis (see next section). Unfortunately, no single test can be used to diagnose NS. Some use the threshold of RPR/VDRL titer of 1:32 to proceed to lumbar puncture (LP) for CSF sample analysis. Others embark on CSF examination for any titer $\geq 1:8$ when in combination with a diagnosis of stroke (or other neurological signs and symptoms), even without a confirmatory test. The decision to perform an LP in the context of low titer RPR/VDRL is a strong indication in patients with HIV infection/AIDS.

CSF analysis for diagnosis of NS/MVS is complex. This is due to low sensitivity of treponemal and NT tests in the CSF. CSF RPR has not been widely studied and is rarely used. CSF VDRL has a sensitivity of 10 percent to 30 percent, but is highly specific for NS. Due to poor sensitivity of CSF VDRL, the diagnosis of NS depends upon various combinations of test results, including CSF leukocyte count and protein. Elevated CSF protein and lymphocytic pleocytosis (>5 cells per mm3) in a patient with syphilis points to a syphilitic meningitis, irrespective of the results of CSF VDRL. CSF FTA-Abs is not routinely done as it is quite expensive; but similar to CSF VDRL, it is highly specific (though poorly sensitive). A reactive VDRL or FTA-Abs in the CSF is diagnostic of NS due to a high level of specificity.

Figure 2 provides a simplified algorithm to assist neurologists in the diagnostic process. This flow-chart is not necessarily a guideline or a universal protocol. The aim of the authors in demonstrating this algorithm was to propose a systematic approach to a stroke patient with positive syphilis serology. Neurologists must bear in mind that the diagnosis of MVS/NS is much more complex and requires meticulous clinical judgment, especially in the context of co-existing confounders such as HIV/AIDS and traditional vascular risk factors. As a final note, the Centers for Disease Control and Prevention (CDC) recommendation is that all patients who have syphilis (with or without evidence for NS) be tested for HIV.

Management
To emphasize, treatment protocols for CNS and non-CNS-associated syphilis are quite different. MVS is a form of NS and therefore the antibiotic regimen is the same. However, further stroke prevention is crucial in patients with MVS and this strategy needs to be realized within the context of the arteriopathy caused by syphilis. In MVS, injury-related morphological changes in vasculature causes steno-occlusive cerebrovascular disease. This may lead to acute platelet aggregation and vessel occlusion, precipitating in cerebral infarcts. Subsequently, implementation of an antiplatelet agent is not an unreasonable strategy in patients with cerebral infarction and MVS. There is no strong evidence for the utility of antiplatelet agents in spinal cord infarcts and therefore no suggestion can be made in that regard.

For antibiotic therapy of NS, CDC recommends aqueous crystalline penicillin G, 18 to 24 million units per day, administered as 3 to 4 million units intravenously (IV) every four hours or continuous infusion, for 10 to 14 days. If compliance with therapy can be ensured, patients may be treated with an alternative regimen of procaine penicillin G, 2.4 million units intramuscularly (IM) once daily plus probenecid 500mg orally four times a day, both for 10 to 14 days. The durations of the recommended and alternative regimens for NS are shorter than that of the regimen used for late syphilis in the absence of CNS involvement. Therefore, some clinicians administer benzathine penicillin G, 2.4 million units IM once per week for up to three weeks after completion of these NS treatment regimens to provide a comparable total duration of therapy. In patients with penicillin allergy, ceftriaxone 2g daily either IM or IV for 10 to 14 days can be used as an alternative treatment for NS. If a concern regarding the possibility of cross-reactivity between ceftriaxone and penicillin exists, the patient should undergo skin testing to confirm penicillin allergy and, if necessary, be desensitized and managed in consultation with an allergist.
If CSF pleocytosis was initially present, an LP should be repeated every six months until the leukocyte count is normal. Follow-up CSF examinations also can be used to evaluate changes in the CSF VDRL or protein after therapy; however, changes in these two parameters occur more slowly than cell counts, and persistent abnormalities might be less important. With effective treatment, CSF should normalize in two years. If the leukocyte count has not declined after six months or if the CSF is not normal after two years, treatment should be repeated. Management of HIV-infected patients with NS is beyond the scope of this article and will not be discussed.

Because MVS is a rare condition, in patients with an initial abnormal cerebral angiogram...
(demonstrating large vessel disease), no specific recommendation has been made with regard to follow up angiography. It is however reasonable to obtain a follow up examination (MRA, CTA or conventional cerebral angiogram) after normalization of CSF to assess the status of large vessel cerebrovascular disease. Until then, antiplatelet agents should be continued. If follow up angiography is normal, consideration can be given to stop antiplatelet therapy, providing the absence of other stroke risk factors. A persistent abnormal angiogram warrants indefinite continuation of antiplatelet medications. Because the progress of small vessel MVS cannot be ascertained via angiography, patients suffering from this type of MVS should perhaps remain on antiplatelet agents for life, unless the patient has contraindications or complications related to these medications. Transcranial Doppler (TCD) ultrasonography has also been used to monitor response to therapy in MVS. TCD may be a useful, non-invasive technology for that purpose; at least in between the angiograms.

**Conclusion**

MVS is a perplexing disease. A high index of suspicion is required in patients who fit the risk factor profile for this condition. In young individuals with cerebral or spinal cord infarcts and in those with unclear etiology to their stroke, screening for syphilis cannot be over-emphasized. It is a disease that can have dire consequences if left untreated. A potentially incapacitating stroke is only one of such consequences. It is also important to consider MVS in a patient who has a working diagnosis of primary or secondary CNS vasculitis (arteritis). In many cases, clinicians excessively focus on autoimmune or rheumatological causes of CNS vasculitis, overlooking infectious etiologies. This may lead to a hasty diagnosis of primary CNS vasculitis when in reality, the patient suffers from MVS. Let us not forget that primary CNS vasculitis and MVS could clinically and radiographically present in a similar fashion. In conclusion, because MVS is a treatable condition, it is not a dubious endeavor to include simple syphilis screening tests in routine stroke laboratory examinations.

Clinicians face many challenges with regard to approaching patients with syphilis and particularly, those with NS/MVS. The increasing rates of syphilis, given the effectiveness of penicillin therapy, suggest a failure in prevention. Changing migration patterns and high-risk behavior may cause thousands of cases to go undetected. With the relentless, diverging appearance and complexity of syphilis, the most effective strategy to battle the “Great Masquerader” is still providing education and implementing preventative measures, focusing especially on our youth.

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