Neurosyphilis: Diagnosis and Response to Treatment

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In this issue of *Clinical Infectious Diseases*, an important article examines the serologic response to treatment of neurosyphilis. Marra et al. [1] show that normalization of the results of the serum antibody test for cardiolipin (rapid plasma reagin [RPR]) is a strong indicator of success after treatment of neurosyphilis. Most of their patients had HIV infection, but their findings are likely to apply to HIV-uninfected persons, as well.

This article [1] provides great practical help to physicians who treat patients for sexually transmitted diseases. Performing a lumbar puncture in a clinical setting is logistically difficult, and furthermore, patients often refuse it. Thus, it is reassuring to learn that normalization of the serum RPR titer is highly predictive of a good response to therapy, even though this finding is somewhat less likely to apply to untreated patients with AIDS.

A full understanding of the article by Marra et al. [1] requires further discussion of 2 important issues—one relating to the diagnosis of neurosyphilis and the other to treatment. In the prepenicillin era [2,3], neurosyphilis was diagnosed clinically; the diagnosis was supported by serologic test results positive for syphilis and detection in CSF of antibody to cardiolipin (initially by the Wassermann reaction, then by the Hahn and other more sensitive modifications, and ultimately by the venereal disease research laboratory [VDRL] test). If the CSF VDRL test result was negative, increased WBC count or protein concentration in CSF provided laboratory support; except in forms of neurosyphilis that are now rare, this was decidedly uncommon [2]. Asymptomatic neurosyphilis was diagnosed on the basis of CSF VDRL test results, although in an occasional case, other CSF abnormalities, in addition to a high serum RPR titer, might have been regarded as diagnostic. Simpy stated, a diagnosis of neurosyphilis or the exclusion of this diagnosis depended largely on the CSF VDRL test result.

In 1972, Hooshmand et al. [4] reported a series of cases in which they diagnosed neurosyphilis on the basis of (1) suggestive neurologic findings, in addition to a positive CSF fluorescent treponemal antibody-absorption test result (this highly sensitive test, now replaced by the equivalently sensitive microhemagglutination *Treponema pallidum* [MHA-TP] test, detects antibody to outer cell wall proteins of *T. pallidum*, and once the result is positive, it remains so for life) or (2) a positive CSF fluorescent treponemal antibody-absorption test result in addition to other CSF abnormalities or neurologic abnormalities for which other causes had been excluded. Only 57% of the patients in the study by Hooshmand et al. [4] had a positive CSF VDRL test result. This article [4] is often cited to support the notion that a reactive CSF VDRL test is not a regular feature of neurosyphilis.

However, MHA-TP testing of CSF samples is not accepted as a diagnostic tool, because it is overly sensitive; passive diffusion of plasma proteins with positive serum MHA-TP yields a positive result even when neurosyphilis is not present [5]. Some European authorities [6] use the CSF MHA-TP assay, but they report the result after calculating the ratios of CSF to serum protein concentration and CSF to serum MHA-TP titer to determine whether its detection reflects passive diffusion from plasma or local synthesis of antibody in the CNS. Hooshmand et al. [4] stated that 100% of their patients had positive CSF fluorescent treponemal antibody-absorption test results, as if to assure the reader of the correctness of their diagnoses. In fact, this has never been a valid basis for diagnosis of neurosyphilis, and it continues to astonish me that this article [4] was ever published in that form.

If the authors overdiagnosed neurosyphilis, which I believe they most certainly did, the true percentage of patients with negative CSF VDRL results should be much lower.

There are other reasons to be suspicious
of the conclusions of Hooshmand et al. [4]. For example, they state that 25% of their patients presented with a seizure. Classic treatises on syphilis [2, 3, 7, 8], none of which is cited by Hooshmand et al. [4], state that, except in advanced paraparesis or some particularly rare forms of syphilitic meningitis, seizures are uncommon in neurosyphilis (I do not recall having seen seizures in an adult that were attributable to neurosyphilis). In summary, in the vast literature that preceded the HIV era, the consensus was that CSF VDRL test results were positive in the great majority of cases of neurosyphilis, and negative CSF VDRL test results, except in the case of certain currently rare forms of neurosyphilis, generally opposed the diagnosis.

Shortly before the recognition of AIDS, a number of cases of acute syphilitic meningitis were reported in young adults, many of whom had recently received treatment with benzathine penicillin. Ehrlich had described “neurorecurrence,” in which neurosyphilis appeared in young adults, often within a year after they received inadequate therapy (cited in [7]). Merritt et al. [2] placed ~5% of all neurosyphilis cases into this category. My colleagues and I [9, 10] postulated that inadequate treatment in an immunologically normal host was analogous to adequate treatment in a greatly immunosuppressed host. In retrospect, these patients were likely to have been infected with HIV before HIV infection or AIDS was recognized.

HIV-infected patients with early neurosyphilis are likely to present with involvement of ≥1 cranial nerve, without other manifestations [9], and this form of syphilis is more likely to be associated with a nonreactive CSF VDRL test. Only approximately three-quarters of the patients reported up to 1990, including many who had only cranial nerve abnormalities, had reactive CSF VDRL tests [9], and all of the patients in a small study involving individuals with asymptomatic neurosyphilis that was performed by Dowell et al. [11] had reactive CSF VRDL tests, as well. However, I remain concerned about overdiagnosis of neurosyphilis in case series in which <60% of all patients had a positive CSF VDRL result [1, 4]. If true cases of neurosyphilis were combined with cases that did not involve neurologic disease, the normalization of serologic measures may not be as reliable in the context of proven neurosyphilis.

The second topic that is worthy of discussion is treatment. Marra and colleagues state that “benzathine penicillin G is not recommended for persons with neurosyphilis, because it yields penicillin concentrations in the CSF that are too low to kill T. pallidum” [1, p. 893]. Through the 1960s, official Centers for Disease Control and Prevention recommendations for treating neurosyphilis included 3 intramuscular doses of benzathine penicillin (2.4 million U each) at weekly intervals [12]. These or similar doses [13] prevented progression of asymptomatic disease and eradicated active disease, although continued evolution of neurologic abnormalities might occur because of CNS damage [13].

In the late 1970s and throughout the 1980s, great attention was given to studies that revealed that, during therapy with benzathine penicillin, drug levels were generally undetectable in the CSF [14, 15]. This finding was expected, because serum levels do not exceed 0.1 μg/mL and CSF levels are only a small percentage of serum levels. Because of reports of neurosyphilis appearing after treatment with benzathine penicillin and the failure to recognize that this was a host problem, rather than an antibiotic problem, some authorities concluded that only large doses of intravenous penicillin could be relied on to treat neurosyphilis. The irony is that 2 weeks of treatment with 24 million U per day of intravenous penicillin is not needed to cure neurosyphilis in the absence of HIV infection but may still fail to do so in patients who are infected with HIV [16].

What difference does all of this make? Consider the hypothetical case of an elderly man, now somewhat demented. The pretest probability that he has neurosyphilis is regarded as low. Nevertheless, he has a reactive serum RPR test (1:1 dilution), a positive serum MHA-TP test result, and a negative HIV ELISA result. Ageing alone may lead to dementia and cause low-level reactivity of the RPR test, and the MHA-TP test result may be the remaining vestige of youthful ardor and/or indiscretion.

May this patient have neurosyphilis? Of course. Is he likely to? No. Does he need a spinal tap? Even if a spinal tap is performed and the CSF sample is normal, those who believe that the CSF VDRL test result is positive in only one-half of cases will not have excluded the diagnosis of neurosyphilis. What treatment should be given? Two weeks of intravenous penicillin requires inpatient therapy in the medical service. On the basis of all of the previous observations, I believe that such patients can be treated with 3 doses of benzathine penicillin (2.4 million U) at weekly intervals and that lumbar puncture probably does not need to be performed. I tried to maintain this position during my 2 terms on the Center for Disease Control and Prevention’s committee to formulate recommendations for sexually transmitted disease therapy, but I was soundly outvoted by my colleagues.

A brief anecdote raises a poignant irony. My colleagues and I were finishing an article that we had worked on for nearly 2 years; the article was about the clinical manifestations of neurosyphilis in patients with AIDS [9]. We wanted the great expert Dr. Rudolph Kampmeier to read the article before we submitted it, and especially for that reason, we continued to polish and refine the manuscript. When I finally called Dr. Kampmeier’s office to inform him that I was sending the article, his secretary told me that he would be unable to read it because he had just experienced a major stroke. Thus, we are left to interpret the older literature without guidance from those who wrote it.

The article by Marra et al. [1] indicates...
that a serological response, manifested by a normalization of the serum RPR reaction, is a reliable predictor of a cure after treatment of neurosyphilis. Despite my reservations about whether all of the patients included in that series actually had neurosyphilis, a sufficient number most certainly did, and I feel quite confident that the conclusion is valid. Much still remains to be learned about the diagnosis and treatment of neurosyphilis, a fascinating and complex disease. Young investigators have a fertile, albeit rocky, field if they choose to till it.

Acknowledgments


References