Symptomatic Relapse of Neurologic Syphilis after Benzathine Penicillin G Therapy for Primary or Secondary Syphilis in HIV-Infected Patients

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We describe 3 symptomatic cases of neurologic syphilis that occurred after the administration of the usual therapy for primary or secondary syphilis in human immunodeficiency virus (HIV)–infected patients. We discuss the difficulty of diagnosing neurosyphilis, the need for lumbar puncture, and risk factors of relapse. Because HIV infection may alter the natural history and response of neurologic syphilis to treatment, scrupulous follow-up and repeated cycles of therapy are warranted.

The incidence of syphilis in US and European cities has recently increased, particularly in the HIV-infected population [1, 2]. During 2004, we observed a similar trend: 29 new cases of syphilis were diagnosed in a cohort of 1236 HIV-infected patients. We describe 3 patients from this cohort who experienced symptomatic relapses of neurologic syphilis, despite having received benzathine penicillin G therapy for primary or secondary syphilis.

Case report. Patient 1 was a 45-year-old man who was referred to our hospital (Hôtel-Dieu Hospital, Lyon, France) for headache and dizziness. He had been HIV infected since 1987 and had been receiving successful antiretroviral therapy. His plasma HIV load was <50 copies/mL, and his CD4 cell count was 356 cells/µL. Two months before hospital admission, he presented with fever and nonpruritic diffuse maculopapular rash, without neurologic symptoms. Biological studies revealed moderate hypertransaminasemia. A serum Venereal Disease Research Laboratory (VDRL) test yielded a titer of 1:16, a serum Treponema pallidum hemagglutination assay (TPHA) yielded a titer of ≥1:20,480, and fluorescent treponemal antibody (FTA)–IgM reactivity test yielded a titer of 1:160. Secondary syphilis was diagnosed, and the patient received weekly intravenous doses (2.4 million U per dose) of benzathine penicillin G for 3 weeks.

At admission, the patient had no recurrent fever and rash. He developed slight malaise, headache, dizziness, and a subjective decrease in vision without ophthalmoscopic abnormalities. There was no stiffness of the neck, and the findings of a neurologic examination were normal except for a right VII cranial nerve palsy. The rest of the physical examination revealed no abnormalities. Biochemical blood test findings were normal. Serum VDRL testing yielded a titer of 1:16, and a TPHA yielded a titer of 1:1280. A CSF specimen was clear, with an elevated WBC count (280 cells/µL; lymphocyte percentage, 97%; no erythrocytes), a normal CSF glucose level, and a protein level of 15 mg/dL. The results of a VDRL test and a TPHA of CSF specimens were negative, and a CSF culture was sterile. Cerebral MRI revealed a fine, contrast-enhancing, bilateral lesion in the frontotemporal meninges compatible with meningitis. A diagnosis of neurosyphilis was considered, and intravenous ceftriaxone treatment (2 g per day for 14 days) was initiated. The patient’s subjective symptoms improved within 5 days. Follow-up serologic testing performed 6 months after the completion of treatment revealed a significant decrease in the VDRL titer (from 1:16 to 1:2) and in the TPHA titer (from 1:1280 to 1:160) (table 1). Lumbar puncture was not repeated.

Patient 2 was a 34-year-old-man who was admitted to our hospital for suspected neurosyphilis. He reported a history of primary HIV infection (diagnosed in March 2003) and subsequent gonococcal urethritis. Seven months before hospital admission, he presented with skin rash but no neurologic symptoms. At that time, secondary syphilis was confirmed by a serum VDRL test (titer, 1:16) and a TPHA (titer, 1:1280), and the patient was treated with weekly intravenous doses of benzathine penicillin G (2.4 million U per dose) for 2 weeks.

At admission, the patient reported right trigeminal neuralgia, followed by involvement of the facial and auditory nerves, with subjective hearing loss, dizziness, and a walking disorder. Physical examination was performed at hospital admission and revealed no fever, no meningism, and no confusion. The findings of a neurologic examination were normal, except for VII cranial nerve palsy. The CD4 cell count was normal (730 cells/µL), and the plasma HIV load was <50 copies/mL while the patient...
was receiving antiretroviral treatment. A serum VDRL test revealed a titer of 1:128, a TPHA revealed a titer of \(\geq 1:20,480\), and FTA-IgM test revealed a titer of 1:80. Lumbar puncture revealed a CSF WBC count of 75 cells/µL (95% lymphocytes), no erythrocytes, a normal glucose level, a protein level of 9 mg/dL, a CSF VDRL titer of 1:8, and a CSF TPHA titer of 1:5120. The CSF culture was sterile. Cranial CT findings were normal. Neurologic relapse was diagnosed even though the patient had received treatment for secondary syphilis, and treatment with intramuscular ceftriaxone (2 g per day for 10 days) was initiated, resulting in a rapid clinical improvement of symptoms. Follow-up serologic tests performed 6 months after the completion of treatment revealed a significant decrease in the VDRL titer (1:128 to 1:8) and in the TPHA titer (1:16 to 1:1280) (table 1). The findings of a follow-up lumbar puncture were normal (i.e., there was no pleocytosis, and the results of a VDRL test and a TPHA were negative).

In July 2004, we therefore decided to perform lumbar puncture for all HIV-infected patients with secondary syphilis. Whenever we found pleocytosis (defined as a CSF WBC count of \(>20\) cells/µL) or a reactive CSF VDRL result, therapy with ceftriaxone or high-dose intravenous penicillin G was provided (rather than repeated injections of benzathine penicillin G). During the period of July 2004 through July 2005, we treated 6 patients with asymptomatic neurosyphilis using this strategy, and no patient experienced relapse.

**Discussion.** Early stage syphilis is often associated with an invasion of the CNS by *Treponema pallidum* [3] that can be controlled without specific neurologic syphilis therapy in immunocompetent individuals. HIV infection may alter the natural history of syphilis, with a higher rate of asymptomatic primary syphilis, secondary manifestations of syphilis, or latent...
infection [4] and relapse [5]. Neurologic syphilis is often asymptomatic in HIV-infected subjects (40%-60%) or combined with cranial nerve palsies, especially facial and auditory nerves [6, 7]. It is also suggested that HIV infection accelerates and changes the clinical course of neurologic syphilis [8] and increase its incidences and rate of relapse, despite the administration of appropriate treatment with benzathine penicillin G [9, 10]. Here, we report 3 cases of syphilitic relapse involving symptomatic neurologic syphilis that occurred in patients who had received high-dose benzathine penicillin G therapy (defined as doses that exceeded the recommended dosage) and who had relatively good immunity while receiving antiretroviral therapy (CD4 cell count, >350 cells/μL). There are additional considerations.

- Repeated doses of benzathine penicillin G (usually 3) failed to prevent neurosyphilitic relapse.

- Did reinfection or relapse occur? Only molecular methods can distinguish between relapse and reinfection in a second episode of syphilis after treatment [11]. The short period between symptom development and previous treatment argue in favor of treatment failure in patients 1 and 3. The second case appears more questionable, but the patient’s interrogatory reported no risky behaviors and was not in favor of reinfection. Also, in the third patient, the high baseline serum VDRL titer (1:512) suggests a risk of early CNS involvement with subsequent neurosyphilis.

- Diagnosis of neurosyphilis in HIV-infected individuals is often difficult. CSF VDRL testing has a high diagnostic specificity but low sensitivity (30%-78%) [7], and mononuclear pleocytosis and elevated CSF protein levels are common [9]. PCR has poor sensitivity [12] and is not helpful. Our 3 cases met the usual criteria for neurosyphilis: a CSF WBC count >20 cells/μL or a reactive CSF VDRL test result [3]. CSF abnormalities may be associated with a higher risk of syphilitic relapse, even without neurologic symptoms. Malone et al. [9] documented that individuals with reactive CSF VDRL test results or a rash caused by secondary syphilis were at higher risk of treatment failure. Marra et al. [3] also demonstrated that a serum rapid plasma reagin titer ≥1:32 was predictive of neurosyphilis in all individuals with syphilis, and that, in HIV-infected individuals, a CD4 cell count ≤350 cells/μL was an additional risk factor. Subjects who do not receive HAART seem more likely to experience syphilis treatment failure [5].

- Many experts recommend lumbar puncture for to detect neurosyphilis in HIV-infected individuals, regardless of syphilis stage [4, 13]. Universal lumbar puncture is both impractical and unnecessary. It may, however, be required in individuals with neurologic, ocular, or psychiatric symptoms in the case of treatment failure, during late syphilis [14], and in the case of a serum rapid plasma reagin titer ≥1:32 or a CD4 cell count ≤350 cells/μL [3]. Our cases had a high rate of relapse of neurologic syphilis, arguing in favor of performing systematic lumbar puncture for HIV-infected patients, even though it is not currently recommended. After treating the 3 patients described here, we treated 6 patients with asymptomatic neurologic syphilis using this strategy for 1 year, without relapse.

- What about optimal treatment? Presently, the recommended first-line treatment for neurologic syphilis is intravenous aqueous crystalline penicillin G potassium (12–24 million U daily for 10–14 days) [4, 14]. Ceftriaxone has excellent activity against T. pallidum, a long half-life in serum, and good CNS penetration [15]. In small pilot studies of HIV-infected individuals, ceftriaxone was at least equivalent to procaine penicillin and benzathine penicillin G [15, 16]. However, more data are required before ceftriaxone can be routinely recommended.

- Without a “test for cure,” syphilis requires monitoring by quantitative nontreponemal tests. Assiduous follow-up studies at 3, 6, 9, 12, and 24 months after the completion of therapy is recommended for serologic evaluation for treatment failure [14]. Ideally, follow-up CSF examinations should be performed at 6-month intervals over the first 2 years or until CSF findings become normal [13]. In our study, it was accepted and performed only for 1 patient. However, serologic evaluation at 6 months revealed a good outcome, without neurologic manifestations.

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References