



Published in final edited form as:

Sex Transm Dis. 2015 June ; 42(6): 347–349. doi:10.1097/OLQ.0000000000000282.

Neurosyphilis and Ophthalmic Syphilis in Persons With Negative Rapid Plasma Reagin and Positive Treponemal Antibody Test Results

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Abstract

The detection of serodiscordant syphilis test results raises several important clinical and public health questions. Based on our retrospective review, the probability of neurosyphilis in persons with serodiscordant serologies is low. The probability of ophthalmic syphilis may be higher, but we lack objective measures for that diagnosis.

Traditionally, syphilis serologic screening begins with a non-treponemal test such as the rapid plasma reagin (RPR) and is then followed by confirmation using one of several treponemal tests. Recently, however, increased availability and decreased expense of automan tests have led many laboratories in the United States to adopt reverse sequence screening in which a treponemal test is performed first, followed by testing of reactive sera with a nontreponemal test.¹ However, the use of these reverse sequence algorithms has led to the detection of a population of “serodiscordant” patients with confirmed reactive treponemal tests and nonreactive nontreponemal tests. Although most of these individuals have treated syphilis resulting in a decline in nontreponemal antibody titers after therapy, this serologic pattern can also be seen in early infection (before the development of detectable antibodies or with the prozone phenomenon) or in individuals with untreated late syphilis who have a decline in nontreponemal antibody titers over time.

In the antibiotic era, in which patients routinely receive β -lactams and other antibiotics with activity against syphilis for a variety of non-syphilis-related indications, the detection of serodiscordant test results in persons without a documented history of syphilis treatment raises several important clinical and public health questions: What are the public health risks of sexual transmission and vertical transmission of syphilis in these individuals? What is the risk that they either currently have or will progress to tertiary syphilis in the future? Studies from the pre-antibiotic era suggest that there is a low risk of sexual transmission in persons with late syphilis,² and recent studies suggest that vertical transmission is rare.³ Determining the risk of progression to tertiary syphilis in the future would involve a protracted and logistically difficult follow-up. In this study, we sought to further characterize the probability of neurosyphilis (NS) or ophthalmic syphilis (OS) at the time of a serodiscordant test result.

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Conflict of interest: None declared.

We conducted a 2-step retrospective review using the Johns Hopkins Patient Database of all inpatient and outpatient visits from 1994 to 2012. Of note, Johns Hopkins initiated reverse sequence syphilis testing in 2011. Before that, the traditional algorithm was used. First, we searched pertinent *International Classification of Diseases (ICD)* codes (*ICD-9* codes 090.0 through 097.9, or equivalent) relating to NS and OS. Second, we searched all records for patients who were seropositive for syphilis (defined as a positive serum treponemal test result) and who underwent a lumbar puncture for any reason. Patients who qualified under one or both of our search criteria were included in our study. We abstracted nontreponemal antibody titers, specifically RPR, and confirmatory treponemal antibody test results. We reviewed discharge summaries, clinic notes, progress notes, and laboratory data for symptoms, signs, HIV antibody testing, CD4 count, HIV RNA, cerebrospinal fluid (CSF) abnormalities, and treatment in the subset of patients who were serodiscordant. We defined “definite NS” as a positive CSF Venereal Disease Research Laboratory (VDRL) and “suspected NS” as a positive serum treponemal test result and a CSF white blood cell count (WBC) greater than 5 cells/mL or a CSF protein greater than 50 mg/dL. Ophthalmic syphilis was defined as compatible ocular findings in a person with a seroreactive treponemal antibody test independent of CSF abnormalities. This analysis was granted approval by the institutional review board of the Johns Hopkins Medical Institutions.

Of 2,685,977 patient encounters in the Johns Hopkins Clinical Database, we identified 470 which met the above *ICD-9* or laboratory criteria. Of these, 48, or 10.2%, were serodiscordant. Thirteen of the 48 were identified under the reverse sequence algorithm. None of these had a positive CSF VDRL result, although no CSF VDRL was done for 8 of the 48 patients. Of the 48 serodiscordant patients, 4 (8.3%) were treated for NS or OS. All of these patients had a negative CSF VDRL result. The clinical course for these serodiscordant patients is summarized in Table 1.

In our study, very few patients with serodiscordant serologies were treated for NS or OS. None met the criteria for definite NS. Of the 2 who were treated for NS, both met the CSF criteria for suspected NS, although in one, HIV status might have explained the mild CSF pleocytosis, and in the other, CNS vasculitis was also on the differential, and might have accounted for the elevated CSF protein. Both had more plausible alternate diagnoses to account for their neurological findings. Confirming the diagnosis of OS is challenging because many cases of OS will have a normal CSF examination. Two of our patients were treated for OS, although neither had any documented CSF abnormalities.

A review of the literature for cases of NS and OS among serodiscordant persons reveals great variability in the quality of these reports. None gives a definitive answer for what the probability of NS or OS is in serodiscordant patients.^{4–13} In one large study, Hooshmand et al.⁴ in 1972 described serodiscordant serum serologies in 51.5% of 241 cases of NS. Only 176 of the 241 patients had CSF tested for a nontreponemal test (the serologic test for syphilis), and of those, 56.7% had a positive CSF serologic test for syphilis. Their criteria for diagnosis of NS were very broad, and there was insufficient information to determine whether any of the serodiscordant patients had confirmed NS. A series by Wohrl and Geusau⁵ found that none of the 265 patients reviewed who had a negative blood VDRL result met the criteria for NS; of note, this applied to both HIV-positive and HIV-negative

patients. A series by Burke and Schaberg¹⁰ described 4 of 30 patients with NS and a negative serum VDRL result. Only 1 of these 4 had a positive CSF VDRL result; however, no further information was available about this patient. A case series by Smith et al.¹¹ described 5 patients with NS and 1 with ocular syphilis who had a negative serum nontreponemal test result and positive treponemal test result, but did not document a single case with a positive CSF nontreponemal test result. Tamesis et al.¹⁴ reported that 8 (32%) of 25 patients with findings consistent with OS had serodiscordant serologies. However, only 2 of these patients had a lumbar puncture, and in both of these patients, CSF VDRL was negative and cell counts, protein, and glucose were normal. A review of 32 articles with a total of 101 HIV-infected patients with ocular syphilis was able to identify only 3 who had a negative serum nontreponemal test result. Two of these patients responded clinically to treatment, and 1 had a CSF pleocytosis which improved after treatment.¹³ Our literature review failed to reveal additional reported cases of serodiscordant HIV-infected patients who were diagnosed as having ocular syphilis.^{13–21}

This study has several limitations. An RPR-first testing strategy was used from 1994 to 2011 so that the diagnosis of NS or OS in persons presenting with neurological or ophthalmological signs and symptoms and a negative RPR result may have been missed. However, we first searched by *ICD-9* codes for NS and OS to try to ensure that we captured all patients who were treated for either condition. Because this was a retrospective chart review, we had to rely on clinician judgment and documentation of diagnostic and therapeutic decisions. A CSF examination was performed for non-syphilis-related reasons in many patients. Finally, although we investigated the occurrence of NS or OS at the time of serodiscordant tests, the risk of progression to tertiary syphilis in the future for these patients remains unknown.

Both the lack of a gold standard test to diagnose OS and NS and our limited understanding of the relationship between serum nontreponemal titers and underlying disease activity have made it difficult to define the public health and clinical risks faced by persons with serodiscordant test results. Comparisons with the pre-antibiotic era are made even more challenging because of significant differences in the nontreponemal tests used. Based on our data and a review of the literature, the probability of NS in persons with serodiscordant serologies is low. Although the probability of OS may be higher, numbers are small and it is unclear whether this observation is confounded by the lack of objective measures to diagnose OS.

Acknowledgments

The authors would like to thank Dr David Thiemann and the Center for Clinical Data Analysis at the Johns Hopkins University School of Medicine for providing the data.

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TABLE 1

Clinical Course of Serodiscordant Patients Treated for Ophthalmic and NS

| Patient | Signs/Symptoms | Laboratory findings | Comments |
|---------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Treated for NS | | | |
| 1 39-y-old male alcoholic | Progressive decline in mental status for 2 mo | HIVAb pos; CD4 653 cells/mm ³ CSF: WBC 8; glucose 67 mg/dL; protein 45 mg/dL | The patient was treated for NS; the more probable diagnosis was Wernicke-Korsakoff. Despite intravenous penicillin and vitamin supplementation, the patient was still significantly confused on discharge. |
| 2 74-y-old woman with a history of dementia and heart failure | Altered mental status and combative throughout her hospitalization | HIV: unknown CSF: WBC 2; glucose: 62 mg/dL; protein 264 mg/dL | Initiated simultaneously on IV penicillin and high-dose steroids as both NS and CNS vasculitis were suspected. Her mental status deteriorated and she died. |
| Treated for OS | | | |
| 3 49-y-old male to female transsexual | Decreased visual acuity in right eye for 3 mo | CD4: 466 cells/mm ³ ; HIV RNA: undetectable; CSF: normal | HIV positive. Anterior uveitis on examination; treated with 10 days of intravenous penicillin with resolution of symptoms |
| 4 42-y-old man with known history of untreated syphilis | Bilateral eye pain, irritation | CSF: normal HIVAb: neg | History of recurrent anterior uveitis of the right eye associated with positive HLA B27. Presents with bilateral uveitis and hypopyon in left eye. Symptoms resolved after penicillin and steroid treatment |

Ab indicates antibody; CNS, central nervous system; pos, positive; neg, negative.