Refer to: Simon RP: Neurosyphilis: An update (Information). West J Med 134:87-91, Jan 1981

Information

Neurosyphilis: An Update

ROGER P. SIMON, MD, *San Francisco*

SEVERAL RECENT STUDIES[1,2] and reviews[3] have suggested that neurosyphilis remains an important and frequently encountered entity. The incidence of late and late-latent syphilis in California from 1974 to 1977 averaged 30 cases per 100,000 persons (written communication, State of California Department of Health, Venereal Disease Control Unit, December 1979). Of these, approximately one case in ten would be expected to be symptomatic neurosyphilis[4]—that is, three newly symptomatic cases of neurosyphilis per 100,000 population represents all cases, the current probably represent only a fraction of the actual incidence, but if one assumes that three per 100,000 population represents all cases, the current incidence of neurosyphilis is similar to that of Huntington chorea, double that of amyotrophic lateral sclerosis, about half that of multiple sclerosis and a seventh that of Parkinson disease.[5,6]

Clinical Spectrum

The frequency and clinical spectrum of neurosyphilis have been documented by Hooshmand[1] from the University of Virginia Hospitals. He reported 241 cases diagnosed between 1965 and 1970.[1] The criteria for diagnosis were (1) a positive FTA-ABS (fluorescent treponemal antibody absorption) test with ocular or neurological findings suggestive of neurosyphilis, (2) reactive serum and spinal fluid FTA-ABS tests with more than 5 lymphocytes per cu mm in cerebrospinal fluid (CSF) or (3) positive FTA-ABS tests in blood and spinal fluid in patients with otherwise unexplained progressive neurological disease in whom penicillin therapy either resulted in significant improvement or produced a transient CSF pleocytosis.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
CSF = cerebrospinal fluid
FTA-ABS = fluorescent treponemal antibody absorption (test)
TPI = *Treponema pallidum* immobilization (test)

The signs and symptoms observed in Hooshmand's series of patients are summarized in Tables 1 and 2. The most common presentation was some unrelated symptom, the diagnosis being made only on routine serological tests; abnormal reflexes or eye signs, or both, compatible with neurosyphilis were noted during evaluation of the reactive serological findings. Of the more specific neurological symptoms, focal or generalized seizures were most common and were usually associated with some other evidence of neurosyphilis. Other common abnormalities included disorders of vision or oculomotor function, dizziness, confusion and stroke. Psychiatric presentations were responsible for only 2 percent of cases in this series.

Although abnormalities on neurological examination were found in more than 75 percent of patients, these were most often nonspecific; for example, reflex changes were noted in 75.8 percent and absent ankle jerks in 66.8 percent of the patients. Of greater value was the evidence of posterior column sensory loss detected in 33.7 percent of the cases. Pupillary abnormalities of some degree (small irregular pupils, absence of light reaction, synechiae or light-near dissociation) were noted in about 45 percent of the cases. Ptosis, occasionally an isolated finding, was noted in nearly 5 percent of cases and felt by the authors to be a minor aspect of tabes dorsalis.

Pertinent laboratory studies in Hooshmand's series of patients included reactive FTA-ABS tests of blood and spinal fluid specimens in 100 percent of the cases, whereas nontreponemal tests were positive in less than 50 percent of serum and 6 percent of CSF specimens. The CSF protein level was normal in greater than 60 percent of cases, and nearly 20 percent of patients had less than five leukocytes per cu mm in the spinal fluid. The CSF gamma globulin fraction was elevated in about 66 percent of the patients examined.

The prognosis of the patients following therapy varied with the presenting symptoms, being poorest in those with clinical features of GPI (general

From the Department of Neurology, San Francisco General Hospital, and University of California, San Francisco, School of Medicine.

Reprint requests to: Roger P. Simon, MD, Neurology Service (4M62), San Francisco General Hospital, San Francisco, CA 94110.

paresis of the insane; dementia paralytica) in combination with seizures, and best in patients with stroke or adult-onset seizures.

Although the epidemiologic and clinical data reviewed above suggest that central nervous system (CNS) syphilis remains a current medical problem, classic cases of tabes dorsalis, general paresis and meningovascular syphilis are uncommon on hospital wards. At the San Francisco General Hospital Neurology Service we saw only 28 such cases between 1970 and 1978.

TABLE 1.—*Signs of Neurosyphilis**

Signs	*Number*	*Percent of Cases*
Reflex changes	183	75.8
Absent ankle jerk	161	66.8
Pupil changes	86	44.8
Sensory abnormalities	57	33.7
Chorioretinitis, retinitis pigmentosa	29	12.0
Organic brain syndrome	21	8.7
Babinski sign	13	5.3
Depression	12	5.0
Ptosis	11	4.6
Optic atrophy	11	4.6
Mania	8	3.3
Personality changes	5	2.0

*Adapted from Hooshmand et al.[1]

TABLE 2.—*Symptoms of Neurosyphilis**

Symptoms	*Number*	*Percent of Cases*
Seizures		
Focal	10	4.2
General	24	10.0
Not specified	24	10.0
TOTAL	58	24.2
Ophthalmic symptoms	28	11.6
Stroke: confusion	27	11.1
Dizziness	19	7.9
Personality changes	5	2.0
Unrelated symptoms	104	43.2
TOTAL	241	100.0

*Adapted from Hooshmand et al.[1]

TABLE 3.—*Serological Tests for Syphilis*

- Nontreponemal tests
  - Flocculation
    - VDRL (Venereal Disease Research Laboratory)
    - Hinton
    - Rapid reagin
  - Complement fixation
    - Kolmer
- Treponemal tests
  - TPI (*Treponema pallidum* immobilization)
  - FTA (fluorescent treponemal antibody)

Several authors have suggested that the clinical presentation of central nervous system syphilis has been altered in the era of antibiotic drugs. It is true that the large numbers of cases of tertiary syphilis that had been expected to result from the documented primary and secondary cases acquired during the Second World War have not occurred.[7] The role of antibiotic therapy in the lack of progression of those infections seems certain; disease modification versus cure following such therapy, however, has not been conclusively documented. Luxon and co-workers,[8] discussing the clinical presentation of CNS syphilis, found no evidence for modified clinical presentations in their 17 recently diagnosed cases. They noted that the presentations were diverse but that all clinical phenomena had been reported in the era before antibiotic therapy.

Pupillary abnormalities remain the most common clinical clue, but the diagnosis remains difficult in many cases. Increased reliance must therefore be placed on serological tests.

Serological Diagnosis

The serological tests for syphilis are treponemal and nontreponemal (Table 3). The nontreponemal tests detect nonspecific antibodies (reagins) that react with lipoidal antigens of *Treponema pallidum* or lipoidal antigens secondary to treponemal host interaction. The most commonly used nontreponemal test is the VDRL. This test relies on the ability of syphilitic serum containing reagin to flocculate a suspension of cardiolipin-lecithin antigen. Unfortunately, this nonspecific antibody (reagin) may also be present in collagen-vascular disease, after febrile illnesses, following immunization, in leprosy or in association with old age and in drug addiction.[9] Most important, however, this test is relatively insensitive in tertiary disease producing a nonreactive VDRL response in as many as a fourth of the cases of late syphilis.[10] In Hooshmand's series, for instance, reagin tests were positive in only 40 percent of cases.

The treponemal tests detect antibodies specific for *T pallidum*. The most widely used is the FTA-ABS test in which the patient's serum is first diluted in a "sorbent" prepared from a nonpathogenic treponeme to minimize false-positive tests and then is layered on a slide coated with dried *T pallidum*. Slides are incubated and then treated with fluorescent-labeled antibody to human gamma globulin. Fluorescence of the dried treponeme organisms indicates antitreponemal anti-

bodies in the patient's serum. This test is clearly more specific and sensitive than the VDRL test; however, it is technically much more difficult to carry out and some variation from laboratory to laboratory has been reported, especially in weakly reactive specimens.[9] In addition, while the quantitative VDRL test shows a falling titer in response to antibiotic therapy, except in so called "serofast" cases, the FTA-ABS test remains reactive indefinitely and therefore is not helpful in documenting a response to therapy. The most important distinction between these two tests in regard to tertiary disease is that the FTA-ABS test remains reactive in greater than 95 percent of patients with late syphilis and therefore greatly assists in the diagnosis of atypical presentation of CNS involvement (Table 4).[10]

In questionable cases an additional specific treponemal test is occasionally used in reference laboratories. This *T pallidum* immobilization (TPI) test detects serum antibodies to *T pallidum* by noting under the microscope a decrease in motility of live organisms when treated with the patient's serum. The study is technically difficult to carry out and not widely available although it is quite specific. Like the FTA-ABS test, it remains positive following treatment.

Cerebral Spinal Fluid Tests

Continued attention to the testing of CSF specimens for evidence of syphilis is the result of the following observations: (1) in the era before antibiotic therapy neurosyphilis was more likely to develop in patients with reactive nontreponemal tests in both spinal fluid and blood than in patients with nonreactive CSF studies[11]; (2) with nontreponemal tests approximately 4 percent of patients with neurosyphilis will have reactivity in the spinal fluid despite normal studies in the blood[12] and (3) in late syphilis treponemal tests have significantly greater reactivity than nontreponemal studies.[10] The availability of the very sensitive fluorescent treponemal antibody tests in tertiary syphilis would seem to be a powerful adjunct to the detection of CNS involvement.

However, the role of the CSF-FTA test and its many modifications in the evaluation of neurosyphilis remains uncertain.[9,11,13] The unabsorbed FTA test, for example, produced a positive response in 4.5 percent of normal CSF.[14] Dilution of specimens and addition of sorbent (CSF-FTA-ABS) will decrease the incidence of these false-positive results but at the expense of sensitivity.[15] To date

TABLE 4.—*Comparative Reactivity of Serological Tests**

Condition	Number	Percent Reactive to Tests		
		FTA-ABS	*TPI*	*VDRL*
Primary syphilis	191	85	56	78
Secondary syphilis ...	270	99	94	97
Late syphilis	117	95	92	77
Latent syphilis	954	95	94	74
Presumably normal ...	384	1	0	0

FTA-ABS = fluorescent treponemal antibody absorption; TPI = *Treponemal pallidum* immobilization; VDRL = Venereal Disease Research Laboratory

*Adapted from Sparling.[10]

no standard approach has been agreed upon. The lack of productivity in the CSF-FTA-ABS was reinforced by Mahony and co-workers,[13] who noted the tests to be positive in only 75 percent of 20 patients with clinical neurosyphilis. Of concern in regard to the interpretation of the CSF-FTA tests is the question of the source of the detected antibody. The finding of a direct correlation between CSF reactivity and higher blood titers[11,16] suggests that the immunoglobulins responsible for the production of the CSF-FTA tests may enter the spinal fluid by diffusion from the blood. This finding has been confirmed in the French literature.[17] The meaning of a positive CSF-FTA test in the absence of other evidence of CNS disease, then, remains uncertain because it may merely represent diffusion of the antibody into the CSF from blood. There is apparent agreement in the literature, however, on an important related point: essentially every patient with a positive CSF-FTA-ABS test will have a positive FTA-ABS reaction in the blood. Therefore, a normal serum FTA-ABS test makes testing of the CSF completely unnecessary.[3,11]

False-Positive Tests

False-positive nontreponemal tests for syphilis are well categorized. Such patients have a positive nontreponemal test and a negative FTA or TPI response and are said to be biologic false-positive reactors. These patients can be divided into two groups, those with transient and those with so-called chronic biologic false-positive reactions (Tables 5 and 6). Transient false-positive reactions are most often associated with acute infections or pregnancy.[18] The large number of cases with unclear causes underline the necessity for several determinations before positivity is assumed to result from syphilis. Chronic false-positive reactive reactions occur mainly in patients with autoimmune disease, especially systemic lupus erythematosus (LE) but also with more benign

abnormalities such as rheumatoid arthritis. Leprosy, heroin addiction and old age are commonly listed causes but are rare in a given population; unknown causes unfortunately continue to lead the list.[17] The association of a chronic false-positive serological response with autoimmune disease is substantiated by the finding of associated serological abnormalities, such as antinuclear antibody, rheumatoid factor, LE cells and hypergammaglobulinemia.[10,18] The quantitative VDRL may assist in the identification of false-positive reactors because such cases usually produce titers of less than 1:8.[10,19]

The issue of false-positive FTA-ABS tests is a more difficult one because this test is specific for treponemal antibodies. Cases of false-positive FTA-ABS responses have been clearly documented, however. One subgroup is the borderline positive FTA-ABS test, which has been reported to occur in 2 percent of celibate nuns[20] and in 8.6 percent of general hospital admissions.[21] Nearly half of such patients will have a normal study on follow-up examination and another half will continue to have chronically borderline positivity, the meaning of which is uncertain. In only a small portion of these patients will clearly positive tests subsequently occur. Strongly reactive FTA-ABS findings that appear to be falsely positive have also been reported in occasional patients. Such patients fall into the categories listed above for false-positive nontreponemal tests. The best documented cases have been associated with abnormal serum globulins (such as in rheumatoid arthritis, autoimmune hemolytic anemia and alcoholic cirrhosis) and pregnancy.[10,16]

TABLE 5.—*Acute Biological False-Positive Reactions**†

Cause	*Number of False-Positive Reactions*
Undetermined	24
Recent smallpox vaccination	11
Recent inoculation	5
Infective hepatitis	5
Infectious mononucleosis	3
Viral pneumonia	3
Chicken pox	2
Measles	2
Viral encephalitis	1
Pregnancy	18
TOTAL	74

*To serological test for syphilis.
†Adapted from Catterall.[18]

TABLE 6.—*Chronic Biological False-Positive Reactions**

Cause	*Number*
Undetermined	74
Systemic lupus erythematosus	10
Rheumatoid arthritis	6
Rheumatic heart disease	6
Possible connective tissue disease	6
Probable multiple sclerosis	6
Discoid lupus erythematosus	4
Hepatic cirrhosis	2
Hemolytic anemia	2
Polyarteritis nodosa	2
Hashimoto thyroiditis	2
Sjögren syndrome	2
Psychotic illness	2
Chronic nephritis	2
Heroin addiction	2
Peripheral vascular disease	2
Systemic sclerosis	1
TOTAL	130

*Adapted from Catterall.[18]

Antibiotic Therapy

The identification of *T pallidum* in multiple body organs (lymph nodes, aqueous humor, CSF, brain, arteries, bone) following full treatment for syphilis has caused much interest in the past decade.[22] This occurrence has been reported most frequently in aqueous humor.[23] The subsequent documentation that many of the alleged organisms were artifacts of glass filament makes this mass of data suspect.[24] More recently, *T pallidum* has been recovered from the spinal fluid of two patients given adequate therapy for neurosyphilis and in whom all CSF determinations had returned to normal.[25] The importance of such findings is a matter of debate.[22] These issues have led to a reevaluation of the adequacy of standard treatment regimens for tertiary syphilis by the measurement of penicillin levels in CSF and a comparison of these results with known spirocheticidal concentrations. The recommended treatment schedules for tertiary syphilis include aqueous procaine penicillin G, 600,000 units per day intramuscularly for 15 days, crystalline penicillin G, 2 to 4 million units intravenously every four hours for ten days and benzathine penicillin G, 2.4 million units intramuscularly per week for three weeks.[26,27] Mohr[28] noted that two patients treated with aqueous penicillin G, 5.0 and 10.0 million units per day had spinal fluid penicillin levels of 0.3 to 2.4 μg per ml, respectively (spirocheticidal levels being greater than 0.3 μg per ml). However, 12 of 13 patients treated with benzathine penicil-

lin G had no detectable penicillin in the CSF. Thus, benzathine penicillin G may be inadequate treatment for CNS syphilis.

Summary

Neurosyphilis has become infrequently diagnosed in recent years, possibly as the result of routine antibiotic treatment of nontreponemal disease. Diagnostic difficulty may be the result of neurosyphilis presenting as a *forme fruste* of classic neurosyphilis (tabes dorsalis, general paresis and meningovascular syphilis) or as an unrecognized but typical form of this now unfamiliar disease. Therefore, increased reliance is placed on serological tests. Because the nontreponemal tests (such as VDRL) may be negative in as many as 30 percent of cases of neurosyphilis, specific treponemal tests (such as FTA-ABS) are required for accurate detection. The role of the FTA test in the evaluation of spinal fluid samples remains uncertain, but a negative serum FTA-ABS response excludes positive serological findings in the CSF. The standard therapy of benzathine penicillin G, 2.4 million units per week for three weeks, may be inadequate treatment for neurosyphilis.

REFERENCES

1. Hooshmand H, Escobar MR, Kopf SW: Neurosyphilis. JAMA 291:726-729, Feb 1972

2. Joyce-Clarke N, Molteno ACB: Modified neurosyphilis in the Cape Peninsula. S Afr Med J 53:10-14, Jan 1978

3. Modified neurosyphilis (Editorial). Br Med J 3:647-648, Sep 1978

4. Syphilis, a Synopsis, Public Health Service Publication No. 1660. 1968, US Dept of Health, Education, and Welfare

5. Merritt HH: A Textbook of Neurology. Philadelphia, Lea & Febiger, 1973

6. Kurtzke JR: Epidemiology of myasthenia gravis, *In* Schoenberg BS (Ed): Neurological Epidemiology, Adv Neurol 19:545-564, 1978

7. Catterall RD: Neurosyphilis. Br J Hosp Med, Jun 1977 pp 585-604

8. Luxon L, Lees AJ, Greenwood RJ: Neurosyphilis today. Lancet 1:90-93, Jan 1979

9. Jaffee HW: The laboratory diagnosis of syphilis. Ann Intern Med 83:846-849, Dec 1975

10. Sparling PF: Diagnosis and treatment of syphilis. N Engl J Med 284:642-653, Mar 1971

11. Jaffee HW, Larsen SA, Peters M, et al: Tests for treponemal antibody in CSF. Arch Intern Med 138:252-255, Feb 1978

12. Dewhurst K: Atypical serology in neurosyphilis. J Neurol Neurosurg Psychiat 31:496-500, Oct 1968

13. Mahony JDH, Harris JRW, McCann JS, et al: Evaluation of the CSF-FTA-ABS test in latent and tertiary treated syphilis. Acta Derm Venereol (Stockh) 52:71-74, 1972

14. Escobar MR, Dalton HP, Allison MJ: Fluorescent antibody tests for syphilis using cerebrospinal fluid. Am J Clin Path 53:886-890, Jun 1970

15. Wilkinson AE: Fluorescent treponemal antibody tests on cerebrospinal fluid. Br J Venereal Dis 49:346-349, Aug 1973

16. Traviesa DC, Prystowsky SD, Nelson BJ, et al: Cerebrospinal fluid findings in asymptomatic patients with reactive serum fluorescent treponemal antibody absorption tests. Ann Neurol 4: 524-530, Dec 1978

17. Ripault J, Colombani J: Le test d'immuno-fluorescence appliqué au diagnostic de la syphilis. Comparaison avec le test de Nelson et la sérologic classique. II Etude de 411 liquides cephalorachidiens. Path Biol (Paris) 12:276-285, Mar 1964

18. Catterall RD: Systemic disease and the biological false positive reaction. Br J Venereal Dis 48:1-12, Feb 1972

19. Tuffanelli DL, Wuepper KD, Bradford LL, et al: Fluorescent treponemal-antibody absorption tests. N Engl J Med 276: 258-262, Feb 1967

20. Goldman JN, Lantz MA: FTA-ABS and VDRL slide test reactivity in a population of nuns. JAMA 217:53-55, Jul 1971

21. Cohen P, Stout G, Ende N: Serologic reactivity in consecutive patients admitted to a general hospital. Arch Intern Med 124:364-367, Sep 1969

22. Dunlop EMC: Persistence of treponemes after treatment. Br Med J 2:577-580, Jun 1972

23. Smith JL, Israel CW: Treponemes in aqueous humor in late seronegative syphilis. Trans Amer Acad Ophthal Otolargyngol 72:63-75, Jan-Feb 1968

24. Montenegro ENR, Nicol WG, Smith JL: Treponema-like forms and artifacts. Am J Ophthal 68:197-205, Aug 1969

25. Tramont EC: Persistence of *Treponema pallidum* following penicillin G. therapy. JAMA 236:2206-2207, Nov 1976

26. Syphilis: Recommended treatment schedules, 1976, Center for Disease Control. Ann Intern Med 85:94-96, Jul 1976

27. Syphilis: Recommended treatment schedules. Medical Letter 19:105, Dec 1977

28. Mohr JA: Neurosyphilis and penicillin levels in cerebrospinal fluid. JAMA 236:2208-2209, Nov 1976