Pitfalls in cerebrospinal fluid test for the diagnosis of neurosyphilis

Abdulaziz M. Al-Semari, MD, Saeed I. Bohlega, FRCPC, Edward J. Cupler, MD, Jehad A. Al-Watban, MD, Donald R. McLean, MD, FRCPC.

ABSTRACT

Objective: To determine the usefulness of cerebrospinal fluid tests in the diagnosis of neurosyphilis.

Methods: Two hundred and seven cerebrospinal fluid-Venereal Disease Research Laboratories tests were performed at King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia between 1992 and 1997. The records of 14 cases with progressive neurological disease and reactive serum fluorescent treponemal absorbent antibodies or treponemal pallidum hemagglutination test were reviewed for clinical presentation, cerebrospinal fluid analysis and Venereal Disease Research Laboratories, neuro-imaging abnormalities and compatibility with the diagnosis of neurosyphilis. The diagnosis of neurosyphilis was made if the patient had reactive serum fluorescent treponemal absorbent antibodies or treponemal pallidum hemagglutination, history of progressive neurological disease and increased cerebrospinal fluid cells or protein.

Results: None of the 207 cerebrospinal fluid-Venereal Disease Research Laboratories tests were reactive. The diagnosis of neurosyphilis was made in 10 out of 14 cases with progressive neurological disease and reactive serum rapid plasma reagin, fuorescent treponemal absorbent antibodies and treponemal pallidum hemagglutination.

Conclusion: We conclude that if reactive cerebrospinal fluid-Venereal Disease Research Laboratories is required to confirm or diagnose neurosyphilis, most cases will be overlooked.

Keywords: Cerebrospinal fluid, neurosyphilis, Venereal Disease Research Laboratories.

Saudi Medical Journal 2001; Vol. 22 (1): 26-29

Neurosyphilis may present in a variety of atypical forms. Unfortunately the signs of neurosyphilis are not pathognomonic and often over-lap those of other diseases, so that diagnosis cannot be made from the clinical picture alone. The Centre for Disease Control recommends the CSF-VDRL test for establishing the diagnosis of neurosyphilis when serological tests are reactive and the patient's history is unknown.[1] The frequency with which active neurosyphilis is associated with a non-reactive CSF-VDRL test has not been established and there has been some concern that the test is insufficiently sensitive to detect all cases of neurosyphilis. We studied 14 patients with progressive neurological disease and reactive serum FTA-ABS, TPHA to assess the validity of CSF-VDRL as a diagnostic marker.

Methods. We reviewed the results of CSF-VDRL tests carried out in the diagnostic laboratory at King Faisal Specialist Hospital and Research Centre between 1992 and 1997. In the 207 patients, 14 cases of progressive neurological disease and reactive serum RPR, FTA-ABS, TPHA were analyzed because of the clinical suspicion of neurosyphilis. We applied the following diagnostic criteria adapted from Bracero et al[2] and Burke and Schaberg:[3] (1) positive CSF-VDRL; (2) negative CSF-VDRL but positive TPHA or FTA-ABS, together with more

From the Department of Neurosciences, King Faisal Specialist Hospital and Research Centre, Riyadh, Kingdom of Saudi Arabia.

Received 26th June 2000. Accepted for publication in final form 13th September 2000.

Address correspondence and reprint request to: Dr. Abdulaziz Al-Semari, Dept. of Neurosciences, King Faisal Specialist Hospital & Research Centre, PO Box 3354, Riyadh 11211, Kingdom of Saudi Arabia. Tel. +996 (1) 464 7272 Fax. +966 (1) 442 4761. Email: lock@kfshrc.edu.sa

than five white cells/ml or more than 450 mg/L protein in CSF. The records of these 14 patients were reviewed as well as the clinical signs, CSF analysis and magnetic resonance imaging (MRI).

Results. None of the 207 CSF-VDRL tests ordered at King Faisal Specialist Hospital and Research Centre between 1992 and 1997 was reactive. In 10 patients the cells and protein were abnormal: five had more than 5 white blood cells (WBC) per millilitre (normal = 0-50), and 10 patients had protein elevated from 507 to 1044 mg/L (normal range 150-450 mg/L). Ten patients met the criteria for neurosyphilis (see Table 1). Patient number 1 had multiple infarcts, and evidence of dilatation and calcification of the ascending aorta. His right pupil was small and non-reactive to light but reactive to accommodation. Patients number 1, 6, 10, 12 and 13 presented with dementia and multiple infarcts were seen on MRI of the brain. Patients number 3, 5, 7 and 12 had MRI findings consistent with leukoaraiosis. Patient number 2 had progressive ataxia: his MRI showed numerous white matter lesions, primarily periventricular in location; there was no enhancement after gadolinium administration. There was cerebral and cerebellar atrophy. His CSF showed 30 WBC, elevated protein and negative oligoclonal bands. He was treated with Ceftraxone intravenously for two weeks. Repeat CSF analysis after 3 months showed no WBC but protein was persistently elevated (516 mg/L). The CSF analysis of patient number 3 showed 12 WBC and high protein; 6 months after treatment with penicillin there were no WBC but protein remained elevated (711 mg/L). Patient number 11 presented with third nerve palsy; MRI of the brain and cerebral angiography were normal, sedimentation rate was normal, antinuclear antibody and vasculitis workup were negative. The patient was not diabetic.

Discussion. Clinically apparent central nervous system (CNS) involvement spans the entire course of syphilis infection with manifestations that vary during the course of the infection.[4-7] This syndrome was designated before the advent of antibiotic agents and currently there is concern that the manifestation or the distribution of different neurosyphilis syndromes may have changed.[8-12] Aseptic meningitis is the most common syndrome in this disease.[13] Later, meningovascular syphilis may develop producing focal CNS signs and endoarteritis.[14,15] In our series, the patients' clinical presentation included dementia, multiple infarcts, leukoaraiosis, chronic aseptic meningitis and mononeuritis. These manifestations of neurosyphilis result from vascular or meningeal inflammation.[14] The peak incidence of meningovascular syphilis is 4 to 10 years after the initial infection.[14] In parenchymatous disease, progressive reversible deterioration is seen with neural loss, demyelination and gliosis.[14] The peak incidence of the parenchymatous neurosyphilis syndrome (general paresis and tabes dorsalis) classically occurs 10 to 15 years after primary infection. It is clear that the clinical signs found in our patients were not pathognomonic and often overlapped signs of other diseases. Patients number 6

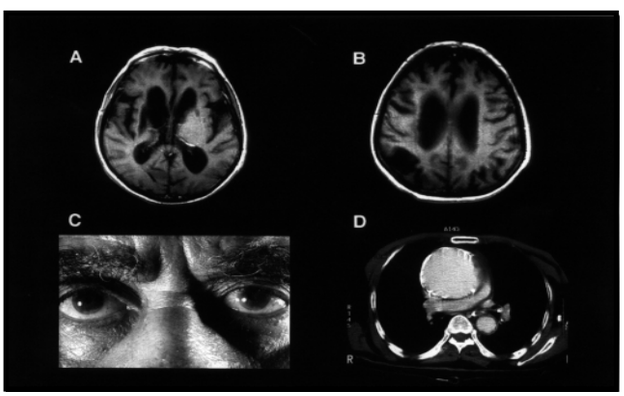

Figure 1 - Patient 1 - A & B - MRI of the brain, T1 sequences in axial projection revealed prominent large lateral ventricles; the cortical sulci and sylvan fissures are moderately enlarged. Several lacunar infarcts involve the basal ganglia and corona radiata. There is a possibility of small cortical infarcts involving the posteroparietal convexity area. C - Right small pupil, non-reactive to light but reactive to accommodation. D - Very marked, aneurysmal widening of the ascending aorta with the largest diameter approximately 9-10 cm.

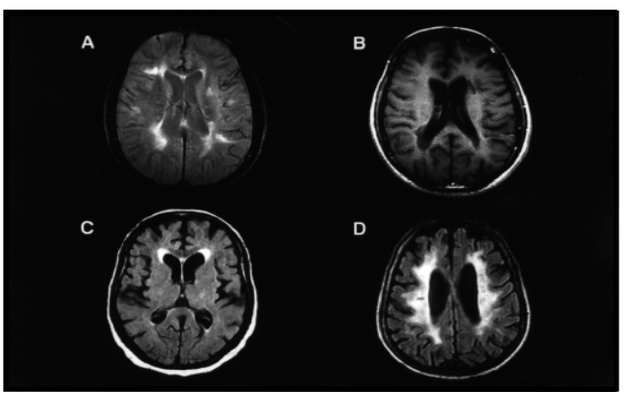

Figure 2 - Patient 2 - A & B - MRI of the brain with and without gadolinium. Both T1 and T2 sequences reveal numerous white matter lesions with sharp margins, primarily located periventricularly with some seen in cortical white matter. Following intravenous administration of gadolinium (B), no significant enhancement was seen in any of the white matter lesions. Patient 3 - C - MRI of brain, FLAIR sequence, shows generalised moderate atrophy with evidence of periventricular white matter disease, most pronounced in the frontal lobe area. Patient 5 - D -MRI of the brain, FLAIR sequence shows a bilateral hyper-intensity combined with brief, interventricular white matter that appears to be confluent.

Table 1 - Data on 14 patients with positive TPHA and FTA-ABS, Negative VDRL Titre in CSF and Progressive Neurological Disease.

Age/sex	Clinical information	WBC/mm (NR 0-50)	RBC/mm (N=0)	Protein mg/L (NR 150-450)	Magnetic resonance imaging	Risk factors for cerebrovascular disease
70/M	Progressive dementia & paralysis, (R) pupil small & non-reactive	1	8	636	Brain atrophy, dilated ventricle multiple infarcts	None
37/M	Progressive ataxia	30	303	526	General cerebral, cerebellar atrophy, periventricular lesions	None
76/M	Dementia, generalized	12	-	539	Atrophy, leukoaraiosis	Smoking
55/M	Amnesia	7	1650	421	(L) thalamic lacunar infarct	None
66/M	Progressive gait apraxia	12	2580	11044	Severe bilateral white matter changes, bilateral basal ganglia lesions, brain stem disease	None
60/M	Dementia	4	3	524	(R) posteroparietal & (L) parietal infarcts	Hypertension & smoking
55/M	Dementia	1	8	599	Leukoaraiosis	None
58/M	Pseudobulbar palsy	6	12	507	Pontine infarct	None
70/F	Dementia	4	1330	547	Brain atrophy, small vessel disease	None
64/M	(L) hemiparesis	5	1	658	Brain atrophy, left cerebellar infarct	None
56/M	(R) 3rd nerve palsy	1	0	637	MRI & angio normal	None
70/M	Dementia, (R) homonymous hemianopia	2	200	432	Brain atrophy, brain stem infarct, leukoaraiosis, (L) occipital infarct	Hypertension
77/M	Dementia	2	0	399	Brain atrophy, (L) temporoparietal infarct, white matter disease	None
65/M	Dementia	<1	0	310	Brain atrophy	None

and number 12 had hypertension and patients number 3 and 6 were smokers; these risk factors for atherosclerosis may have contributed to the clinical and MRI signs. The serodiagnosis of neurosyphilis is discussed extensively in the literature. No laboratory test has proved sufficiently sensitive or specific to be pathognomonic for neurosyphilis.[16] The serum FTA-ABAS and TPHA tests are positive in 96% to 100% of patients with neurosyphilis. Endemic syphilis (bejel), which has similar FTA-ABS and TPHA sensitivity,[17] causing persistent leg pain, radiological evidence of osteoperiostitis and facial deformity and defects but not associated with neurolgoical disease, has been reported from Saudi Arabia.[18-20] However, the treponemes isolated from patients with yaws, endemic and venereal syphilis are genetically identical sub-species of Treponema pallidum.[21] The CSF-VDRL test is regarded as the best available test for active neurosyphilis, despite its low sensitivity leading to some false negative results. The sensitivity ranges from 22% to 70% and is lowest in symptomatic neurosyphilis and tabes dorsalis.[2,22] In 1988, Davis and colleagues[23] diagnosed active neurosyphilis if the patient had reactive CSF-FTA-ABS tests, recent onset of neurolgoical signs consistent with neurosyphilis or abnormal CSF and no other recognized causes of neurological illness. Of 15 patients so classified, four had reactive CSF-VDRL tests. In 1986, Danz and colleagues[24] reviewed the records of 226 patients who had a positive or borderline serum FTA-ABS test; only three had reactive CSF-VDRL. Similarly low rates of sensitivity with the CSF-VDRL test have been reported from the United Kingdom.[25]

In 1985, Burke and Schaberg reviewed 30 patients with neurosyphilis diagnosed between 1970 and 1981.[3] They followed the criteria discussed above. The serum VDRL was positive in 86% and CSF-VDRL was positive in 53%. Meningovascular and vascular syphilis were relatively more common than before the discovery of penicillin; tabes dorsalis and general paresis were unchanged in the comparative frequency. Based on the criteria adapted from Bracero et al[2] and Burke and Schaberg[3] we diagnosed neurosyphilis in 10 of our patients. Their clinical presentation was varied and included progressive dementia, generalized paralysis, progressive ataxia, amnesia, third nerve palsy, pseudobulbar palsy and multiple infarcts. In two patients with increased WBC, repeat CSF analysis after treatment showed

resolution of the pleocytosis although the protein remained elevated. The remaining four patients had progressive neurological disease with normal CSF and VDRL. They were classified as "unlikely neurosyphilis".

Normal CSF leukocyte and protein concentration have been reported in small numbers of patients with clinically active, symptomatic neurosyphilis.[9,26,27] In 1994, Chesney and Kemp[28] inoculated CSF from untreated patients with early syphilis into rabbits and demonstrated spirochetæ in 15% of 34 patients with normal CSF. Later, Lukehart and colleagues[29] validated these results when 30% patients with spinal fluid samples from 40 cases of early syphilis demonstrated viable T.pallidum by rabbit inoculations, even though one third of these samples had normal cell count and protein with non-reactive CSF-VDRL. The significance of spirochetal invasion in patients without other CSF abnormalities remains unclear. For most clinical purposes, the use of readily available CSF laboratory tests (such as CSF-VDRL, cell count and protein determination) are adequate for clinical decision-making on CNS syphilis.

In summary, the CSF-VDRL test is insensitive and limited and should not be used to diagnose or to exclude neurosyphilis. Unfortunately, the clinical signs of neurosyphilis are not pathognomonic and often over-lap signs of other disease, limiting the usefulness of the clinical picture in making a diagnosis. Cerebrospinal fluid analysis is most often used to diagnosis CNS neurosyphilis but is not specific. Thus the diagnosis of neurosyphilis is not easy. No single or combination test is sufficiently sensitive or specific for diagnosis. However, we recommend that patients with a recent history of progressive neurological disease, reactive serum FTA-ABS and TPHA and abnormal CSF cells and protein, be treated for neurosyphilis. Cerebrospinal fluid pleocytosis is the first abnormality to resolve with treatment, usually within 3 to 6 months. Elevation of CSF protein may persist despite treatment.

References

1. Jaffe HW, Kabins A. Examination of cerebrospinal fluid in patients with syphilis. Rev Infect Dis 1982; 4(suppl): 842-848
2. Bracero L, Wormser GP, Bottone EJ. Serologic tests for syphilis: a guide to interpretation in various states of disease. Mt Sinai J Med (NY) 1979; 46: 289-292
3. Burke JM, Schaberg DR. Neurosyphilis in the antibiotic era. Neurology 1985; 35: 1368-1371
4. Clark EG, Danbolt N. The Oslo study of the natural course of untreated syphilis. An epidemiologic investigation based on a re-study of the Boeck-Bruusgaard material. Med Clin North Am 1964; 48: 613-623.
5. Moore JE, Hopkins HH. Asymptomatic neurosyphilis. VI. The prognosis of early and late asymptomatic neurosyphilis. JAMA 1930; 95: 1637-1641
6. Rockwell DH, Yobs AR, Moore MB Jr. The Tuskegee study of untreated syphilis. The 30th year of observation. Arch Intern Med 1964; 114: 792-798
7. Sparling PF. Natural history of syphilis. In: Holmes KK, March PA, Sparling PF (eds) Sexually Transmitted Diseases, 2nd ed, New York: McGraw-Hill; 1990. p. 213-219.
8. Dans PE, Vernon T, Russell B. Cerebrospinal fluid serology - is its routine use justifiable? Public Health Rep 1977; 92: 260-262
9. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis: a study of 241 patients. JAMA 1972; 219: 726-729
10. Joffe R, Black MM, Floyd M. Changing clinical picture of neurosyphilis: report of seven unusual cases. Br Med J 1968; 1: 211-212
11. Kofman O. The changing pattern of neurosyphilis. Can Med Assoc J 1956; 74: 807-812.
12. Editorial. Modified neurosyphilis. Br Med J 1978; 2: 647-648
13. Merritt HH, Moore M. Acute syphilitic meningitis. Medicine (Baltimore) 1935; 14: 119-183.
14. Merritt HH, Adams RD, Solomon HC. Neurosyphilis. New York: Oxford; 1946.
15. Holmes MD, Brant-Zawadzki MM, Simon RP. Clinical features of meningovascular syphilis. Neurology 1984; 34: 553-556
16. Hook EW III. Ventral nervous system syphilis. In: Scheld WM, Whitely RJ. Durack DT (eds) Infections of the Central Nervous System. New York: Raven Press; 1991. p. 639-656.
17. Treponemal infections. WHO Tech Rep Ser 1982; 674: 16-20.
18. Ghuouroury AA. The syphilis problem in Asir province, Saudi Arabia. Bull WHO 1954; 10: 691-702.
19. Pace JL, Csonka GW. Endemic non-venereal syphilis (bejel) in Saudi Arabia. Br J Vener Dis 1984; 60: 293-297.
20. Erdelyi RL, Moll AA. Burned out endemic syphilis (bejel): facial deformities and defects in Saudi Arabia. Plast Reconstr Surg 1984; 74: 589-602
21. Roman GC, Romm LN. Occurrence of congenital, cardiovascular, visceral, neurological and neuro-ophthalmic complications in late yaws: a theme for future research. Rev Infect Dis 1986; 8: 760-770.
22. Luger A, Schmidt BL, Steyrer K, Schonwald E. Diagnosis of neurosyphilis: examination of cerebrospinal fluid. Br J Vener Dis 1981; 57: 232-237.
23. Davis LE, Schmitt JW. Clinical significance of cerebrospinal fluid tests for neurosyphilis. Ann Neurol 1989; 25: 50-55.
24. Dans PE, Cafferty L, Otter SE, Johnson RJ. Inappropriate use of the cerebrospinal fluid Venereal Disease Research Laboratory (VDRL) to exclude neurosyphilis. Ann Intern Med 1986; 104: 86-89.
25. Editorial. Routine tests for syphilis on cerebrospinal fluid. Lancet 1977; 2: 595.
26. Byrne TN, Bose A, Sze G, Waxman SG. Syphilitic meningitis causing paraparesis in an HIV-negative woman. J Neurol Sci 1991; 103: 48-50.
27. Kolar OJ, Burkhart JE. Neurosyphilis. Br J Vener Dis 1977; 53: 221-225.
28. Chesney AM, Kemp JE. Incidence of spirochetal pallida in cerebrospinal fluid during early stage of syphilis. JAMA 1924; 83: 1725-1728.
29. Lukehart SA, Hook EW III, Baker-Zander SA, Collier AC, Critchlow CW, Handsfield HH. Invasion of the central nervous system by Treponema pallidum: implications for diagnosis and therapy. Ann Intern Med 1988; 109: 855-862.