The usefulness of cerebrospinal fluid tests for neurosyphilis

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To determine the usefulness of cerebrospinal fluid (CSF) tests for syphilis at a large academic hospital, clinical and laboratory data on 644 patients in whom such testing was requested over a 12-month period were analysed. In 198 cases (31%) the *Treponema pallidum* haemagglutination (TPHA) screening test could not be performed because of insufficient fluid. Thirty-eight of the remaining patients were diagnosed as having active neurosyphilis. Examination of 22 files of patients who had a positive TPHA and fluorescent treponemal antibody absorption (FTA-Abs) test together with a negative CSF Venereal Disease Research Laboratory (VDRL) test revealed that other CSF measures indicating disease activity (CSF protein, cells or IgG index) were not utilised optimally. In 10 (45%) of these patients neurosyphilis was not diagnosed despite either abnormal or incomplete CSF biochemical analysis, indicating that if the CSF VDRL is used as the sole marker for disease activity, some cases of neurosyphilis are likely to be missed.

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Notwithstanding the fact that neurosyphilis remains an important cause of psychiatric morbidity, particularly in developing countries such as South Africa,[1] uncertainty still exists about the application and interpretation of cerebrospinal fluid (CSF) tests for syphilis.[2-5] This applies particularly to patients whose clinical picture is not clear cut when the CSF *Treponema pallidum* haemagglutination (TPHA) or fluorescent treponemal antibody absorption (FTA-Abs) tests are positive in the presence of a negative CSF Venereal Disease Research Laboratory (VDRL) test.

The CSF VDRL test is generally regarded as the best available test for active neurosyphilis, despite its low sensitivity, which can result in some false negative results. This sensitivity ranges between 10% and 89%, and is lowest in asymptomatic neurosyphilis and tabes dorsalis.[3] The TPHA and FTA-Abs tests are more sensitive and are valuable as routine screening tests, but both remain positive for an indefinite period after successful treatment,[6] which

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limits their usefulness in the diagnosis of recurring neurosyphilis activity. An elevated CSF cell count, protein content or IgG index are also indicative of activity, but are nonspecific measurements and, furthermore, may be normal in patients with active neurosyphilis.[5]

In a study performed at Johns Hopkins Hospital in 1980, Dans *et al.*[2] concluded that the CSF VDRL test is used inappropriately, without regard for clinical findings and results of blood serology. This opinion was based on the finding that, out of 2 536 CSF VDRL tests requested, only 3 (0,1%) were reactive. However most of these CSF VDRL tests were requested without clear indications and without regard for blood serology. The value of the CSF VDRL test to exclude symptomatic neurosyphilis has also been questioned because of the limited advantage CSF analysis has over the empirical treatment of patients with asymptomatic late syphilis (i.e. untreated syphilis of more than 1 year's duration).[7,8] Also, tests with a high rate of false- negative results cannot be used with confidence to exclude neurosyphilis.

The current study was undertaken to evaluate the usefulness of CSF tests for neurosyphilis in a large academic hospital. We were particularly interested in assessing whether available markers were being optimally utilised and correctly interpreted — especially where there was doubt about disease activity.

Method

Results of all the tests for syphilis performed on the CSF of adult patients during the 12-month period from 1 July 1990 to 30 June 1991 at Tygerberg Hospital were analysed retrospectively. Tests for syphilis were requested for 644 adults' CSF specimens during this period.

At the time of the study, the following laboratory protocol for CSF analysis was followed. The TPHA and FTA IgG and IgM tests were performed on each specimen. The VDRL test was performed only in the event of any of these tests being positive.

We applied the following criteria, adapted from Burke and Schaberg,[9] to diagnose neurosyphilis: (*i*) positive CSF VDRL test; or (*ii*) negative VDRL test, but positive TPHA or FTA-Abs test, together with a raised cell count (more than 5 cells/ml), protein concentration (> 0,45 g/l) or IgG index (> 0,6).

The number of patients who met these criteria and in whom treatment for neurosyphilis had been initiated was also determined, and the follow-up management of those who had not received any treatment was investigated. Also, in the patients with a negative CSF VDRL test together with a positive TPHA or FTA-Abs test, a more detailed analysis was performed.

Results

Of the 644 specimens tested, 379 (59%) had negative TPHA and FTA IgG and IgM tests, and no further analyses were performed. In 198 patients (31%), there was insufficient fluid present for the TPHA test; this resulted in possible missed diagnoses. Forty-five (31%) of these 198 specimens had a positive FTA-Abs IgG test, but had to be excluded from the study as the CSF VDRL test had not been performed.

The TPHA and FTA-Abs IgG tests were both positive in 64 cases (10%). In 4 of these, there was insufficient fluid for the VDRL test. Of the remaining 60 specimens, 31 (52%) had positive VDRL tests, and 29 (48%) negative VDRL tests. Thus out of a total of 442 CSF specimens with sufficient fluid for a complete analysis, 7% had a positive CSF VDRL titre.

Table I. Relevant data of 22 patients with positive TPHA and FTA-Abs tests, but negative VDRL titre in CSF

Age (yrs)	Presenting symptoms	Clinical diagnosis	Serum VDRL titre	IgG index	CSF protein (g/l)	CSF cells (/mm³)
72	Delirium	Multi-infarct dementia	Neg	ND	N	1
53	Delirium; hallucinations	Delirium tremens	ND	ND	ND	ND
34	Memory impairment	Post-traumatic amnestic disorder	Neg	0,55	0,29	0
46	Progressive weakness in legs	Neurosyphilis	1:64	5,55	2,20	15
43	Delirium	Neurosyphilis	1:20	ND	0,45	1
34	Seizures	Epilepsy	Neg	0,05	ND	ND
46	Hallucinations	Neurosyphilis	1:64	ND	1,30	0
24	Hallucinations	Schizophreniform disorder	Neg	0,48	0,11	0
31	Aggression	Neurosyphilis	1:64	ND	0,35	1
30	Fainting	Diabetes mellitus	Neg	ND	0,42	2
48	Delirium	Epilepsy	1:80	0,48	0,16	0
45	Headache	Migraine	Neg	0,58	0,25	0
32	Weakness in legs	Idiopathic proximal muscular atrophy	1:16	0,46	0,28	1
34	Weakness in legs; ataxia	Epilepsy; phenytoin toxicity	Neg	ND	1,00	3
72	Weakness in legs	Cerebellar degeneration	Neg	ND	0,70	ND
41	Monoparesis; memory impairment	Factitious disorder	Neg	0,66	0,02	2
46	Hallucinations	Bipolar mood disorder	1:20	ND	0,15	1
60	Memory impairment	Diabetes mellitus	Neg	ND	0,80	0
21	Headache; fever	Meningococcal meningitis	Neg	2,30	2,60	0
27	Headache; fainting	Previously treated neurosyphilis	1:20	0,73	0,15	2
38	Personality change, cognitive decline	Previously treated neurosyphilis	Neg	0,77	0,82	2
50	Delirium	Previously treated neurosyphilis	1:40	2,02	0,14	0

ND = not done; N = normal; Neg = negative.

The 29 patients with a negative CSF VDRL but positive TPHA or FTA-Abs test, were selected for further analysis. We regarded this group as a potential source of missed diagnoses, because of the high false-negative rate of the VDRL test. Seven of the 29 files could not be traced. Relevant clinical and laboratory data for the remaining 22 patients are given in Table I.

According to the diagnosis noted in the files by the attending doctor, 7 of the 22 patients were diagnosed as having active neurosyphilis on the basis of factors other than a reactive CSF VDRL test (raised cells, protein content or IgG index in 5, suggestive symptomatology in 2 in the presence of a positive CSF TPHA and FTA-Abs test). These patients were treated and followed up accordingly. Assuming that the 31 patients with a reactive CSF VDRL test were diagnosed and treated as having neurosyphilis, we obtained a positive yield of 38 (5,9%) from the 644 patients in whom tests for syphilis had been requested. However, when we applied our criteria to the 22 cases with a negative CSF VDRL but a positive TPHA or FTA-Abs test, 10 patients met the criteria for neurosyphilis. In a further 7 cases the diagnosis could not be excluded because a full biochemical analysis was not requested, while only 5 had completely normal CSF chemistry. Ten patients therefore were not diagnosed as having neurosyphilis by the attending doctor, despite either meeting our criteria for neurosyphilis on the basis of abnormal biochemistry or the fact that the diagnosis could not be ruled out because of incomplete biochemical analyses. In only 1 patient could the abnormal CSF chemistry be ascribed to other central nervous system pathology. The remaining 9 patients had routine follow-up arranged for them. However, at the time of discharge, no reference was made to a consideration of the possibility of neurosyphilis at follow-up.

Discussion

Given the grave consequences of a missed diagnosis, we believe that a positive yield of 5,9% from all CSF specimens tested for neurosyphilis confirms the usefulness of these tests as a screening device in a population where the disease is still relatively frequently encountered.

However, our findings also highlight a number of potential pitfalls that may seriously jeopardise the usefulness of CSF tests for neurosyphilis.

The fact that 6 of the 10 patients who met our study criteria for neurosyphilis had a negative serum VDRL titre, emphasises the limitations of this test as the sole indicator for further investigation. It would seem prudent, therefore, to perform a lumbar puncture should *any* of the serological parameters for syphilis (TPHA, FTA-Abs and VDRL) be abnormal in the blood of patients who present with neurological or psychiatric symptoms.

The large number of specimens with insufficient fluid for a complete analysis (31%) was an unexpected finding. In our laboratory a minimum of 1,5 ml fluid is necessary for the microbiology and at least 2 ml for the chemistry in order to perform the complete analysis, without which the value of these tests is greatly diminished. Although it is sometimes difficult to obtain sufficient fluid, this finding points to a lack of communication between the laboratory and clinicians. This could be explained by the rapid turnover of staff in an academic hospital.

It is generally accepted that a positive VDRL titre in the CSF is indicative of disease activity. However, we found that in the presence of a negative VDRL titre, neurosyphilis was not considered, and that the other measurements in the CSF were not adequately utilised, as revealed by the large number of patients in whom an IgG index was not requested (50%). Although the IgG index is not routinely requested in patients with suspected neurosyphilis, we suggest that it be used in such patients, in order to obtain a higher detection rate.

It was also interesting to note the high proportion of patients with positive TPHA and FTA-Abs tests but negative VDRL tests who had biochemical abnormalities in the CSF (45%). This again indicates that a negative VDRL test does not necessarily exclude neurosyphilis.

According to our criteria, there were 3 patients who had false-negative CSF VDRL tests and 9 who were possible false-negatives. Furthermore, the fact that 31% of our cases could not be analysed because of insufficient CSF samples indicates that this is probably an underestimation. If such a large percentage of cases is missed in a tertiary hospital, one can surmise that even more are missed at lower levels of care.

Like Stingl *et al.*,[10] we found that follow-up of patients with neurosyphilis was inconsistent, particularly for those initially suspected to have neurosyphilis but who were subsequently found to have a negative CSF VDRL test. Because of the insensitivity of the VDRL test and the poor predictive value of CSF cell and protein content or IgG index, we suggest that all patients presenting with psychiatric or neurological symptoms who have a positive TPHA or FTA-Abs test of the CSF be carefully followed up for signs of active infection, including a repeat lumbar puncture after 1 - 2 months. The lack of infallible markers for the diagnosis of active neurosyphilis underlines once again the need for further research in this area.

To increase the awareness of the volume of CSF required to perform these tests, we suggest that the minimum volume be printed on the laboratories' request forms. We also suggest that the IgG index be performed routinely in the event of positive CSF TPHA and FTA-Abs tests. The laboratory staff may also be required to suggest follow-up testing on the laboratory report form. After the implementation of these suggestions, follow-up studies are indicated to determine their success in improving the utility of CSF tests for neurosyphilis.

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REFERENCES

1. Roberts MC, Emsley RA, Jordaan G. Screening for syphilis in acute psychiatric admissions. *S Afr Med J* 1992; **82:** 16-18.
2. Dans PE, Cafferty L, Otter S, Johnson RJ. Inappropriate use of the cerebrospinal fluid venereal disease research laboratory (VDRL) test to exclude neurosyphilis. *Ann Intern Med* 1986; **104:** 86-89.
3. Davis LE, Schmitt JW. Clinical significance of cerebrospinal fluid tests for neurosyphilis. *Ann Neurol* 1989; **25:** 50-55.
4. Luger A, Schmidt BL, Steyrer K, Schonwald E. Diagnosis of neurosyphilis by examination of the cerebrospinal fluid. *Br J Vener Dis* 1981; **57:** 232-237.
5. Hoosmand H, Escobar MR, Kopf SW. Neurosyphilis. *JAMA* 1972; **219:** 726-729.
6. Felman YM, Nikitas JA. Syphilis serology today. *Arch Dermatol* 1980; **116:** 84-89.
7. Wiesel J, Rose D, Silver A, Sacks HS, Bernstein RH. Lumbar puncture in asymptomatic late syphilis; an analysis of the benefits and risks. *Arch Intern Med* 1985; **145:** 465-468.
8. Graham PS, Trupei M, Reichman RC. Evaluation of cerebrospinal fluid in asymptomatic late syphilis. *Sex Transm Dis* 1987; **14:** 205-208.
9. Burke JM, Schaberg DR. Neurosyphilis in the antibiotic era. *Neurology* 1985; **35:** 1368-1371.
10. Stingl B, Hänny P, Waespe W. Neurolues 1982-1989. *Schweiz Med Wochenschr* 1990; **120:** 1575-1583.

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