Pitfalls in cerebrospinal fluid test for the diagnosis of neurosyphilis

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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 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, fluorescent 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.

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Neurosyphilis may present in a variety of atypical forms. Unfortunately the signs of neurosyphilis are not pathognomonic and often overlap 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. 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 and Burke and Schaberg (1)
positive CSF-VDRL; (2) negative CSF-VDRL but positive TPHA or FTA-ABS, together with more 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 were 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 endarteritis.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 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-ABAS and TPHA sensitivity,17 causing persistent leg pain, radiological evidence of osteoperiostitis and facial deformity and defects but not associated with neurological 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.22 In 1988, Davis and colleagues3 diagnosed active neurosyphilis if the patient had reactive CSF-FTA-ABS tests, recent onset of neurological 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 colleagues24 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 1981.1 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 al2 and Burke and Schaberg3 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

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

<table>
<thead>
<tr>
<th>Age/sex</th>
<th>Clinical information</th>
<th>WBC/mm³ (NR 0-50)</th>
<th>RBC/mm³ (N=0)</th>
<th>Protein mg/L (NR 150-450)</th>
<th>Magnetic resonance imaging</th>
<th>Risk factors for cerebrovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>70/M</td>
<td>Progressive dementia &amp; paralysis, (R) pupil small &amp; non-reactive</td>
<td>1</td>
<td>8</td>
<td>636</td>
<td>Brain atrophy, dilated ventricle multiple infarcts</td>
<td>None</td>
</tr>
<tr>
<td>37/M</td>
<td>Progressive ataxia</td>
<td>30</td>
<td>303</td>
<td>526</td>
<td>General cerebral, cerebellar atrophy, periventricular lesions</td>
<td>None</td>
</tr>
<tr>
<td>76/M</td>
<td>Dementia, generalized</td>
<td>12</td>
<td>-</td>
<td>539</td>
<td>Atrophy, leukoaraiosis</td>
<td>Smoking</td>
</tr>
<tr>
<td>55/M</td>
<td>Amnesia</td>
<td>7</td>
<td>1650</td>
<td>421</td>
<td>(L) thalamic lacunar infarct</td>
<td>None</td>
</tr>
<tr>
<td>66/M</td>
<td>Progressive gait apraxia</td>
<td>12</td>
<td>2580</td>
<td>11044</td>
<td>Severe bilateral white matter changes, bilateral basal ganglia lesions, brain stem disease</td>
<td>None</td>
</tr>
<tr>
<td>60/M</td>
<td>Dementia</td>
<td>4</td>
<td>3</td>
<td>524</td>
<td>(R) posteroparietal &amp; (L) parietal infarcts</td>
<td>Hypertension &amp; smoking</td>
</tr>
<tr>
<td>55/M</td>
<td>Dementia</td>
<td>1</td>
<td>8</td>
<td>599</td>
<td>Leukoaraiosis</td>
<td>None</td>
</tr>
<tr>
<td>58/M</td>
<td>Pseudobulbar palsy</td>
<td>6</td>
<td>12</td>
<td>507</td>
<td>Pontine infarct</td>
<td>None</td>
</tr>
<tr>
<td>70/F</td>
<td>Dementia</td>
<td>4</td>
<td>1330</td>
<td>547</td>
<td>Brain atrophy, small vessel disease</td>
<td>None</td>
</tr>
<tr>
<td>64/M</td>
<td>(L) hemiparesis</td>
<td>5</td>
<td>1</td>
<td>658</td>
<td>Brain atrophy, left cerebellar infarct</td>
<td>None</td>
</tr>
<tr>
<td>56/M</td>
<td>(R) 3rd nerve palsy</td>
<td>1</td>
<td>0</td>
<td>637</td>
<td>MRI &amp; angio normal</td>
<td>None</td>
</tr>
<tr>
<td>70/M</td>
<td>Dementia</td>
<td>2</td>
<td>200</td>
<td>432</td>
<td>Brain atrophy, brain stem infarct, leukoaraiosis, (L) occipital infarct</td>
<td>Hypertension</td>
</tr>
<tr>
<td>77/M</td>
<td>(R) homogenous hemianopia</td>
<td>2</td>
<td>0</td>
<td>399</td>
<td>Brain atrophy, (L) temporoparietal infarct, white matter disease</td>
<td>None</td>
</tr>
<tr>
<td>65/M</td>
<td>Dementia</td>
<td>&lt;1</td>
<td>0</td>
<td>310</td>
<td>Brain atrophy</td>
<td>None</td>
</tr>
</tbody>
</table>
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.\textsuperscript{5,26,27} In 1994, Chesney and Kemp\textsuperscript{28} inoculated CSF from untreated patients with early syphilis into rabbits and demonstrated spirochete in 15% of 34 patients with normal CSF. Later, Lukehart and colleagues\textsuperscript{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-VDR. 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-VDR, 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

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