Neurosyphilis in a tertiary care hospital in north India

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Background & objectives: The clinical diagnosis of neurosyphilis is very rarely encountered today in the developed world although syphilis remains a significant health problem in few areas of the industrialized countries and in most of the third world nations. This apparent decline may be due to increase in number of asymptomatic neurosyphilis and cases presenting as subtle, ill-defined syndromes rather than classic presentation of tabes dorsalis and general paresis in the post penicillin era. This retrospective study was carried out to report the neurosyphilis cases diagnosed at a tertiary care hospital in North India, and to analyse the laboratory and clinical parameters of these cases.

Methods: Suspected cases of neurosyphilis presenting at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh over a period of 13 yr (January 1990 to December 2002) were identified. Diagnosis of neurosyphilis was based on clinical presentation, prior history of syphilis, routine CSF biochemistry (protein and leukocytes) and serological evidence [serum and CSF venereal disease research laboratory (VDRL) and Treponema pallidum particle agglutination (TPPA) tests].

Results: A total of 25 cases of neurosyphilis were identified, 18 (72%) with reactive CSF-VDRL, 22 (88%) with elevated CSF protein and 24 (96%) with CSF mononuclear leukocytosis. Serum VDRL was reactive in all 25 cases. Three patients were asymptomatic (2 primary syphilis; 1 early latent stage), 8 had secondary and 14 had tertiary syphilis. Two of the neurosyphilis cases were also seropositive for HIV. Radiology was abnormal in 7 (28%) patients.

Interpretation & conclusion: Neurosyphilis still remains a problem in a country like India and a high index of suspicion and clinical expertise are required for appropriate diagnosis and proper management especially in the era of AIDS pandemic.

Key words Clinical presentation - neurosyphilis - north India
Over the past decade, syphilis has emerged coincidental with socio-economic upheavals, behavioural changes and spread of the AIDS pandemic. Reports from South-West Asia and Africa estimated the prevalence of syphilis to range from 0.35 to 15 per cent. Data on prevalence of syphilis in India are scanty and seroprevalence has been estimated to be 1.4 and 2.4 per cent in Kerala and Aurangabad in Maharashtra. In cases of syphilis, appropriate therapy can lead to complete cure and progression of disease is rare. Syphilitic involvement of the central nervous system has consequently become a very elusive entity. It is believed that the spectrum of neurologic involvement in patients with syphilis may have shifted away from the classic parenchymatous and meningovascular neurosyphilis to asymptomatic disease or subtle, ill defined syndromes which are more liable to escape clinical diagnosis. These problems of clinical recognition of cases of neurosyphilis are compounded by difficulties in laboratory diagnosis. There are sporadic reports of cases of neurosyphilis with atypical clinical presentation and radiological changes in world literature, however documentation of neurosyphilis cases from India is very limited.

This retrospective study was carried out to identify and report cases of neurosyphilis diagnosed over a period of 13 yr (January 1990 to December 2002) at Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, a tertiary care institute in north India. The efficacy of laboratory diagnosis of these cases was evaluated and associated with the clinical presentation of the patients.

Material & Methods

Study population: Serological tests for syphilis Venerable Disease Research Laboratory (VDRL) test and the Treponema pallidum particle agglutination test (Serodia TP-PA Fujirebio, Japan) were performed for patients suspected to be suffering from sexually transmitted infections and associated with high risk behaviour (history of contact, intravenous drug abuse, HIV seropositivity). All these patients either presented to the out patient department or were admitted in Nehru Hospital of PGIMER, Chandigarh, over a period of 13 yr (January 1990 to December 2002). The records of the patients clinically suspected to be suffering from neurosyphilis were reviewed further.

Laboratory and clinical evaluation: Diagnosis of neurosyphilis in clinically suspected cases was established by performing VDRL test in both serum and cerebrospinal fluid (CSF) of the patients. The TPPA test was also performed in some of the suspected cases. Blood (4-5 ml) was obtained from each patient for quantitative VDRL testing and TPPA test when required. CSF (5-6 ml) was obtained by lumbar puncture and sent for determination of leukocyte count, protein concentration and serologic testing. Serum and CSF-VDRL were performed according to standard procedures. The TP-PA test was performed as per manufacturer’s instructions. CSF leukocytosis was defined as leukocytes >5x10^6/l (5 leukocytes/mm^3), and protein concentrations of >0.4 g/l were considered abnormal. The stage of syphilis in each patient was determined by clinical presentation (chancre, skin rash, lymphadenopathy) and VDRL reactivity (absolute titre and rise in titre). Information about sexual history, intravenous drug use and history of neurologic complaints (headache, dizziness, visual or hearing disturbances) was obtained.

Results

Routine serum VDRL test done in 15,500 patients clinically suspected to be suffering from sexually transmitted infections (presence of genital lesions, high risk behaviour, HIV seropositivity) was found to be reactive in 630 (4.1%) cases. Further laboratory evaluation was carried out in those patients who were diagnosed or suspected to be suffering from neurosyphilis on the basis of clinical presentation and past history of syphilis. On the basis of clinical parameters, laboratory (serological, biochemical) evaluation and radiological abnormalities, 25 cases of neurosyphilis were identified over a period of 13 yr from 630 serumVDRL positive patients (4%).

Serum VDRL was found to be reactive (up to 64 dilutions) in all the 25 cases where as CSF VDRL was reactive in 18 (72%) patients. The TP-PA test could be performed in only 10 patients (including 7 CSF VDRL negative cases) and the test was positive in all these cases (Table I). Two of the patients were seropositive for HIV. CSF protein was elevated in 22 patients and leukocytosis was found in 24. Of these 25 patients, 20 were males (age range 20 to 60 yr).
and 5 were females (age range 18 to 45 yr). The stage of syphilis was determined on the basis of clinical presentation and VDRL reactivity. Asymptomatic neurosyphilis could be identified in three patients by reactive CSF VDRL test. Two of these patients were suffering from primary syphilis (genital ulcers) with abnormal CSF biochemistry. Early latent syphilis was identified in only one pregnant woman who was asymptomatic, with normal CSF biochemistry but had a reactive CSF VDRL. CSF and serum VDRL were repeated twice in this patient after a gap of two weeks and the results were consistently positive and the titre also remained the same. The TP-PA test was also positive in this case. Secondary syphilis (rash, lymphadenopathy and meningitis) with reactive CSF VDRL, elevated CSF protein and leukocytosis was seen in eight cases. Tertiary syphilis (meningeal, meningovascular and parenchymal) was identified in 14 patients. Positive association with laboratory parameters in the cases of tertiary syphilis was possible in 7 (50%) patients with a reactive CSF VDRL (Table II). Meningitis was the commonest manifestation in the patients (28%) followed by systemic features and dementia (Table III).

### Table I. Laboratory parameters in neurosyphilis patients (n=25)

<table>
<thead>
<tr>
<th>VDRL</th>
<th>Reactive</th>
<th>Non-reactive</th>
<th>TPPA*</th>
<th>Increased protein concentration (&gt;0.40 g/l)</th>
<th>Increased no. of leukocytes (&gt;5x10^6/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td>18</td>
<td>7</td>
<td>10</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Blood</td>
<td>25</td>
<td>0</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

VDRL, Venereal disease research laboratory  
*TPPA could be performed in only 10 patients and was not done in the other 15 cases  
Two patients were HIV seropositive

### Table II. Stages of syphilis in neurosyphilis patients

<table>
<thead>
<tr>
<th>Stages</th>
<th>Primary</th>
<th>Secondary</th>
<th>Latent</th>
<th>Tertiary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Late</td>
<td>Reactive</td>
<td>Non-reactive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CSF VDRL</td>
<td>CSF VDRL</td>
</tr>
<tr>
<td>Reactive</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>CSF VDRL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-reactive</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serum-VDRL</td>
<td>2</td>
<td>8</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table III. Clinical presentation of neurosyphilis patients

<table>
<thead>
<tr>
<th>Signs/symptoms</th>
<th>Number of patients (%)</th>
<th>CSF VDRL Positive</th>
<th>TP-PA** positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningitis</td>
<td>7 (28)</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Stroke syndrome (meningovascular)</td>
<td>1 (4)</td>
<td>1</td>
<td>ND</td>
</tr>
<tr>
<td>Dementia (parenchymal)</td>
<td>5 (20)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Optic atrophy</td>
<td>3 (12)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cranial nerve involvement</td>
<td>1 (4)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Quadripareesis/Paraplegia (myelopathy)</td>
<td>3 (12)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Systemic*</td>
<td>4 (16)</td>
<td>4</td>
<td>ND</td>
</tr>
<tr>
<td>Asymptomatic (antenatal)</td>
<td>1 (4)</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Rash, lymphadenopathy, genital ulcers, fever, headache.  
ND, not done  
**Done in only 10 cases and was positive in all  
VDRL, Venereal disease research laboratory  
TP-PA, Treponema pallidum particle agglutination
Computed tomographic (CT) scan, contrast enhanced CT (CECT), magnetic resonance imaging (MRI) and gadolinium enhanced MRI (contrast MRI) were performed in 21 of 25 patients, and radiology was abnormal in seven (28%) cases. MRI revealed temporal lobe atrophy in two patients presenting with dementia. A young male presenting with stroke had hypodensity conforming to left middle cerebral artery (MCA) territory on CT scan. Two patients with paraplegia and one patient with quadripareesia had hyperintensities on T2-weighted sequences in MRI of the thoracic and cervical region respectively.

**Discussion**

Since the beginning of the antibiotic era, *Treponema pallidum* remains exquisitely sensitive to penicillin thus making cure of the disease possible and halting progression of syphilis through various stages. CNS syphilis represents a continuum comprising early invasion, usually within the first weeks or months of infection and asymptomatic involvement which may or may not lead to neurologic manifestations. The spectrum of neurologic manifestations include meningitis, stroke, myelopathy, cranial nerve involvement, symptoms of demyelination, seizures and headache which can be confused with many neurological diagnoses. High index of suspicion and clinician’s awareness is thus very important in diagnosis of neurosyphilis. Lack of a gold standard for the laboratory diagnosis also contributes to missing the diagnosis in some instances. CSF VDRL is the most widely used test for diagnosis and is generally considered definitive evidence of neurosyphilis. In our study reactive CSF VDRL was observed in 72 per cent of the patients, reactive serum VDRL in all cases, elevated CSF protein in 88 per cent and CSF leukocytosis in 96 per cent. All the patients suffering from primary, secondary and latent syphilis had a reactive CSF VDRL whereas only 50 per cent patients with tertiary disease were reactive. The CSF VDRL is highly specific but relatively insensitive and may be non reactive even in cases of progressive disease. The sensitivity of serum VDRL was found to be 100 per cent (positive in all 25 cases, irrespective of stage of the disease) and that of CSF VDRL was 72 per cent in our study. All the seven patients who were CSF VDRL negative, but serum VDRL positive had tertiary syphilis. Degree of sensitivity of CSF VDRL is known to be lower in asymptomatic neurosyphilis and tabes dorsalis. The TP-PA test performed in only 10 cases, was found to be 100 per cent sensitive and specific. The degree of sensitivity is highest in meningo-vascular syphilis and lower in asymptomatic neurosyphilis however, in our study all the cases of asymptomatic neurosyphilis were positive by CSF VDRL. CSF abnormalities are estimated to be demonstrable in up to 90 per cent cases of primary or secondary syphilis and 25 per cent of latent syphilis, but the rate of laboratory detection in our patient population was found to be higher. Isolation of *T. pallidum* from CSF (rabbit infectivity test), demonstration of the organism in CSF by dark field microscopy, immunofluorescence and silver staining have been evaluated by various investigators but found to be cumbersome and compromised by presence of artifacts. Based on these observations, the benefits of CSF examination becomes more apparent and can also have potential role in detection of patients with early syphilis.

Several investigators have reported a change in the clinical spectrum of neurosyphilis with more patients presenting with vague, ill defined neurologic complaints. The classic manifestations of tertiary neurosyphilis (tabetic gait, lancinating pains, Argyll Robertson pupil) could not be found in any case, though 20 per cent patients had dementia.

There has been speculation that concurrent infection with HIV may alter the natural history and therapeutic response of syphilis, particularly with regard to neurologic manifestations. Rompalo et al report that the only significant difference among HIV infected and uninfected persons suffering from syphilis was an increase in median number of genital ulcers. In our study, only two patients were HIV seropositive and they had no atypical manifestation or increased severity of disease. Radiological abnormalities were present in 28 per cent patients and syphilitic myelitis was seen in four cases although this finding is rarely reported.

CSF examination remains the most essential tool in the evaluation of any seropositive patient with neurologic signs and symptoms and should be
recommended for all patients with untreated syphilis of unknown duration or of $>$ 1 yr duration, although asymptomatic cases with early syphilis may still be missed. We reported 25 cases of neurosyphilis over a 13 yr period, however, this might be an underestimate because the asymptomatic cases of neurosyphilis are liable to be missed because of lack of proper recommendations of CSF screening. There has been no significant change in the clinical manifestations of neurosyphilis, but asymptomatic cases and meningovascular manifestations are seen more often than in the pre antibiotic era.

**References**


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