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Usefulness of routine lumbar puncture in non-HIV patients with latent syphilis of unknown duration

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ABSTRACT

Objectives To evaluate the usefulness of routine lumbar puncture in non-HIV patients with untreated latent syphilis.

Methods We conducted a prospective study in Seoul National University Bundang Hospital from May 2003 to December 2005. Participants in routine health check-ups of the healthcare system were screened for serological evidence of syphilis by the Treponema pallidum particle agglutination (TPPA) test. Lumbar puncture was performed, with consent, on untreated latent syphilitic patients. Neurosyphilis was defined as positivity for cerebrospinal fluid Venereal Disease Research Laboratory (CSF VDRL) or pleocytosis with positivity for CSF TPPA or elevation of CSF protein with IgG index exceeding 0.85.

Results Of 21 507 participants, 282 (1.4%) had serological evidence of syphilis. Among the 163 non-HIV patients with untreated latent syphilis, 70 (43%) underwent lumbar puncture. All the patients had VDRL titres less than 1:16. Abnormal neurological signs or symptoms were present in eight (11%) patients. CSF abnormalities were seen in 57 (81%), but no patient (0%, 95% CI 0 to 6.2) was diagnosed with neurosyphilis.

Conclusions The estimated prevalence of neurosyphilis among non-HIV patients with untreated latent syphilis and serum VDRL < 1:16, was below 6.2%.

INTRODUCTION

In the era before antibiotics, lumbar puncture was part of the clinical work-up for latent syphilis because latent syphilitic patients with abnormal cerebrospinal fluid (CSF) findings were at risk of developing symptomatic neurosyphilis.¹ In the modern antibiotic era, the incidence of neurosyphilis appears to be declining possibly because antibiotic treatment for other diseases treats unsuspected syphilis.² Hence, recent guidelines for the management of syphilis recommend that lumbar puncture should only be performed in selected patients.³ ⁴ However, because recent reports of the possibility of neurosyphilis among latent syphilitic patients are controversial,⁵ ⁶ there is debate about the usefulness of lumbar puncture in asymptomatic latent syphilitic patients.³ To address this issue, we prospectively evaluated the prevalence of neurosyphilis in patients diagnosed with latent syphilis by screening tests.

METHODS

Study population

This prospective study was conducted in Seoul National University Bundang Hospital. All participants in health check-ups of the healthcare system from May 2003 to December 2005 were considered for enrolment. Patients with primary, secondary or tertiary syphilis and patients with HIV infection were excluded.

Study design

Treponema pallidum particle agglutination (TPPA) test was performed at the first visit. For all patients with reactive TPPA, board certified infectious disease specialist conducted a history taking for previous syphilis treatment, clinical examinations for signs or symptoms of primary and secondary syphilis, and careful neurological examinations. Each patient was tested for HIV infection, fluorescent treponemal antibody absorption (FTA-ABS) and serum Venereal Disease Research Laboratory (VDRL) titre. Lumbar puncture was performed on consenting untreated latent syphilitic patients by other physicians. The CSF was evaluated for white blood count, protein, albumin and IgG concentrations, and reactivity in the VDRL, Treponema pallidum haemagglutination (TPHA) and FTA-ABS tests. CSF IgG index was calculated as CSF IgG index = (CSF IgG/serum IgG)/(CSF albumin/serum albumin).⁷ Neurosyphilis was defined as CSF VDRL positivity or pleocytosis with CSF TPHA positivity or CSF protein elevation with IgG index exceeding 0.85.³ ⁴

RESULTS

Of 21 507 participants in health check-ups during the study period, 282 (1.4%) had serological evidence of syphilis. One hundred and fifteen participants had histories of syphilis treatment, two were diagnosed with tertiary syphilis and patients with HIV infection were excluded. Among the 163 non-HIV participants with untreated latent syphilis, 93 (57%) refused lumbar puncture. Of the 70 who consented to lumbar puncture, 39 (55%) were male with median age 59 years (range: 31–84). Abnormal neurological signs or symptoms were present in eight (11%) patients. CSF abnormalities were seen in 57 (81%), but no patient (0%, 95% CI 0 to 6.2) was diagnosed with neurosyphilis. None of the patients met the diagnostic criteria for neurosyphilis (95% CI 0 to 6.2% by modified Wald method). Pleocytosis was observed in four patients, but none of these had positive CSF TPHA. Although the cause for pleocytosis was unclear, none had developed any neurological signs or...
symptoms in follow-up duration. Positive CSF TPHA was observed in three patients; none with pleocytosis. Protein elevation was observed in 57 patients, but none had a CSF IgG index exceeding 0.85. CSF abnormalities were not associated with neurological symptoms (table 1).

**DISCUSSION**

In this study, the estimated prevalence of neurosyphilis among latent syphilitic patients of unknown duration was below 6.2% and a diagnosis of neurosyphilis could be excluded in 96% because the results of the highly sensitive CSF TPHA were negative.3 4 This finding suggested that it is possible that some of patients had received antibiotics effective against *Treponema pallidum* in the interval between acquisition of syphilis and lumbar puncture.

A previous study reported that none of the 52 patients admitted to hospital with latent syphilis detected by routine screening showed evidence of neurosyphilis.5 However, Marra et al reported that 12 (15%) of 79 non-HIV patients with late latent syphilis or syphilis of unknown duration had neurosyphilis.6 In that study, substantial numbers of patients had serum VDRL $<1:16$, which predicts CSF abnormalities compatible with neurosyphilis.6 The absence of a neurosyphilis high-risk group in our study (none had serum VDRL $<1:16$) might explain the difference.

Elevated CSF protein was the most common CSF abnormality in our study group (median age: 59 years; range: 39–87 years), perhaps because CSF protein increases as patients get older.8 We also noted the increasing tendency of CSF protein levels over age. CSF IgG index is often elevated in neurosyphilis, presumably because of intrathecal synthesis of antitreponemal immunoglobulins.9 None of our patients had an elevated CSF IgG index suggesting that antitreponemal immunoglobulins were not the major contributors to the elevated CSF protein levels.

**Table 1** Cerebrospinal fluid analyses of 70 patients with untreated latent syphilis of unknown duration

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>95% CI* of prevalence (%)</th>
<th>Neurological symptoms (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleocytosis (WBC&gt;5 cells/μl)</td>
<td>4 (5.7)</td>
<td>1 to 14</td>
</tr>
<tr>
<td>Protein elevation (&gt;0.45 g/l)</td>
<td>57 (81.4)</td>
<td>71 to 89</td>
</tr>
<tr>
<td>CSF IgG index elevated (&gt;0.85)</td>
<td>0</td>
<td>0 to 6</td>
</tr>
<tr>
<td>CSF TPHA/FTA-ABS positive</td>
<td>3 (4.3)</td>
<td>1 to 12</td>
</tr>
<tr>
<td>CSF VDRL positive</td>
<td>0</td>
<td>0 to 6</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid; FTA-ABS, fluorescent treponemal antibody absorption; TPHA, *Treponema pallidum* haemagglutination; VDRL, Venereal Disease Research Laboratory.

*CI was calculated by modified Wald method.

Among latent syphilitic patients with serum VDRL $<1:16$, none had clinical findings of neurosyphilis. This outcome supports current guidelines recommending restriction of lumbar puncture for asymptomatic patients with latent syphilis to patients at high risk.

**Key messages**

- Among 70 non-HIV patients with untreated latent syphilis and serum Venereal Disease Research Laboratory $<1:16$, none had clinical findings of neurosyphilis.
- This study supports current guidelines recommending restriction of lumbar puncture for asymptomatic patients with latent syphilis to patients at high risk.

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**Contributions** Pyong Gun Choe collected and analysed the data and wrote the paper; Jin Su Song contributed to the study design and reviewed the paper; Kyoung Ho Song contributed to the study design and reviewed the paper; Jei Hyun Jeon contributed to the study design and reviewed the paper; Nam Joong Kim contributed to the study design and reviewed the paper; Myoung-don Oh contributed to the study design and reviewed the paper; Hong Bin Kim was the principal investigator on the project, recruited patients, performed medical interview and neurological examination, and took part in the writing and editing of the paper.

**Competing interests** None.

**Ethical approval** The study protocol was obtained from the Institutional Review Board of Seoul National University Bundang Hospital.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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