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CLINICAL REPORT

Neurosyphilis is Unlikely in Patients with Late Latent Syphilis and a Negative Blood VDRL Test

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Patients with latent syphilis or syphilis of unknown duration should be evaluated for tertiary disease and neurosyphilis. The aim of this retrospective study was to determine relevant serological parameters for the identification of those individuals with syphilis who are most likely to have neurosyphilis and who therefore require lumbar puncture. After excluding repeated estimates and patients whose blood syphilis serology had either been negative or not been determined within 3 months of lumbar puncture, 265 out of 710 cerebrospinal fluids from 1988 to 2004 were analysed. In each of those patients the earliest available pairs of serum and cerebrospinal fluid samples were evaluated. The diagnosis of neurosyphilis was based on criteria according to established guidelines. Forty-three of 265 patients (16.2%; 5 women, 38 men; mean age 47±16 years) had neurosyphilis. Seven of 72 (9.7%) of those testing HIV-positive, fulfilled the criteria of neurosyphilis. Not a single patient with neurosyphilis tested Venereal Disease Research Laboratory test (VDRL)-negative in peripheral blood, an effect which was highly significant ($p<0.01$, χ^2-test). The median blood-VDRL titre was significantly higher in patients with neurosyphilis than in those without (1:32 vs. 1:0; p<0.01, t-test, two-sided). Hence, neurosyphilis is very unlikely in patients with a negative blood-VDRL. Therefore, lumbar puncture is not recommended in these patients. ***Key words: syphilis; neurosyphilis; screening; lumbar puncture; diagnosis; VDRL; cerebrospinal fluid.***

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Endemic transmission of syphilis had been considered to be almost eliminated in Western Europe. However, recent surveys have found increases in the prevalence of infectious syphilis in the USA and several European countries (1–6). Accordingly, neurosyphilis or tertiary syphilis, such as cardiovascular syphilis, still needs to be considered. Neurosyphilis develops in about 5% of untreated patients infected with *Treponema pallidum* (7). The diagnosis of neurosyphilis is usually based on laboratory findings from analysis of the cerebrospinal fluid (CSF), and no single test can be used to establish the diagnosis. It depends on various combinations of reactive serological test results, abnormalities of CSF-cell count or protein, and/or a reactive Venereal Disease Research Laboratory test (VDRL) -CSF with or without clinical manifestations. The Centers for Disease Control and Prevention (CDC) and European guidelines on sexually transmitted diseases (STD), consider various combinations of reactive serological test results, including a reactive CSF VDRL test, together with an augmented CSF leukocyte count and evidence of intrathecal immunoglobulin production with or without clinical manifestations to be indicative of neurosyphilis (8).

According to the CDC published guidelines for neurosyphilis, lumbar puncture (LP) is indicated in patients with syphilis who have clinical evidence of neurological symptoms, including motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, and symptoms or signs of meningitis regardless of the stage of infection, in patients with treatment failure or evidence of active tertiary disease such as gummata and cardiovascular disease, as well as in HIV-positive patients (8, 9). However, there is a subset of patients with late latent syphilis, who meet the laboratory criteria of neurosyphilis without specific symptoms ("asymptomatic neurosyphilis") (10). CSF examination may therefore be indicated in a particular subset of patients with late latent syphilis, without clinical and historical findings, who have an unknown duration of infection and no history of treatment (4, 9). LP is an invasive procedure with side-effects and should therefore be carried out only when indicated. According to literature, nausea, tinnitus and persistent headache may occur in up to 37% of those who undergo LP (11).

The aim of this retrospective study was to determine serological parameters in peripheral blood, which, apart from clinical signs, can be used as criterion for the indication of LP in patients with late latent syphilis.

MATERIALS AND METHODS

Between January 1988 and June 2004, 710 CSF samples obtained from patients with latent syphilis (defined by a positive treponemal specific test (see below) in the peripheral blood) in the departments of dermatology, neurology, psychiatry or

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other specialists were analysed in the syphilis laboratory of the Department of Dermatology, Medical University of Vienna. Indications for performing LP had been established by each referring centre and were: neurological symptoms, patients with treatment failure, evidence of active tertiary disease or HIV-positive patients.

Blood and CSF were analysed by non-treponemal tests, such as the VDRL, and treponemal specific tests, such as the *T. pallidum* particle haemagglutination (*TPHA*) test and the fluorescent treponemal antibody-absorbed (FTA-Abs) test. A positive test result in at least one of the treponemal specific antibody tests was required to establish the diagnosis of syphilis infection. After excluding repeated estimates and patients whose syphilis serology was either negative or had not been determined within 3 months of LP, blood/CSF pairs of 265 patients (79 women and 186 men) were retained for analysis (Table I). Due to the retrospective study design, clinical information about the stage of infection, details on medical history and treatment was not available for every single patient but, if available, are shown for all patients in Table II.

The TPHA test was initially performed by the micro-haemagglutination assay technique (Fujirebio Inc., Japan); after 1996 a variation of the test, the *T. pallidum* particle agglutination (TP-PA) test was used instead (Serodia®-TP-PA, Fujirebio Inc., Japan). For quantitative testing of TPHA, serial dilutions of each serum in 0.9% saline (TPHA 1:2, 1:10, 1:40, 1:80, 1:160) were prepared. The TPHA was considered reactive at a titre ≥1:160. In most of the cases, a positive TPHA was confirmed by another commercial treponemal specific IgG/IgM antibody test (FTA-Abs test, BioMerieux, France). The VDRL slide flocculation test (VDRL Cardiolipin Antigen Test, Dade Behring Austria, Vienna, Austria), detects IgM and IgG antibodies directed against membrane phospholipids and was performed according to a standard protocol (12). Serial dilutions of each serum in 0.9% saline (VDRL undiluted =1:0, 1:2, 1:4, 1:8, 1:16, etc.) were prepared.

The diagnosis of neurosyphilis was based either on a reactive CSF VDRL test according to the CDC guidelines (9), and/or if the patient met additional criteria defined in the European STD guidelines (positive CSF TPHA and/or FTA-Abs test, augmented CSF white blood cell count (>10/mm^3), intrathecal synthesis of IgG and/or IgM quantified by the respective indices (IgG index ≥0.7; IgM index ≥ 0.10; IgG index = {(total CSF IgG (mg/l)) × (serum albumin (mg/l)) / (total serum IgG (mg/l)) × (CSF albumin (mg/l)) }; IgM index likewise) (8). The TPHA-index, which quantifies intrathecal production of *T. pallidum*-specific IgG antibodies, served as an additional diagnostic tool (TPHA-index = CSF-TPHA titre/{albumin quotient ×1000}; albumin quotient = {CSF albumin (mg/l) in CSF ×1000/serum albumin (mg/l)}; according to (8)). Neurosyphilis is most probable at results between 70 and 500, and an outcome above 500 is diagnostic (12).

Table I. *Gender, age, HIV-status and diagnosis of neurosyphilis according to the following criteria: neurosyphilis was diagnosed with a positive cerebrospinal fluid – VDRL-test according to the CDC (9); with three additional detection rules according to the European STD-guidelines (8); or with a TPHA index of more than 70 according to Luger et al. (13)*

Neurosyphilis according to European STD criteria			
	+	–	Σ
Female (n)	5 (11.6%)	74 (33.3%)	79 (29.8%)
Male (n)	38 (88.4%)	148 (66.7%)	186 (70.2%)
Mean age (years±SD)	46.7±14.8	48.5±17.2	48.2±16.8
HIV-positive (n)	7	65	72
Σ	43	222	265

Statistical analysis was performed with the software package SPSS 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Two hundred and sixty-five patients met the criteria for inclusion into this study, 72 of them being HIV-positive. The patients' gender, age and HIV status are depicted in Table I. Forty-three of the 265 patients (16.2%; 5 women, 38 men; mean age 46.7±14.8 years) met the laboratory criteria of neurosyphilis according to their CSF findings. In 38 of them the laboratory criteria of neurosyphilis according to the criteria of the CDC guidelines, i.e. tested positive in the CSF-VDRL, were applicable (9). However, a negative CSF-VDRL does not exclude neurosyphilis. Extended diagnostic criteria by laboratory analysis of abnormalities CSF are defined in the European STD guidelines (8), leading to the inclusion of the 5 further patients #7, #15, #16, #22 and #24 (Table II), who exhibited CSF pleocytosis, CSF-TPHA reactivity (the TPHA-titre was only available in 22 patients), elevated IgG and IgM indices, but negative in the CSF-VDRL. Thirty-eight patients fulfilled both CDC and European STD criteria.

Another criterion for neurosyphilis is the TPHA-index. A value above 70 is considered suggestive for neurosyphilis (13). In our study population, however, the TPHA-index was available in only 22 patients, and was elevated in 17 patients. Each of those patients additionally fulfilled established criteria for neurosyphilis. Fifteen patients (#2–4, #20, #23, #24, #29–32, #34, #35, #37, #41, #42 in Table II) fulfilled all criteria (CDC, European STD and positive TPHA-index).

Due to the retrospective study design, the complete medical reports were available for only 41 out of the 45 patients who met the laboratory criteria of neurosyphilis in their CSF findings. For patients #37–40 the clinical details were unknown, but LP had been carried out because syphilis serology indicated active disease ("syphilis infection", Table II). Two patients (#34, #35) with secondary syphilis underwent LP because of clinical evidence of neurological symptoms (hemiparesis and facial nerve palsy (#34), optical nerve neuritis (#35)). Ten patients were diagnosed clinically with neurosyphilis, suffering from tabes dorsalis or progressive paralysis or other symptoms classically seen in neurosyphilis patients such as Argyll Robertson pupils. Seven patients had late latent syphilis who exhibited neurological symptoms also seen under other conditions such as headache, single cranial nerve palsy, ocular symptoms, anomia or dementia. Three patients met criteria of tertiary syphilis with cardiovascular stigmata (aortic insufficiency, aneurysm of the ascending aorta) and an additional 3 patients experienced treatment failure years after appropriate treatment. Overall, 10 patients with neurosyphilis were asymptomatic and had late latent syphilis of unknown duration.

Table II. *Details of the patients who met the European STD criteria of neurosyphilis according to the criteria listed in the legend of Table I. All but patients 7, 15, 16, 22 and 24 additionally fulfilled the CDC criteria (9). "Clinical diagnosis" was the diagnosis established by the referring centre, which led to lumbar puncture (LP). "Secondary Syphilis" was syphilis infection for less than 1 year, "late latent syphilis" was of >1 year, according to CDC classification (9). "Neurosyphilis" indicates that symptoms suggestive for neurosyphilis were already known at the time of LP. "Tertiary syphilis" meant other sequelae of syphilis than neurosyphilis, e.g. cardiovascular syphilis. There was no clinical information about patients #37–40 filed under "syphilis infection".*

#	Sex	Age (years)	HIV	Clinical information and diagnosis at LP	Blood[1]	CSF[2]				
					VDRL (titre)	VDRL (titre)	White blood cells (mm^{-3}) >10	IgG-quotient ≥0.7	IgM-quotient ≥0.1	TPHA-Index >70
1	M	33	–	Late latent infection, serological treatment failure	1:32	1:2	209	*nd*	nd	*nd*
2	M	38	–	Late latent syphilis	1:512	1:4	257	11.7	2.7	163
3	M	56	–	Late latent syphilis	1:128	1:4	19	9.3	0.9	158
4	M	36	–	Late latent syphilis	1:128	1:0	79	*nd*	*nd*	107
5	F	30	–	Late latent syphilis	1:32	1:2	105	4.2	2.2	55
6	M	42	–	Late latent syphilis	1:32	1:0	91	4.4	*nd*	37
7	M	45	–	Late latent syphilis	1:16	–	51	5.9	*nd*	15
8	M	32	+	Late latent syphilis	1:16	1:8	62	28.9	10.1	*nd*
9	F	24	+	Late latent syphilis	1:256	1:4	53	6.6	3.1	*nd*
10	M	44	–	Late latent syphilis	1:128	1:4	10	*nd*	*nd*	*nd*
11	M	27	+	Late latent syphilis	1:64	1:4	*nd*	*nd*	*nd*	*nd*
12	M	51	–	Late latent syphilis	1:16	1:4	*nd*	*nd*	*nd*	*nd*
13	M	53	–	Late latent syphilis	1:8	1:0	*nd*	*nd*	*nd*	*nd*
14	M	39	–	Late latent syphilis	1:512	1:0	*nd*	*nd*	*nd*	*nd*
15	F	50	–	Late latent syphilis	1:8	–	38	1.8	*nd*	*nd*
16	M	38	+	Late latent syphilis	1:64	–	13	2	*nd*	*nd*
17	M	40	–	Late latent syphilis, anomia, motoric aphasia	1:128	1:32	*nd*	*nd*	*nd*	*nd*
18	M	37	–	Late latent syphilis, epilepsia	1:16	1:4	*nd*	*nd*	*nd*	*nd*
19	M	48	–	Late latent syphilis, facial nerve palsy	1:256	1:0	*nd*	*nd*	*nd*	*nd*
20	F	31	–	Late latent syphilis, headache	1:2	1:4	30	6.6	*nd*	90
21	M	69	–	Late latent syphilis, neurodegeneration process	1:128	1:0	5	5.9	*nd*	53
22	M	57	–	Late latent syphilis, presenile dementia	1:16	–	13	5.9	*nd*	85
23	M	24	+	Late latent syphilis, seizures	1:64	1:8	81	7.9	*nd*	721
24	M	70	–	Late latent syphilis, uveitis posterior	1:8	–	11	4.4	*nd*	853
25	M	40	–	Neurosyphilis, Argyll Robertson pupil, organic mental syndrome	1:512	1:0	15	11.2	*nd*	368
26	M	59	–	Neurosyphilis, optic atrophy	1:8	1:4	96	1.71	0.3	nd
27	M	49	–	Neurosyphilis, optic atrophy with pupilloplegia	1:16	1:4	50	nd	nd	nd
28	M	35	–	Neurosyphilis, progressive paralysis	1:32	1:32	78	59.5	8.1	nd
29	M	50	–	Neurosyphilis, progressive paralysis with tetraspasm	1:2	1:8	106	11.3	1.9	4096
30	M	44	–	Neurosyphilis, tabes dorsalis, Charcot joints, neuritis nervi optici, Argyll Robertson pupil	1:8	1:2	14	9.5	nd	1652
31	M	55	–	Neurosyphilis, tabes dorsalis, hearing loss	1:4	1:8	248	47	10.1	128
32	M	40	–	Neurosyphilis, tabes dorsalis, optic atrophy, ophthalmoplegia	1:8	1:2	5	10	nd	191
33	M	80	–	Neurosyphilis, tabes dorsalis, treatment failure	1:4	1:0	*nd*	nd	nd	nd
34	M	35	–	Secondary syphilis, hemiparesis, facial nerve palsy	1:128	1:32	109	12.7	29.4	166
35	M	32	+	Secondary syphilis, neuritis nervi optici	1:512	1:2	368	4.6	6.5	96
36	M	32	+	Secondary syphilis, serological treatment failure	1:128	1:0	30	3.3	*nd*	31
37	M	50	–	Syphilis infection	1:64	1:4	*nd*	*nd*	*nd*	91
38	M	65	–	Syphilis infection	1:512	1:4	*nd*	*nd*	*nd*	*nd*
39	M	62	–	Syphilis infection	1:16	1:2	*nd*	*nd*	*nd*	*nd*
40	M	58	–	Syphilis infection	1:8	1:2	*nd*	*nd*	*nd*	*nd*
41	M	67	–	Tertiary syphilis, aortic aneurysm	1:4	1:8	5	4.9	nd	413
42	M	61	–	Tertiary syphilis, cardiovascular syphilis	1:128	1:16	105	22.2	14.5	939
43	F	54	–	Tertiary syphilis, cardiovascular syphilis	1:8	1:4	8	9.9	*nd*	*nd*

[1]All patients were TPHA (>1:180) and FTA-Abs positive (>1:80) in the peripheral blood.
[2]All but patient 34 were TPHA and FTA-Abs positive (>1:80) in the cerebrospinal fluid (CSF).
nd: not done; –: negative; +: positive.

Each of the 43 patients with neurosyphilis tested positive in the blood-VDRL and none of the patients with a negative blood-VDRL had evidence of neurosyphilis, an effect which was statistically significant ($p<0.001$, χ^2 test). Grouping the patients according to their HIV-status, this difference remained highly significant (HIV-negative: 36/157, $p<0.001$; HIV-positive 7/65, $p<0.002$, χ^2 test; Fig. 1). In our patients, a blood-

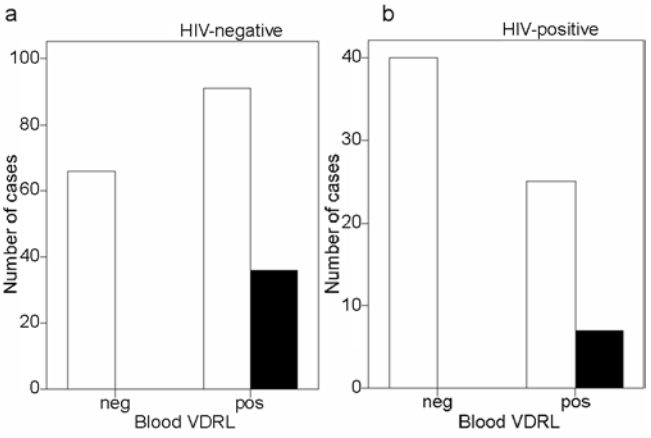

Fig. 1. None of the patients with neurosyphilis had a negative blood–VDRL test, either in (a) the HIV negative or (b) the HIV-positive patients. The diagnosis of neurosyphilis was according to current guidelines (for details refer to Material and Methods). □ neg. ■ pos.

VDRL ≥1:2 showed an extraordinary sensitivity for predicting neurosyphilis of 100% with a specificity of 62.6% (Table III). However, we did not find clear-cut blood-VDRL cut-off titres above which the likelihood for a positive CSF was high enough that they could be used as indicators for performing LP in insecure cases. In contrast, the derived negative likelihood-ratio of a negative blood-VDRL was impressively low at 0.024 (95% confidence interval (CI) 0.002–0.376). This means that, according to our calculations, less than 3 out of 100 patients with late latent syphilis infection and negative blood-VDRL tests would suffer from neurosyphilis defined by laboratory criteria.

In patients with neurosyphilis, the median blood-VDRL titre was ≥1:32, significantly higher than 1:0 in those without neurosyphilis (Fig. 2), $p<0.001$, *t*-test of means, 2-sided). In none of the 43 patients with neurosyphilis was a correlation found between blood- and CSF-VDRL-titres.

Table III. *Sensitivity and specificity of blood–VDRL test for predicting cerebrospinal fluid-defined neurosyphilis in patients with a positive T. pallidum haemagglutination assay blood test (see Table II for details)*

	Blood-VDRL	
Cut off titre	Sensitivity	Specificity
1:0	1.00	0.48
1:2	1.00	0.63
1:4	0.95	0.73
1:8	0.88	0.80
1:16	0.70	0.87
1:32	0.53	0.91
1:64	0.44	0.94
1:128	0.35	0.95
1:256	0.16	0.98
1:512	0.12	0.99
1:1024	0.00	1.00

DISCUSSION

In our series, all patients with neurosyphilis exhibited a positive VDRL in peripheral blood and a blood VDRL titre of <1:2 was 100% sensitive and 62.6% specific in excluding CSF-findings compatible with the diagnosis of neurosyphilis.

We identified astounding 15 clinically asymptomatic patients with CSF-findings compatible with neurosyphilis that would have been missed by applying the standard indications for LP in patients with late latent syphilis or syphilis of unknown duration indicated by a positive TPHA. Perhaps all of these patients should be submitted to LP for CSF analysis, as was already recommended before (14, 15). However, this broad approach had been abandoned from the CDC guidelines in 1998 (16).

We looked for screening parameters in the peripheral blood that could be used as indicators for performing LP in patients with late latent syphilis or syphilis of unknown duration. A recent study by Marra et al. indicated that higher titres of the non-treponemal specific Rapid plasma Reaginin (RPR) could increase the likelihood for a positive CSF-VDRL (17). In our patients, a negative blood-VDRL was 100% sensitive for excluding neurosyphilis in our patients (Table III). Increasing the cut-off to 1:2 increased the specificity while still remaining at 100% sensitivity. Higher titres decreased the sensitivity. Due to the limited sample size, however, our study might be under-powered to find patients with a positive blood-TPHA, a negative blood-VDRL while still suffering from asymptomatic neurosyphilis. Therefore, we suggest to rely on a completely negative blood-VDRL as criterion for not performing LP in insecure cases and not on a titre <1:4 as suggested by our data.

According to the CDC guidelines, in patients with late latent syphilis of unknown duration, one of the indications for LP is a serum anti-treponemal antibody titre ≥1:32 (9). Marra et al. (17) found an RPR titre of ≥1:32 to increase the probability for neurosyphilis 5-fold. We observed 3 patients without clinical symptoms but CSF-findings compatible with asymptomatic neurosyphilis with lower serum VDRL titres (Table II #7, #13, #15).

Our findings were valid for both HIV-positive and HIV-negative patients, although significances were lower in the HIV-positive cohort due to the smaller number of patients. There were relatively more HIV-positive patients who had undergone LP and did not meet the serological criteria of neurosyphilis compared to the HIV-negative cohort (29.3% vs. 16.3%, Table I). The reason is that LP is frequently performed in HIV-positive patients because of neurological complications related to various infections (e.g. cerebral toxoplasmosis) and STD-treatment guidelines requires LP regardless of the syphilis stage and activity (5, 6).

In summary, we suggest that in patients with a reactive TPHA but a negative VDRL from the peripheral blood,

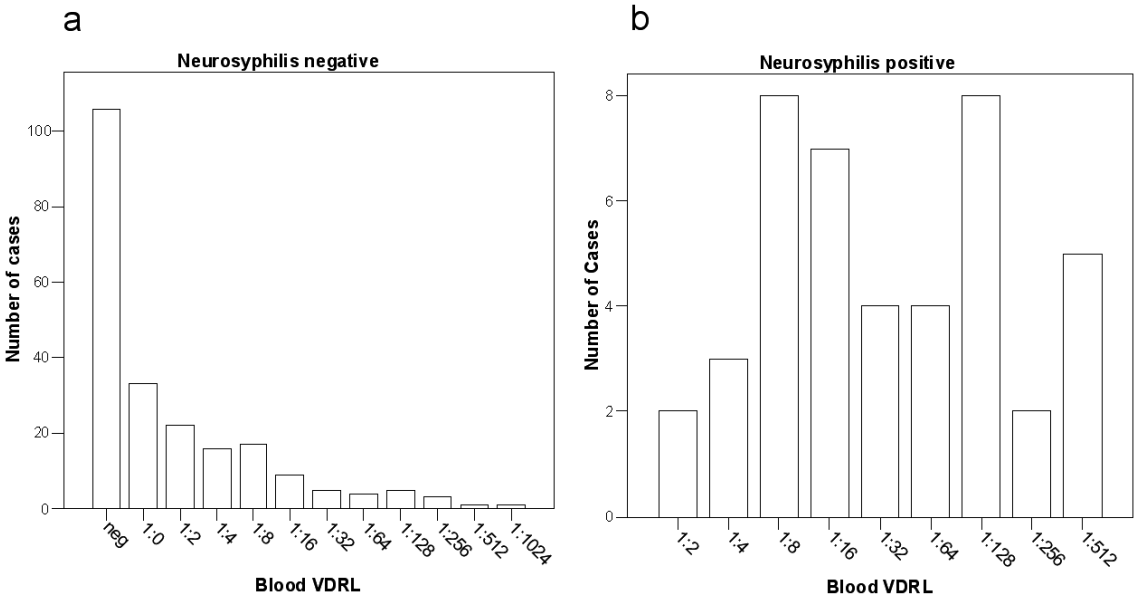

Fig. 2. Distribution of VDRL titres in neurosyphilis negative (a) and positive (b) patients. The median VDRL test titre in (a) was 1:0 (= undiluted) and in (b) the 1:32. The difference was highly significant ($p<0.001$, *t*-test of means, two-sided).

LP for the exclusion of neurosyphilis in late latent syphilis is not recommended. This is true for HIV-negative as well as HIV-positive patients.

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