

Diagnosis of neurosyphilis by examination of the cerebrospinal fluid

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SUMMARY Thirty-six patients with reactive results in the cerebrospinal fluid to the *Treponema pallidum* haemagglutination assay (CSF-TPHA) were investigated by further serological tests for confirmation of active neurosyphilis. The results of the TPHA and fluorescent treponemal antibody tests were reactive in all CSF samples from patients with acute untreated neurosyphilis and from most patients with late latent syphilis but no signs of involvement of the central nervous system.

The demonstration of 19S-IgM antibodies against *Treponema pallidum* in the CSF was a better indication of activity of the disease than the Venereal Disease Research Laboratory test. Ten of 11 patients with untreated acute neurosyphilis had reactive results in the solid-phase haemadsorption test for CSF-IgM (CSF-IgM-SPHA test). The TPHA index, which relates the CSF-TPHA titre to the albumin quotient and thus excludes errors from disturbed function of the blood-brain barrier, was above 100 in all but one of the patients with acute neurosyphilis but below 100 after treatment. Patients with late latent syphilis and without CNS signs had TPHA indices below 5. Thus a non-reactive CSF-TPHA test result excludes neurosyphilis but reactive CSF-IgM-SPHA results and TPHA indices above 100 strongly indicate active disease.

Introduction

A precise diagnosis of neurosyphilis is usually difficult to establish but may be easier in patients with classical clinical symptoms as well as pathological findings in the cerebrospinal fluid (CSF). The presence of pleocytosis, raised protein concentrations (Dattner-Thomas formula),¹ and a reactive Venereal Disease Research Laboratory (VDRL) test result have for many years been taken as indications of active disease.^{2,3}

CSF reagin tests, like the VDRL, may give non-reactive results in up to 30% of patients with neurosyphilis.⁴ Other workers⁵ have found a reactive CSF-VDRL test result in only 56.7% of 176 patients with neurosyphilis. Therefore, the CSF-VDRL test is of very low diagnostic value.⁶⁻⁸

Of the assays using *Treponema pallidum* as antigen,⁹ the CSF fluorescent treponemal antibody-absorption (FTA-ABS) test seems to be a very

sensitive method. Non-reactivity in this test apparently excludes neurosyphilis.¹⁰ A reactive FTA-ABS result, however, is not a reliable indicator of active disease since reactivity may be caused by transudation of immunoglobulins from the serum into the CSF.¹⁰ Immunoglobulins of the IgG class directed against *T pallidum* can often be found in the serum as well as in the CSF many years after adequate treatment.¹²

The *T pallidum* haemagglutination assay (TPHA) and its microversion, the automated microhaemagglutination assay using *T pallidum* antigen (AMHA-TP) or the manually performed MHA-TP,¹³ give even more sensitive results in the CSF than the FTA-ABS test¹⁴ and so may not indicate whether or not the disease is active or the CNS affected.

Recent investigations have shown that *T pallidum* can survive in the CSF after treatment with three doses of benzathine penicillin of 1 200 000 IU each at weekly intervals.¹⁵ Injections of 600 000 IU of procaine penicillin daily⁶ do not provide the treponemocidal CSF concentration of 0.03 IU/ml,¹⁶⁻¹⁹ which is recommended by the World Health Organisation. This has led to doubts about the efficacy of the current schedules^{20,21} and to a search for a "better therapy."²² High doses of water-soluble

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benzyl penicillin G,²³ such as 2-4 megaunits intravenously at four-hourly intervals for 10 days,^{24 25} have been suggested; three injections of 2 400 000 IU of benzathine penicillin at seven-day intervals are also effective for treating active neurosyphilis.^{22 24-26}

Ineffective treatment during the early stages of syphilis increases the possibility of late neurosyphilis.²⁷⁻²⁹ Furthermore, the widespread use of antibiotics for treating unrelated conditions may have led to some patients with unsuspected syphilis receiving suboptimal doses. Many cases were detected accidentally during routine serological tests.³¹⁻³⁵

Material and methods

Thirty-six samples of CSF from patients with suspected or clinically diagnosed neurosyphilis, which gave reactive results in the TPHA test, were submitted for serological examination. A serum specimen was taken from each patient on the day of lumbar or cisternal puncture and the paired samples were, if possible, examined shortly after arrival in the laboratory or stored at -70°C . CSF specimens contaminated with blood were excluded.

CLINICAL DIAGNOSIS

The clinical diagnosis was established by the neurologists; the criteria generally agreed with the classification of Hooshmand *et al.*³⁶ The final diagnosis was based on the predominant signs and, for this evaluation, was classified simply into asymptomatic and meningovascular forms, tabes, general paresis, and taboparesis.

LABORATORY TESTS

The cell count and VDRL and FTA-ABS (serum and CSF) tests were performed as previously described¹⁴; reagents used for the AMHA-TP test were obtained from Fujizoki Pharmaceutical Co Ltd, Tokyo, Japan. The CSF-TPHA results were considered to be reactive at a dilution of $\geq 1/10$; a series of fourfold dilutions were used starting at a dilution of 1/10. The solid phase haemadsorption assay (SPHA-IgM) technique was performed as described.³⁷

$$\text{The TPHA index} = \frac{\text{CSF-TPHA titre}}{\text{albumin quotient}} \quad \text{and}$$

$$\text{the IgG index} = \frac{\text{IgG quotient}}{\text{albumin quotient}}$$

$$\left(\text{IgG quotient} = \frac{\text{CSF IgG (mg/dl)} \times 10^3}{\text{serum IgG (mg/dl)}} \right) \text{ were}$$

calculated by the above formulas. The albumin quotient indicates the function of the blood-brain barrier and is calculated by the formula:

$$\frac{\text{CSF albumin (mg/dl)} \times 10^3}{\text{serum albumin (mg/dl)}}$$

The Bio-Rad (California) kit was used for the determination of total CSF protein.

Results

Fourteen of the 36 samples giving reactive CSF-TPHA test results had insufficient clinical or serological evidence or both to support the diagnosis of neurosyphilis and were therefore excluded from the analysis. Data on the samples from the remaining 22 patients are given in table I. The mean age was 61.4 years; four patients were under 50 years and had asymptomatic meningovascular disease, taboparesis, and asymptomatic neurosyphilis (two cases) (table I).

HISTORY OF SYPHILIS

Four of the 22 patients had been diagnosed and treated 38, 24, 45, and 34 years previously in the early stage of the disease (table I). Seventeen patients (Nos 6-22) did not know when they had been infected. In at least seven patients (Nos 5, 6, and 18-22) syphilis was detected by routine serological tests during the investigation of diseases other than syphilis.

TREATMENT

Eleven patients were examined before effective therapy (table I). Of these, two (Nos 1 and 4) had been treated in the pre-antibiotic era and probably received arsenobenzol and bismuth. Two patients (Nos 10 and 18) did not have serological evidence of active disease and had not received antisyphilitic treatment. They were classified as having "burnt out" neurosyphilis.

Three patients (Nos 2, 15, and 18) had been treated with antibiotics for diseases other than syphilis with regimens which were inadequate for the treatment of syphilis. The other 19 patients denied ever having received antibiotics before their present disease had been diagnosed. Eleven patients were examined after the beginning or completion of antisyphilitic therapy (table I).

Treatment failure occurred in two patients (Nos 2 and 5); both had received inadequate amounts of penicillin.

DIAGNOSIS

Meningovascular syphilis was diagnosed in six patients, general paresis in three, tabes in five, taboparesis in three, and asymptomatic neurosyphilis in

TABLE 1 Serological results in serum and CSF of 22 patients with neurosyphilis

Patient No	Age	Sex	Antisiphilic treatment (year)	Interval between treatment and examination	Present diagnosis	Serological results										Patient No					
						Serum					Cerebrospinal fluid										
						Year*	VDRL titre	FTA-ABS	AMHA-TP titre	SPHA-IgM titre	Year*	VDRL titre	FTA	TPHA titre	SPHA-IgM titre	Cell count ($\times 10^6/l$)	Total protein (g/l)	Albumin quotient	IgG index	TPHA index	
1	75	F	1942	†	Taboparesis (active)	1980	8	++++	10 240	64	1980	4	++++	10 240	4	42	1.35	11.3	3.5	906	1
2	63	M	1939 1948 1978	10 y	Tabes (active)	1978	2	++++	20 480	16	1979	2	++	10 240	ND	2	ND	6	1.7	1700	2
3	76	M	1935	3 d	Tabes (treated)	1980	NR	+	5120	NR	1980	NR	++	10 240	NR	1	0.72	11.7	1.94	875	3
4	65	M	1946	†	Taboparesis (active)	1979	1	+	5120	NR	1979	NR	+++	2560	4	3	1.23	18	1.7	144	4
5	47	M	1978	8 m	Asymptomatic (active)	1979	8	++	40 960	NR	1979	NR	+	40 960	NR	4	0.54	3	2.3	12 375	5
6	52	M	1976 1978	3 y	Meningovascular (treated)	1979	1	+	1280	ND	1979	NR	+	160	NR	2	ND	6	1.7	27	6
7	70	M	1978 1979	9 m	Meningovascular (treated)	1979	NR	+	2560	NR	1979	NR	NR	40	NR	2	0.75	5	1.3	8	7
8	71	M	1975	3 y	Meningovascular (treated)	1978	2	++	10 240	NR	1979	2	++	10 240	NR	2	0.64	7	2.4	1530	8
9	71	M	1978	1 y	Meningovascular (treated)	1979	NR	++	5120	NR	1979	NR	NR	10	NR	5	0.47	4.5	0.8	2	9
10	66	F	1978	†	Meningovascular ("burnt out")	1978	1	+	10 240	NR	1978	NR	NR	10	NR	2	0.53	7.0	0.7	1	10
11	78	F	1967 1973 1976	11	General paresis (treated)	1978	16	++	20 480	16	1978	2	+	10 240	4	3	2.12	24	4.8	435	11
12	59	F	1957-72	7 y	General paresis (treated)	1979	NR	+	1280	NR	1979	NR	+	640	NR	2	0.56	7	1.0	90	12
13	55	M	1978	†	General paresis (active)	1978	4	++	20 480	16	1978	1	++	2560	4	52	1.16	16	3.7	160	13
14	53	F	1979	†	Tabes (active)	1979	4	++	20 480	8	1979	4	++	10 240	8	85	2.11	380	0.3	27	14
15	59	M	1977	2 y	Tabes (treated)	1979	NR	+	2560	NR	1979	NR	±	640	NR	3	0.41	7	0.8	87	15
16	77	F	1979	†	Tabes (active)	1979	16	++	81 920	32	1979	NR	+++	40 960	8	2	ND	5	3.1	8200	16
17	38	M	1980	2 w	Taboparesis (treated)	1980	32	++	20 480	64	1980	8	++	10 240	16	37	1.10	9	3.7	1130	17
18	74	F	None	†	Asymptomatic ("burnt out")	1978	1	+	20 480	8	1978	NR	NR	160	NR	2	0.40	3.3	1.0	50	18
19	67	F	1980	†	Asymptomatic (active)	1980	128	++++	40 960	32	1980	4	+	163 840	32	102	ND	27	2.3	6000	19
20	58	F	1980	†	Asymptomatic (active)	1980	16	+	10 240	4	1980	4	+	2560	2	3	0.69	5	1.4	502	20
21	49	M	1980	†	Meningovascular (active)	1980	128	++++	20 480	64	1980	8	+++	10 240	64	24	1.20	11.5	2.2	879	21
22	28	F	1980	†	Asymptomatic (active)	1980	8	+++	81 920	32	1980	NR	++	40 980	2	79	0.87	9.3	1.2	4530	22

* Of examination

† If patients examined before effective treatment

NR = non-reactive; ND = not done

five (table I). One patient (No 3) had finished treatment three days before examination and another (No 17) was still being treated with penicillin at the time of lumbar puncture. The findings of both patients therefore indicate almost unchanged signs of active neurosyphilis.

All patients with active neurosyphilis (including two who had started treatment within four weeks of examination, Nos 3 and 17) had reactive TPHA and FTA-ABS test results in the CSF, whereas the VDRL test gave a reactive result in eight (61.5%) of 13, and a cell count above $5 \times 10^6/l$ ($5/mm^3$) was found in only six (46%) of 13. Increased cell counts were also found in the CSF of four patients with no further serological signs of neurosyphilis. Raised total protein concentrations occurred in a similar number.

ANTITREPONEMAL ANTIBODIES

T pallidum-specific 19S-IgM antibodies were detected by the 19S-IgM-SPHA and the 19S-IgM-FTA assay. The SPHA technique is obviously more sensitive than the fluorescence method (table II). Reactivity to IgM in the CSF apparently occurs predominantly in patients with a breakdown in function of the blood-brain barrier as indicated by the albumin quotient.

The TPHA index relates the TPHA titre to the albumin quotient and thereby attempts to exclude errors from disturbed function of the blood-brain barrier. TPHA indices of patients with active neurosyphilis were above 500 in 10 of 13 cases, while those of patients who had been effectively treated two years before examination were all below 100 (except for patients 8 and 11) (figure).

Results of tests for *T pallidum*-specific IgA antibodies are described elsewhere.³⁸

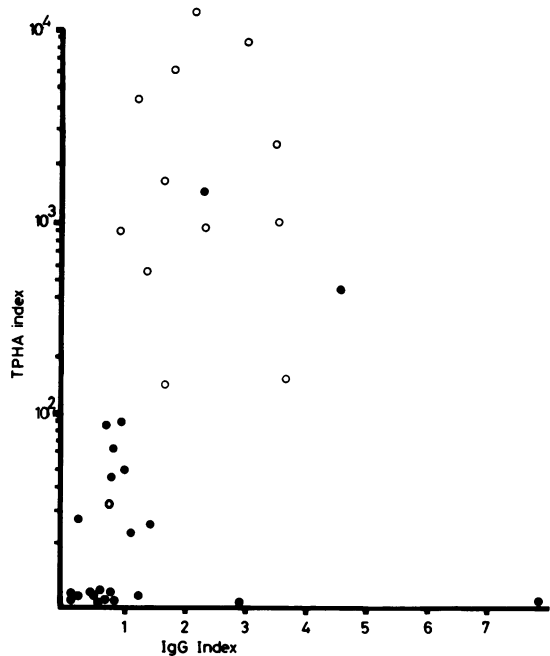


FIGURE TPHA and IgG indices of 13 patients with active neurosyphilis (○) and of 23 patients effectively treated two years before examination (●).

Discussion

The diagnosis of neurosyphilis may be suspected but cannot be based on clinical symptoms alone; this, as well as the occurrence of atypical oligosymptomatic forms, often presents the physician with the dilemma

TABLE II Results of SPHA-IgM in cerebrospinal fluid and serum of patients with active neurosyphilis compared with those of the FTA-IgM test and albumin quotient

Patients	Cerebrospinal fluid		Albumin quotient	Serum
	SPHA-IgM titre	FTA-IgM titre		SPHA-IgM titre
Untreated active neurosyphilis				
No 1	4	-	11	64
No 2	ND	ND	6	16
No 4	4	-	18	ND
No 5*	-	-	3	4
No 13	4	++	16	16
No 14	8	+	380	8
No 16	8	ND	5	32
No 19	32	+	27	32
No 20	2	-	5	4
No 21	64	-	11	64
No 22	2	-	13	64
Treated active neurosyphilis†				
No 3	-	-	12	-
No 17	16	+	9	64

* Patient inadequately treated six months previously ND = not done
 † Treated within four weeks before examination

of deciding whether or not treatment is necessary. Laboratory findings are not always helpful because the commonly used tests for the detection of syphilis have a wide margin of error. Criteria, such as raised CSF cell counts and increased total protein, may give evidence of an inflammatory process in the CNS but these examinations are not specific for neurosyphilis. In addition, normal CSF counts and total protein values do not exclude absolutely involvement of the CNS.

The present study indicated that only six (46%) of 13 patients with active neurosyphilis had $>10 \times 10^6$ cells/l ($10/\text{mm}^3$). On the other hand, five (21.7%) of 23 patients with latent syphilis who had no CNS signs or had been adequately treated for neurosyphilis more than two years previously and had reactive results in the CSF-TPHA test had $>10 \times 10^6$ cells/l ($10/\text{mm}^3$) and eight (34.8%) of 23 had total protein concentrations above 0.5 g/l (50 mg/100 ml).

The CSF-VDRL test was non-reactive in five (38.5%) of 13 patients with active neurosyphilis and these results are in agreement with the findings of other workers.^{3 4 11} The CSF-FTA and CSF-TPHA test results were both reactive in all patients with active neurosyphilis. Thus a non-reactive CSF-TPHA or CSF-FTA test result or both apparently excludes active neurosyphilis.

The detection of 19S-IgM antibodies specific for *T pallidum* in the serum depends on the presence of antigen and consequently indicates the need for treatment.³⁸⁻⁴³ All patients with untreated active neurosyphilis showed specific 19S-IgM antibodies in the serum and in the CSF by the SPHA technique, except for patient 5 who, surprisingly, had a non-reactive result to this assay in both the serum and the CSF. This patient had been inadequately treated with 800 000 IU clemizol penicillin (which is equivalent to approximately 600 000 IU of procaine penicillin) twice daily for seven days eight months before examination. This seems to suggest that even sub-curative doses of penicillin may abolish reactivity in the CSF-19S-IgM-SPHA test. 19S-IgM antibodies could be detected by the fluorescent technique in only three of 11 patients with untreated neurosyphilis (table II); (two with active disease were not tested). All but one of the patients with a reactive 19S-IgM-SPHA test had disturbed function of the blood-brain barrier as indicated by the albumin quotient. One patient (No 3) had finished treatment three days before examination (group B, table II) and already showed a non-reactive CSF-19S-IgM-SPHA test result. Such a result could be expected, since 19S-IgM antibodies not only have a short half-life of five days but are also the first immunoglobulins to disappear after adequate treatment.⁴⁴⁻⁴⁷

One patient (No 11) gave a reactive result in the

19S-IgM-SPHA test in the serum (titre 1/16) and in the CSF (titre 1/4). This patient died from a stroke. Necropsy showed severe intracerebral and extracerebral arteriosclerotic changes but no signs of active neurosyphilis. The disturbed function of the blood-brain barrier was apparently a sequel of arteriosclerosis, but the presence of 19S-IgM antibodies as well as the markedly increased IgG index cannot be explained.

Pathological IgG indices were found in 12 of 13 patients with active neurosyphilis. This indicates that the IgG antibody concentration in the CSF was greater than could be accounted for by mere transudation from the serum to the CSF. A raised IgG index, however, is no more than a sign of a specific perivascular inflammation in the close vicinity of the CSF and does not necessarily indicate neurosyphilis.

CSF-TPHA titres seem to be of minor diagnostic value unless these titres are related to the function of the blood-brain barrier. This function is an essential factor which has to be assessed at each CSF protein determination. The TPHA test detects only a small portion of the total protein—that is, the immunoglobulins specifically directed against *T pallidum*. A commonly used indicator of the function of the blood-brain barrier is the albumin quotient; normal values of this range between 3 and 8 depending on the age of the patient.⁴⁸

The TPHA index relates the function of the blood-brain barrier to *T pallidum*-specific antibodies.¹⁰ The individual TPHA indices of the patients in the present study are shown in the figure. All samples, except one, from patients with active neurosyphilis had TPHA indices above 100. The indices of the patients who had been adequately treated more than two years before examination were below 100 (except in the case of patients 8 and 11). Both had been treated three years before examination, one (No 8) with 1.2 million units procaine penicillin for 10 days which may have been inadequate; the other (No 11) received three courses of penicillin for 14, 20, and 23 days, which should provide serum concentrations of 0.03 IU. Serologically patient 11 would be classified as having active neurosyphilis; however, neurohistopathological examination at necropsy did not show any evidence of CNS involvement; she was, therefore, classified as having had treated neurosyphilis.

Ineffective treatment apparently does not decrease the TPHA index (patients 2 and 5). All patients with late latent syphilis but no symptoms affecting the CNS had TPHA indices of <5 .

The TPHA and IgG indices found on examination of the CSF in 36 patients in the present study showed that 14 (Nos 22-36) had no signs of neurosyphilis; the weak CSF-TPHA results could be explained by

transudation of specific antibodies from the blood. All the CSF samples had non-reactive results in the IgM-SPHA and had TPHA indices below 5.

The TPHA index, as well as the sensitive tests for demonstrating *T pallidum*-specific IgM antibodies in the CSF, may help to determine whether or not neurosyphilis is active and whether treatment should be given.

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