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Neurosyphilis

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SUMMARY In patients with abnormal neuropsychiatric symptoms and a reactive fluorescent treponemal antibody absorption (FTA-ABS) test in the cerebrospinal fluid (CSF) or serum, a normal CSF cell count and total protein concentration does not exclude late syphilis involving the central nervous system. In these patients, the presence of plasma cells in the CSF cytogram, increased concentration of CSF immunoglobulin G (IgG), immunoelectrophoretic abnormalities in the precipitates of the IgG and of the Fab fragments of IgG in the CSF immunoelectropherogram, and an increased serum level of immunoglobulin M (IgM) suggest an active, potentially treatable neurosyphilis.

Introduction

During the last two decades the textbook description of neurosyphilis and the laboratory findings in late syphilis involving the central nervous system (CNS) have been modified, probably by the widespread use of antibiotics and corticosteroids for treating unrelated diseases. The atypical presentation of neurosyphilis often leaves the clinician with the question to treat or not to treat a patient with clinical symptoms compatible with late syphilitic CNS involvement.

In patients with abnormal or absent reflexes, alterations in pupils, sensory abnormalities, involvement of cranial nerves, personality changes or mental disturbances, cerebrovascular accidents, symptoms to the spinal cord, seizures or altered states of consciousness and with clinical signs compatible with chronic meningitis, neurosyphilis represents one of the differential diagnostic possibilities (Wetherhill *et al.*, 1965; Hooshmand *et al.*, 1972; Ghosh and Holt, 1975). An increasing proportion of cases with vascular manifestations of neurosyphilis has been reported (Kochetkov, 1974; Matiar-Vahar and Müller, 1974).

Non-treponemal or lipoidal serological investigation is rarely omitted during the investigation of neurological disorders (Tomecki and Plaut, 1976). On the other hand, in the absence of a clinical history of neurosyphilis, treponemal serological tests are seldom requested when the non-treponemal tests are found to be non-reactive. In the late stages of syphilis, non-treponemal serological tests have been reported to have negative results in as many as 39% of patients (Harner *et al.*, 1968).

The fluorescent treponemal antibody absorption (FTA-ABS) test is more often reactive in cases of late syphilis than non-treponemal tests (Mahony *et al.*, 1972); however, it may be negative in patients with neurosyphilis (Matiar-Vahar and Müller, 1974). There are authors who do not recommend the FTA-ABS test to be done on the cerebrospinal fluid (CSF) (Jaffe, 1975), advocating instead the non-treponemal quantitative Venereal Disease Research Laboratory (VDRL) test. In about 3% of cases of neurosyphilis, non-treponemal tests were reported to be reactive in CSF and simultaneously negative in serum (Dewhurst, 1969).

Treponema pallidum has been demonstrated in CSF by means of dark ground microscopy (Smith and Israel, 1967) and isolated from CSF specimens with normal cell counts and total protein concentration (Tramont, 1976). Over 30% of patients with neurosyphilis have been found to have fewer than 5 cells/mm^3 of CSF and/or CSF total protein concentration below 0·6 g/l (Dewhurst, 1969). Normal CSF cell counts or total protein concentration (Dattner *et al.*, 1951) are therefore unreliable indicators of neurosyphilitic inactivity.

Patients with untreated syphilis have an increased concentration in one or more serum immunoglobulins (Norredam and Clausen, 1963); an

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increased serum IgM level in cases of neurosyphilis was considered to be a sign of activity of the disease. IgM detected in the CSF of patients with untreated neurosyphilis could not be measured several months after a course of treatment. Return to normal of the elevated CSF, IgG, and IgA takes a longer period of time (Oxelius *et al.*, 1969).

The FTA-ABS antibodies are represented by IgG and IgM (Musher and Schell, 1975). Correlation between the results of the CSF FTA-ABS test and the CSF IgG level has been reported (Heitmann, 1972). As well as increased CSF IgG levels in cases of general paresis, higher CSF concentration of albumin was noticed, suggesting changes in the blood-CSF barrier (Schmidt *et al.*, 1971). In the CSF immunoelectropherograms of patients with syphilis studied by Norredam and Clausen (1963) the presence of proteins of larger molecular weight than 200 000 and anodal elongation in the IgG precipitate were observed.

In the attempt to obtain laboratory data to help in the diagnosis of active, potentially treatable neurosyphilis, CSF cytomorphology, and CSF, and serum protein electrophoresis and immunoelectrophoresis were examined in 11 consecutive patients with progressive CNS symptoms and positive non-treponemal and/or treponemal results to serological tests.

Materials and methods

All patients in our series were admitted to the Indiana University Medical Center Hospitals between 1969 and 1976. There were six men and five women.

The age range of the men was 26 to 57 years (average 46) and the age range in women was 34 to 86 years (average 52). All the patients were admitted because of progressive CNS symptoms. The most frequent abnormal neurological symptoms were alterations in reflexes and muscle weakness secondary to an upper motor neurone involvement in six, sensory disturbances in five, decline in intellectual functions or personality changes in three, and pupillary changes in three patients. Seven of the 11 patients had a history of venereal disease. Only two patients (cases 3 and 9) had another concurrent disease.

The CSF cytomorphology, protein electrophoresis and immunoelectrophoresis, and the serum protein

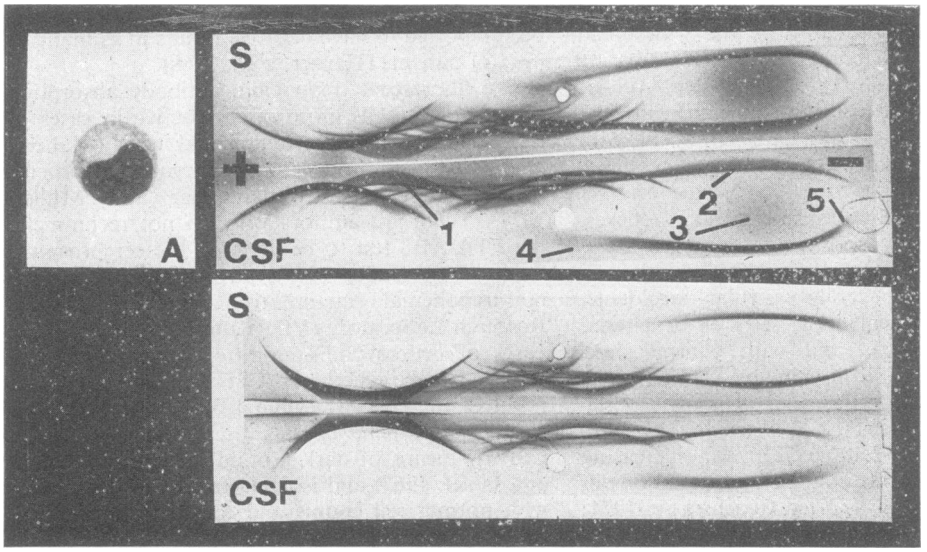

Figure *A—Plasma cell in CSF cytogram serum (S) and CSF immunoelectropherograms: Upper immunoelectropherograms* (46-*year-old woman with neurosyphilis; CSF total proteins*—0·45 *g/l). In the middle groove, rabbit antiserum to human serum and in the marginal grooves rabbit antiserum to Fab fragments of IgG were used. Increased density in the alpha-1 glycoprotein precipitate* (1), *cathodal and anodal elongation and 'shadow' formation in the IgG precipitation arc* (2), *increased concentration of glycoproteins with electrophoretic mobility of gammaglobulins* (3), *anodal elongation and split in the precipitate of Fab fragments of IgG* (4), *and cathodal elongation of the precipitation arc of Fab fragments of IgG* (5) *in the CSF immunoelectropherograms are demonstrated. For comparison, lower immunoelectropherograms* (39-*year-old woman with trigeminal neuropathy; CSF total proteins* 0·72 *g/l) with no abnormalities.*

Table 1 *Cerebrospinal fluid findings in* 11 *patients with neurosyphilis*

Case	*Age (years)*	*Sex*	*Last treatment*	*CSF and serum data obtained*	*Cell count*	*Cytomorphology*	*Total proteins (g/l)*	*Electrophoretic increase in gammaglobulins*	*Immunoelectrophoretic abnormalities*		*IgG concentration (g/l)*	*Serological tests*	
									Fab fragments of IgG	*IgG*		*VDRL*	*FTA*
1	46	F	1968	1969	0	Plasma cells	0·45	+	+	+		1:16	
2a	53	M	——	1972	0	Normal	0·29	+		+	0·096	+	
b			1972	1972	0	Normal	0·33	+	+	+	0·116	+	
3a	26	M	——	1976	1744	Plasma cells	3·06	+;AGPG	+	+	0·2>	1:32	+
b			1976	1976	40							1:16	
c			1976	1976									
d			1976	1976	8	Normal	0·59	+	+	+	0·2>	1:8	
4	40	M	1952	1975	0	Normal	0·27	+	+	+	0·068	NR	+
5a	54	M	——	1976	430	Plasma cells	1·5	+;AGPG	+	+	0·2>	1:128	+
b			1976	1976		Plasma cells	0·67	+;AGPG	+	+	0·196		
6	34	F	1966	1976	0	Normal	0·47			+	0·093	NR	
7	56	F	1961	1976	6	Normal	0·67			+	0·138	NR	+
8a	46	M	1953	1976	1	Normal	0·94	+;AGPG	+	+	0·128	NR	+
b			1976	1976	3	Normal	0·61	+;AGPG		+	0·058		+
c			1976	1976	1	Normal	0·59				0·03		
9a	86	F	——	1976	35		0·75					1:32	+
b			——	1976	7		0·61					1:32	+
			1976	1976	0	Normal	0·75	+;AGPG	+	+	0·2>	1:32	+
10	42	F	——	1976	7	Normal	0·39	+	+	+	0·08	NR	+
11	57	M	1955	1976	0	Normal	0·75	+;AGPG	+	+	0·142	NR	+

Cell count/mm³
AGPG—abnormal glycoproteins with electrophoretic mobility of gammaglobulins
NR—non-reactive

electrophoresis and immunoelectrophoresis were examined by means of the previously published techniques (Kolar *et al.*, 1970).

The serum and CSF protein electrophoresis and immunoelectrophoresis were performed simultaneously. Rabbit antisera to human serum and to Fab fragments of IgG (Behring Diagnostics, Sommerville, NJ) were applied in the immunoelectrophoretic studies. CSF IgG concentration was examined using the electroimmunodiffusion technique (Merrill *et al.*, 1967). Serum IgG, IgM, and IgA concentrations were determined by means of the radial immunodiffusion technique (Mancini *et al.*, 1965).

Results and comments

In our series, the CSF cell count was normal in six patients (Table 1). The CSF cytograms revealed plasma cells (Figure (*A*)) in three cases including one patient with a normal CSF cell count. The CSF total protein concentration was normal (0·45 g/l and lower) in four of the patients examined. In nine cases, the CSF gammaglobulins were increased (over 16% of CSF total proteins) including four patients with normal CSF total protein concentration. One to four bands in the CSF gammaglobulin field of the CSF electropherograms were noticed in six of the patients, including one with a normal CSF concentration of gammaglobulins. Increased density in the CSF alpha-$_1$ glycoprotein precipitate (Figure) was seen in seven patients. Cathodal and anodal elongation and increased density in the CSF IgG precipitate and/or in the CSF precipitation arc of the Fab fragments of IgG were found in all patients examined. Increased concentration of CSF glycoproteins with electrophoretic mobility of gammaglobulins was established in five patients. Immunoelectrophoretic abnormalities in the precipitates of the CSF, IgG, and Fab fragments of IgG correlated with an increased CSF IgG concentration (over 12% of the CSF total protein level). Higher CSF IgG levels were found in all patients examined including three cases with normal CSF total proteins.

The spinal fluid VDRL test was performed in all 11 patients. The results were reactive in five and non-reactive in six. In all six patients on whom the VDRL test was non-reactive, the CSF IgG concentration was increased, thus demonstrating no correlation between the results of the VDRL test and the CSF IgG concentration.

Spinal fluid FTA-ABS test was performed in eight of the 11 patients and was reactive in all eight including five cases with non-reactive CSF VDRL test. In all patients with positive CSF FTA-ABS test, increased CSF IgG concentration was established.

Two of the three patients in our series (Cases 3, 5, 9) with the most recent onset of neurological symptoms, demonstrated the highest concentration in CSF total proteins and in the CSF IgG. In both cases, plasma cells were present in the CSF cytograms.

There was no correlation between the time elapsed from the last treatment and the CSF IgG levels.

The serum IgM concentration (Table 2) was found to be raised in eight of the 11 patients examined. There was no correlation between elevation of the serum IgM concentration and duration of the neurological symptoms. The serum was re-examined after treatment in four patients. In three of them the IgM concentration was found to be lower than the pretreatment levels and in two of the four cases the IgM concentration returned to normal. The CSF immunoelectropherograms in our patients did not reveal IgM precipitates. In untreated neurosyphilis, Oxelius *et al.* (1969) reported elevated CSF IgM levels which fell rapidly after treatment with penicillin. Absence of IgM precipitates in the CSF immunoelectropherograms of our patients would suggest that we were dealing with partially treated neurosyphilis.

In 10 of the 11 cases, the results of both the serum VDRL and the FTA-ABS tests were reactive. In one case, the serum VDRL and also the FTA-ABS tests were negative; however, the CSF FTA-ABS test was positive. In our patients, there was no correlation between the serum VDRL titre and the serum IgM concentration.

Current methods of diagnosing and treating neurosyphilis require thorough re-evaluation. On examining indications for treatment in cases of potentially active neurosyphilis, determination of the CSF concentration of total proteins and of the CSF cell count is inadequate. Increased level of CSF gammaglobulins established by CSF protein electrophoresis in patients with possible neurosyphilis must not necessarily represent an indication for treatment. Examination of the CSF using cytological and immunochemical techniques and extensive serological screening is necessary to establish an active, treatable stage of neurosyphilis. The currently recommended treatment for neurosyphilis by the World Health Organisation appears to be inadequate (Mohr *et al.*, 1976; Tramont, 1976). After a course of treatment in patients with neurosyphilis, neurological CSF and serum examinations are necessary to establish the effectiveness of such treatment.

Table 2 *Serum findings in 11 patients with neurosyphilis*

Case	*Age (years)*	*Sex*	*Last treatment*	*CSF and serum data obtained*	*Serological tests*		*Total proteins (g/l)*	*Electrophoretic increase in gammaglobulins*	*Immunoglobulin concentration (g/l)*		
					VDRL	*FTA*			*IgG*	*IgM*	*IgA*
1	46	F	1968	1969	1:8	+	0·087		20·0		5·24
2a	53	M	——	1972	1:16	+	0·07		10·35	1·50	3·17
b			1972	1972	1:8		0·074		10·2	0·92	2·58
3a	26	M	——	1976	1:16	+	0·083		12·65	1·39	3·35
b			1976	1976	1:32	+					
c			1976	1976			0·087		14·5	1·04	3·65
d			1976	1976	1:8		0·076		9·0	1·35	3·10
4	40	M	1952	1975	1:8	+	0·083	AGPA	10·7	1·01	3·85
5a	54	M	——	1976	1:128	+	0·067	+;AGPG	18·0	5·8	6·40
b			1976	1976			0·083	+;AGPG	11·8	2·9	3·85
6	34	F	1966	1976	NR	+	0·083		5·1	1·98	2·14
7	56	F	1961	1976	1:2	+	0·07	+	11·4	1·61	4·80
8a	46	M	1953	1976	NR	NR	0·076	+;AGPG	13·05	1·47	3·50
b			1976	1976			0·078	+	8·6	0·96	4·43
c			1976	1976		+	0·077	AGPG	12·2	1·35	3·50
9a	86	F	——	1976	1:256	+					
b			——	1976							
c			1976	1976	1:128	+	0·068	+	18·9	2·12	2·85
10	42	F	——	1976	1:16	+	0·089		15·4	1·45	5·45
11	57	M	1955	1976	1:1	+	0·08	AGPG	15·0	0·55	2·40

NR—non-reactive
AGPG—abnormal glycoproteins with electrophoretic mobility of gammaglobulins
Normal values IgG 10·68±2·46 g/l (2 sigma)
IgM 0·90±0·38 g/l
IgA 2·92±1·63 g/l

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