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Central Nervous System Involvement in Early Syphilis

Part I. Intrathecal Immunoglobulin Production

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The immunological activity in the cerebrospinal fluid (CSF) was studied in 47 patients with early syphilis. The immunoglobulin production within the central nervous system (CNS) was estimated by analysing immunoglobulin G and albumin in CSF and serum and constructing an IgG index according to Tibbling et al. and calculating daily CNS IgG synthesis, according to Tourtellotte.

In 10 (21%) of the 47 patients, intrathecal immunoglobulin production was observed. The immunoglobulin production within the CNS was significantly correlated to the presence of syphilis antibodies and to pleocytosis. Eight of the patients demonstrated oligoclonal bands on electrophoresis. Total protein usually did not reveal an increased CNS immunoglobulin production but reflected a blood–brain barrier lesion. One year after penicillin treatment, 2 out of 9 patients still had slight intrathecal immunoglobulin production. *Key words: Early syphilis; Cerebrospinal fluid; Immunoglobulin G (IgG)-index; Central nervous system IgG synthesis; Albumin quotient.* (Received February 1, 1983.)

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The central nervous system (CNS) becomes involved early in syphilitic infection. Before the antibiotic era, clinical experience indicated that some patients with early asymptomatic CNS involvement subsequently develop neurosyphilis (11). Since the introduction of penicillin, however, neurosyphilis has become a rare disease. The widespread present-day use of antibiotics may lead to administration of suboptimal penicillin doses in patients with undiagnosed syphilis. Actually, some authors have reported an increased frequency of atypical cases of neurosyphilis (8, 10), while others find the same clinical pattern as in the pre-antibiotic era (24). The controversy is probably due to the use of different clinical and laboratory criteria for diagnosis.

There is currently a search for reliable indicators of active CNS involvement in syphilis. Two parameters suggested by the WHO (32) to be further studied in this context are the albumin quotient and the immunoglobulin G (IgG) index. The albumin quotient is the ratio between albumin in cerebrospinal fluid (CSF) and serum and reflects the function of the blood–brain barrier (28). An increment of immunoglobulin G in the CSF can be found secondary to an increase of this protein in serum, damage of the blood–brain barrier, or increased synthesis within the CNS. The IgG index (28) is a measure of the local immunoglobulin G production within the CNS. The daily intracerebral IgG synthesis can also be extrapolated from serum and CSF levels according to Tourtellotte (29).

The aim of this work was to evaluate the extent of CNS involvement in early syphilis and to correlate possible intrathecal immunoglobulin production to other signs of immunological activity in CSF before and after penicillin treatment.

PATIENTS

Forty-seven patients with early syphilis (44 men and 3 women, aged 19–69, mean 37 years) were included in the study. They were admitted to our Department of Dermatology between 1976 and 1982. Clinical and serolgical examination were performed and lumbar puncture was carried out in all cases before treatment. Routine neurological examination was normal in all patients.

Twenty-four of the 47 patients had a clinical picture and serology consistent with secondary syphilis and 23 cases were diagnosed as early latent syphilis viz. seropositive patients without clinical signs of syphilis and with a history and/or serological data indicating an infection of less than 2 years' duration. Seventeen patients had a history and serological data indicating a duration of infection of 6–24 months, while 6 patients had a more recent infection (<6 months).

Nine of 10 patients with increased intrathecal immunoglobulin production were monitored with repeated CSF analyses after treatment. The patients received our standard treatment for early syphilis, i.e. procaine penicillin 600000 IU daily by intramuscular injection for 17 days, except for 2 patients who were given benzyl penicillin 6 g (10 million IU) intravenously three times a day for 10 days. One patient had moved abroad and was not available for follow-up.

METHODS

CSF samples (15–20 ml) were obtained by lumbar puncture under standardized conditions. At the same time, blood was drawn.

Serological techniques

The Wasserman reaction (WR) and the Venereal Disease Research Laboratory (VDRL) test were used as screening tests for syphilils, and the fluorescent treponemal antibody absorption (FTA-ABS) test (2) and/or *Treponema pallidum* immobilization (TPI) test (21) for confirmation. Both serum and CSF were analysed with these tests. FTA-abs tests on CSF were not performed in 13 patients.

CSF-cell studies

Cells were routinely counted in a Fuchs-Rosenthal chamber. Samples with blood contamination were not included. Pleocytosis was defined as ≥ 5 mononuclear cells $\times 10^6$/l.

Cytological preparation was done in all patients except 10, with normal cell counts (0–2), by sedimentation in a suction chamber modified after Sayk (4). The specimens were stained with May–Grünwald–Giemsa solution.

CSF and serum protein determinations

The protein content in CSF was determined as described by Lowry et al. (15). Reference value: 200–500 mg/l for patients aged 15–45 years, 200–600 mg/l for those over 45 years.

Albumin and immunoglobulin G were assayed by immuno-electrodiffusion *ad modum* Laurell (12). Reference value for serum IgG: 7–14 g/l. Reference value for CSF IgG: 8–36 mg/l for patients aged 15–45 year, 10–42 mg/l for those over 45 years.

The albumin quotient (CSF albumin $\times 10^3$/serum albumin) was estimated as a measure of blood–brain barrier function. Reference value: <6.0 for patients aged 15–45 years, <7.0 for those over 45 years.

The IgG-index was calculated as:

$$\frac{\text{CSF IgG}}{\text{serum IgG}} \Big/ \frac{\text{CSF albumin}}{\text{serum albumin}}$$

according to Tibbling et al. (28).

IgG-index values above 0.7 have been considered pathological (14).

IgG synthesis within the CNS was calculated according to Tourtellotte (29), viz.

$$\left[\left(\mathrm{IgG_{CSF}} - \frac{\mathrm{IgG_s}}{369}\right) - \left(\mathrm{Alb_{CSF}} - \frac{\mathrm{Alb_s}}{230}\right)\left(\frac{\mathrm{IgG_s}}{\mathrm{Alb_s}}\right) 0.43\right] \times 5$$

CSF = cerebrospinal fluid; *s* = serum

The upper normal limit according to Tourtellotte is 3.3 mg/day.

Agar gel electrophoresis for study of the protein pattern was performed *ad modum* Wieme (33). In the results, 'immunopathic pattern' means oligoclonal bands not detectable in serum, and 'barrier lesion' means a plasma-like protein pattern.

The immunological assay of albumin and immunoglobulin G and the agar gel electrophoresis were performed on serum and CSF simultaneously within one week of collection of the sample. The samples were stored at 5°C until analysis.

Statistical analysis

Fisher's exact test (1) was used for analysing correlations between CSF tests. For significant correlation $p<0.05$.

RESULTS

Before treatment (Table I)

Fifteen (of 24) patients with secondary syphilis and 13 (of 23) patients with early latent syphilis showed pathological findings in at least one of the tests. Nineteen patients had normal findings.

Cell counts and cytology

Seventeen of the 47 patients had a pleocytosis. Nineteen patients, including all those with pleocytosis, had pathological cytology. The predominant finding was a lymphocytic reaction. Small lymphocytes, medium-sized and, occasionally, typical plasma cells were seen. In 6 patients, all with secondary syphilis, there was a pathological presence of neutrophilic granulocytes.

Protein determinations

Albumin quotient was increased in 8 of 24 patients with secondary syphilis and in 4 of 23 with early latent syphilis. All but one of 12 patients with a pathological albumin quotient had increased total protein values.

IgG values in CSF were increased in 31 of the 47 patients (range 37–130 mg/l). IgG in serum was increased in 29 of the 47 patients (range 16–29 g/l).

IgG index was pathologically increased (>0.7) in 8 patients, all with early latent syphilis of more than 6 months' duration. Full details of the CSF findings in these patients are presented in Table II.

IgG synthesis (>3.3 mg/day) in the CNS according to Tourtellotte was found in 10 patients, presented in Table II.

All patients with IgG index >0.7 had IgG synthesis >8.9 mg/day. Four of the patients had a pathologically increased total protein level, in 3 cases probably reflecting a blood–brain barrier lesion.

Table I. *Frequency of pathological CSF findings in 47 patients with early syphilis before treatment*

I = Immunopathic pattern; B = Barrier lesion pattern

Stage	No. of patients	Mononuclear cells	Total protein	Albumin quotient	IgG index	Electrophoresis		IgG synthesis	Pos. VDRL, WR, FTA-ABS and/or TPI
						I	B		
Secondary syphilis	24	10	10	8	0	1	7	2	5
Early latent syphilis	23	7	4	4	8	7	5	8	12
Total	47	17	14	12	8	8	12	10	17

Electrophoresis. Seventeen of the 47 patients showed a pathological electrophoresis pattern. Eight patients demonstrated an immunopathic pattern, with oligoclonal bands not detectable in serum, and 12 patients showed a barrier lesion pattern with increased plasma proteins. Three patients showed both an immunopathic and a barrier lesion pattern. There was a good correlation between an immunopathic pattern in electrophoresis and increased IgG index and IgG synthesis. As expected, a good correlation was also found between a barrier lesion pattern in electrophoresis and an increased albumin quotient.

Syphilis serology in CSF (Table III)

Seventeen of the patients had one or more positive serological tests in CSF. Sixteen patients were positive in TPI, 8 in WR, 5 in FTA-ABS and 2 in VDRL.

Correlation between CSF tests

Intrathecal IgG/cell number (Fig. 1): Nine of 10 patients with intrathecal IgG production had an increased cell count (significant correlation, $p<0.01$).

Intrathecal IgG/WR (Fig. 1): Eight of 10 patients with intrathecal IgG production had positive WR in CSF (significant correlation, $p<0.001$).

Table II. *CSF findings before and after treatment in 10 patients with early syphilis and intrathecal immunoglobulin production*

L = Early latent syphilis; S = secondary syphilis; I = immunopathic pattern; B = barrier lesion pattern; R = reactive; NR = non-reactive; Total protein in mg/l; IgG synthesis in mg/day

Pat. no.	Sex	Age	Stage	Treatment	Time (months)	Cerebrospinal fluid			
						Mononuclear cells 10^6/l	Total protein	Electro-phoresis	IgG index
1	♂	23	L	Procaine pc	0	11	419	I	1.45
					4	2	401	I	0.87
					12	0	408	N	0.69
2	♂	48	L	Procaine pc	0	2	390	N	1.0
					6	0	420	N	0.72
3	♂	19	L	Procaine pc	0	24	459	I, B	0.88
					4	9	443	B	0.62
					12	2	437	B	0.57
4	♂	63	L	Procaine pc	0	9	569	I	0.88
					2	2	579	N	0.67
					10	4	554	N	0.76
5	♂	20	L	Procaine pc	0	152	849	I, B	1.0
				Benzyl pc, i-v	5	19	719	I	0.85
					7	4	658	I, B	0.78
					13	4	548	I	0.75
6	♂	37	L	Benzyl pc, i-v	0	32	405	I	1.22
					2	2	390	I	1.0
					8	1	343	N	0.55
					16	2	328	N	0.64
7	♂	43	L	Benzyl pc, i-v	0	42	488	I	0.76
					4	3	450	N	0.57
8	♂	39	L	Procaine pc	0	16	515	I	1.57
9	♂	36	S	Procaine pc	0	13	572	I, B	0.67
					6	1	510	N	0.55
10	♂	52	S	Procaine pc	0	19	875	B	0.61
					2	2	584	N	0.62

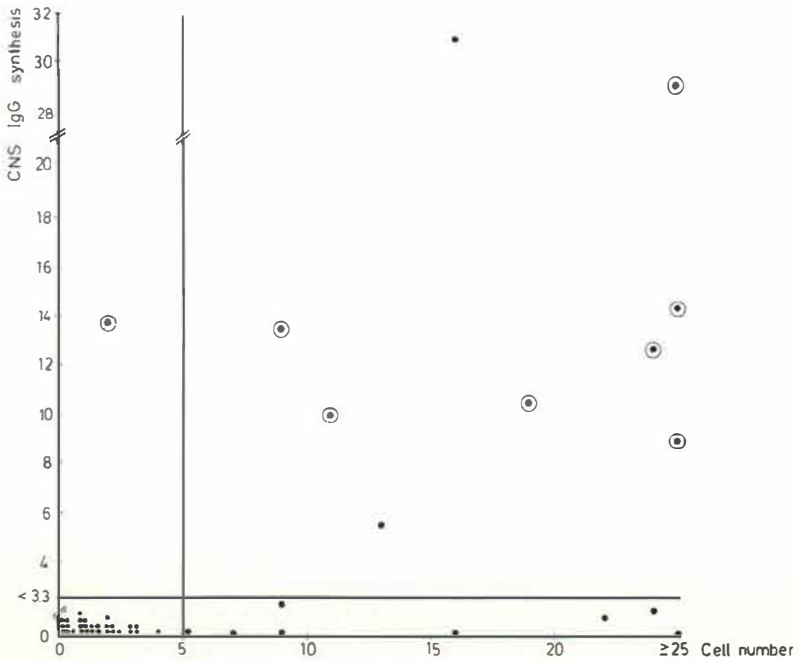

Fig. 1. Relationship between CNS IgG synthesis and cell count in 47 patients with early syphilis. Upper normal limits for cell count (5×10^6/l) and CNS IgG synthesis (3.3 mg/day) are indicated by bars. Encircled points indicate positive WR in CSF.

IgG synthesis	Albumin quotient	WR	VDRL	FTA-ABS IgG	FTA-ABS IgM	TPI
10.0	3.2	R	NR	R	NR	R
4.5	3.7	–	NR	R	NR	R
3.4	3.6	NR	NR	NR	NR	NR
13.7	4.2	R	NR	–	–	R
1.3	4.2	NR	NR	–	–	R
12.6	5.7	R	NR	–	–	R
0.1	4.7	NR	NR	–	–	R
−1.5	4.7	NR	NR	NR	NR	NR
13.1	5.6	R	NR	NR	NR	R
4.2	5.4	NR	NR	NR	NR	R
7.5	5.7	NR	NR	NR	NR	R
29.1	8.1	R	R	R	NR	R
11.9	5.8	R	NR	R	NR	R
10.7	6.8	R	NR	R	NR	R
6.3	5.2	R	NR	NR	NR	NR
14.4	3.4	R	R	R	NR	R
4.4	2.8	NR	NR	NR	NR	NR
−3.5	3.0	NR	NR	NR	NR	NR
−2.5	2.3	NR	NR	NR	NR	NR
8.9	5.7	R	NR	R	NR	R
−1.4	4.6	NR	NR	NR	NR	NR
31.3	5.3	NR	NR	–	–	R
5.5	6.7	NR	NR	–	–	R
−1.1	6.0	NR	NR	–	–	NR
10.5	10.8	R	NR	NR	NR	NR
1.0	5.0	NR	NR	NR	NR	NR

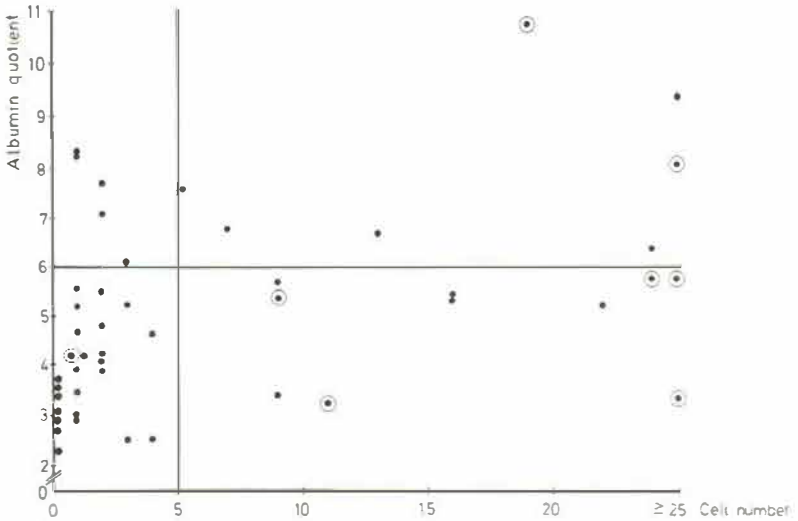

Fig. 2. Relationship between albumin quotient and cell count in 47 patients with early syphilis. Upper normal limits for cell count (5×10^6/l) and albumin quotient (6.0, age group 15–45 years) are indicated by bars. All patients with albumin quotient between 6.0 and 7.0 are <45 years old. Encircled points indicate positive WR in CSF.

Albumin quotient/cell number (Fig. 2): Pleocytosis was observed in 7 of 12 patients with an increased albumin quotient and in 10 of 35 with a normal albumin quotient (no significant correlation).

Albumin quotient/WR (Fig. 2): WR antibodies were detectable in 2 of 12 patients with a pathologically increased albumin quotient and in 6 of 35 patients with a normal albumin quotient (no significant correlation).

After treatment (Table II)

Lumbar puncture was performed after treatment in 9 of 10 patients with incrased CNS IgG synthesis.

Cells. In 7 of 9 patients, the cell number was normalized 2–6 months after treatment. Two patients (nos. 3 and 5) still had pleocytosis after 4–5 months. Patient no. 5 was retreated with benzylpenicillin 6 g (10 million IU) three times a day for 10 days, whereas patient no. 3 received no further treatment. Both patients showed normal cell numbers after 7–12 months. The cytological changes normalized concomitant with the decrease in cell number.

CNS IgG synthesis and IgG index: After 2–6 months, 5 of 9 patients demonstrated

Table III. *Pretreatment results of WR, VDRL, FTA-ABS and TPI in CSF in 17 patients with early syphilis*

n = number patients, R = reactive, NR = non-reactive

n	WR	VDRL	FTA-abs	TPI
2	R	R	R	R
2	R	NR	R	R
1	R	NR	NR	R
2	R	NR	–	R
1	R	NR	NR	NR
1	NR	NR	R	R
4	NR	NR	NR	R
4	NR	NR	–	R

normal IgG values, while 4 (nos. 1, 4, 5 and 6) still had signs of intrathecal immunoglobulin production. Two of these patients (nos. 4 and 5) still did not have normal IgG values after 10–13 months.

Concomitant with the normalization of the IgG production, the immunopathic pattern in electrophoresis disappeared or regressed.

Syphilis serology in CSF. Of 9 patients, 8 were WR-positive, 2 VDRL-positive, 4 FTA-ABS-positive and 9 TPI-positive in CSF before treatment. After 2–6 months, only one (no. 5) of the 9 patients had a positive WR; none was VDRL-positive, 2 (nos. 1 and 5) were positive in FTA-ABS and 5 still had a positive TPI. Re-examination after 10–16 months in 4 patients (nos. 1, 3, 4 and 5) revealed a positive WR in patient no. 5, positive TPI in patient no. 4 and negative FTA-ABS in all 4 patients.

DISCUSSION

Elevated immunoglobulin levels in CSF have been reported repeatedly in neurosyphilis (6, 7, 23) and also in early syphilis (31). Flodén (5) reported increased globulin values in CSF in 30% of patients with secondary syphilis. Von Engel (31) found elevated IgG levels in CSF in 70% of patients with early syphilis. The significance of an increased immunoglobulin value in CSF cannot be judged without knowing whether it reflects an intracerebral production of globulin or a diffusion from serum secondary to elevated serum levels and/or damage to the blood–brain barrier.

Norredam (22) found, by immuno-electrophoresis, α_2-lipoprotein and α_2-macroglobulin in CSF, indicating a blood–brain barrier defect in 12 of 13 patients with early syphilis. An increased albumin quotient reflecting blood–brain barrier dysfunction was also found in 26% of our patients. Increased values of immunoglobulins, both IgG and IgM, in serum have been reported in early syphilis (3, 13, 22) and were found for IgG in 62% of our patients. In CSF, 31 (66%) of the 47 patients demonstrated pathologically elevated IgG levels. By correcting for elevated serum levels and barrier lesions (albumin quotient) according to the formulas given by Tibbling et al. and Tourtellotte, it was found that in 10 of the patients the IgG level reflected an intrathecal production of IgG. In 8 of these patients, oligoclonal bands were also demonstrated in electrophoresis. By calculating the IgG index and/or IgG synthesis, a quantitative estimate of the IgG production was obtained.

All but one patient with intrathecal immunoglobulin production had an increased cell count. The positive correlation between pleocytosis, characterized by lymphocyte activation, and intrathecal immunoglobulin production demonstrated in this study, indicates that immunocompetent cells within the brain are stimulated to immunoglobulin production early in syphilitic infection. In contrast, no correlation was found between albumin quotient and cells. There was also a significant correlation between positive WR in CSF and intrathecal immunoglobulin production, thus supporting intrathecal antibody production. It has recently been demonstrated in two studies (27, 30), by antibody immunofixation, that oligoclonal bands in CSF in patients with neurosyphilis represent *Treponema pallidum* antibodies.

When evaluating the significance of syphilis antibodies in CSF in the individual case, the titre in serum as well as the function of the blood–brain barrier must be considered. The *Treponema pallidum* haemagglutination (TPHA) index according to Luger (16) corrects for the barrier lesion but not for the serum titre. A linear correlation between serum and CSF titres for TPI, FTA as well as for TPHA antibodies has been demonstrated by Müller (20).

With conventionally recommended penicillin treatment for syphilis, detectable penicillin concentrations in CSF are not achieved (17, 19). For neurosyphilis, new treatment

regimens with high doses of benzyl penicillin have been proposed (19, 25). Two of 10 patients with increased CNS IgG synthesis were accordingly given benzyl penicillin 6 g (10 million IU) three times a day i.v. for 10 days. After one year, irrespective of treatment, all CSF tests were normalized in 7 patients, while 2 patients still had signs of slight intrathecal immunoglobulin production. Thus, procaine penicillin, although not giving measurable concentrations in CSF, seemed to be an adequate mode of therapy. This may be explained by a recent observation demonstrating that sub-inhibitory levels of penicillin may co-operate with the immune system to eliminate invading bacteria (9).

The early syphilitic CNS involvement characterized by an increased cell count and increased total protein has been assumed to reflect meningeal inflammation (11). With few exceptions, it is asymptomatic and progression to neurosyphilis after adequate therapy is a rarity (24).

Local immunoglobulin production within the CNS, was found in as many as 21% of 47 patients with early syhilis in this study. None of the patients with intrathecal immunoglobulin production had any neurological symptoms. Nevertheless, Rosenhall & Roupe (26) demonstrated, by auditory brainstem responses, signs of subclinical lesions in the brainstem in patients with late as well as early syphilis. A comparison between these disturbances and CSF abnormalities will be reported in a following paper (18).

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