Cerebrospinal Fluid Immunoglobulins: Their Diagnostic Role in Neurosyphilis*

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SUMMARY **Cerebrospinal fluid immunoglobulins G, A and M were determined by electroimmunodiffusion method in patients with neurosphilis, secondary and latent syphilis and in normal controls. The highest and most frequent increase in IgG and IgA occurred in patients with symptomatic neurosyphilis. IgM was detected in only two patients, but its presence appears to indicate activity of the disease process and possibly relate to an unfavourable clinical outcome. In secondary syphilis, the significantly high mean concentration of IgG in patients with reactive Fluorescent Trepronemal Antibody Absorption test in the cerebrospinal fluid seems to suggest local immunoglobulin synthesis, thereby implying that the responsible infectious agent has invaded the central nervous system.**

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Diagnosis of neurosyphilis is, at present, difficult because presenting clinical features are often atypical and serological tests for syphilis on the cerebrospinal fluid (CSF) are not necessarily reactive. Elevation of CSF proteins and gamma-globulin have been used as supportive evidences for the presence and for the probable activity of the disease. Recent studies,[1,2] however, showed that determination of CSF immunoglobulins seemed to be more valuable. The aim of our study was to determine whether concentrations of immunoglobulins G, A and M would have any significant role in the diagnosis of neurosyphilis and in the assessment of its activity. We also observed the behaviour of these immunoglobulins in the CSF of patients with secondary syphilis in whom CSF fluorescent treponemal antibody absorption (FTA-ABS) test was reactive and compared it with that found in patients with secondary syphilis with non-reactive CSF FTA-ABS.

PATIENTS AND METHODS

CSF samples from 7 patients with classical neurosyphilis, 33 patients with clinically diagnosed neurosyphilis with reactive blood but non-reactive CSF FTA-ABS, four patients with asymptomatic neurosyphilis, 20 patients with latent syphilis, 50 patients with secondary syphilis and 12 normal controls were examined. CSF immunoglobulin G, A and M concentrations were measured in duplicates from each sample by the electroimmunodiffusion method of Lopez, Tsu and Hyslop.[3]

Table 1 CSF IgG and IgA concentrations in patients with late syphilis and normal controls

Diagnosis	No. of Patients	IgG (mg/dl) Mean	IgG (mg/dl) Range	IgA (mg/dl) Mean	IgA (mg/dl) Range
Classical neurosyphilis	7	10.3	3.7 –20.0	1.72	0–7.2
Neurosyphilis c̄ -ve CSF FTA-ABS	33	4.01	1.4 – 7.2	0.30	0–1.06
Asymptomatic neurosyphilis	4	5.60	4.0 – 8.0	0.22	0–0.49
Latent syphilis	20	2.93	1.08– 5.65	0.08	0–0.32
Normal controls	12	2.84	1.08– 5.20	0.06	0–0.30

Conversion : Traditional units to SI - Immunoglobulin concentration
: 100 mg/dl = 1g/L

RESULTS

CSF IgG and IgA concentrations in patients with neuro- and late

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Table 2 CSF IgG and IgA concentrations in patients with secondary syphilis and normal controls

Patients with	No. of patients	IgG (mg/dl) Mean ± SD	IgG (mg/dl) Range	No. of patients	IgA (mg/dl) Mean	IgA (mg/dl) Range
(1) +ve CSF FTA-ABS	13	5.5* ± 0.96	3.2 –12.5	7	0.06	0–0.38
(2) -ve CSF FTA-ABS, +ve CSF FTA	30	3.98* ± 0.29	2.5 – 9.1	28	0.14	0–0.53
(3) -ve CSF FTA-ABS and FTA	7	3.36* ± 0.28	2.6 – 4.0	6	0.11	0–0.49
Normal controls	12	2.84 ± 1.09	1.08– 5.20	12	0.06	0–0.3

IgG*(1) vs (2) + (3) : $P < 0.05$

Table 3 Detectable CSF IgA in various types of syphilis and normal controls

Types	No. of patients tested	Detectable IgA No. of patients	Detectable IgA %
Classical neurosyphilis	7	6	85.7
Neurosphilis c̄ -ve CSF FTA-ABS	33	21	63.6
Asymptomatic neurosyphilis	4	2	50.0
Secondary syphilis:			
c̄ +ve CSF FTA-ABS	7	4	57.1
c̄ -ve CSF FTA-ABS	34	11	32.3
Latent syphilis	20	4	20.0
Normal controls	12	3	25.0

Table 4 CSF IgM concentrations in patients with syphilis and normal controls

Diagnosis	No. of patients tested	No. of patients c̄ detectable IgM (mg/dl)
Classical neurosyphilis	7	1 (3.8)
Neurosyphilis c̄ -ve CSF FTA-ABS	33	1 (5.5)
Asymptomatic neurosyphilis	4	0
Latent syphilis	20	0
Secondary syphilis	50	0
Normal controls	12	0

syphilis, and in normal controls are recorded in Table 1, whilst those in patients with secondary syphilis are separately shown in Table 2 and are divided into subgroups according to the results of CSF FTA-ABS and FTA. Table 3 shows the number and percentage of detectable CSF IgA in various groups of patients studied. CSF IgM was detectable in only two patients both of whom had neurosyphilis. The number of patients tested for CSF IgM together with the results are recorded in Table 4, whilst Table 5 shows immunoglobulin G, A and M concentrations in the sera and CSF's of the two patients with detectable CSF IgM and their clinical outcome.

Immunoglobulin G

IgG was present in the CSF of all patients, the highest mean concentration belonging to those with classical neurosyphilis. In latent syphilis, i.e. the condition based solely on positive serology and other clinical forms of the disease having been excluded, the mean CSF IgG concentration hardly differed from that of normal controls. In patients with secondary syphilis, CSF IgG concentrations were increased, compared with those in normal controls. Moreover, the mean CSF IgG concentrations of the 13 patients in whom CSF FTA-ABS results were reactive was significantly higher than that of the remaining 37 patients with non-reactive CSF FTA-ABS ($p < 0.05$).

Immunoglobulin A

The mean CSF IgA concentrations among patients of all categories of neurosyphilis were significantly higher than that of normal controls. Moreover, the immunoglobulin was detectable in increased number of patients with secondary and neurosyphilis.

Immunoglobulin M

In the two patients with neurosyphilis in whom CSF IgM's were detectable (3.8 and 5.5 mg/dl), CSF

Table 5 CSF and blood IgG, IgA and IgM concentrations in patients with detectable CSF IgM and clinical outcome

Patients			IgG (mg/dl)		IgA (mg/dl)		IgM (mg/dl)		Clinical
Sex	Age	Diagnosis	CSF	Blood	CSF	Blood	CSF	Blood	outcome
F	54	Classical GPI	20.0	1875	0.21	282	3.8	225	dead
F	43	Sy-myelitis	3.1	1750	0.64	217	5.5	220	permanent paraplegia
Normal controls			1.08–5.20	800–1500	0–0.30	140–400	0	50–200	

IgA was detectable in both and in the patient with classical General Paralysis of the Insane (GPI), the CSF IgG level of 20 mg/dl was the highest recorded in the present series.

DISCUSSION

Our findings of abnormally high concentrations of CSF IgG and IgA and increased IgA detectability in patients with neurosyphilis were in agreement with previously reported studies.[2,4] Kabat[5] was the first to point out that the increase in the immunoglobulin level of the CSF in many neurological diseases including neurosyphilis is often disproportionate to the rise in total protein and suggested that it was due to antibody synthesis in the nervous system. This was finally proved by Frick and Scheid-Seydel.[6] At present the IgG index[7] which is derived from the CSF: Serum IgG and albumin ratios is widely used as an indicator of immunoglobulin synthesis in the central nervous system and it has been found to be raised in a majority of patients suffering from multiple sclerosis, subacute sclerosing panencephalitis and neurosyphilis. The presence of IgM in the CSF of only 2 out of our 44 patients with neurosyphilis is also comparable to previous observations.[1,4] Oxelius, Rorsman and Laurell[8] suggested that CSF IgM could be of value in evaluating the activity of the neurosyphilitic process. It is thus noteworthy that of our 2 patients with detectable CSF IgM, one had active GPI and another had acute syphilitic myelitis and that their clinical outcome in spite of treatment were poor.

The abnormal increase in CSF IgG and IgA levels in patients with secondary syphilis is of great interest in that the difference in the mean CSF IgG concentrations among those with reactive and non-reactive CSF FTA-ABS are statistically significant though clinical features in those patients were similar. The significant increase in CSF IgG in those patients with reactive CSF FTA-ABS seems to suggest that immunoglobulin synthesis has occurred in the central nervous system (CNS) and this would mean that *Treponema pallidum* (TP) has already invaded the CNS and has acted as the responsible antigen for antibody synthesis. If that indeed is the case, then those patients should also, perhaps, be regarded as having asymptomatic neurosyphilis and may require a regimen of treatment with penicillin different from that for secondary syphilitic patients with non-reactive CSF FTA-ABS. Recently, Vartdal *et al*[9] reported on the presence of oligoclonal IgG in the CSF of patients with neurosyphilis and also demonstrated that it represents TP antibodies, reflecting a specific immune response in the CNS to the infectious agent. Such a study in patients with secondary syphilis with and without reactive CSF FTA-ABS would further help to clarify the matter.

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