

Cellular and Humoral Immunity in Subacute Sclerosing Panencephalitis

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Cellular and humoral immunity was studied in 26 patients with subacute sclerosing panencephalitis. Results were compared with those of 14 normal controls and 11 patients suffering from other neurological disorders. It was shown that cellular and humoral immune responses are adequate in subacute sclerosing panencephalitis. The persistently elevated levels of serum immunoglobulin G (IgG) and IgA indicated a persistent infection, and their progressive rise in later stages correlated with the progressive nature of the illness. IgG progressively increased with the clinical stage in the cerebrospinal fluid unaccompanied by a corresponding rise in the measles antibody titer. This suggests that antigenic determinants other than those tested play a role in the production of IgG in the cerebrospinal fluid. The progressive increase in the ratio of cerebrospinal fluid to serum IgG with the advance of the disease suggests synthesis of IgG locally in the central nervous system. Elevated measles antibody titer in serum and cerebrospinal fluid is a consistent aid in the diagnosis of subacute sclerosing panencephalitis. It is more specific in cerebrospinal fluid than in serum. Its level did not vary significantly with the clinical stages or duration of illness. Depressed serum complement activity has been detected in some subacute sclerosing panencephalitis patients in whom serum levels of the third and fourth components of the complement were normal.

Subacute sclerosing panencephalitis (SSPE) is a slow virus infection of the central nervous system related to measles. It afflicts children and young adults and usually follows measles infection by several years. It is characterized by a progressive course that ends in disability and death.

Six clinical stages have been recognized (24). Stage 0 is that of subtle psychointellectual symptoms recognized retrospectively. Stage I is the stage of overt psychointellectual or nonspecific neurological symptoms or both. Stage II is characterized by stereotyped jerks, and stage III is characterized by a vegetative psychomotor condition. Stage IV is the stage of spontaneous improvement, modest in substage IVa and substantial in substage IVb. Stage V is that of relapse.

Criteria for the diagnosis of SSPE (9) include: a characteristic clinical picture; a characteristic electroencephalographic pattern of generalized bilaterally synchronous bursts of spike and wave complexes; a parietic type colloidal gold curve; an elevated cerebrospinal fluid (CSF) immunoglobulin G (IgG), or elevated ratio of IgG to total protein; and elevated measles antibody titer (MAT) in serum and CSF. The brain biopsy shows intranuclear Cowdry type A inclusion

bodies or evidence of panencephalitis or both.

Whereas the involvement of a measles-like virus in the etiology of SSPE is well substantiated (3, 7, 10, 23), the pathogenesis of this disease remains unclear. Attempts to uncover factors that heighten the susceptibility of individuals to this virus have been conducted through various approaches. One such approach was immunological. Investigators questioned the competence of the immune system to eliminate the infection. Studies evaluating this competence revealed controversial and sometimes contradictory results, especially regarding cell-mediated immunity (8, 12-14, 20, 24, 26; R. M. Blaese and H. Hofstrand, *Arch. Neurol.* **32**:494-495, 1975). The relationship of the immunological findings to the clinical stage of SSPE and duration of illness has been barely touched upon. These factors prompted us to study the immune system in SSPE by evaluating T-cell function, humoral immunity, and the complement system and their relation to the clinical stage and duration of illness.

MATERIALS AND METHODS

Patients. Twenty-six SSPE patients, 17 males and 9 females, were included in this study. The diagnosis

was established on clinical, electroencephalographic, and serological grounds (9). Nineteen patients were Lebanese, five were Syrians, and two were Palestinians; all were living in Lebanon. The age of the patients at the time of obtaining the samples ranged between 5 and 17 years. There were 4 patients in stage I, 10 in stage II, 7 in stage III, and 5 in stage IV. There were no patients in stage 0 or V. The duration of illness at the time the samples were obtained ranged in over 50% of the cases between 0.5 and 5 months. The remaining patients had been ill for up to 84 months. Serum studies were done on 25 patients, CSF studies were done on 26 patients, and skin testing was done on 15 patients.

Controls. Controls consisted of two subgroups. Subgroup I included normal, healthy individuals, 11 males and 3 females between 8 and 26 years of age. Three were brothers of SSPE patients. Skin testing was done on 14 normal individuals who came from the same area as SSPE patients. Data on isohemagglutinin titers, complement levels, and complement activity were available from studies done on normal individuals by the same technician. Data on normal, age-specific, immunoglobulin levels from the same population were reported previously (2).

Subgroup II included non-SSPE patients, seven males and four females. Five had encephalitis, one had meningitis, one had Sydenham's chorea, two had multiple sclerosis, and two were suspected to have an immune deficiency. Serum and CSF studies were done on 10 patients, and skin testing was done on 7 patients.

Specimens. Twenty-five serum samples and 26 CSF samples from SSPE patients were studied, in addition to control samples. Serum and CSF samples from patients and controls were stored at -20°C for comparable periods to minimize the effects of storage.

Reagents. Skin testing antigens were supplied by the Industrial Drug Supplies Inc., Jamaica, N.Y. Immunodiffusion plates for immunoglobulin and complement level determinations and antigens for MAT determination were obtained from Behring Diagnostics, Hoechst Pharmaceuticals, West Germany.

Evaluation of cellular immunity. Assessment of T-lymphocyte function was done by the skin testing method. A panel of six of the following seven antigens were used: *Candida* (1:100, 1:10), coccidioidin (1:100, 1:10), measles (1:10, 1:1), PPD (5 U, 250 U), streptokinase-streptodornase (5 U, 50 U), staphage lysate (1:5, 1:1), and trichophyton (1:30). For the sake of conformity all skin tests were performed and the results were interpreted by one of us (S.S.D.J.) 24 to 48 h later. The interpretation was confirmed by one or more independent observers. A response to a particular test antigen was considered positive when the area of induration was 5 mm or more in diameter 48 h after intradermal injection. A patient was considered to have diminished delayed hypersensitivity reaction if he responded to fewer than two of the six antigens used.

Evaluation of humoral immunity and complement system. Evaluation of B-lymphocyte function was done by detecting the levels of isohemagglutinins and various immunoglobulins in the serum as well as the level and activity of the complement. The different immunoglobulins and the third and fourth components of the complement (C3 and C4, respectively)

were determined by the single radial immunodiffusion technique of Mancini et al. (19). Determination of the complement activity was done by the method of Lachmann et al. (16). Measles specific antibody levels were determined by the hemagglutination inhibition (HI) test using strain 1677, supplied by G. Enders, as described by Norrby (21) and by the complement fixation (CF) test with the Kolmer microtechnique (18).

RESULTS

Skin testing. Of the 15 SSPE patients, 12 (80%) reacted to two or more antigens. There was no significant difference in the response to two or more antigens when the results obtained in SSPE patients were compared with those of 14 normal controls ($P > 0.3$) and 7 non-SSPE controls ($P > 0.2$).

Isohemagglutinin titers. SSPE patients had normal isohemagglutinin titers as compared with those of controls. Log_2 geometric mean titers were 4.14 in 14 SSPE patients, as compared with 4.52 in 10 non-SSPE patients.

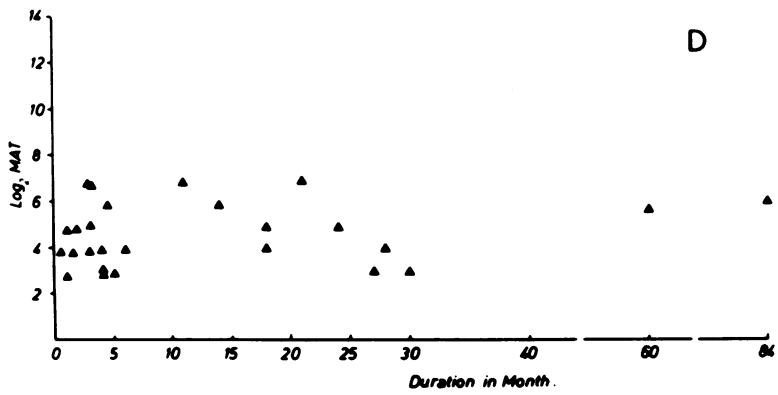
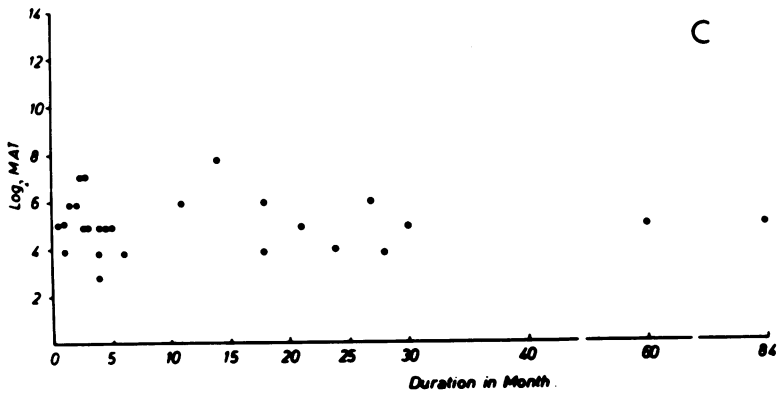
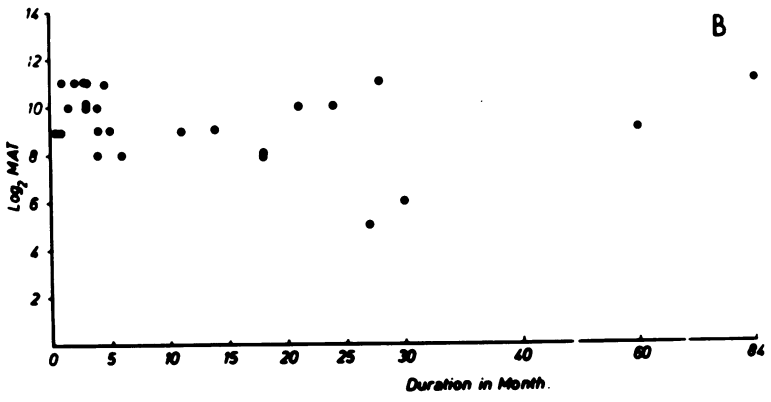
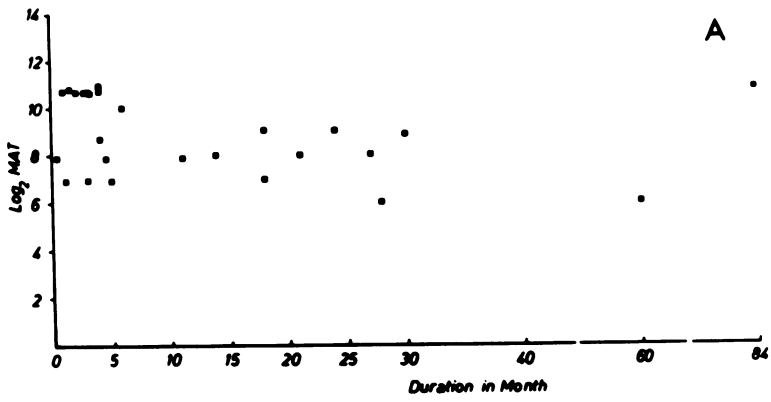
MAT. All SSPE patients had elevated MAT in serum ($\geq 1:64$) and CSF ($\geq 1:8$) as determined by CF and HI when compared with controls (Table 1). Of 10 controls in subgroup II, 4 had elevated MAT in serum and none had elevated MAT in the CSF. These four consisted of two patients with encephalitis (MAT, 1:1,024), one patient with Sydenham's chorea (MAT, 1:256), and one patient with multiple sclerosis (MAT, 1:2,048). CF and HI geometric mean MAT in serum were approximately double those in CSF (Table 2). There was little, if any, variation of the geometric mean MAT with the clinical stage of SSPE in serum and CSF (Table 2). No significant correlation could be found between the duration of illness and the levels of MAT in serum and CSF (Fig. 1).

TABLE 1. Log_2 geometric mean MAT in 26 SSPE patients, 10 non-SSPE patients, and 14 normal subjects

Condition	HI titer		CF titer	
	Serum	CSF	Serum	CSF
Normal	<6	<3	<6	<3
SSPE	9.32	4.74	8.73	4.87
Non-SSPE	6.56	1.25	4.52	1.00

TABLE 2. Correlation of log_2 geometric mean MAT and clinical stage of SSPE

Clinical stage	No. of subjects	HI titer		CF titer	
		Serum	CSF	Serum	CSF
I	4	9.66	4.00	9.32	5.00
II	10	9.60	4.60	9.46	5.00
III	7	9.83	5.40	8.13	5.60
IV	5	8.20	4.40	8.11	5.00



Immunoglobulins. In each of the 24 SSPE patients tested, the IgG level was higher than the normal age-specific mean, and in 16 patients it was above the upper limit for age-specific normal range. The mean IgG level in SSPE patients was significantly higher when compared with that of normal controls matched for age and subgroup II controls (Table 3). IgG levels in stages II and III were significantly higher than those in stage I ($P < 0.02$ and $P < 0.05$, respectively). Differences between other stages were not statistically significant (Table 4). There was no correlation between serum IgG level and the duration of illness ($r = -0.12$).

CSF IgG level was always within normal limits in subgroup II controls (normal range in our laboratory was 2 to 5.3 mg/dl). It was elevated in 22 of 26 SSPE patients. This elevation was significantly higher in stages III and IV compared with stages I and II (Table 5). There was a positive but statistically insignificant correlation between the IgG level and the duration of illness ($r = 0.22$).

Serum IgA level was above the age-specific mean in 20 to 24 SSPE patients, and in 4 of those 20 it was greater than the age-specific normal range. The mean IgA level of the 24 SSPE patients was significantly higher when compared with that of normal controls matched for age, but it did not differ significantly from that of subgroup II controls (Table 3). IgA level was significantly higher in stage IV than in stage I ($P < 0.05$). Differences in other stages were insignificant (Table 4). IgA level did not correlate with the duration of illness ($r = -0.18$).

In the CSF IgA was detected in only 6 of the 26 SSPE patients (Table 6) and in two subgroup II controls who were suffering from encephalitis (1.7 and 1.45 mg/dl).

Serum IgM was elevated above the upper limit of the age-specific normal range in 2 of 24 SSPE patients. In the remaining patients it was above or close to the normal mean level. The mean IgM level in the 24 SSPE patients was significantly higher than the normal mean, but did not differ significantly from that in subgroup II controls (Table 3). IgM level did not vary significantly with the clinical stage (Table 4). It correlated negatively but not significantly with the duration of illness ($r = -0.48$).

In the CSF IgM was detectable in only 6 of the 26 SSPE patients (Table 6) and in two subgroup II controls suffering from encephalitis (3.7 and 0.31 mg/dl).

Serum IgD was above the upper limit of the age-specific range in 2 of 19 SSPE patients, greater than the age-specific mean level in 14, and undetectable in 3. The mean IgD level did not differ significantly when compared to the mean in normal controls matched for age (Table 3). IgD level did not vary with the clinical stage of SSPE (Table 4), nor did it bear a significant correlation with the duration of illness ($r = -0.18$). IgD was undetectable in the CSF (Table 6).

Complement. C3 was normal in all except one of 24 SSPE patients tested. It did not vary significantly with the clinical stage (Fig. 2) and did not bear a strong correlation with the duration of illness ($r = 0.25$). Subgroup II controls had normal serum C3 levels.

C3 was detectable in the CSF of two SSPE patients (2.00 and 2.40 mg/100 ml) and in one subgroup II control suffering from post-measles encephalitis (1.75 mg/dl).

C4 was low in 3 of the 24 SSPE sera tested. In the remaining 21 it was normal or slightly elevated. Its level did not vary significantly with the clinical stage (Fig. 3). There was a positive but statistically weak correlation between the duration of illness and C4 level ($r = 0.39$). C4 was normal in the sera of subgroup II controls. It was not tested in the CSF.

Complement activity. Complement activity was low in 12 of 19 (63%) SSPE sera tested. It did not vary significantly with the clinical stage (Fig. 4). It did not correlate with the duration of illness ($r = 0.39$). Subgroup II controls had normal serum complement activity. None of the CSF samples had detectable complement activity.

DISCUSSION

T-cell function. The functional competence of T-lymphocytes in SSPE patients has been questioned (1, 26, 27). Response to skin testing has been controversial (8, 12, 13). Jabbour et al. (12) have shown a positive response to *Candida* in all eight patients tested. Only two patients responded to histoplasma and mumps, and none showed a response to measles antigen from two different strains of live measles virus. However, none of their controls showed a response to any of the above-described measles strains. Gerson and Haslam (8) reported on four SSPE patients who did not express delayed responses to six common skin test antigens and failed to become sensitized to dinitrochlorobenzene. They sug-

FIG. 1. Correlation ($r =$ correlation factor) of serum and CSF \log_2 MAT and the duration of illness in 26 SSPE patients. Panels: A, CF serum MAT ($r = -0.28$); B, HI serum MAT ($r = -0.30$); C, CF CSF MAT ($r = 0.14$); D, HI CSF MAT ($r = -0.006$).

TABLE 3. Comparison of mean serum immunoglobulin levels of 24 SSPE patients, 10 non-SSPE patients, and 14 normal subjects

Condition	Mean serum immunoglobulin level \pm standard deviation			
	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgD (U/ml)
Normal	1,031.25 \pm 66.03	110.92 \pm 15.29	126.70 \pm 12.37	35.19 \pm 2.73
SSPE	1,882.91 \pm 447.54	170.16 \pm 75.34	164.83 \pm 55.78	48.47 \pm 38.43
Non-SSPE	1,595.55 \pm 442.01	173.66 \pm 87.62	160.00 \pm 84.42	25.05 \pm 32.05
<i>P</i> -values ^a	<0.001 ^b <0.01 ^c	<0.001 ^b >0.7 ^c	<0.02 ^b >0.6 ^c	>0.1 ^b <0.001 ^c

^a *P*-values are significant at $P < 0.05$.

^b SSPE values versus normal values.

^c SSPE values versus non-SSPE values.

TABLE 4. Correlation of mean serum immunoglobulin levels and clinical stage in 24 SSPE patients

Clinical stage (no. of patients)	Mean serum immunoglobulin level \pm standard deviation			
	IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgD (U/ml)
I (3)	1,353.33 \pm 285.46	106.33 \pm 45.08	107.33 \pm 14.19	39.00 \pm 37.58
II (10)	2,095.00 \pm 430.80	172.90 \pm 80.53	200.2 \pm 80.74	66.8 \pm 62.83
III (6)	1,970.00 \pm 411.14	158.6 \pm 83.47	149.16 \pm 16.24	43.5 \pm 15.80
IV (5)	1,672.00 \pm 359.75	216.80 \pm 77.67	147.4 \pm 36.37	41.8 \pm 33.16

TABLE 5. Comparison of CSF total protein (TP) and IgG in four clinical stages of SSPE by the paired *t*-test

Clinical stage (no. of patients)	Mean TP (mg/dl)	Mean IgG (mg/dl) \pm standard deviation	<i>P</i> -value ^a
I (4)	17.66	7.40 \pm 2.53	>0.5
II (10)	30.32	8.59 \pm 4.73	<0.02
III (7)	38.94	19.28 \pm 8.38	>0.5
IV (5)	22.46	22.2 \pm 9.32	

^a Comparison of one stage to the next. Significant at $P < 0.05$.

gested that subtle abnormalities of the immune system may be present in the rare individuals in whom SSPE develops. Their study involved too small a number of patients and lacked controls. Klajman et al. (13) reported a positive response to *Candida albicans* and PPD skin tests in two SSPE patients.

The majority of our patients reacted to either two or three antigens (common in Lebanon and Syria) of the six antigens used. Two SSPE patients failed to respond to any test antigen, probably because only the low-strength dilutions of *Candida* and streptokinase-streptodornase were used. Only one SSPE patient reacted to the attenuated live measles virus (Attenuvax) used as a skin test antigen. None of the control subjects showed a positive skin response to Attenuvax.

From the above data we conclude that SSPE

patients have a functional delayed hypersensitive response to general recall antigens; no severe deficit was demonstrated in this study.

Humoral immunity. Studies of humoral immunity in SSPE showed normal B-lymphocyte count in peripheral blood, increased levels of serum IgG and IgE, normal levels of serum IgA and IgM, and normal antibody response to antigenic stimulation like brucella, diphtheria, tetanous toxoid, and typhoid vaccines (Blaese and Hofstrand, Arch. Neurol. 32:494-495, 1975). Some authors, having demonstrated a lower avidity of SSPE antibodies to the antigen, questioned the functional ability of the measles-specific IgG to eliminate the infection (22).

The present study revealed elevated levels of serum IgG, IgA, IgM, and MAT, but normal IgD levels and isohemagglutinin titers. These findings are suggestive of a normal B-lymphocyte function in agreement with the findings of K. W. Sell and A. Ahmed, Arch. Neurol. 32:495, 1975 and Blaese and Hofstrand (Arch. Neurol. 32:494-495, 1975). Hence the evidence is in favor of an accrued humoral immune response in SSPE rather than its impairment.

The persistently high serum IgM during the different clinical stages of SSPE speaks for a continuous antigenic stimulus. The finding of high serum IgG and its progressive rise between stages II and III, which coincides with the severest clinical deterioration, suggests that it might be important in the pathogenesis of SSPE. It is noted that the ratio of CSF to serum IgG increases with the clinical progression of SSPE

TABLE 6. Log_2 MAT by HI, total protein (TP), and CSF immunoglobulin levels in the six SSPE patients in whom CSF IgA and IgM were detectable.

Patient no.	Clinical stage	Log_2 MAT		TP (mg/dl)	CSF immunoglobulin level			
		Serum	CSF		IgG (mg/dl)	IgA (mg/dl)	IgM (mg/dl)	IgD (U/ml)
1	I	11	4	36	9.5	0.7	2.5	UD ^a
2	II	8	3	36	6.0	0.7	3.1	UD
3	III	11	7	35	24.0	1.45	2.55	UD
4	III	11	6	42	6.2	0.71	UD	UD
5	III	11	4	37	23.0	1.45	2.5	UD
6	IV	11	6	40	18.9	1.45	2.2	UD

^a UD, Undetectable.

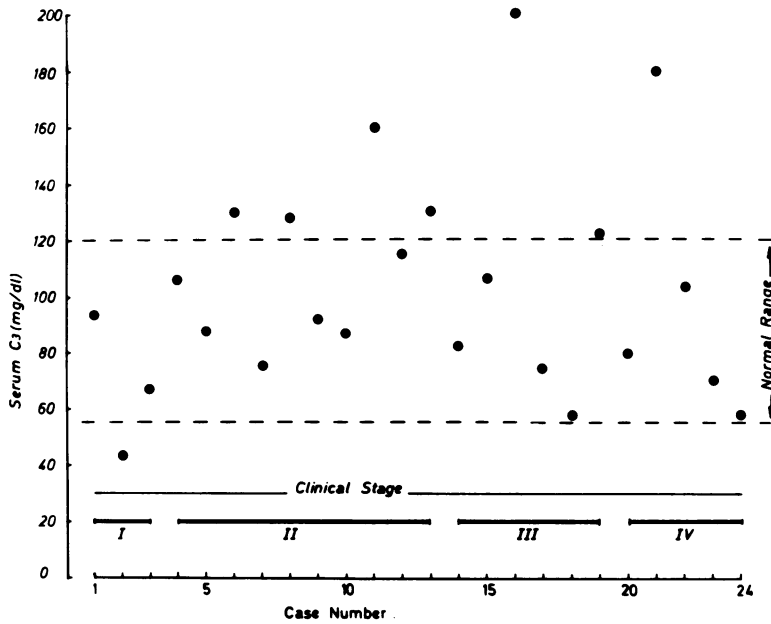


FIG. 2. Correlation of serum C3 levels and clinical stage in 24 SSPE patients.

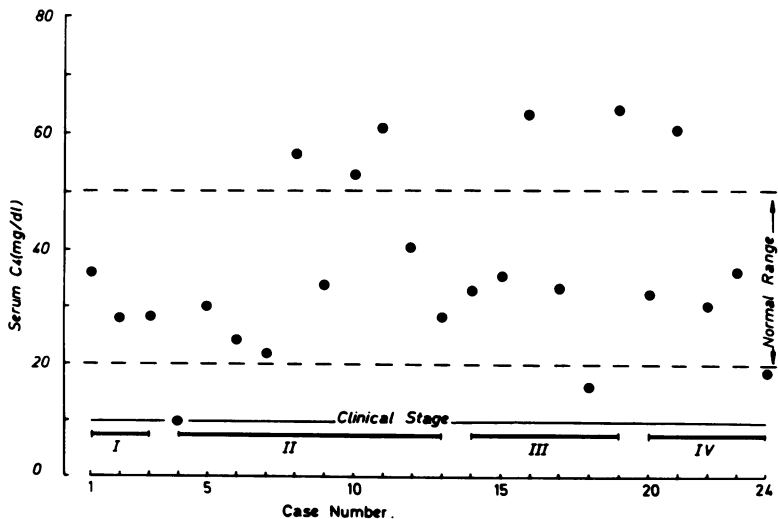


FIG. 3. Correlation of serum C4 levels and clinical stage in 24 SSPE patients.

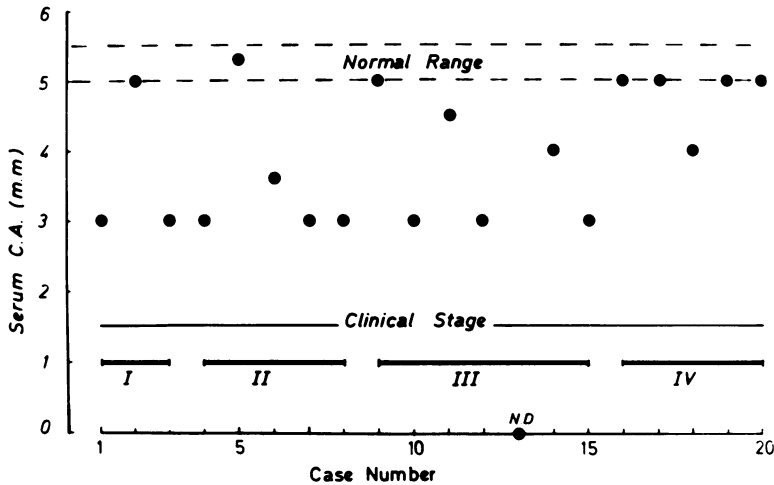


FIG. 4. Correlation of serum complement activity (CA) and clinical stage in 19 SSPE patients. ND, Not done.

(Fig. 5). It suggests that IgG is locally synthesized in the central nervous system. This suggestion is supported by the studies of Cutler et al. (5) and Ewan and Lachmann (6).

Although IgA and IgM are not normally present in CSF, their presence in six SSPE patients is noteworthy. Their presence could be due to an altered blood-brain barrier or to endogenous CNS production. The former reason is less likely, because of (i) undetectable IgD in the CSF in the presence of normal levels of IgD in the serum and (ii) the presence of normal CSF total proteins (Table 5). The presence of CSF IgA and IgM did not correlate with the clinical stage of the illness. In these same six cases, we found an unusually elevated MAT as determined by HI in the serum (Table 6); we have no explanation for this finding.

The progressive increase in the CSF IgG with the progression of the disease without a corresponding rise in MAT (Fig. 6) suggests that antigenic determinants other than those tested play a role in the production of IgG in the CSF. This suggestion derives support from the demonstration of auto antibodies against a water-soluble brain extract in the CSF of SSPE patients (14).

MAT. The presence of elevated MAT in the serum and CSF is almost a universal finding in SSPE (4, 25). The finding of elevated MAT in the sera of four non-SSPE patients makes the serum MAT a nonspecific test for SSPE. The presence of elevated MAT in the CSF of all SSPE patients included in this study and in none of the non-SSPE patients used as controls, including those with high serum MAT, suggests that elevated CSF MAT is a more specific aid in

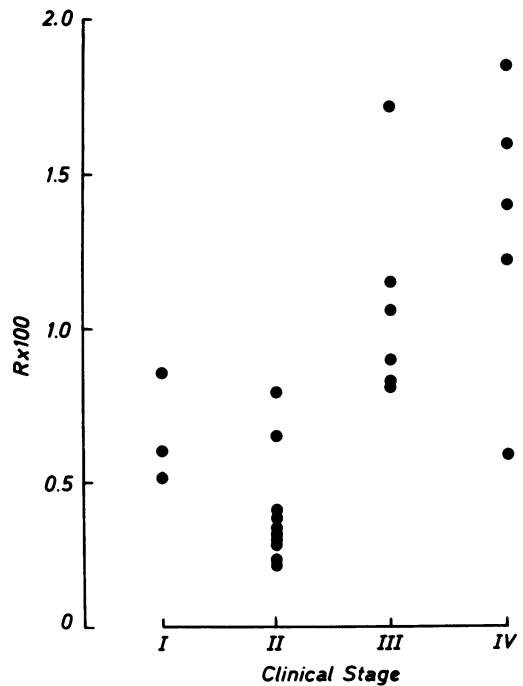


FIG. 5. Correlation of the ratio of CSF to serum IgG (R) and clinical stage in 24 SSPE patients.

diagnosis, in agreement with the report of Sever et al. (25).

Horta-Barbosa et al. (11) reported that serum MAT as determined by CF and HI were significantly increased in stage III compared with stage II, that serum HI levels were also significantly increased in stage IV compared to stage II, and

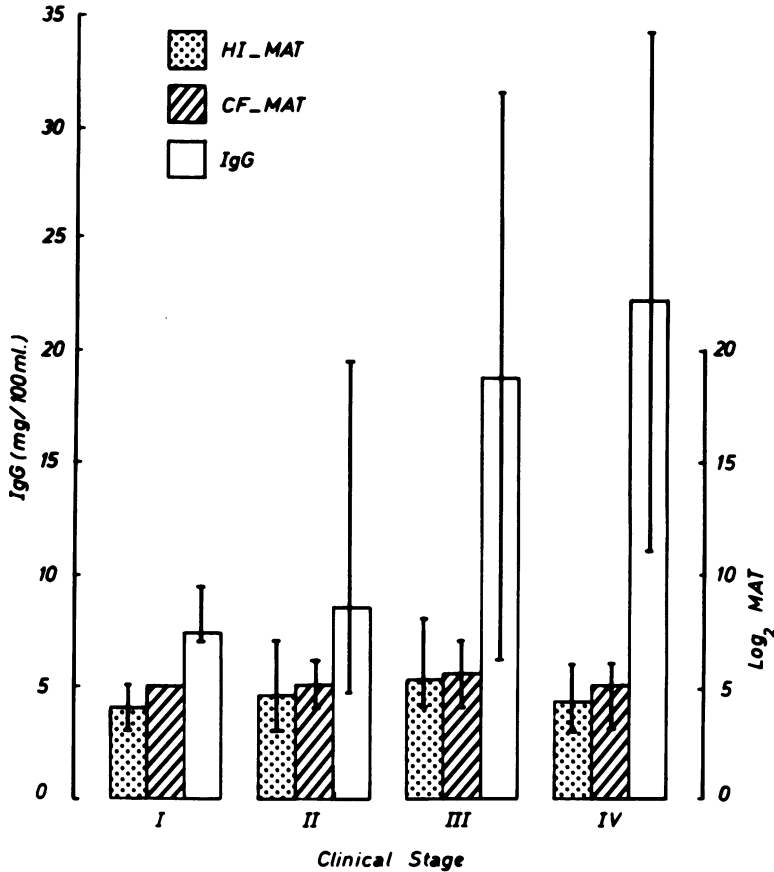


FIG. 6. Variation of the CSF IgG and \log_2 MAT with the clinical stage of SSPE.

that CSF HI levels were also significantly increased in stages III and IV when compared with stage II, using the multiple-range test. Our study did not show a significant variation of the serum and CSF MAT with the clinical stage when the \log_2 geometric means of MAT in each stage were compared. This is in agreement with the study of Legg (17), who found no significant rise in the MAT in the serum of 22 SSPE patients as their disease progressed. This and the lack of correlation of MAT with the duration of illness suggest that CF and HI measles antibodies are not necessarily involved in the pathogenesis of SSPE. This suggestion gains support from a report on the occurrence of SSPE in a patient with agammaglobulinemia who lacked measles antibodies in his serum and CSF (28).

Complement. An interesting finding is the demonstration of low complement activity in the sera of some SSPE patients in the presence of normal C3 and C4 values (Fig. 2, 3, and 4). This finding could be explained by one or more of the following: (i) alteration *in vitro*, e.g., improper handling; (ii) increased consumption *in vivo*, e.g.,

immune complex diseases; and (iii) decreased synthesis, e.g., inborn errors. We are currently investigating these possibilities. Joseph et al. (B. S. Joseph, N. R. Cooper, and M. B. A. Oldstore, *Arch. Neurol.* 32:500, 1975) have demonstrated that antibody-mediated, complement-dependant lysis occurred with measles virus-infected lymphocytes, glia, and neuroblastoma cells. This piece of information, added to our finding of low complement activity, may explain, at least in part, why the elevated measles antibodies fail to kill the neurons infected with measles in SSPE patients.

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