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Quantitative Determination of Immunoglobulins in CSF and Plasma of Chronic Schizophrenic Patients

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Summary: Immunoglobulins, IgG, IgA and IgM were quantified in cerebrospinal fluid (CSF) and plasma from chronic schizophrenic patients and controls using an immunofluorescent antibody technique. A generalized reduction in immunoglobulin levels was observed in the schizophrenic patients compared with controls. While this study supports other reports of abnormal immune functioning in schizophrenia, it failed to replicate previous findings of elevations in CSF IgG and elevations in serum IgA. The aetiology and significance of these findings are hypothesized but remain elusive.

An association between abnormal immune functioning and schizophrenia has been reported by several investigators (Heath and Krupp, 1967a, b, c; Heath *et al*, 1967; Vartanian *et al*, 1978; Liedeman and Prilipko, 1978; Friedman *et al*, 1967; Vaughn *et al*, 1949; Jankovic *et al*, 1979). Although the aetiology of altered immunological function in schizophrenia is unknown, several possibilities have been proposed. They include a reaction to a viral-like substance in some schizophrenic patients (Torrey *et al*, 1978; Crow *et al*, 1979; Dwyer, 1979; and Tyrell *et al*, 1979), a manifestation of an autoimmune disease (Heath and Krupp, 1967b; Werthheimer, 1961), and the result of pharmacological treatment (Lovett *et al*, 1978; Ferguson *et al*, 1978; Fieve *et al*, 1966; Zarrabi *et al*, 1979).

The most accessible and extensively studied components of the immune system are the immunoglobulins. Of the five major classes of immunoglobulins, IgG normally comprises 70–80 per cent of the serum and almost all of the CSF antibodies, while IgA comprises about 20 per cent and IgM approximately 7 per cent of serum immunoglobulins. IgA and IgM are present in CSF in trace amounts (for review see Thaler *et al*, 1977; and Fishman, 1980). Each of the possibilities for altered immunological functions in schizophrenia mentioned above might effect the concentrations of these components of the humoral immune system. Increased concentrations could reflect recent or past infection or antigen load. Decreased concentrations might reflect diminished immunological competence.

Studies of immunoglobulins in schizophrenic patients have produced contradictory findings. Solomon *et al* (1969) demonstrated significantly higher serum IgA and IgM in psychiatric inpatients, although they found no difference between the schizophrenic and other psychiatric patient groups. While the elevation of serum IgA was confirmed by others (Strahilevitz and Davis, 1970; Hendrie *et al*, 1972), Bock *et al* (1970) found serum IgM to be decreased in schizophrenic patients and Domino *et al* (1975) found IgA to be decreased in acute schizophrenic patients. Pulkkinen (1977) showed that a good prognosis appeared to be connected with higher than average IgA and IgG concentrations at the beginning of treatment but Amkraut *et al* (1973) found patients with IgA and IgG levels below average to be more likely to recover than those with higher levels.

While Hunter *et al* (1969) found 13 per cent of unselected admissions to a psychiatric unit had raised total CSF immunoglobulin levels, only two reports of CSF immunoglobulin classes in schizophrenic patients have appeared and these have been contradictory. Torrey *et al* (1978) found an increase in CSF IgG concentrations in 35 per cent of chronic schizophrenic patients, although, in a subsequent report, Albrecht *et al* (1980) failed to replicate this finding.

The reason for these discrepancies is not clear. It is possible that the heterogeneity of the populations studied as well as lack of control of many environmental factors affecting immunoglobulin production (e.g. drug treatment, endemic viruses) could have led to the contradictory results. The CSF studies also may have suffered from a CSF gradient artifact. A recent study (Fossan and Larsen, 1979) has shown that IgG

levels vary significantly depending upon which fraction of CSF is assayed.

In a further attempt to examine immunoglobulin concentrations in schizophrenic patients compared with controls, we have measured IgG, IgA, and IgM concentrations in CSF and plasma from chronic poor prognosis schizophrenic patients who had not received medication for at least three weeks before the sampling procedures. In addition, we have controlled for a potential CSF gradient artifact.

Methods

Thirty-five chronic schizophrenic patients (diagnosed by Research Diagnostic Criteria, Spitzer *et al*, 1977), hospitalized on NIMH research wards at Saint Elizabeths Hospital, Washington, D.C., had spinal fluid and plasma samples taken simultaneously after a medication withdrawal period of at least three weeks. The sample consisted of 27 males and 8 females, mean age 28.7 (s.d. 17.4); 28 were Caucasian and 7 were black. They were all patients with unremitting illness whose symptoms failed to respond to neuroleptic medication sufficiently to be maintained outside a hospital; mean length of illness was 10.4 (s.d. 7.2) years. To assess the potential effect of neuroleptic drugs, a subgroup of seven patients had additional CSF and plasma samples taken while on at least two months of stable doses of neuroleptic medication. Spinal taps were performed in the morning on all subjects and fluid from the 10th to 15th cc used in all immunoglobulin analyses. CSF from 16 neurological controls was obtained for comparison; their mean age was 38.3 (s.d. 19.21), 13 were male, and 3 females, 12 were Caucasian and 4 were black; they were non-psychiatric patients presenting to a neurology service for evaluation of miscellaneous symptoms such as headache, tremors, or seizures of unknown aetiology; none had specific physical findings. Written consent was obtained from all subjects prior to spinal taps. For those patients who were unable to give informed consent, permission from close relatives was obtained. Since no matching plasma was available from the neurological patients plasma samples were obtained from 17 healthy laboratory workers (mean age 26.2 ± 6, 13 males, four females, 16 Caucasian, one black). All blood was drawn into heparinized vacutainer tubes. Plasma was prepared by centrifuging at 2,000 xg and stored at $-70°C$ until assayed. CSF samples also were stored at $-70°C$ until assayed.

Immunoglobulin assays were performed randomly in duplicates without knowledge of diagnosis using the Immuno-fluor procedure (Bio-Rad Laboratories)

TABLE I

Mean (±SEM) CSF and plasma immunoglobulins

	CSF						Plasma		
	IgG		IgA		IgM				
	µg%	% Total protein	µg%	% Total protein	µg%	% Total protein	IgG	IgA	IgM
Published Normal means Range	1.9 (1.4)‡ 4.6 (1.9)§	.028–.106*	.08 (.05)§	0–.02*	17.0 (.0005)§		800–1600†	120–230†	60–200†
Controls CSF N = 16 Plasma N = 17	2.26 (.41)	.066 (.01)	2.93 (.05)	.0088 (.001)	59.55 (16.5)	.0015 (.0004)	860 (61.7)	256 (21.9)	170 (14.01)
Schizophrenic patients N = 35	1.14 (.25)	.050 (.007)	.134 (.02)	.0038 (.0005)	11.53 (2.2)	.0005 (.0001)	630 (48)	127 (15.2)	123 (14.5)
t**	2.41	1.18	3.99	4.5	2.96	3.01	2.84	2.97	1.99
P**	> .02	NS	> .001	> .001	> .01	<.005	> .01	> .01	> .05

* Torrey *et al*, 1978

** Schizophrenic patients vs. controls

† Established by Bio-Rad Laboratories using the Immuno-Fluor method

‡ Weisner *et al*, 1975

§ Fishman *et al*, 1980

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for determination of IgA, IgG, and IgM in plasma and spinal fluid. Antibody to each immunoglobulin was covalently coupled to hydrophilic polyacrylamide beads to form an immunoadsorbent. Sample was added for all present immunoglobulin to bind to the immunoadsorbent. Fluorescently labeled monospecific antiserum was then added in excess to combine with all complexes in the solution. After centrifugation and pelleting of the fluorescent complexes, the pellets were washed twice in a buffer (pH 7.5 containing .15 mol NaCL and .01 mol sodium phosphate diluted in distilled water) and the fluorescence measured at an excitation wavelength of 485 mm and an emission wavelength of 525 mm on a standard laboratory fluorometer. Split sample coefficients of variation for samples assayed on separate days was 10.6 per cent (IgG), 7.6 per cent (IgA), and 5.3 per cent (IgM).

Four patients had immunoglobulins assayed twice from several different fractions collected from the same spinal tap in order to determine if a gradient existed in immunoglobulin levels in CSF. CSF protein levels were determined using the turbidometric method described by Annino (1964). Statistical analyses of all results were performed using two-tailed independent t-tests, unless otherwise stated.

Results

CSF and plasma IgG, IgA, IgM concentrations in mg per cent were significantly lower in the chronic schizophrenic patients compared with control groups. When expressed in mg/total protein, CSF IgG was not significantly lower, but IgA and IgM levels in the schizophrenic patients remained lower (Table I).

In the patient sample CSF and plasma IgA and IgM levels were positively correlated (Pearson $r = .39$, $P < .05$ and $r = .42$, $P < .02$ respectively) but the correlation between the IgG levels was not significant ($r = .06$). In the seven patients who were studied both on and off neuroleptic medication there was no difference between mean CSF or plasma concentrations of any of the immunoglobulins.

Sample storage time, a potential source of artifact not considered in previous studies, ranged from four years to less than a month. There was no significant correlation between time in freezer and immunoglobulin levels in CSF or plasma. When multiple CSF fractions from four patients' spinal taps were assayed, there was a clear trend toward lower levels of IgG, IgA and IgM with CSF samples taken from higher fractions (Table II) (mean 32 per cent decline in IgG; 25 per cent in IgA and 47 per cent in IgM).

TABLE II

Spinal fluid fraction. Mean (±SEM) IgG, IgA, IgM concentrations for four patients from different fractions of CSF used for analyses

	1–5 cc	9–15 cc
IgG (mg/100 ml)	1.78± .30	1.35± .5
IgA (mg/100 ml)	.2160± .13	.0871± .04
IgM (μg/100 ml)	48.75±17.0	33.7±8.0

Discussion

We did not find an increase in IgG, IgA and IgM levels in CSF and plasma of chronic schizophrenic patients. In demyelinating and infectious diseases of the CNS, on the other hand, relative increases in CSF gamma globulins, possibly due to CSF synthesis, have been found (Fishman, 1980). The finding that IgA and IgM levels in plasma and CSF of the schizophrenic patients correlate while IgG levels do not, is consistent with the notion that there is independent production of IgG in the central nervous system. In our patients, however, we found no evidence of increased production. Although antibody producing cells are known to be present in normal CSF (Manconi *et al*, 1976), their significance is unknown.

While we did not confirm the previous findings of elevations in IgG (Torrey *et al*, 1978), IgA and IgM (Solomon *et al*, 1969; Strahilevitz *et al*, 1970, 1976), in either CSF or plasma, our results may be consistent with the notion that neuroleptic medication may suppress the immune response. Although the patients in our study were withdrawn from all medications for about three weeks, they had previously received long-term neuroleptic treatment. The time period necessary for return to normal immune functioning after years of suppression is not known.

That neuroleptics affect the immune system is supported by several lines of evidence. Chlorpromazine has been linked to the presence of abnormal lymphocytes in the blood of schizophrenic patients (Fieve *et al*, 1966) and the development of systemic lupus erythematosis an immune complex disorder (Dubois *et al*, 1972; Fessel and Solomon, 1960; and Ananth *et al*, 1973). Antinuclear antibodies have also been associated with long-term neuroleptic treatment (Zarrabi *et al*, 1979; Gallien *et al*, 1976; Johnstone and Whaley, 1975). Lovett *et al* (1978) has reported a decrease in antibody production *in vitro* associated with chlorpromazine and Ferguson *et al* (1978) reported a suppressive effect of chlorpromazine on several measures of lymphocyte responsiveness. Our data could be interpreted as consistent with these findings. Whatever the aetiology of depressed immunoglobulins levels, it is interesting to speculate about the

possible clinical relevance of this state for those schizophrenic patients who manifest it.

There have been reports of a reduced life span among schizophrenic patients (Niswander *et al*, 1961 and 1963; Tsuang and Woolson, 1977). Two major categories of illness that conceivably would lower the life span of a population and could be associated with reduced immune responsiveness are infections and neoplasms. Some studies in the literature report an increase in infections among hospitalized mental patients (Tsuang *et al*, 1980; Alstrom, 1942; Babigian and Odoroff, 1969), while there is at least one report of increased resistance to infection (Doust, 1952). Whether more schizophrenics die of infectious diseases than the general population (Baldwin, 1979) remains unclear.

Although controversial (Baldwin, 1979; Fox, 1978), it has long been thought that the death rate from cancer is lower in schizophrenic patients than in the general population (Alstrom, 1942; Katz *et al*, 1967; Lindelius and Kay, 1973; Modrzewska and Book, 1979); however some studies of schizophrenic patients, treated with neuroleptics, report a relative rise in the incidence of cancer. Breast cancer, which has been associated with immune changes (Conesa *et al*, 1979) has been reported to be associated with neuroleptic use (Ettigi *et al*, 1973; and Overall, 1968); while this association has yet to be clarified (Thompson and Weissman, 1979), it may be related to a rise in prolactin levels induced by neuroleptic drugs (Meltzer and Fang, 1976) rather than immunologic alterations. Baur (1967) suggested that an excess of fatal blood dyscrasias, including neoplasms, reported among schizophrenic patients may be due to phenothiazines. Chronic administration of immune suppressive drugs, such as following organ transplantation, can lead to subsequent neoplastic development (Montie, 1979). Nevertheless, none of the patients we studied had evidence of a decreased resistance to infections and none were known to have neoplasms.

Alternatively, it is possible that abnormal immunity plays a role in the development of schizophrenia. Although abnormalities of lymphocytes as well as abnormal immune responses may be associated with neuroleptic treatment, some indirect measures of immune status, such as the alleged decreased prevalence of rheumatoid arthritis (Gregg, 1939; Nissen and Spencer, 1936) and decreased prevalence of allergy in schizophrenic patients (McAllister and Hecker, 1949; Beauchemin, 1936) were noticed before the advent of neuroleptics. Even decreased serum (Vaughn *et al*, 1949) and cellular immune responses were noted (Molholm, 1942). No recognizable immunological pattern has yet been reported and furthermore there is no consistency in findings among the published studies of schizophrenic patients. Thus, the interpretation of these findings remains largely speculative.

Future studies of 'first episode' schizophrenic patients, before medication commences, will be necessary to determine if abnormal immune functioning plays a role in the development of schizophrenia.

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