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Immunoglobulins, Autoantibodies and other Serum Protein Fractions in Psychiatric Disorders

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Summary. The levels of IgM, IgG and IgA were measured in the serum of 337 psychiatric inpatients (92 patients with bipolar depression, 150 patients with unipolar depression and 95 schizophrenics) and compared to 150 healthy subjects. A significantly higher level of IgM was found in all psychiatric groups compared with the controls, and IgM levels were more elevated in female patients than in male patients for the bipolar and unipolar groups. There were no differences for the other immunoglobulins (IgG, IgA) among the groups studied. In 51 of the patients (17 bipolar, 34 unipolar), other measurements were performed (C-reactive protein, antinuclear antibodies, lymphocyte antibodies, thyroid antibodies, complement and the third and fourth factors of complement). The unipolar group showed a significant rise of C-reactive protein values and the presence of antinuclear antibodies. Interestingly all patients with antinuclear antibodies were females. No difference was found between psychiatric patients and controls in lymphocyte antibodies, thyroid antibodies and values of complement.

Key words: Unipolar – Bipolar – Schizophrenia – Autoantibodies – Immunoglobulins

Introduction

During the last decade, several clinical investigators have reported a higher frequency of immunological disturbances in psychiatric patients (Pearson 1973, Bech and Rafaelsen 1974, Strahilewitz et al. 1976, Pulkkinen 1977). Some of these studies are difficult to interpret because of the lack of sophistication in diagnostic procedures, insufficient control of potential interfering factors such as concomittant drug treatment and concurrent somatic illnesses. Therefore, the question remains open as to whether any of these abnormalities are primary or secondary to environmental aggression (e.g. viruses). The purpose of this study was to investigate plasma protein factors in normal subjects and in psychiatric drug-free patients and to evaluate the effect of sex on these parameters.

Patients and Methods

A total of 337 psychiatric patients who had been hospitalized between March 1975 and February 1976 at the University Psychiatric Institute Brugmann were included in the present study. The age distribution of these patients was 25 to 68 years with a mean age of 42. All diagnoses were made according to the criteria of Feighner et al. (1972); 92 patients were suffering from bipolar depression (51 females, 41 males), 150 from unipolar depression (68 females, 82 males) and 95 patients were diagnosed as schizophrenics (49 females, 46 males). Patients with a diagnosis of alcoholism, drug addiction, organic psychosis or with somatic illnesses were excluded from the study.

All patients were drug-free for at least 8 weeks and studied during the same period. Patients who had been treated with lithium salts, MAOI or neuroleptics within 1 month prior to the wash-out period were not included in the study. The control group consisted of 105 healthy subjects (35 females, 70 males) of similar age span (25 to 65).

The serum levels of IgG, IgA and IgM were immunologically measured by classical single radial immunodiffusion using antisera commercially available (Behring) (Mancini et al. 1965). The same technique (classical single radial immunodiffusion) was used to measure C-reactive protein (CRP), and the third and the fourth factors of complement with Behring Werke antisera. Antinuclear antibodies (ANA), and the lymphocyte and thyroid antibodies were detected by indirect immunofluorescence on tissue sections (rat liver for ANA) (McCluskey 1971). Total hemolytic complement was measured according to the method of Kabat and Mayer (Kabat and Mayer 1961). The Student *t*-test was used for statistical analysis.

Results

Table 1 includes the serum levels of IgM, IgG and IgA in the three groups of patients and controls. All psychiatric patients had significantly higher serum IgM compared to normal subjects (normals compared to unipolars, $P < 0.001$; normals compared to bipolars, $P < 0.001$; normals compared to schizophrenics, $P < 0.001$). Table 2 shows the distribution of IgM according to sex in the three groups of patients and in the controls. The differences in IgM levels between females and males were not significant in normal and in schizophrenic subjects.

There was however a difference according to sex for the bipolar patients ($P < 0.05$) and the unipolar patients ($P < 0.05$) with higher IgM levels in females than in males. Significant differences were also found in IgM levels for unipolar and

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Table 1. Immunoglobulin levels of pychiatric patients and normal subjects

Immunoglobulin levels (g/l)	Schizophrenia $n = 95$	Unipolar depression $n = 150$	Bipolar depression $n = 92$	Normal subjects $n = 105$
IgM	171.4 ± 98.1*	194.6 ± 126.2*	269.3 ± 160*	115.2 ± 62.3
IgG	1041.9 ± 335	1060.7 ± 299.6	1073.0 ± 264.9	1107.0 ± 313.0
IgA	224.6 ± 119.6	222.3 ± 100.9	243.5 ± 122	235.0 ± 110

* $P < 0.001$ compared to normal subjects

Table 2. Distribution of IgM according to sex

IgM (g/l)	Female	Male	P values
Bipolar depression	299.2 ± 173.3 ($n = 51$)	219.1 ± 119.9 ($n = 41$)	< 0.05
Unipolar depression	234.5 ± 152 ($n = 68$)	152 ± 84.2 ($n = 82$)	< 0.05
Schizophrenia	170.4 ± 93 ($n = 49$)	155.2 ± 83.3 ($n = 46$)	NS
Normal	129.2 ± 75 ($n = 35$)	106 ± 52.9 ($n = 70$)	NS

The P values have been calculated using the Student t-test comparing males and females of each group

Table 3. Levels of CRP and complement in unipolar and bipolar depression

	Unipolar depression ($n = 34$)	Bipolar depression ($n = 17$)
CRP (mg/ml)	1. 5 ± 1.15	1.21 ± 0.89
C total (units)	433.24 ± 150.54	507.65 ± 94.11
C3 (mg/ml)	110.62 ± 34.59	111.53 ± 29.46
C4 (mg/ml)	43.59 ± 15.28	40.71 ± 14.99

bipolar females compared to the control group (unipolar compared to normals, $P < 0.001$; BP compared to normals, $P < 0.001$). This was not the case for schizophrenics. Significant differences were found in IgM values of the male psychiatric patients compared to the male controls (unipolars compared to normals, $P < 0.001$; bipolars compared to normals, $P < 0.001$; schizophrenics compared to normals, $P < 0.001$). Conversely, none of the diagnostic groups had significantly elevated serum IgG levels compared to the controls and no significant differences in IgA were found between the various diagnostic groups and the controls (Table 1). The levels of CRP, ANA, lymphocyte antibodies, thyroid antibodies, factors of complement are also documented. Among the 92 bipolar depressed patients 17 sera were tested for CRP, ANA and other protein fractions, and 34 sera were tested from the 150 unipolars. We found 10 of the 34 unipolar patients with elevated CRP (> 1 mg/ml) compared to only 1 of the 17 bipolar patients (Table 3). We found ANA at a titer varying between 1/40 and 1/320 in 7 of the 34 unipolar patients and all of them were females. In contrast, ANA were only found in 1 of the 17 patients in the bipolar group. We found no correlation between CRP and ANA. There was no difference between psychiatric patients and controls for lymphocyte antibodies, thyroid antibodies and values of complement as the third and the fourth factor (Table 3).

Discussion

Our results in drug-free schizophrenics and depressed patients confirm the interest in performing immunological studies in psychiatric patients. Elevated IgM levels were found in all psychiatric groups. There is much controversy about serum IgM values in the literature. Salomon et al. (1969) found elevated serum IgM in schizophrenic patients, and Bech et al. (1971, 1976) found significantly lower serum IgM in schizophrenics when compared with controls. Pulkkinen (1977) differentiated withdrawn schizophrenic patients and paranoid schizophrenic patients, and found elevated serum IgM in withdrawn schizophrenic patients and lower serum IgM in paranoid schizophrenics. Strahilewitz and Davis (1970) however observed normal serum IgM in schizophrenic patients. The present study documents differences in serum IgM levels between males and females. Higher IgM levels were observed in females than in males in the bipolar and the unipolar groups in contrast with normals and schizophrenics. This sex difference has never been reported previously in the literature. In relation to this observation, it appears important to mention that Fuller Torrey (1982) in a recent study found a significant increase in IgM antibodies to cytomegalovirus in the CSF of some schizophrenics and some bipolar patients. The mean level of IgM antibody in the CSF of the females was significantly higher than in the CSF of the males. These observations are consistent with the hypothesis that elevated IgM levels represent active (viral) infection, reactivation of latent (viral) infection, or abnormally persistent antibodies after some (viral) infection. Concerning IgG, no differences were found between psychiatric patients and controls. This is consistent with previous reports of serum immunoglobulin studies (Salomon et al. 1969; Strahilewitz and Davis 1970; Bech et al. 1971; Hendrie et al. 1972; Domino et al. 1975; Bech 1976; Strahilewitz et al. 1976). As for IgA, none of the diagnostic groups had significantly different serum IgA values compared to the controls. This is also consistent with the studies of Bech et al. (1971), Hendrie et al. (1972) and Domino et al. (1975). Strahilewitz and Davis (1970) found significantly elevated serum IgA in schizophrenics but later reported that the elevated IgA were found only in females and black schizophrenics (the patients of the present study were all Caucasian). Salomon et al. (1969) reported significantly elevated serum IgA in psychiatric patients but not particularly in schizophrenics. Later, they reported an association between elevated serum IgA and poor diagnosis of schizophrenia (Amkraut et al. 1973). Vecchio et al. (1975) found elevated serum IgA only in schizophrenics with a positive family history of schizophrenia.

We also found 10 of the 34 unipolar patients had significantly elevated CRP values. This protein represents an acute phase reactant protein and is normally increased in inflammatory processes. This has not been previously described in the literature for unipolar patients. Our results concerning ANA were particularly unexpected. Indeed, 7 of the 34 unipolar patients had these autoantibodies at a low titer and all 7 patients were females; these results are consistent with some previous studies. Von Brauchitsch (1972), Johnstone and Wholey (1975) and Deberdt et al. (1976) have found positive antinuclear factors in 25% to 36% of depressive patients, but they did not find any relation to sex. In contrast, Shopsin et al. (1973), Mellsop et al. (1973), Gottfries and Gottfries (1974), Ghose et al. (1977), Gastpar and Müller (1980), Fontana et al. (1980) did not observe a higher frequency of these antibodies in psychiatric patients compared with controls. No difference between psychiatric patients and controls was found for values of total hemolytic complement and the third and the fourth factors of complement. In contrast, Fontana et al. (1980) reported a significant serum increase in C4 concentration in patients with bipolar psychosis. The lack of concordance in the literature on these abnormalities may be due to several reasons: differences in diagnotic criteria or in time of hospitalization, diet, treatment and analytical methods. Finally, recent studies along with the present investigation indicate that psychiatric patients have humoral immunological abnormalities which may represent a response to a variety of antigenic aggressions like viral infections. Whether these immune disturbances are related to the etiopathogeny of psychiatric disorders or are secondary to the disease process remains to be proven. Prospective studies on larger samples are needed to clarify the relationship between the immune system and subgroups of psychiatric patients.

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