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# IMMUNOGLOBULINS AND VIRAL ANTIBODIES IN DEPRESSIVE PATIENTS

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**SUMMARY**

Patterns of serum and C.S.F. IgG, IgA and IgM, and haemagglutination inhibiting (HI) antibodies and complement fixing (CF) antibodies against rubella and cytomegaloviruses respectively and total CSF protein were investigated in 30 depressives, 20 each in neurological and surgical patients. Significant changes in total CSF protein and immunoglobulins in depressives and neurological patients in comparison to surgical subjects indicate an etiological similarity between the two groups. Failure to detect antibodies in C.S.F. of these subjects and statistically insignificant seropositivity refute the claim of viral hypothesis for depression but similar alterations in these body proteins in depressives and neurological patients raise other aetiological possibilities.

The last couple of decades have led to advancement of biological psychiatry. One of the many biological advances involve the immunochemical analysis and virological study of blood and cerebrospinal fluid (C.S.F.) of patients of functional psychoses towards understanding of their etiology. Investigations done in this area are in favour of the hypothesis that some individuals who are lebelled as schizophrenics have acute or chronic brain disease, possibly acquired in utero or early infancy or from the environment, whose cause is supposed to be a viral agent (Torrey and Paterson, 1974).

Similar claims have been made for depressive psychosis too, specially in association to herpes simplex virus (Lycke et al; 1974; Rimon and Halonen, 1969) and influenza virus (Deo, 1958 and Bental and Jerusalam, 1958). Even in the face of evidence of specific blood factors in patients with depression, some physicians reject the idea of a biochemical defect being involved in a disease that affects the mind. The occurrence of depression after influenza (Meninger, 1926; Deo, 1958) and after other viral encephalitis and reports of serum and CSF protein abnormalities in depression (Fontana et al., 1980; Hunter et al., 1968) all point out towards an infectous agent, possibly a virus, being involved in the aetiopathology of depression. Not only laboratory data but clinical and epidemiological data as well indicate a possibility of viral aetiology of functional psychoses (Torrey and Paerson, 1976).

Although the work in this direction has been going on for the last two decades in the west, only a few reports and that too regarding serum porteins only have emerged from this country (Alias et al., 1969; Kuruvilla et al., 1973 and Prakash et al., 1978). None of the Indian investigators have attempted to study the issue of viral aetilogy of functional psychoses and therefore, the present study was undertaken in depressives to address this issue.

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**Material and Method**

The sample for the present study consisted of depressive, neurological and surgical patients. The depressed patients were drawn from indoor department of psychiatry and control group (Neurological and Surgical patients) from the indoor departments of Neurology and Surgery of G. M. and Associated Hospitals and K.G.'s Medical College, Lucknow. The patients of the experimental group were between 17-50 years, weighing more than 35 Kg and fulfilled the diagnostic criteria of Feighner et al. (1972) for depression. The neurological patients included in the study were having illness of either unknown or doubtful or multiple etiology and were given the diagnostic level according to ICD-9 classification. Surgical patients included in the study were having noninfective, non-neoplastic, non-neurological, noninflamatory and non-immunological surgical problems and were planned to be operated under spinal anaesthesia. The neurological controls were those who were scheduled for lumber puncture as advised by the incharge neurophysician.

The patients having any associated physical illness, pregnancy, raised intracranial tension and use of immunosuppressant drugs were excluded from the study. All the patients of the experimental group selected for the study were then kept drug free for 15 days and were given barbiturate hypnotics as and when required.

10 cc of venous blood was drawn from the experimental, as well as, control group. It was then centrifuged and serum was separated. 109 cc of CSF was collected from both the groups within 24 hours of serum collection. The serum and CSF samples for immunoglobulins and viral antibodies estimations were blindly coded and were kept in deep freeze at $-20^{0}$C till further estimation. Three immunoglobulins viz. IgG, IgA and IgM were estimated in serum and CSF of all the subjects by single radial immuno diffusion method as described by Mancini et al. (1965).

For estimation of viral antibodies in serum and CSF two viruses-rubella and cytomegalo virus were selected. The estimation of rubella antibodies was done by haemaglutination inhibition test as described by Halonen et al. (1967) and cytomegalo virus antibodies were estimated by complement fixation test as described by Lannette and Schmidt (1964). Total CSF protein estimation was done by turbidometric method based on the technique described by Mulemans (1965).

**Results**

Thirty patients of depression and twenty each of neurological and surgical problems completed the study. Among the neurological controls, patients of Guillian Barre Syndrome and epilepsy formed more than half the total, while the others were suffering from motor neuron disease, cerebellar ataxia and parkinson's disease. Hernia and haemorrhoids formed the major bulk among the surgical controls, others being varicocoel, vesicular calculus, foreign body in thigh, fissure in anus and vesico-vaginal fistula. Majority of the subjects were male, hindu and married. The mean weight was above 50 Kg in all the groups.

The normal mean total CSF protein for healthy surgical controls was 30.7 mg/dl while the same in the depressives and neurological controls was 42.7 mg/dl and 115.5 ml/dl respectively (Table-1).

*TABLE-I Mean CSF Protein in experimental and control groups (mg/dl)*

| | (A) Depression (N = 30) | (B) Neurological Controls (N = 20) | (C) Surgical Controls (N = 20) |
|---|---|---|---|
| Mean | 42.7 | 115.49 | 30.71 |
| S. D. | 15.5 | 134.19 | 7.22 |

A Vs. B : t = 3.00, d.f. = 48, p <.01
A Vs. C : t = 3.27, d.f. = 48, p <.01
B Vs. C : t = 2.80, d.f. = 38, p <.01

Total C.S.F. proteins were, thus, significantly increased in depressives (p 0.01) as well in neurological subjects (p 0.01) as compared to surgical controls. A comparison of neurological and dépressive patients indicated that the former had significant increase ($p<0.01$). The mean serum values of IgG, IgA and IgM were found to be higher in depressives and in neurological controls as compared to surgical controls (Table-II). The mean values of IgG and IgA in serum were significantly higher in depressives and neurological controls (p 0.05) as compared to surgical controls. However, there is no significant increase for mean IgM.

*TABLE II Serum Immunoglobulins in experimental and control groups (mg/dl)*

| Immunoglobulin | Depression (N = 30) A | Neurological (N = 20) B | Surgical (N = 20) C |
|---|---|---|---|
| *IgG* | | | |
| Mean±s.d. | 1290.4±82.6 | 1305.3±83.4 | 1232.5±110.6 |
| *IgA* | | | |
| Mean±s.d. | 208.0±23.7 | 207,5±13.2 | 172.3± 48.9 |
| *IgM* | | | |
| Mean±s.d. | 100.4±13.6 | 102.4±11.2 | 96.2± 12.7 |

*Significances*

| | IgG | | IgA | | IgM | |
|---|---|---|---|---|---|---|
| | t | p | t | p | t | p |
| A Vs. C | 2.07 | <0.05 | 3.45 | <0.001 | 1.12 | N.S. |
| A Vs. B | 0.62 | N.S. | 0.09 | N.S. | 0.52 | N.S. |
| B Vs. C | 2.33 | <0.05 | 3.07 | <0.01 | 1.62 | N.S. |

The CSF immunoglobulins are expressed as % of total protein. CSF IgG was detected in all the subjects, IgA in only 7 depressives and 5 neurological patients while IgM only in 5 neurological patients. In CSF lower limit of detection for IgG was 1.0 mg/dl, for IgA 3.3 mg/dl and for IgM 2.6 mg/dl. IgA and IgM were detected only when total CSF protein was 53 mg/dl or more and 300 mg/dl or more respectively. Mean CSF IgG/TP% was found to be higher in depressives and neurological subjects as compared to surgical controls (Table-III). Mean CSF IgA/TP% is found to be significantly increased in neurological controls as compared to depressives (p 0.05).

*TABLE-III C.S.F. Immunoglobulins in experimental and control group expressed in mg/dl as a%of the total C.S.F. protein (TP) (CSF Ig/TP%)*

| Ig/TP | Depression (N = 30) A | Neurological (N = 20) B | Surgical (N = 20) C |
|---|---|---|---|
| *IgG/TP* | | | |
| Mean±s.d. | 8.0±2.6 | 10.2±2.9 | 6.6±1.9 |
| *IgA/TP* | (N = 7) | (N = 5) | – |
| Mean±s.d. | 6.7±0.5 | 8.0±0.9 | – |
| *IgM/TP* | | (N = 5) | – |
| Mean±s.d. | – | 0.9±0.2 | – |

*Significances*

| | CSF IgG/TP% | | CSF IgA/TP% | |
|---|---|---|---|---|
| | t | p | t | p |
| A Vs. C | 2.10 | 0.05 | – | – |
| A Vs. B | 3.17 | 0.01 | 2.65 | 0.05 |
| B Vs. C | 4.63 | 0.001 | – | – |

Haemagglutination inhibiting (HI) antibodies against rubella virus and complement fixing (CF) antibodies against

dytomegalo virus were estimated in serum and CSF of all subjects. The lowest and highest dilutions tested for HI and CF antibodies were 1:10 and 1:1280 and 1:8 and 1:256 respectively. In none of the CSF samples HI and CF antibodies were detected.

The incidence of seropositive cases for HI antibodies against rubella virus and geometric mean of antibodies titres were found to be higher in depressives and in neurological patients as compared to surgical controls but application of test of significance on log values of antibody titres revealed these differences to be insignificant. A similar trend was noticed for C.S.F. antibodies against cytomegalo virus.

**Discussion**

One of the important observations in this study revealed significanlty higher total C.S.F. proteins in depressives and neurological subjects. Similar observations, were made by Hunter et al., as early as in 1968 and their 8 out of 17 patients (47%) with depressive syndrome had raised total CSF protein ( 60 mg/dl.). In the present study, however, only 13.3 of patients of depression had more than 60 mg/dl total CSF protein. Hunter and his associates were able to correlate total CSF protein with the clinical picture and course of illness but did not specify the pathological mechanism for protein increase. Nonetheless, based on clinical picture of their patients, these workers speculated that an encephalitis or encephalitic type of illness or flaring up of an original infection or onset of a similar one or an encephalopathic process could be considered possible pathological processes responsible for protein increase in C.S.F.

The findings of mean serum IgG, IgA and IgM in surgical controls is consistent with the findings of Schultze and Heremann (1966), Samuel et al. (1970) and Gupta et al. (1980) for normal values. IgG and IgA were found to be significantly increased in depressives and neurological patients whereas increments in IgM could not reach statistical significance. The observations in this study are similar to one of the reported studies in literature (Gowdy, 1980), but contrary to others (Soloman et al., 1969., Torrey et al., 1978, Fontana et al., 1980). Although, the observations are inconclusive, yet they point out towards an important fact that depressives and neurological patients are similar in respect of serum immunoglobulins.

In a given condition immunological abnormalities could be due to various factors viz. it may be an autoimmune phenomenon or it may be due to antigenic stimulation of any nature. In autoimmune disease such as, systemic lupus errythematoses, pernicious anaemia, rheumatoid arthritis and thyroiditis, low serum IgA concentrations are quite frequently found. But in this study a reverse trend has been observed which does not favour the possibility of an autoimmune phenomenon. Hence, it is more likely that these immunological abnormalities as found in the present work could be due to an antigenic stimulation.

The mean CSF IgG/TP% ratio (6.6 ± 1.9%) found for the surgical controls is consistent with the reported values of 6.1% (Link and Muller, 1971) and 6.4% (Torrey et al., 1978). Mean CSF IgG/TP% ratio was found to be higher in depressives and neurological patients as compared to surgical controls. In neurological patients such an increases is frequently reported for variety of neurological disorders (Link and Muller, 1971). Torrey et al. (1978) investigated CSF IgG/TP% in manic-depressive patients and found elevated CSF IgG/TP% in two patients, but they related this to an experimental drug melationin which these patients were taking. CSF IgA/TP% in this work was found to be significantly increased in depressives and neurological patients as compared to the normal values reported by Torrey et al. (1978).

Incidence of HI antibodies were found to be 80% in serum of surgical controls which is consistent with the studies of Seth (1971) and Mathur et al. (1974). In depression 83.3% patients were found to be seropositive for HI antibodies against rubella virus which is slightly less than that reported by Torrey et al. (1978) and Halonen et al. (1974) who found 90% depressives to be seropositive but this increase is statistically non- significant when compared to surgical con- trols. In none of the patients HI antibodies were detected in the CSF. Incidence of CF antibodies against cytomegalo virus were found to be 75.0% in surgical controls. Mathur et al. (1981) studied only female subjects and found 83.5% females seropositive. The geometric mean titre in serum was also found to be higher in depressives (17.8%) and neurological controls (18.7%) in comparison with surgical controls (12.7%). But this difference was statistically non-significant. Lycke et al. (1974) found significanly higher incidence of CF antibodies against cytomegalo virus in depressives (69%) as compared to controls (50%). Torrey et al. (1978), however, failed to find such a higher incidence. None of the patients studied in the present work were fond to be positive for CF antibodies against cytomegalo virus in CSF. Torrey et al. (1978) also failed to find any patient positive for CF antibodies in CSF except for patients of multiple sclerosis. Higher incidence of HI and CF antibodies against rubella and cytomagalo viruses respectively and higher geometric mean titre of these antibodies in depressives and neurological subjects in compariosn to surgical controls raises the possibility of an etiological relationship between these viruses and depressive and neurological disorders. However, in view of statistically insignificant differences and non-detection of these antibodies in C.S.F. of these subjects make this speculation questionable.

This study, therefore, has failed to establish viral hypothesis for primary depression. However, certain observations deserve consideration. Increased total C.S.F. protein, raised levels of IgG and IgA and significant increase in CSF IgG/TP and CSF IgA/TP% ratios in depressives and a similar pattern in neurological patients (of unknown aetiology) indicate an etiological similarity between two groups. Had there been a similar trend for viral antibodies, the pathogenic process behind these findings could have been easily explained. But in view of inconclusive trends with viral antibodies, other possibilites arise. Changes in CSF immunoglobulins may be a reflection of changes in serum immunoglobulins (Schultze and Horeman, 1966) or it may be due to local immunoglobulin production similar to seen in multiple sclerosis and SSPE patients (Cutler et al; 1970) for which slow virus aetiology is now being proposed (Adams and Bell, 1976). Further, it may be due to increased enothelial cell permeability secondary to local inflammation (Fishman, 1980) or it may be result of an encephalitis like process as proposed by Hunter et al. (1968). Thus, clear understanding of these issues will require simultaneous study of a number of variables such as blood brain barrier, histopathology etc. The findings of C.S.F. proteins and serum and C.S.F. proteins and serum and C.S.F. immunoglobulings in this work, therefore, prompt for further work to elucidate the mechanism behind those alterations.

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