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IMMUNOGLOBULIN PATTERNS IN SCHIZOPHRENIC PATIENTS[1]

S. C. TIWARI[2]
NAROTTAM LAL[3]
J. K. TRIVEDI[4]
J. SAYEED[5]
L. M. BAHAUGUNA[6]

SUMMARY

Immunoglobulins G, M and A were estimated in serum and cerebrospinal fluid (CSF) of 30 schizophrenics, 20 neurological controls and 20 surgical controls. Significant increased levels of serum Ig A and M were detected in schizophrenics. An association was observed beiween increasing levels of serum IgA and IgM with the duration of disease and the number of episodes. CSF IgG/TP% was also significantly increased with the severity of the disese. On the basis of viral aetiology of schizophrenia it can be concluded that the increase in immunoglobulins synthesis might be due to the persistent antigenic stimulation.

Psychotic disorders have generated much interest regarding their aetiopathology and various aspects of these disorders have been explored during last few decades. Currently, the emphasis centres upon immunological and virological aspects of the illness. However, only a few reports have appeared from India, which deal with elementary serum protein studies only (Alias *et al.*, 1968; Kuruvilal *et al.*, 1973; Prakash and Sethi, 1978). The present work was undertaken to study the pattern of immunoglobulins and to establish the relationship, if any, with the severity of the schizophrenia.

MATERIAL AND METHODS

The cases for the present study consisted of 30 schizophrenics (experimental group), 20 cases of neurological diseases and 20 surgical patients (control group). The diagnosis of schizophrenia was based on the criteria proposed by Feighner *et al.* (1972). The age ranged between 17-50 (mean 32) years and body weight 45 kgs. or more. Those with physical illness, pregnancy, mental retardation (primary or secondary) or history of intake of drugs, e.g. immunosuppressives and phenothiazines and/or drug addiction and ECT in past three years were not included. For surgical controls patients were taken up who did not have any past or family history of neuropsychiatric illness. These patients did not report any psysical sickness except minor surgical problems and were scheduled to be operated under spinal anaesthesia. For neurological controls patients with unknown, doubtful or multiple aetiological conditions (viz. Mortor Neuron Diease, Guillian Barre Syndrome, Parkinson's Disease, Epilepsy and Cerebellar Ataxia) were taken. They had negative past and family history of psychiatric disorders and were free from any active spychiatric and other physical sickness at the time of investigation. The criteria for age, weight,

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[2]Senior Research Officer,
[3]Reader,
[4]Lecturer,
Department of Psychiatry, K. G.'s Medical College, Lucknow.
[5]Research Assistant
[6]Pool Officer
Upgraded Deparemnt of Pathology and Bacteriology, K.G's Medical College, Lucknow.

etc. for control groups were same as in schizophrenia. All the patients in experimental and control groups were thoroughly examined and investigated to rule out any overt or occult psysical illness.

The schizophrenic patients were kept only on barbiturates for 15 days from the date of hospitalization. 4.0 ml. of venous blood and 3.0 ml. CSF were collected for the study. Total CSF proteins were estimated by the turbidometric method (Meulemans 1960) and immunoglobulins were estimated by single radial immunodiffusion technique (Manicini *et al.*, 1965).

RESULTS

Mean serum IgA value was found to be significantly higher in schizophrenics and in neurological controls compared to surgical controls. There was no significant increase in serum IgM in schizophrenics and neurological controls as compared to surgical controls (Table-1).

IgG in CSF could be detected in all subjects but IgA and IgM only in five neurological controls Mean IgG/TP% in CSF was found to be significantly higher in schizophrenics and in neurological controls when compared with surgical controls. Further comparison revealed that CSF IgG/TP% was significantly higher in neurological controls than in schizophrenics (Table-1).

Regarding the relationship of various immunoglobulins with the number of episodes it was found that mean levels of serum IgG, Ig M and IgA register a rise with increasing number of episodes. Only IgA was significantly higher in schizophrenic patients with 3 or more than 3 episodes as cmpared to patients with first episode. Serum IgM was significantly higher in schizophrenic patients with 3 or more than 3 episodes

TABLE 1. *Statistical analysis of serum and CSF Immunoglobulins (mg%) in different groups*

Groups	IgG Mean±S. D.		IgM Mean±S. D.		IgA Mean±S. D.	
	Serum	C. S. F./ TP%	Serum	C. S. F./ TP%	Serum	C. S.F/ TP%
Schizophrenia (30) Vs. Surgical Control (20)	1285.7±95.6 / 1232.5±110.6	8.4±2.6** / 6.6±1.9	100±12.4 / 96.2±12.7	— / —	210±24.9*** / 172.5±48.9	— / —
Schizophrenia (30) Vs. Neurological control (20)	1285.7±95.6 / 1305.3±83.4	8.4±2.6** / 10.2±2.9	100.12.4 / 102.4±11.2	— / —	210±24.9 / 207.5±13.2	— / —
Surgical control (20) Vs. Neurological control (20)	1232.5±110.6* / 1305.3±83.4	6.6+1.9*** / 10.2±2.9	96.2±12.7 / 102.±+11.2	— / —	172.5±48.9** / 207.5±13.2	— / —

The value represent the % of total protein only for CSF immunoglobulins.
Figures in parentheses indicate number of cases.
Significant differences with control groups, p value *<0.05, **<0.01, ***<0.001

as compared to both the first and the second episode patients, but this increase was more marked in the former. Serum IgG was not found to be significantly related to number of episodes of schizophrenia. Similarly IgG/TP% in CSF was also found to be increasing as the number of episodes increased, but this increase was significant only for the patient with 3 or more than 3 episodes on comparison with the patients of first episode. These results are shown in table-2.

A positive relationship was noted in the levels of immunoglobulins IgA and IgM and duration of illness (time from the onset of first episode till the day of present investigation). Levels of these proteins were significantly higher in patients with 5 years duration on comparison with 1 year duration. Significant increase in IgM was also detectable even in patients with 1 to 5 years of duration when compared to 5 years of sickness. In contrast to above, no significant alteration in the level of serum IgG was noted with the duration of disease.

Statistically significant differences were observed in the ratio CSF IgG/TP%, when patients with 5 years of illness were compared with patients having 1 year and 1 to 5 years=duration of illness.

Data obtained in the present study were further analysed in relation to the family history of neuropsychiatric illness in patient's first degree relatives. There were 8 patients with family history of schizophrenia and one patient with family history of neurological problem (bilateral congenital deafness). No significant relationship was noted tetween the levels of serum immunoglobulins with the positive familial history of schizophrenic illness, however, CSF IgG/TP% was found to be statistically significant in in such patients (10.0±1.3)when com-

TABLE 2. *Statistical analysis of Serum and C.S.F. Immunoglobulin* (mg%) *in different groups of episodes in Schizophrenia.*

Groups in Schizophrenia	IgG Mean±S. D.		IgM Mean±S .D.		IgA Mean±S. D.	
	Serum	C. S.F./ Tp%	Serum	CSF/ TP%	Serum	CSF/ TP%
1st Episode (14) VS	1266±106.4	6.9±2.3	93.9±11.9	—	196.3±20.0	—
2nd Episode (7)	1278±68.3	8.8±2.6	99.6±8.7	—	212.8±25.5	—
2nd Episode (7) Vs.	1278±68.3	8.8±2.6	99.6±8.7*	—	212.8±25.5	——
3rd or>3 episode (9)	1321.8±85.5	10.3±1.4	110.8±7.9	—	229.4±16.3	——
1st Episode (14) Vs.	1266±106.4	6.9±2.3***	93.9±11.9**	—	196.3±20.0***	—
3rd or>3 Episode(9)	1321.8±85.5	10.3±1.4	110.8±7.9	—	229.4±16.3	——

Figures in parentheses indicate number of cases.
Significant differences with control groups, 'p' value *<0.05, **<0.01, ***<0.001

TABLE 3. *Statistical analysis of Serum and C. S. F. immunoglobulin (mg%) in different duration of illness in Schizophrenia.*

	IgG Mean±S.D		IgM Mean±S.D.		IgL Mean±S.D.	
Duration	Serum	CSF/Tp%	Serum	CSF/TP%	Serum	CSF/TP%
<1 year (4) Vs.	1293.5± 41.6	4.9±0.5	90.5± 3.9	—	182.8±16.1	—
1-5 year (9)	1250.3±106.6	7.4±2.3	92.7±1.2	—	205 ±21.4	—
<1 year (4) Vs.	1293.5± 41.6	4.9±0.5***	90.5± 3.9***	—	182.8±16.1**	—
5 years (17)	1302.5± 93.6	9.7±2.0	106.6± 10.5	—	219.2±22.8	—
1-5 years (9) Vs.	1250.3±106.6	7.4±2.3*	92.7± 11.2**	—	205 ±21.4	—
5 years (17)	1302.5± 93.6	9.7±2.0	106.6± 10.5	—	219.2±22.8	—

Figures in parasentheses indicate number of cases.
Significant differences with control groups, 'p' value *<0.05, **<0.01, ***<0.001.

pared with patients having no family history of neuropsychiatric illness (7.5 ±2.5;p<0.05).

DISCUSSION

A continuing problem with immunological studies in regard to psychiatric disorders has been lack of concordance among numerous reports in literature and also with that of this work (Solomon *et al.*, 1969; Fontana *et al.*, 1980; Bock *et al.*, 1971; Bock and Rafaelsen, 1974; Amkraut *et al.*, 1973; Gowdy, 1980). This has chiefly been because several factors such as age, race, sex, diagnostic criteria, duration of disease, hospitalization, ECT and drugs (Fregusson *et al.*, 1978; Kolyaskina, 1967) influence immunological studies and hardly ever all factors have been controlled. It would, therefore, be a farfetched conclusion if any cause-effect relationship is inferred out of this controversial situation. Nevertheless, we have been able to demonstrate significant elevation of serum IgA and CSF/TP% in both schizophrenics and neurological subjects and in schizophrenics these elevations and that of surum IgM are significantly related to increasing number of episodes and duration of illness. The serum levels of IgA and IgM is reported to increase with the duration of hospitalization (Solomon *et al.*, 1969) and similarly Torrey *et al.*, (1978) have demonstrated elevation of CSF IgG/TP% in multiple admission schizophrenics. These reports favour our observations. None of the other immunological studies done so far have investigated this association.

The most remarkable finding to emerge from the study is significant increase of CFS IgG in both schizophrenics and neurological subjects in the absence of similar increase of serum IgG, which is consistent with the observations of Torrey *et al.* (1978), Riddoch and Thompson, (1970) and Link and Muller, (1971). This indicates a *de novo* synthesis of IgG in the CNS (Tourtellotte, 1970; Lumsden, 1972); and such a pattern has frequently been reported to

occur in various viral, bacterial and other inflamatory conditions of CNS (Fishman, 1980).

Increase in serum and CSF immunoglobulin for neurological patients can be easily explained, as for the most of the neurological conditions included in the present study, a slow virus aetiology is now being proposed (Adams and Bell, 1976). The evidence in this regard is still not conclusive and is mainly from epidemiological data (Timakov and Zuev, 1980, Adams and Bell, 1976). Zilber *et al.* (1963), Khondkarian *et al.* (1971) and Gardashyan (1972) have been able to demonstrate clinical and pathological features resembling motor neuron disease in rhesus monkeys inoculated with brain suspension obtained from patients of motor neuron disease indicating a viral aetiology. A number of evidences indicate that Parkinson's disease is also caused by common viruses which attain latent form of infection (Bojinov, 1971; Gajdusek *et al*, 1971). An infectious (viral) aetiology is similarly claimed for Gullian Barre Syndrome (Brain and Walton, 1969).

Does a similar pattern of immunological alteration in schizophrenics indicate a viral aetiology as in neurological subjects. At present the answer is only inferential not conclusive. In the light of recent evidence of viral aetiology of schizophrenia, number of episodes may be thought to represent either recurrent attacks by a virus or activation of virus which was quiescent previously. If an attack can be related to increase in viral particles, it is possible that spillage of these particles lead to activation of immunological defence of the body, as indicated by increased synthesis of immunoglobulins. It is therefore tempting to assume that familial incidence observed in schizophrenia is due to some inherent succeptibility of brain to a virus for which countless environmental factors may be responsible. These arguments, however, at best, are only assumptions and a concrete evidence of viral etiology can only be provided by demonstration of a specific agent coupled with experiments that aspire to fulfill Koch's postulates.

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