

Protein Electrophoresis in Schizophrenias

By M.S.A. Gawad and Z. Abdel Gawad

ABSTRACT

The fractions of serum proteins in 19 male schizophrenic patients were analysed quantitatively by paper electrophoresis. The α_2 -globulin was found to be distinctly increased above average normal. The trend of increase was also found for the α_1 and the B-globulin fractions. The γ -globulin was almost normal in our schizophrenics. In some patients the albumin was slightly increased. The total proteins were significantly increased in all schizophrenic patients studied. The A/G ratio was decreased. These findings may be interpreted by an increased globulin synthesis in schizophrenic patients especially of the α_2 -globulin fraction, and this protein fraction may contribute to the etiology of the schizophrenic syndrome.

INTRODUCTION

One of the oldest recognized illnesses of mankind is the disturbance that we now call schizophrenia. Even 3300 years ago its characteristics were noted and differentiated from other mental conditions. In spite of this long history, it is almost as baffling to us today as it was when it was first described in the Ayura Veda of the ancient Hindus (Kety, 1970).

Thudichum, who has been called the father of modern neurochemistry, in the preface of his monumental "Treatise on the Chemical Constitution of the Brain", published in 1884, stated, "many forms of insanity are unquestionably the external manifestations of the effects upon the brain-substance of poisons fermented within the body" a concept which continues to motivate much of our current research.

Through the years, ever since the studies of Kraepelin, there has been speculation that some types of schizophrenia may be the result of, or influenced by, a toxic factor. Numerous studies have been conducted but none has led to definite conclusions.

Biochemical theories of mental disease have been modified and reformulated during the past 15 years. It remains true that there is as yet no unified theory of schizophrenia which can reconcile all the available evidence.

Recent advances in psychiatric research utilizing chromatography, electrophoresis and density gradient ultracentrifugation, have managed to isolate a plasma protein factor in a relatively pure form without losing very much of its metabolic effect. The study of the isolated substance indicates that it is an α -2-globulin.

MATERIAL and TECHNIQUE

19 male schizophrenics whose ages ranged between 23 and 35 years and duration of symptomatology from 2 to 9 years, were admitted to the in-patient psychiatric department at Kasr El-Aini Hospital. They presented with different types of schizophrenia, but none was in an acute phase. They were kept on the ordinary hospital diet, without any medication for one week before taking blood sample for analysis. Their general physical condition was satisfactory without clinical manifestations of malnutrition or undernutrition. There was neither hepatosplenomegaly in any one of them, nor any evidence of active infection.

The apparatus used for electrophoresis is that described by El-Marsafy *et al.* (1965). The electrophoretic patterns were quantitatively evaluated by direct photometry, using the Spinco Analytrol Unit.

The total proteins in each sample was determined by the refractive index method.

RESULTS

The results of the analysis of the various protein fractions of the schizophrenic patients are tabulated in Tables No. 1 and 2. Table No. 1 indicates the percentage of each fraction. In the last two lines of the table the average normal percentage of each fraction is indicated. The standard deviation is also quoted.

Table No. 2 indicates the value of the total serum proteins as determined refractometrically for each patient. The calculated gm. protein fraction/100 ml. serum is tabulated for all the patients together with the average normal and the standard deviation.

The detailed analysis of the variations in the different globulin fractions and the albumin fraction in schizophrenic patients is presented in Fig. (1). In this diagram the normal range is indicated by solid arrows extending vertically from the average normal value of each fraction which is represented as an open circuit. This normal range is considered as $\pm 2 \sigma$, the value of which is indicated for each fraction in the normal values quoted in Table No. 2.

A dotted idealised electrophoretic pattern representing a normal case is traced by a dotted line interconnecting the average normal values of each protein fraction.

The average normal level of the γ -globulin fraction is 1.88 gm/100 ml. with a rather high standard deviation of 0.36. This fraction in schizophrenic patients approaches very closely to the normal average, only 4 patients had a slightly reduced γ -globulin fraction representing about 21% of the cases studied. One patient only had a high γ -globulin value of 3.4 gm/100 ml. This may have been due to a recent chance infection. The B-globulin fraction is also generally increased in schizophrenic patients. Three patients only had a very slightly decreased B-globulin fraction. Five patients were within the normal range. The remaining 11 patients had their B-globulin fraction above the higher normal limit of 0.80 gm %, reaching the level of 1.45 gm % in one patient.

The α -2 and α -1 fraction in schizophrenic patients were increased, compared to the normal range. Only two cases had α -1 fraction of normal values. Six patients (31.7%) had an α -2 fraction higher than 200% of the high normal limit.

Eight of the schizophrenic patients had an albumin fraction higher than the normal range. Six patients are within the normal range. The remaining five patients had a very slightly reduced albumin fraction.

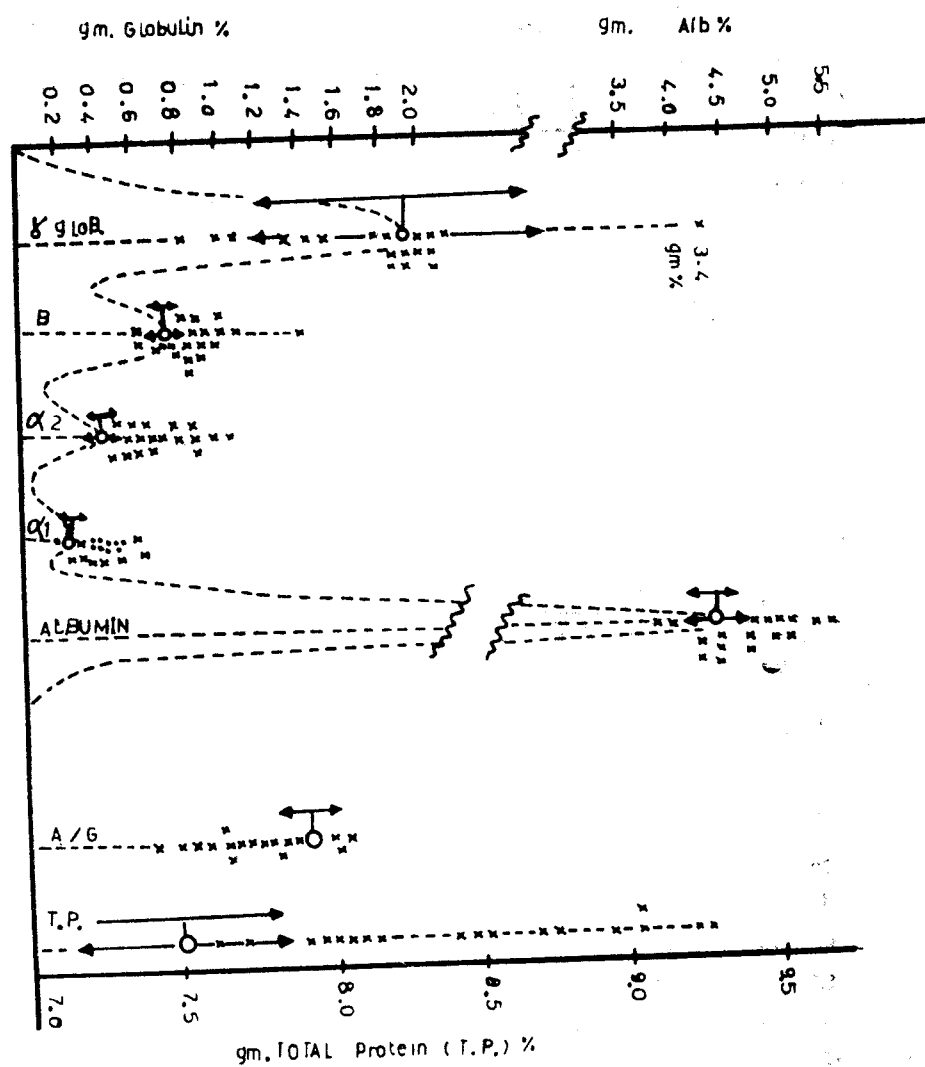
TABLE I

Case No.	Globulin Fractions					Albumin	Albumin
					Total		Globulin
	γ	β	α_2	α_1	Globulin		
1	22.3	13.9	10.4	3.4	50.0	50.0	1.00
2	22.7	12.4	12.4	3.6	51.1	48.9	0.96
3	21.9	9.4	10.4	5.2	46.9	53.1	1.13
4	22.9	6.1	8.4	6.1	43.5	56.5	1.30
5	23.5	8.9	11.3	4.7	48.3	51.7	1.07
6	20.8	6.9	9.2	4.6	41.5	58.5	1.41
7	18.4	8.4	10.6	3.9	41.3	58.7	1.42
8	39.1	7.9	8.7	5.2	60.9	39.1	0.64
9	23.8	7.2	7.7	3.0	41.7	58.3	1.40
10	15.6	17.0	7.1	5.0	44.7	55.3	1.24
11	18.6	13.4	8.8	2.6	43.4	56.7	1.31
12	25.3	11.1	7.6	2.7	46.7	53.3	1.14
13	12.8	10.6	12.3	7.3	43.0	57.0	1.33
14	22.3	10.9	7.3	5.1	45.6	54.4	1.19
15	25.7	10.2	9.7	6.6	52.2	47.8	0.92
16	25.2	11.1	11.9	7.7	55.9	44.4	0.80
17	20.5	11.7	6.8	4.4	43.4	56.6	1.30
18	17.4	10.2	8.3	4.2	40.1	59.9	1.49
19	22.8	12.7	9.1	5.4	50.0	50.0	1.00
Normal	24.7	9.7	5.3	2.7		57.6	1.36
S.D. σ	3.8	1.3	0.7	0.4	42.4	2.2	0.13

TABLE II

Case No.	gm. Protein & Protein Fraction/100 ml.							Total Protein
	Globulin Fractions					Albu- min	Albumin Globulin	
	α 1	α 2	β	γ	Total			
1	0.31	0.94	1.25	2.00	4.50	4.50	1.00	9.0
2	0.32	1.12	1.12	2.04	4.60	4.40	0.96	9.0
3	0.44	0.87	0.79	1.84	3.94	4.46	1.13	8.4
4	0.46	0.64	0.46	1.74	3.30	4.29	1.30	7.5
5	0.42	1.01	0.79	2.08	4.30	4.60	1.07	8.9
6	0.37	0.74	0.55	1.68	3.34	4.74	1.41	8.1
7	0.36	0.99	0.78	1.71	3.84	5.46	1.42	9.3
8	0.45	0.76	0.69	3.40	5.30	3.40	0.62	8.7
9	0.24	0.63	0.58	1.93	3.38	4.72	1.40	8.1
10	0.43	0.60	1.45	1.33	3.81	4.70	1.24	8.5
11	0.21	0.69	1.06	1.47	3.43	4.48	1.31	7.9
12	0.20	0.57	0.83	1.90	3.50	4.00	1.14	7.5
13	0.58	0.97	0.84	1.01	3.40	4.50	1.33	7.9
14	0.44	0.64	0.95	1.94	3.97	4.73	1.19	8.7
15	0.56	0.83	0.87	2.18	4.44	4.06	0.92	8.5
16	0.59	0.95	0.89	2.02	4.45	3.55	0.80	8.0
17	0.41	0.63	1.09	1.91	4.04	5.26	1.30	9.3
18	0.32	0.64	0.79	1.34	3.09	4.61	1.49	7.7
19	0.43	0.73	1.02	1.82	4.00	4.00	1.00	8.0
Normal	0.20	0.40	0.73	1.88	3.15	4.35	1.36	7.5
S.D. or	0.02	0.04	0.07	0.36		0.15	0.13	0.35

Fig 1. Deviation of the Schizophrenic Serum Protein Fractions (X) from the average normal values



This general trend in increased globulin fractions of the α -2, α -1 and B-globulins is reflected in the A/G ratio for the schizophrenics. This ratio is appreciably decreased in most patients. This ratio has been found to be as low as 0.64 compared with the average normal range of 1.36. Only 4 schizophrenic patients had an A/G ratio higher than the average normal, but not exceeding the level of 1.49 which is still in the normal range.

DISCUSSION

In a symposium on recent developments in schizophrenia (Coppen and Walk, 1967) it was stated that there are three separate lines of evidence all pointing in the same direction. Firstly, it is likely that most of the hallucinogens (mescaline, psilocybin, dimethyltryptamine) are methylated derivatives of the cerebral neurohumours (dopamine, serotonin, noradrenaline. Secondly, there is evidence that schizophrenic patients excrete an excess of a compound possibly DMPE, not commonly found in normal urine. Thirdly, feeding methyl donors to schizophrenic patients makes their symptoms worse. These three facts all suggest that some disorder of methylation is concerned in the aetiology of schizophrenia.

One of the consistent puzzles has been the fact that the elevation of the α -2-globulin is characteristic of about 60% of the typical schizophrenic population. Various pathophysiological manifestations have been observed in these patients. For example, Caldwell *et al* (1967) reported that stage 4 sleep is reduced significantly in those patients characterized by an elevation of the α -2-globulin. Similarly, Rodin *et al.* (1968) reported that photic evoked potentials and proprioceptive feedback mechanisms appear to be disturbed in these patients.

An alternate hypothesis would consider all of the patients as being affected by a mechanism which is in various stages of evolution. Lozovsky *et al.* (1967) suggest that the α -2-globulin reaches its height during the first year of the illness and that, as chronicity develops, it becomes less until, after about 7 years, it is no longer elevated. This supports the hypothesis that this substance is an important component of

a stress mechanism which is initially out of control and eventually goes into a stage of failure somewhat similar to the stress concept as proposed by Selye.

Frohman et al. (1969) in their studies of the effect of the α 2-globulin on the metabolism of tryptophan showed that it increased both influx and efflux of tryptophan, but the influx is greater under the influence of the α 2-globulin than is the efflux. The fact that the α 2-globulin is 80% lipid permits the hypothesis that true interaction with the lipids of cell membranes would in some way affect selectively the mechanism of transport across the membrane. Tryptophan and 5-hydroxytryptophan are the precursors of serotonin, which plays an important regulatory function in the processing of information within the brain.

Kety (1970) showed that excessive N-methylation may occur in patients with schizophrenia, resulting in the formation of psychotomimetic substance such as N-dimethyl serotonin or bufotenine.

Stowik (1964) examined blood serum proteins in chronic schizophrenics and control cases using the electrophoretic method. The electrophoretic picture of blood serum proteins in schizophrenic patients exhibited a constant abnormality as compared to the normal protein pattern. This consisted in a decrease of serum albumin level and an increase in the globulin level. Changes in β and γ -globulin levels were statistically significant. They concluded that the results of their study seem to support Ushakoff's theory of hepatocerebral homeostasis in the pathogenesis of schizophrenia.

Fessel et al. (1961) reported their electrophoretic and analytic ultracentrifuge studies in sera of chronic psychotic patients (mainly schizophrenics). 10% showed splitting in α 2-globulin, 17% showed a sharp line superimposed on γ -globulin and 32% an abnormally shaped γ -globulin curve in densitometric analysis. A mean hypergammaglobulinemia was found in all groups of patients and some sera showed significantly an elevation of S-19-macroglobulins. The possibility of other secondary factors coincidental to psychosis influencing serum proteins was considered.

The extensive literature precludes an exhaustive survey in this discussion, and the studies cited above constitute a representative rather than comprehensive survey of the literature.

In our study, as evident from discussion of the results, the level of plasma albumin in our schizophrenic patients is not significantly different from the average normal. The general trend, however, is increased globulin fractions of the α -2, α -1 and B-globulin. This result is consistent with most published reports. γ -globulin level in our patients is very close to the normal average.

From the suggested relationships of these various studies, it would appear most probable that, within the immediate years ahead, the results of painstaking investigations by a number of different investigators will define a pathophysiological mechanism which is important to the understanding of the mechanisms involved in the schizophrenic illness.

REFERENCES

- Caldwell, D.F. and Domino, E.F. (1967) Electroencephalographic and eye movement patterns during sleep in chronic schizophrenic patients. *Electroenceph. Clin. Neurophysiol.*, **22** : 414.
- Coppen, A. and Walk, A. (1967) (Eds.) *Recent Development in Schizophrenia. Symposium. R.M.P.A.*
- El-Marsafy, M.K. and Abdel-Gawad, Z.J. (1965) *Chem. U.R.A.*, **8** : 19.
- Fessel, W.J. and Granbaum, B.W. (1961) Electrophoretic and analytical ultracentrifuge studies in sera of psychotic patients. *Ann. Intern. Med.*, **54** : 1134—1145.
- Frohman, C.E., Warner, K.A., Barry, C.T. and Arthur, R.E. (1969) Amino acid transport and the plasma factor in schizophrenia. *Biol. Psychiat.*, **1** : 201.
- Kety, S. S. (1970) *Biochemistry, Schizophrenias and Affective Illnesses* (Introduction). Edited by : Himwich, H.E. Baltimore : The Williams and Wilkins Co.

- Lozovsky, D., Krasnova, A., Factor, M., Polyanskaya, N. and Popova, N. (1967) The effect of the serum of schizophrenic patients upon certain glucose transformations. In *Transactions of the Symposium on Biologic Research in Schizophrenia*. p. 151. Moscow: Lenin Printing Co. (Pravda).
- Rodin, E.A., Grisell, J.L. and Gottlieb, J.S. (1968) Some electrographic differences between chronic schizophrenic patients and normal subjects. In Wortis, J. (Ed.) *Recent Advances in Biological Psychiatry*. Vol. 10. p. 194. New York: Plenum Press.
- Stowik, S. (1964) Electrophoretic study of the blood serum proteins in chronic Schizophrenia. *Neurol., Neurochir. Psychiat. Pol.*, 14/1: 119 – 126.

AUTHORS

- M.S.A. Gawad, M.D., M.R.C. Psych., D.P.M. (London), D.M., Professor of Psychiatry, Cairo University, Egypt.
- Zeinab Abdel Gawad, B.Sc., M.Sc. (London), Egyptian Organization for Biological and Vaccine Production, Virus Research Laboratory, Agouza, Cairo.

الموجز

التحليل الكهربائي لبروتينات الدم في حالات الفصام

أجرى التحليل الكهربائي لبروتينات الدم في تسعة عشر فصامياً، وقد تبين ارتفاع الألفا - ٢ جلوبيولين بدرجة دالة بالمقارنة بالعينة الضابطة، كذلك تبين ارتفاع نسبة الألفا - ١ والفي٢ جلوبيولين، أما الجاما جلوبيولين فقد كانت نسبتها في حدود مثيلتها للعينة الضابطة.

وفيما يتعلق بالالبومين فقد لوحظت زيادة طفيفة في بعض الحالات ولكنها ليست دالة احصائياً.

وعليه، فإن الكمية الكلية لبروتينات الدم في مرضى الفصام أعلى من مثيلتها في العينة الضابطة، ويمكن تفسير تلك الزيادة أنها ناجمة عن زيادة في تصنيع أو تكوين الجلوبيولين خصوصاً الألفا - ٢؛ وقد يوكن لهذه الظاهرة علاقة ببياثولوجيا مرض الفصام.

ABSTRAIT

L'électrophorèse des protéines chez les schizophrènes

Les fractions sériques de protéines ont été analysées chez dix-neuf malades schizophréniques par l'électrophorèse à papier. Nous avons trouvé que le nouveau de α -2-globulins est distinctivement élevé, au-dessus de la limite normale. Aussi, les fractions de α -I et β -globulins ont été élevées. Le niveau de γ -globulins fut presque normal chez les dix-neuf schizophrènes, tandis que l'albumine fut un peu élevée. Le total des protéines fut élevé chez tous les malades schizophréniques de l'échantillon examiné. Le rapport entre l'albumine et les globulins (A/G) fut abaissé. Ces résultats peuvent être attribués à l'augmentation de la synthèse des globulins, et particulièrement nous désignons la fraction de α -2-globulins chez les malades schizophréniques. De même nous concluons que cette dernière fraction peut contribuer à la genèse de la maladie schizophrénique.