

Electrophoresis in Psychiatry: Autoimmune Hypothesis for Schizophrenias

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ABSTRACT

Out of 19 Schizophrenic patients screened for their electrophoretic protein pattern, five were selected, on basis of their high protein content, for further study by immunoelectrophoresis (I E P). Anti-Total Human Serum was used for the five cases while Anti IgG, IgM, and IgA was used for the three cases that revealed increased gamma-globulins. The results of I E P indicated presence of antibodies. A short review of the studies of the mechanism involved in the formation of antibrain antibodies and their nature was attempted.

INTRODUCTION

There are data indicating that in schizophrenia there may be a disturbance of membrane permeability. However, these ideas do not go beyond a hypothesis and have still not received convincing experimental proof.

It is well known that the changes in cell membrane permeability, or even the destruction of the membranes, are accompanied by a diffusion of the intracellular contents, especially the cell proteins, into the environment. If the human lymphoid system has never previously been in contact with a cell protein, then contact with protein in lymph nodes or in the spleen will result in corresponding antibodies to these proteins. This principle is the basis for all contemporary noninfectious immunobiology and particularly the concept of autoimmune diseases of man and animals.

Towards this end, we carried out this immunoelectrophoretic study aiming at the identification of the factor that may be responsible for the hypothesized autoimmune process.

TABLE I

Case	gm. Protein and Protein fraction/100 ml.							
No.	GLOBULIN FRACTIONS					Albu-	Albumin	Total
	α 1	α 2	β	γ	Total	min	Globulin	Protein T.P.
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	0.78	1.84	3.54	4.46	1.13	8.4
4	0.46	0.64	0.46	1.74	3.31	4.29	1.30	7.6
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	3.36	4.74	1.41	8.1
7	0.36	0.99	0.78	1.71	3.84	5.46	1.42	9.3
8	8.45	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	3.80	4.70	1.24	8.5
11	0.21	0.69	1.06	1.47	3.42	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	3.44	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	7.0
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		7.5
S.D.	0.02	0.04	0.07	0.36		0.15	1.36	0.35

MATERIAL AND METHOD

Out of the 19 schizophrenic patients screened for the electrophoretic protein pattern (Gawad & Abdel Gawad, 1979), five were selected for further study by immunoelectrophoresis (IEP). Their selection was on basis of their high protein content, 9 gm/100 ml. in two cases, 9.3, 8.7 and 8.1 gm/100 ml. in the other three cases respectively. Table (1). IEP using antitotal human serum was carried out for the five samples. Three cases out of the five revealed increased α -globulins, for these further analysis using specific anti IgG, IgM, IgA was conducted.

The precipitin arcs formed for each patient's sample is compared to the arcs of a normal serum sample on the same slide. Changes from the normal arcs include :

1. Length of the arc.
2. Thickness of arc and dye concentration.
3. Distance of the arc from the antibody basin.

Identification of the different arcs in the IEP slide is guided by the use of charts, in text publication.

RESULTS

The results of IEP using Anti Total Human Serum for the five cases are shown in Table (2). All cases revealed dense arcs for α globulin. Three cases revealed long and dense arcs for IgG and IgM. All cases showed normal arc for IgA.

The results of IEP using specific Anti IgG, IgM, and IgA for the three case that revealed increased α -globulins are shown in Table (3). All three cases showed near and dense arc of IgG. Two cases showed long and dense arc of IgM. All three showed normal arc of IgA.

Significance of findings :

1. Increased IgG indicates presence of antibodies.
2. Increased IgM indicates an active process of stress whether infection or otherwise.
3. IgA is indicator for secretory antibodies.

TABLE II

Immunoelectrophoresis using Anti Total Human Serum

Case	cc-2	IgG	IgM	IgA
1	+	+	+	N
2	+	+	+	N
3	+	N	N	N
4	+	N	N	N
5	+	+	+	N

TABLE III

Immunoelectrophoresis using specific Anti IgG, IgM, and IgA

Case	IgG	IgM	IgA
1	Near and dense	Long and dense	N
2	Near and dense	N	N
5	Near and dense	Long and dense	N

DISCUSSION

Snezhnevsky *et al.* (1970) studied the state of cell membranes in schizophrenic patients. They chose erythrocytes of the peripheral blood stream as the object of investigation. The state of erythrocyte membranes was determined by their degree of resistance of hemolysis to a weak solution of hydrochloric acid (0.004 N HCl) in vitro. Study of the resistance of erythrocytes in patients with different forms of schizophrenia revealed the following regularities. The position of the circle in Fig. (1) shows the resistance of the erythrocytes of corresponding groups of pa-

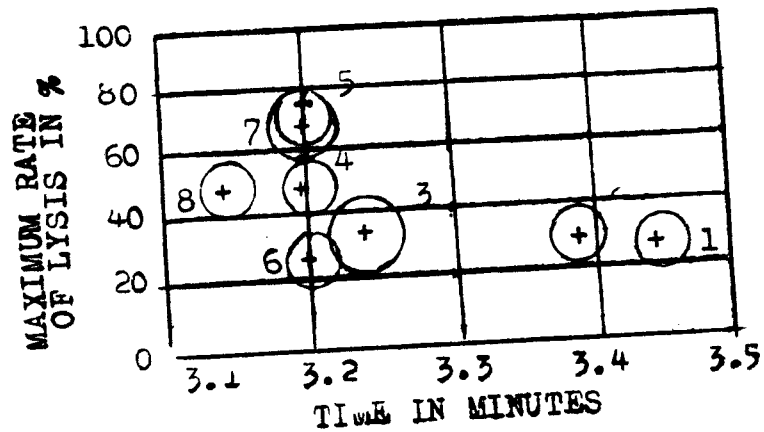


Fig. 1: The resistance of erythrocytes of schizophrenic patients in comparison to that in individuals with other mental disorders and in normals. The position of the circles from the left to the right of the figure indicates increasing resistance, i.e., the erythrocytes of the group of paranoid schizophrenics (circle No. 8) show the least resistance, whereas those of the normals (circle No. 1) show the greatest. The radii of the circles reflect the average deviations. Circles : 1, normals; 2, epileptics and patients with organic psychoses; 3, nuclear schizophrenia; 4, periodic forms of schizophrenia; 5, circular form of periodic schizophrenia; 6, shift-like schizophrenia; 7, manic-depressive psychoses; 8, paranoid schizophrenia.

tients : the further to the right, the greater the resistance. The figure demonstrates that the resistance of normals is the greatest. The radius of each circle reflects the average deviation of the results. The dispersion of results for normals is very small, i.e. the group of normals is a relatively homogeneous one. The group of epileptic patients and patients with organic lesions of the brain differs slightly from the normals, but these differences are not statistically significant. Quite different results were found in studying the resistance of schizophrenic erythrocytes. Their resistance was significantly lower than in controls. Also schizophrenic patients differ from epileptics, from patients with organic psychoses as well as from normals. These facts are evidence for disturbed functions of cell membranes in schizophrenic patients. It has also been shown that the schizophrenic serum brings on significant destructive processes which can involve other body cells than the erythrocytes and especially cells of the nerve tissues.

In the Institute of Psychiatry in Russia Snezhnevsky et al. (1970) carried out extensive studies devoted to the isolation of the biologically active factor from the blood of schizophrenic patients. The use of different preparative methods including column chromatography and electrophoresis has shown that this biological factor is related to a protein fraction of the serum. It also possesses the mobility of B-globulin Fig. (2), and contains in its structure B-lipoproteins. These pathological compounds have the ability to change the structure of membranes in cell systems, leading to diffusion of intracellular contents, especially the cell proteins, into the environment. Contact of these proteins with the lymphoid tissue will result in corresponding antibodies to these proteins. It was possible to establish that, in patients with a nuclear form of schizophrenia, "pathological" lymphocytes were seen significantly more often than in normals.

It was assumed that the antigens which sensitized the lymphocytes in schizophrenic patients may be of nervous tissue proteins. To verify this assumption the lymphocytes of schizophrenics were introduced into a culture of human nervous tissue (Gosheva et al. 1966). When the lym-

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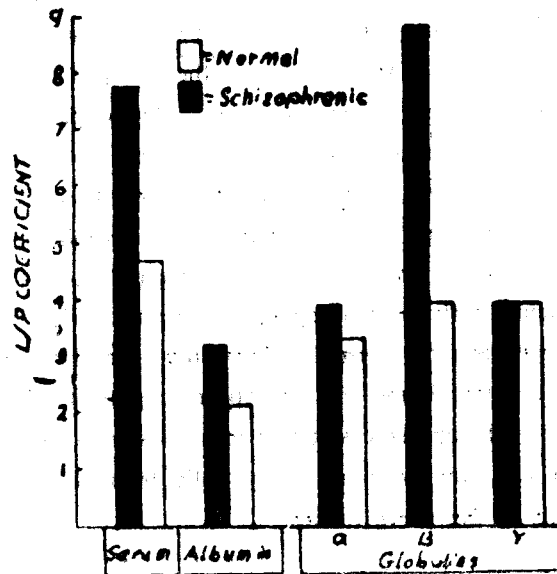


Fig. 2: The activity of different protein fractions of the blood serum of schizophrenic patients as shown by the lactate/pyruvate (L/P) ratio. The fractionization of the globulins was accomplished by electrophoresis.

phocytes of normals were introduced into the culture of human nervous tissue there were no significant changes in the cells of the tissues nor in the lymphocytes. However, when the lymphocytes of schizophrenic patients were introduced into a similar culture, a destruction of the cells of the nervous tissue as well as of the lymphocytes themselves was seen. These changes were expressed in marked vacualization, granular destruction of the cytoplasm, reduction of the cell axons, nuclear pyknosis and lysis.

A study of the preliminary stage of incubation of lymphocytes with cells of nervous tissue permitted the observation of an interesting phenomenon. After 24 hours of incubation in the tissue culture a formation of peculiar "bridge" between the lymphocytes and cells of the brain tissue culture took place. The lymphocytes of schizophrenic patients formed these bridges five times more frequently than did the lymphocytes

of the controls (Fig. 3). A study of the nature of the bridges has shown that they contain large amounts of DNA. These data permit one to make a preliminary conclusion indicating that the proteins of the nervous tissue participate in the sensitization of lymphocytes in schizophrenic patients. In addition antibodies active against soluble human brain proteins were tested in schizophrenic serum using the complement fixation test at cold temperatures.

A series of experiments was carried out for the study of the mechanism involved in the formation of antibrain antibodies and their nature.

Schizophrenia and Biological Correlates



Fig. 3: "Bridge" between a lymphocyte and the cells of nerve tissue in culture. (Used by kind permission of the Honorary Editors of the Proceedings of the Royal Society of Medicine.)

It was established that after a prolonged and rather intense psychic and somatic loading (a marked state of stress) it was also possible to find antibrain antibodies in titers 1:40 and 1:80 in the blood of normal volunteers. In other words, an intensive state of stress can bring on an immunological reorganization in relation to tissue of the "suprabarrier" organs.

These data are evidence for the fact that, in schizophrenic patients with the nuclear form, the development of a pathological process is accompanied by a diffusion of the nerve tissue proteins through the cell system of the brain into the blood stream. As a result some immunological changes occur in response to the appearance of the so-called foreign antigens.

Heath et al. (1957) showed that a protein fraction isolated from the sera of schizophrenic patients induced transient symptoms characteristic of schizophrenia when given intravenously to nonpsychotic volunteer subjects. The name "taraxein" was given to the presumed active factor. Developments in recent years have shown that the psychosis-inducing component of taraxein is the γ -G immunoglobulin (IgG) fraction.

In our study, there is definite increase in IgG fraction which indicates the presence of a homeostatic process leading to the formation of antibodies. The increase in IgM fraction is an indicator for an active stress situation; this biochemical finding is positively correlated with the clinical condition of the three patients in whose sera the phenomenon was detected, as they were in acute psychotic state.

To sum up, the current hypothesis is that the schizophrenic patient has an unusual globulin of fluctuating titer, possibly genetically determined and probably antibody. This globulin can combine with cells in the septal region of the brain (an activation center involved in integration of pleasure and emotional expression) to impair physiological activity at this site probably by altering neurohumoral conduction, and thereby induce disturbed behaviour. The nature of the antibody and of the specific brain antigen requires further definition.

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المسوح

التحليل الكهربائي في مجال الطب النفسي : فرض المناعة الذاتية

(أوتواميوني) لحالات الفصام

لقد اختار الباحثان خمس حالات من بين تسعة عشر فصاميا سبق أن أجرى لهم تحليل كهربائي لبروتينات الدم ، وذلك على أساس ارتفاع كمية البروتينات في هذه الحالات الخمس ، حتى يتسنى إجراء التحليل الكهربائي المناعي (الأميوني) لهم . ولقد استخدم لهذا الغرض مضاد للمصل الكلي للإنسان وذلك في الحالات الخمسة ، بالإضافة الى ذلك استخدمت مضادات نوعية في الثلاث حالات التي أظهرت ارتفاعا في الجاما - جلوبيولين ، وهذه عبارة عن مضادات لأجزاء الجاما - جلوبيولين المختلفة (ج ، م ، ١) .

والنتيجة التي توصل اليها البحث بواسطة هذا النوع من التحليل الكهربائي هي وجود أجسام مضادة ، ولقد قام الباحثان باستعراض الدراسات السابقة التي تعرضت للميكانيزم المسئول عن تكوين هذه الأجسام المضادة للمخ ، وكذلك طبيعة هذه الأجسام .

ABSTRACT

L'Electrophorèse en Psychiatrie : Une Hypothèse Autoimmune pour les Schizophrénies

Parmi dix-neuf patients schizophréniques chez qui on avait étudié le modèle d'électrophorèse de protéines, cinq présentant un taux élevé de protéines ont été choisis pour des études d'immunoelectrophorèse plus poussées. L'évaluation du total de l'antiserum humain a été faite pour cinq sujets, par ailleurs l'anti IgG, IgM, et IgA ont été calculés pour les trois sujets révélant une élévation des globulins. Les résultats de l'IEP ont montré la présence d'anticorps. Une revue brève des études des mécanismes responsables dans la formation des anticorps contre le cerveau et de leur nature a été tentée.