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Serum Proteins in Huntington's Chorea

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Introduction

Huntington's chorea is transmitted by a rare autosomal Mendelian dominant gene. Its hereditary transmission is facilitated by a late onset of the condition in many cases. Often the first signs are not seen until late in the reproductive period, so that it is not uncommon for a patient already to have produced a number of children before the diagnosis is made. On a theoretical basis, 50 per cent. of these offspring are at risk for carrying the gene and consequently for developing the condition themselves.

It is, therefore, highly desirable that some means of detecting the carrier state should be sought. It has been suggested that carriers of the Huntington's chorea gene are prone to show psychopathic personality changes which may antedate the onset of choreic signs by many years (Mayer-Gross, Slater and Roth, 1960). This is not always so. About half of the 44 patients with Huntington's chorea reported by Minski and Guttmann (1938) had normal premorbid personalities. Furthermore, abnormality of personality is too unspecific an observation for use as a clinical marker for the carrier state in genetical counselling. Electroencephalographic changes have been reported to appear before the onset of chorea (Patterson, Bagchi and Test, 1948). These findings, however, remain to be confirmed.

There have been relatively few biochemical studies of Huntington's chorea, and in most instances the subjects of investigation have been selected because the diagnosis has been already established. There have been no consistently positive findings, and no prospective study in which possible candidates for the condition in families with Huntington's chorea have been studied from a biochemical point of view and followed up to correlate biochemical with genetical results. In a recent study (Cowie and Seakins, 1962) two sons of a mother with Huntington's chorea were found to have raised levels of serum alanine. No sign of Huntington's chorea was at that time apparent in these boys. Two other sibs gave normal values. Delinquency in this sibship (age range: 21 to 14 years) was considered as a possible early manifestation of the gene for Huntington's chorea, but it has not been possible to follow this family for further study.

In a search for genetical markers of the carrier state, it would seem logical to seek first for biochemical or other changes amongst those in whom the morbid state of Huntington's chorea has already been reached. If changes are found, these can then be looked for in relatives who may be carriers. Our report is concerned with a study of serum proteins in a group of patients in whom the diagnosis of Huntington's chorea was already established. This approach was stimulated by the work of McMenemey (1961) who suggested the study of immunity mechanisms in Huntington's chorea and other neurological diseases characterized by the degeneration of large numbers of nerve cells. He suggested the possible emergence of mutants which might fail to produce metabolic substances essential for the survival of neurons, and might stimulate the formation of antibodies. If such mechanisms were in fact responsible, it would not be unreasonable to suppose that immunity reactions would antedate the onset of clinical signs in Huntington's chorea. If so, the study of immunological changes might prove remunerative by indicating a dynamic process rather than the accumulation of by-products of degenerative change once the condition was established.

McMenemey studied serum from patients with a variety of neurological diseases by electrophoresis and reported some suggestive changes in Huntington's chorea. In the present study a larger group of Huntington's chorea patients have been investigated.

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Material and Methods

Blood was obtained from 14 patients with Huntington's chorea and from a series of 14 control patients admitted to the same mental hospital for conditions other than Huntington's chorea. The control patients were selected to match the Huntington's chorea patients for sex and as nearly as possible for age and length of residence in the same ward at time of examination. A variety of tranquillizing drugs were being taken by patients of both groups. These included chlorpromazine, thiopropazate, meprobamate, perphenazine, thioridazine and trifluoperazine. Although it has been shown that various drugs may have a small effect in raising serum globulins (Faurbye and Clausen, 1965), it was considered unlikely that any clear-cut changes would emerge affecting the comparison between the two groups of patients (Table I).

Serum was prepared from the blood samples and frozen immediately for storage at −20° until analysed. Electrophoretic analysis was performed on cellulose acetate strips, using the procedure described by Gammack and Hector (1965), but with minor modifications. Approximately 0·5 μl. aliquots of serum were applied to individual 20 cm. by 5 cm. cellulose acetate strips (Oxoid Division of Oxo Ltd., London) by means of a Unostencil pen, size No. 1 (A. West & Partners, Ltd., London), which was drawn across a line 2·2 cm. in length. The conditions used for electrophoresis and for the staining of the strips and the method of densitometric analysis were exactly as described by Gammack and Hector (1965).

The modified procedure for the application of serum samples removed the difficulty in obtaining a uniform distribution of serum across the strip experienced with the use of a micropipette, so that densitometric analysis was possible on two separate sections of each strip. The standard deviation and standard error of the mean, however, calculated for a number of analyses carried out on a single sample of serum were rather greater in magnitude than those previously reported (Gammack and Hector, 1965). The reason for this increased variability is obscure, but the modified procedure was nevertheless adopted since it depends less on the dexterity of the experimenter than does the use of a micropipette.

Results

The results of the densitometric analyses of the cellulose acetate electrophoretic separations are given in Table II. The values given are the means of two determinations carried out on each sample. The t-test was applied, based on the hypothesis that the mean of the differences in the protein composition of the serum of the paired individuals was zero. There was no significant difference in the levels of the serum protein fractions in the two groups of subjects, except in the case of the γ-globulins which showed a small but statistically significant elevation in the Huntington's chorea patients (Table II).

Table I

Huntington's Chorea Patients					Control Patients					
Patient	Sex	Age (completed years)	Length of Stay in Hospital yrs.	mths.	Patient	Sex	Age (completed years)	Length of Stay in Hospital yrs.	mths.	Diagnosis
S.L.	M	66	4	0	W.H.	M	65	24	11	Epilepsy
S.S.	M	38	11	0	R.C.	M	39	13	0	Schizophrenia
W.C.	M	39	3	6	S.V.	M	35	3	2	Schizophrenia
E.R.	M	62	7	1	J.C.	M	63	45	4	Schizophrenia
W.J.	M	45	—	5	E.H.	M	49	—	5	Schizophrenia
J.P.	M	47	—	4	K.F.	M	43	—	4	Schizophrenia and pulmonary tuberculosis
R.W.	M	44	2	10	S.F.	M	45	23	2	Schizophrenia
R.J.	F	58	1	8	M.B.	F	59	28	3	Schizophrenia and breast carcinoma
V.F.	F	48	—	1	E.W.	F	51	—	1	Schizophrenia
S.C.	F	49	1	0	E.B.	F	51	21	0	Schizophrenia
M.L.	F	52	—	8	R.H.	F	52	27	10	Cerebral diplegia
I.G.	F	46	1	8	A.R.	F	58	3	7	Schizophrenia
D.P.	F	41	8	5	E.F.	F	46	28	7	Schizophrenia
N.B.	F	72	3	4	E.W.	F	71	17	7	Schizophrenia

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TABLE II

Protein Composition of Serum from Huntington's Chorea Patients and Control Patients

(Protein composition from densitometric analysis of electrophorograms; mean of two analyses per serum sample; expressed as per cent. of total protein)

Fraction	Huntington's Chorea Patients (n = 14)				Control Patients (n = 14)				t-Values for Mean Differences within Matched Pairs
	Mean	±	Standard Error	Standard Deviation	Mean	±	Standard Error	Standard Deviation	
Albumin ..	53·1	±	4·1	15·4	56·5	±	3·4	12·8	1·66 N.S.
α_1-globulin ..	4·5	±	1·2	4·0	4·0	±	1·1	4·1	1·32 N.S.
α_2-globulin ..	14·9	±	3·2	11·9	14·1	±	2·0	7·7	0·58 N.S.
b-globulin ..	12·7	±	1·3	4·7	13·4	±	1·9	7·1	1·31 N.S.
γ-globulin ..	14·9	±	2·4	9·0	12·0	±	2·4	9·0	2·25 $p<·05$

DISCUSSION

McMenemey (1961) described the appearance of the characteristic patterns obtained on paper electrophoresis of sera taken from three cases of chorea, one of which was clearly a case of Huntington's chorea and another was described as resembling the disease clinically. In all three cases the serum β-globulin level was raised and the γ-globulin fraction had a "plateau-like" appearance on the densitometric scans. The latter peculiarity appears to be associated with an increased level of γ-globulin as judged by the appearance of the scans. More recently, Bruyn and Leguin (1964) have observed quantitative differences in the immunoelectrophoresis of serum from 27 cases of Huntington's chorea when compared with 27 samples of pooled normal human serum. These workers noted an elevation in five distinct protein fractions including γ_1-A-globulin and 7S-γ-globulin and the α_2-macroglobulin in from 12 to 23 of the 27 diseased individuals, although the extent of the elevation of each fraction was not specified. In general only large increases can be detected on visual inspection of immunoelectrophoretic separations, and the density of the precipitin lines may be extremely variable owing to factors other than variations in the amount of antigen present.

Results obtained in the present investigation have provided evidence for a minor quantitative change in the serum proteins in Huntington's chorea, without any detectable qualitative abnormalities comparable to those described by McMenemey (1961).

The inclusion of twelve schizophrenic patients in the control group was considered valid. There are discordant findings with respect to the level of serum γ-globulin in schizophrenia. On the one hand, Fessel and Grunbaum (1961) demonstrated an increase of this fraction in all the groups of psychotic patients they studied, including schizophrenics. On the other hand, Gammack and Hector (1965) were unable to find such changes in the serum of a group of ten subjects with acute schizophrenia. In the case of all but three of the control patients in the present series the serum γ-globulin fraction was within normal limits. If in fact a raised level of serum γ-globulin is associated with schizophrenia, our findings suggest that the effect is only a very small one compared with the increase in the serum γ-globulin fraction seen in the group of Huntington's chorea patients.

The finding of a raised level of serum γ-globulin in Huntington's chorea is of interest, although it is difficult to interpret. There is likely to be little specificity in such an observation, since γ-globulins are commonly found to be raised in a variety of conditions, notably diseases of the liver, and hypergammaglobulinaemias are a sequel to all types of infectious disease. The finding, however, fits in with the suggestion by McMenemey (1961) of possible immunological reaction in Huntington's chorea. As a next step, it would be of interest

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to study the unaffected sibs and offspring of patients with Huntington's chorea to find whether similar changes can be detected in their serum, and if so, to find by follow-up study whether such changes antedate the onset of the condition.

Summary

The levels of the major protein fractions in the serum of 14 cases of Huntington's chorea have been compared with those in a group of matched controls by means of densitometric analysis of electrophoretic separations.

There were no obvious qualitative differences in the electrophoretic patterns obtained for the two groups, but a statistically significant elevation of γ-globulin in the group of Huntington's chorea patients was noted.

The possible significance of this observation with respect to immunity mechanisms in the disease is discussed.

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