TOTAL AND DIFFERENTIAL PROTEIN LEVELS IN THE BLOOD AND CEREBROSPINAL FLUID IN RHEUMATOID ARTHRITIS

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The results obtained by accurate chemical estimation of the blood and cerebrospinal-fluid (C.S.F.) proteins in 23 cases of severe chronic active rheumatoid arthritis are described in the following paper.

Boland and others (1948) reviewed the subject authoritatively, pointing out that very few studies on the C.S.F. proteins in cases of rheumatoid arthritis had been published. They were able to quote only four, and only one other additional study (Sundelin, 1947) appears to exist apart from our own.

Graber-Duvernay and Gerbay (1939) studied the C.S.F. in eighteen cases of "chronic polyarthritis" (most, if not all, probably being cases of rheumatoid arthritis), and found a raised protein level in the C.S.F. of all but one. They concluded that the protein level in the C.S.F. paralleled the activity of the disease and that the estimation of it was more useful as a guide to progress and therapy than the erythrocyte sedimentation rate.

Piaggio Blanco and Sciuto (1941) studied the C.S.F. in 21 cases of "sciatica of vertebral origin". Boland and others (1948) consider that seven of these cases were probably suffering from "rheumatoid spondylitis" (ankylosing spondylitis). In five the protein level in the C.S.F. was raised, with results ranging from 59 to 100 mg. per 100 ml.

Ludwig and others (1943) did various biochemical estimations on the C.S.F. in 101 patients, 59 of whom had rheumatoid arthritis and 42 ankylosing spondylitis with or without peripheral joint involvement.

Taking 45 mg. protein per 100 ml. C.S.F. as the upper limit of normal, they found a raised total protein (46 to 70 mg.) in 6.8 per cent. of the rheumatoid arthritics, and in 28.6 per cent. of the ankylosing spondylitics (range 47 to 105 mg.). They found no correlation between the level of protein in the C.S.F. and the erythrocyte sedimentation rate, the severity of the disease process, and its duration, although there seemed to be some correlation with the activity of the disease.

Polley (1945) found a raised C.S.F. protein level in three out of 24 cases of "rheumatoid spondylitis".

Boland and others (1948) studied fifty cases of ankylosing spondylitis, seventeen with peripheral joint involvement. The C.S.F. protein estimations were done

by the method of Johnston and Gibson (1938), a non-specific colorimetric test. They accept the range of normal C.S.F. protein as 15 to 45 mg. per 100 ml. and they found an increased C.S.F. protein level (46 to 98 mg.) in 21 cases (42 per cent.). The blood protein (method of estimation not given) was slightly raised (over 8 g.) in four cases, and in only one of the four was the C.S.F. protein raised. They conclude there is no correlation between the blood and C.S.F. protein levels, or between the latter and the severity or duration of the disease process. They also conclude that:

- (1) the spine need not be affected to have a raised C.S.F. protein level and hence the meninges are not necessarily the source of the protein,
- (2) the choroid plexus is perhaps unduly permeable to protein in cases of rheumatoid spondylitis,
- (3) the protein may possibly enter the C.S.F. by way of perivascular and perineural channels,
- (4) the estimation of the C.S.F. protein in cases of rheumatoid spondylitis is of little clinical value.

Sundelin (1947) studied the total and differential protein levels in the C.S.F., by the method of Izikowitz (1941), in 141 cases of rheumatoid arthritis, three of whom had "rheumatoid spondylitis". The results were analysed carefully in great detail in an endeavour to correlate the protein changes with the severity or duration of the disease process. The abnormality of the C.S.F. protein level found was approximately proportional to the severity, and inversely proportional to the duration, of the disease, but the findings were not highly significant. Sundelin found a raised total protein level in 58 cases (35.1 per cent.).

Izikowitz (1941) estimated the proteins in the C.S.F. in 72 normal persons by an accurate chemical method of his own (modified micro-Kjeldahl). His figures give a wider range of normal than is normally accepted, but there seems little doubt of their accuracy (Tables II and III). Sundelin's findings are keyed to these figures, but those of other workers are not, so that the percentage of abnormals reported in other workers' papers appears unduly high. No one has reported a C.S.F. protein level in uncomplicated rheumatoid arthritis more than half as high again as the upper limit of normals so that the abnormalities reported are not very marked.

Eeg-Olofsson (1948) using Izikowitz's method found it less accurate than Izikowitz claims, but even so the error was no more than about 1 per cent.

Estimation	Standard Errors (mg. per cent.)	
	Izikowitz (1941)	Eeg-Olofsson (1948)
Total Protein	± 0.17	± 1.4
Globulin	± 0.08	± 0.39
Albumin	± 0.14	± 1.0

We consider that the disease process in ankylosing spondylitis is not the same as that in rheumatoid arthritis. All the previous investigations, except that of

Grabner-Duvernay and Gerbay (1939), come from the other side of the Atlantic, where the opposite view is held, and their findings have been reviewed in that light. The figures of Ludwig and others (1943) and Sundelin (1947) were thus the only ones we felt could be safely taken as indicating the findings to be expected in cases of what we term rheumatoid arthritis.

Present Investigation

The results just mentioned indicated that a high C.S.F. protein level or alterations in the differential protein content in the C.S.F. occur in a proportion of cases of rheumatoid arthritis.

It has long been known that plasma total and differential protein levels may be abnormal in the majority of long-standing or severe cases of rheumatoid arthritis, the commonest findings being a low total protein level and increased levels of globulin and fibrinogen (Fletcher, 1947) or various combinations of the above. It is not altogether certain whether the low total protein reported by many observers is due to rheumatoid arthritis *per se*, or to undernutrition, resulting from the fact that many of these patients have a poor appetite and, because of their locomotor disability, are unable to get about to do the shopping and cooking, and thus in many cases may live on little more than bread-and-butter, tea, and jam. This fact has been eliminated in the present study, because all cases were on adequate hospital diet for several weeks before the investigation.

It was thought of interest to compare the findings in the blood and C.S.F. to see if any light could be thrown on the aetiology of rheumatoid arthritis (Sundelin's study was undertaken because he thought that there was much clinical evidence that rheumatoid arthritis was, in part, at least, a disease of the central nervous system). In the present study the blood (serum) and C.S.F. total and differential proteins have been estimated by an accurate chemical method.

Lumbar puncture is not a procedure to be embarked upon lightly, so it was considered advisable to do a pilot experiment before embarking on a large-scale investigation. Hence only chronic active severe cases have been studied, for it was thought that the changes, if any, would be most marked in such cases, and hence most easily detected.

Clinical Criteria

Diagnosis of Rheumatoid Arthritis.—Polyarticular destructive arthritis, involving the small joints (metacarpophalangeal and proximal interphalangeal) of the hands in all cases; constitutional upset (loss of weight, weakness, and fatiguability); raised E.S.R.; characteristic radiological appearances of juxta-articular osteoporosis, loss of joint space, and erosions of the joint surface (the last symptom was not present in all, and all patients were afebrile).

Chronicity.—More than 4 years since onset of symptoms and signs of disease (range 4 to 15 years; average 7.4 years).

Severity.—Involvement of nearly all limb joints (spine involved in none of the cases); marked constitutional upset; E.S.R. over 30 mm. first hour (Westergren), highest reading 140 mm. first hour; marked crippling; radiological or clinical evidence of subluxation or ankylosis of joints.

Activity—joints hot, swollen, and painful; marked radiological evidence of decalcification; combination of high E.S.R. and iron-resistant anaemia.

Age and Sex.—The patients' ages ranged from 23 to 69 years (average 52). There were twelve females (aged 23 to 64 years, average 48) and eleven males (aged 42 to 69 years, average 56.3).

Experimental Details.—In accordance with the view that the constitution of the C.S.F. varies with the level from which it is taken (Izikowitz, 1941) it was considered advisable to do all lumbar punctures at the same level—between L3 and L4. All punctures were done without any premedication and in the lateral position.

The blood and C.S.F. samples were taken at the same time, and sent to the laboratory in plain bottles, and the protein estimations were begun at once.

Methods

ANALYSIS.—All determinations of the proteins were done by the micro-Kjeldahl method. The globulin was precipitated from the blood serum by 42 per cent. (W/V) crystalline sodium sulphite (Campbell and Hanna, 1937). The procedure adopted for the precipitation of the proteins from C.S.F. was that used by Izikowitz (1941), but the method was altered so that the combusted protein could be treated in the same way as the blood serum proteins. Though, in blood, fractionation of the proteins by half-saturation with ammonium sulphate gives slightly higher results for the albumin than when 42 per cent. (W/V) crystalline sodium sulphite is used, it was thought advisable not to change the Izikowitz method of globulin precipitation as we intended to relate our results to those obtained by Izikowitz in his studies of the C.S.F. proteins in normal subjects. The technique used was as follows:

Blood

Total Protein.—0.5 ml. serum was diluted to 10 ml. with water. 2.5 ml. of this mixture was taken, 2.5 ml. water added, and the protein precipitated by 0.2 ml. 7.5 per cent. sodium molybdate and 0.2 ml. 2/3 N sulphuric acid. After spinning this mixture for 5 mins., the supernatant fluid was decanted and the tube allowed to drain on filter paper. The protein was then heated with 1.5 ml. digestion reagent (50 per cent. sulphuric acid containing 1 per cent. selenium dioxide). Heating was continued until the mixture cleared and then for one hour after.

Albumin.—0.5 ml. serum was diluted to 10 ml. with 42 per cent. (W/V) crystalline sodium sulphite, and after 15 mins. at room temperature the mixture was filtered through a No. 42 Whatman paper. 2.5 ml. of the filtrate was taken, and 2.5 ml. water and 2.5 ml. 10 per cent. sulphuric acid added. To drive off the sulphur dioxide liberated from the sodium sulphite the tube was shaken and, if necessary, warmed slightly. The protein was precipitated by adding 0.5 ml. 7.5 per cent. sodium molybdate. The mixture was spun and the tube drained as before. Digestion was carried out in the same way as for total protein.

Globulin.—This was calculated by subtracting the albumin from the total protein.

Cerebrospinal Fluid

Total Protein.—2 ml. C.S.F. were diluted to 17 ml. with 10 per cent. trichloroacetic acid. After mixing, the tube was placed in a water-bath at 56° C. for 60 min. to precipitate the protein. It was then centrifuged for 45 min. and the supernatant fluid decanted. The precipitate was washed with 17 ml. 9 per cent. trichloroacetic acid and centrifuged again for 30 min. Combustion was carried out as for blood proteins.

Albumin and Globulin.—The globulin was precipitated from 5 ml. C.S.F. by the addition of 5 ml. of a saturated solution of ammonium sulphate. After mixing, the tube was placed in a water-bath at 56° C. for 60 min. and then centrifuged for 45 min. 4 ml. of the centrifugate was taken for the albumin estimation. The precipitate was dissolved in 4 ml. water and 13 ml. 10 per cent.) trichloroacetic acid was added to re-precipitate the protein. The tube was incubated at 56° C. for 60 min. and then centrifuged for 45 min. The supernatant fluid was poured off, the tube drained, and the precipitate washed with 17 ml. 9 per cent. trichloroacetic acid. The tube was re-centrifuged for 30 min. This washing was repeated. Combustion was carried out as for blood proteins.

For the albumin determination 13 ml. (10 per cent.) trichloroacetic acid were added to 4 ml. of the centrifugate (from globulin fractionation). The tube was placed in a water-bath at 56° C. for 60 min. and then centrifuged for 45 min. The supernatant fluid was decanted and the precipitate washed with 17 ml. 9 per cent. trichloroacetic acid and centrifuged again. This washing was repeated making two washings altogether. The protein was combusted in the same way as the blood proteins.

In all the C.S.F. protein estimations, the tubes were thoroughly drained and the inside of each dried with filter paper after they had been centrifuged.

DISTILLATION.—5 ml. 40 per cent. caustic soda (W/V) was used for the liberation of the ammonia and the distillate was collected in N/70 sulphuric acid, 10 ml. N/70 sulphuric acid being used for the blood proteins and 2 ml. N/70 sulphuric acid (measured from the burette used for the final titration) for the C.S.F. proteins. The excess acid was titrated against N/70 sodium hydroxide. A 10-ml. burette was used for the blood proteins and a 2-ml. burette graduated in hundredths for the C.S.F. proteins. The factor 6.25 was used to convert nitrogen to protein values.

CHECK ON ACCURACY OF RESULTS.—The following precautions were taken.

Blood Proteins.—All estimations were done in duplicate.

C.S.F. Proteins.—Where the quantity of C.S.F. allowed the total protein estimations were done in duplicate. Two 4-ml. portions of filtrate from the globulin fractionation were taken for estimation of the albumin. The globulin was always estimated as a further check; results agreed to about 1 per cent.

Normal Values

There is very little in the literature about the absolute values of the differential protein levels in the C.S.F. There are plenty of crude tests indicating an excess of the globulin moiety, but no absolute figures for normal apart from these of Izikowitz (1941). In view of this we have no other course than to accept his values (Tables II and III) in spite of the fact that the total protein figures disagree with those of most workers. Izikowitz's method has been used in this investigation.

Results

The C.S.F. pressure was normal in all our cases, as in all previously reported cases. All relevant results are given in Table I (overleaf). They are grouped for comparison with Izikowitz's figures for normal cases in Tables II and III.

Discussion

Table II shows that the mean C.S.F. total protein levels in rheumatoid arthritis cases of both sexes are similar and above the normal mean. The increase is

TABLE I
CONSOLIDATED RESULTS SERUM (g. per cent.) AND
C.S.F. (mg. per cent.)* TOTAL AND DIFFERENTIAL PROTEINS

Case No.	Sex	Age	Total Proteins		Albumin		Globulin	
			Serum	C.S.F.	Serum	C.S.F.	Serum	C.S.F.
2	F	40	9.6	57	3.4	36	6.2	20
1	F	65	9.4	90	4.1	60	5.3	30
7	M	69	7.7	56	3.6	38	4.1	18
17	M	53	7.7	62	4.8	42	2.9	20
5	F	47	7.6	58	4.2	47	3.4	12
13	F	60	7.5	35	4.8	30	2.7	5
16	M	65	7.5	39	3.9	27	3.6	12
8	F	39	7.4	31	4.7	26	2.7	5
10	F	23	7.4	31	4.7	25	2.7	6
12	F	36	7.4	33	4.1	27	3.3	6
14	F	40	7.2	31	4.4	23	2.8	9
6	M	52	7.1	39	4.0	31	3.1	8
9	M	53	7.1	55	3.6	43	3.5	12
11	F	55	7.1	33	4.2	28	2.9	5
3	F	64	7.0	38	4.2	30	2.8	8
22	M	42	7.0	39	5.0	33	2.0	6
23	M	60	7.0	32	4.3	25	2.7	7
21	F	50	6.9	34	4.2	28	2.7	6
20	F	63	6.8	32	4.5	25	2.3	7
4	M	57	6.7	53	4.3	36	2.4	17
18	M	52	6.4	26	3.2	17	3.2	9
19	M	49	6.3	24	4.0	19	2.3	5
15	M	67	6.0	29	3.0	12	3.0	17

* Apparent discrepancies are due to taking C.S.F. figures to the nearest whole number.

significant only in the female cases, although not markedly so. The mean C.S.F. globulin is raised in both sexes, but to a significant degree only in the male cases. The mean C.S.F. albumin is normal in the male cases and significantly raised in the female cases. The mean C.S.F. G/A ratio is significantly increased.

The total protein serum levels are within normal limits except in two cases where they were found to be rather high. No clinical reason for this was evident. The serum albumin figures were normal, but the serum globulin figures and the serum G/A ratio were both high in nearly all cases (Table IV).

The correlation between the serum total proteins and serum globulin is very high, whereas it is almost nil between the serum total proteins and serum albumin. From this it may be deduced that high serum protein levels in these cases are due solely to the globulin fraction (Table V).

As might be expected serum albumin and globulin are inversely related. Serum albumin is not correlated to a significant degree with anything else.

Serum protein levels are significantly correlated with both C.S.F. albumin and globulin levels, as well as C.S.F. total protein levels. The C.S.F. albumin levels are significantly related to the C.S.F. globulin, which suggests that abnormalities have the same cause in both. The serum and C.S.F. globulin levels are significantly correlated. The C.S.F. total protein figures in the rheumatoid arthritis cases show quite a wide range in view of the fact that the cases were essentially analogous.

TABLE II
MEAN OF RESULTS IN NORMAL CONTROLS AND
RHEUMATOID ARTHRITIS PATIENTS

Cerebrospinal Fluid		Normal Controls (Izikowitz) N. Mean± Standard Error (mg. per cent.)	Rheumatoid Arthritis Patients N. Mean± Standard Error (mg. per cent.)	Difference± Standard Error (mg. per cent.)
Total Protein	Male	39.46±1.2 (45)*	40.64±3.89 (11)	1.18±4.1 NS
	Female	30.99±1.16 (27)	42.5 ±4.89 (12)	11.51±5.0 S
Globulin	Male	7.71±0.30 (45)	11.82±1.56 (11)	4.11±1.59 S
	Female	6.27±0.29 (27)	10.00±2.10 (12)	3.73±2.12 NS
Albumin	Male	31.74±1.03 (45)	29.2±3.26 (11)	2.54±3.42 NS
	Female	24.80±0.91 (27)	32.5 ±3.0 (12)	7.70±3.11 S
G/A Ratio†	Combined Male and Female	0.245±0.006 (72)	0.373±0.053 (23)	0.128±0.055 S

* Figures in brackets represent number of persons in each group.

NS=not significant. S=significant.

† G/A ratio given in all Tables rather than A/G for ease of comparison with Izikowitz's figures.

TABLE III
EXTREME PHYSIOLOGICAL LIMITS
(from Izikowitz)

Cerebrospinal Fluid	Males (mg. per cent.)	Females (mg. per cent.)
Protein	14-65	13-49
Globulin	2-14	2-11
Albumin	11-52	11-38
G/A Ratio	0.14-0.34	0.14-0.36

It has not been found possible to correlate this variation with the clinical findings or the course of the disease, which confirms the view of Boland and others (1948) that the estimation of the C.S.F. proteins in rheumatoid arthritis is of little clinical importance.

To summarize, the abnormality in the serum appears to be due to the globulin fraction, but variations in the C.S.F. total protein, albumin, and globulin fractions, occur simultaneously and in the same direction. It is difficult to think of any explanation for this, except that, as suggested by Boland and others (1948), the haemato-encephalic barrier is unduly permeable in rheumatoid arthritis, with the result that some serum protein of high G/A ratio leaks into the C.S.F., thus producing a rise in C.S.F. total proteins, both albumin and globulin. Increase in the C.S.F. globulin will be more evident because of its lower normal level and because of the high G/A ratio of the entering proteins.

The regrettable lack of normal controls limits the conclusions which can be

TABLE IV
SERUM AND CEREBROSPINAL FLUID G/A RATIOS

Case No.	Sex	Serum	Cerebrospinal Fluid
1	F	1·3/1	0·5/1
2	F	1·79/1	0·56/1
3	F	0·67/1	0·27/1
4	M	0·56/1	0·46/1
5	F	0·8/1	0·25/1
6	M	0·77/1	0·26/1
7	M	1·14/1	0·48/1
8	F	0·59/1	0·19/1
9	M	0·97/1	0·28/1
10	F	0·59/1	0·24/1
11	F	0·71/1	0·18/1
12	F	0·83/1	0·22/1
13	F	0·56/1	0·17/1
14	F	0·63/1	0·37/1
15	M	1/1	1·43/1
16	M	0·91/1	0·43/1
17	M	0·59/1	0·48/1
18	M	1/1	0·53/1
19	M	0·59/1	0·26/1
20	F	0·53/1	0·28/1
21	F	0·63/1	0·21/1
22	M	0·4/1	0·27/1
23	M	0·63/1	0·28/1

drawn. Nevertheless, it is felt that the results obtained have yielded some useful information. It is particularly unfortunate that so little is known about the absolute values for the albumin and globulin ratios in the C.S.F. Pemberton (1935) suggested that the capillaries may be abnormal in rheumatoid arthritis, and it is possible that local vascular derangement may be important in producing some of the symptoms and signs of the disease, although it seems unlikely that this is of basic importance in the aetiology.

One possible explanation of the changes in the serum protein is that some degree of liver dysfunction is present in rheumatoid arthritis. Swanson (1949) found

at some time or other abnormal serum colloidal gold reactions, in approximately half of 72 cases of rheumatoid arthritis, and he quotes other authorities as finding abnormal serum colloidal gold reactions in up to 76 per cent. of cases. Another possible reason for the appearance of excess globulin is that it comes from the lymphocytes (Dougherty and White, 1947), being an antibody response to an unknown causative antigen.

TABLE V
CORRELATION COEFFICIENTS

Total Proteins Serum / Total Proteins C.S.F.	0.734 S
Total Proteins Serum / Albumin Serum	0.075 NS
Total Proteins Serum / Albumin C.S.F.	0.702 S
Total Proteins Serum / Globulin Serum	0.839 S
Total Proteins Serum / Globulin C.S.F.	0.594 S
Total Proteins C.S.F. / Albumin Serum	0.027 NS
Total Proteins C.S.F. / Albumin C.S.F.	0.942 S
Total Proteins C.S.F. / Globulin Serum	0.652 S
Total Proteins C.S.F. / Globulin C.S.F.	0.835 S
Albumin Serum / Albumin C.S.F.	0.181 NS
Albumin Serum / Globulin Serum	-0.480 S
Albumin Serum / Globulin C.S.F.	-0.340 S
Albumin C.S.F. / Globulin Serum	0.510 S
Albumin C.S.F. / Globulin C.S.F.	0.634 S
Globulin Serum / Globulin C.S.F.	0.704 S
G/A Serum / G/A C.S.F.	0.47 S

These results provide further confirmation for the current idea that rheumatoid arthritis is a generalized disease (Ellman and Ball, 1948).

Summary

- (1) The literature on C.S.F. protein in rheumatoid arthritis is reviewed.
- (2) The total and differential serum and C.S.F. protein was investigated in 23 cases of chronic active severe rheumatoid arthritis with the following results:
 - (a) serum globulin and G/A ratio were found to be significantly increased.
 - (b) high C.S.F. total protein level correlated with high serum protein level.
 - (c) high C.S.F. globulin and G/A ratios were common findings.
- (3) It was not possible to correlate the results with the clinical findings. It is concluded that the estimation of the C.S.F. protein is of no clinical importance.

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Taux total et différentiel des Protéines du Sang et du Liquide Céphalo-rachidien dans l'Arthrite Rhumatismale

RÉSUMÉ

- (1) Les auteurs passent en revue la littérature sur les recherches concernant les protéines du L.C.R. dans l'arthrite rhumatismale.
- (2) Le taux des protéines, total et différentiel, dans le sérum et dans le L.C.R. fut déterminé dans 23 cas d'arthrite rhumatismale chronique, active et grave, et les résultats suivants furent obtenus:
 - (a) augmentation appréciable dans le sérum de la globuline et du rapport globuline/albumine;
 - (b) taux élevé des protéines totales du liquide céphalo-rachidien en corrélation avec le taux des protéines sériques;
 - (c) taux de la globuline et le rapport globuline/albumine dans le L.C.R. augmentés.
- (3) Il n'a pas été possible de trouver un rapport entre ces résultats et le tableau clinique et on en conclut que la détermination des protéines du L.C.R. n'a pas d'importance clinique.

Cifras totales y diferenciales de Proteinas de la Sangre y del Líquido Cefalorraquídeo en la Artritis Reumatoide

RESUMEN

- (1) Los autores pasan en revista la literatura sobre las investigaciones respecto a las proteínas del líquido cefalorraquídeo en la artritis reumatoide.
- (2) Las cifras de la proteína, total y diferencial, en el suero y en el líquido cefalorraquídeo fueron determinadas en 23 casos de artritis reumatoide crónica, activa y grave y los resultados siguientes fueron obtenidos:
 - (a) aumento notable en el suero de la globulina y de la razón globulina/albumina;
 - (b) cifra alta de las proteínas totales del líquido cefalorraquídeo en proporción con el aumento de las proteínas del suero;
 - (c) cifra de la globulina y la razón globulina/albumina en el líquido cefalorraquídeo aumentadas.
- (3) No se pudo establecer relación entre estos resultados y los resultados clínicos. En conclusión, la determinación de las proteínas del líquido cefalorraquídeo no tiene importancia clínica.