THE CEREBROSPINAL FLUID IN RHEUMATOID SPONDYLITIS

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Abnormalities in the chemistry of cerebrospinal fluid in cases of rheumatoid arthritis and of rheumatoid spondylitis have been reported: the total protein may be increased in amount, and at times there may be abnormalities in the colloidal gold reaction. The present study was designed to determine how often and at what stages of rheumatoid spondylitis such abnormalities are present, and to evaluate their possible significance.

The diagnosis of rheumatoid spondylitis may be difficult in the early stages of the disease when physical and radiographic signs are minimal or absent, when constitutional reactions may be lacking, and when in mild cases even erythrocyte sedimentation rates may be normal. During the early stages of the disease sciatica is present in about 20 per cent. of cases (Boland and Present, 1945). Hence rheumatoid spondylitis must be differentiated at times from other causes of chronic low-back disability accompanied by sciatica, especially from cases of ruptured intervertebral disks, in which the total protein content of cerebrospinal fluid is frequently increased. In these and other circumstances it would be helpful if biochemical studies on cerebrospinal fluid afforded data upon which clear and early differentiations could be made.

Previous Studies on Cerebrospinal Fluid in Rheumatoid Arthritis and Spondylitis

Although the blood and synovial fluid of patients with rheumatoid arthritis have been studied extensively, the cerebrospinal fluid has been rather neglected. This is somewhat surprising in view of the fact that certain European internists and neurologists during the last century sponsored the "neurogenic theory" of rheumatoid arthritis, the idea that the disease results from inflammatory or

trophic changes in the central nervous system. These ideas were still current when Quinke introduced lumbar puncture in 1891. In 1909 rheumatoid arthritis was regarded by Jones, an outstanding British rheumatologist, as being "due to a cerebrospinal toxemia", and rheumatoid spondylitis was considered to be a form of spinal meningitis. Although these ideas have been generally discarded, some modern rheumatologists believe that in cases of rheumatoid arthritis the neurologic manifestations may be numerous and at times striking enough to simulate disease of the central or peripheral nervous system.

Graber-Duvernay and Gerbay.—In 1939 Graber-Duvernay and Gerbay studied certain biochemical reactions of the cerebrospinal fluid in eighteen patients with "chronic polyarthritis". They did not classify precisely the types of "chronic polyarthritis" studied by them, but their descriptions lead one to believe that, although several sub-varieties were encountered, all were cases of rheumatoid arthritis, one case representing also rheumatoid spondylitis. The total and differential leucocyte counts on the cerebrospinal fluid, as well as sugar determinations and Wassermann tests, were normal in all their cases. But frequent abnormalities were noted in the total protein content of the cerebrospinal fluid. A normal concentration was found in only one of the eighteen cases; and in ten of these, including the one with spondylitis, the concentrations of total protein were increased. They found that the height of the protein paralleled the activity of the disease, and that concentrations were usually highest in the cases "in which the toxic infectious character was clinically most prominent". They used the concentrations of spinal fluid protein somewhat as a guide to the desirability of such

treatments as gold therapy, orthopaedic manipulations, etc., and regarded such estimations as being more informative than erythrocyte sedimentation rates.

Blanco and Sciuto.—In 1941 Blanco and Sciuto studied twenty-one cases of so-called sciatica of vertebral origin. Of these, seven were diagnosed as sciatica with "lumbar arthritis", and in view of the relative youth of the patients in this group they probably had rheumatoid spondylitis. The cerebrospinal fluid protein was raised in five (71 per cent.) of the seven cases of probable rheumatoid spondylitis with sciatica, with values ranging between 59 and 100 mg. per 100 c.cm.

Ludwig, Short, and Bauer.—Various biochemical tests on cerebrospinal fluid were made in 1943 by Ludwig, Short, and Bauer on 101 patients with rheumatoid arthritis. Of these, fifty-nine had rheumatoid arthritis of peripheral joints without spinal involvement, and forty-two had rheumatoid spondylitis with or without additional involvement of peripheral joints.

Estimations of pressure, total cell count, sugar, and chlorides were essentially normal. The only significant abnormalities noted were increased concentrations of protein, abnormal colloidal gold curves, or combinations of the two.

Total Proteins.—The spinal fluid protein was increased (46 to 70 mg.) in 6.8 per cent. of the fifty-nine patients with rheumatoid arthritis of peripheral joints, in 28.6 per cent. (47 to 105 mg.) of the forty-two patients with rheumatoid spondylitis, and in 15.8 per cent. of the total 101 patients. No significant relation was established between the level of the spinal fluid protein and the patient's erythrocyte sedimentation rate or the duration or "total severity" of the disease. However, they stated that "severe pain or sciatica or both were much more frequent in the high-protein group", which suggested to them that these patients were suffering from more active disease.

Colloidal Gold Reactions.—The colloidal gold reactions were abnormal in 8.5 per cent. of the fifty-nine patients with peripheral rheumatoid arthritis and in 14.3 per cent. of the forty-two patients with rheumatoid spondylitis.

Summary of Findings.—The findings of Ludwig, Short, and Bauer can be summarized thus: (1) Increased concentrations of protein in spinal fluid, noted only occasionally in patients with peripheral rheumatoid arthritis, were present quite often (in fact four times as often) among patients with rheumatoid spondylitis. (2) Abnormal gold-sol curves were found only occasionally in both groups of patients but were noted about twice as often among the spondylitics as among those with

peripheral rheumatoid arthritis. (3) Four of their patients with peripheral rheumatoid arthritis but with no objective evidence of spondylitis had increased protein in the cerebrospinal fluid. Three of these had "clinical symptoms suggestive of spondylitis" even though no definite diagnosis of spondylitis was justified. Because fifteen of the sixteen patients with increased spinal fluid proteins had either spondylitis or symptoms suggestive thereof, they made this tentative conclusion: when a patient with peripheral rheumatoid arthritis exhibits an increased spinal fluid protein, one should suspect that spinal or sacro-iliac joints are already affected even though definite evidence for spondylitis is not yet at hand.

Polley's Investigation.—Examinations of cerebrospinal fluid were made in twenty-four of 1,035 cases of rheumatoid spondylitis reviewed in 1945 by Polley. In most of the twenty-four cases fluids were examined because of a history of sciatic, intercostal, or segmental pain with features of nerve-root irritation but with no neurologic abnormalities on physical examination. The total protein content was slightly raised in five of the twenty-four cases, and two of these had other reasons than spondylitis for the increased protein; one had a protrusion of the fourth lumbar disk and the other a hypertrophied ligamentum flavum, both substantiated by surgical operations.

Scope of Investigation

Fifty cases of rheumatoid spondylitis were studied*; in each case active symptoms and radiographic signs of the disease were present. All the patients were males, young soldiers sent to the Army's Rheumatism Centre from various foreign theatres or from various posts in the United States. In thirty-three of the fifty cases spondylitis alone was present; in seventeen cases spondylitis was associated with rheumatoid arthritis of peripheral joints. No cases of peripheral rheumatoid arthritis without spondylitis were studied in this series.

The cerebrospinal fluid was obtained by lumbar puncture with patients in the recumbent position and under fasting conditions.

Results of Investigation

Manometric Pressure.—Considering only the definite abnormalities (that is, pressures over 200 mm. of water) we noted that the initial manometric pressures were raised in nine of the fifty cases; in six of these nine cases the increased pressures were unaccompanied by any other abnormality of cerebrospinal fluid; therefore we agree

* Studies were conducted at the United States Army's Rheumatism Centre, Army and Navy General Hospital, Hot Springs, Arkansas.

with Ludwig, Short, and Bauer that such occasional increases of pressure in the spondylitic patients probably represent improper muscular relaxation of the patients.

Total Leucocyte Count.—Leucocyte counts on spinal fluid were normal (less than five cells per c.mm.) in every case.

Sugar.—The concentrations of spinal fluid sugar were normal (between 50 and 80 mg. per 100 c.cm.) in thirty-five cases, slightly low (between 43 and 49 mg.) in six cases, and slightly increased (between 81 and 89 mg.) in nine cases. We could attach no particular significance to these nine "borderline values".

Colloidal Gold Reactions.—An abnormal colloidal gold reaction was present in only one (2 per cent.) of our fifty cases, and in this case no other cerebrospinal fluid abnormality was present. Ludwig, Short, and Bauer noted abnormal colloidal gold reactions in 14 per cent. of their spondylitic patients. The low incidence of abnormal gold-sol curves in our cases is all the more striking in view of the fact that we noted increased spinal fluid proteins more often than did Ludwig, Short, and Bauer.

Concentration of Total Protein.—For the determination of total proteins in cerebrospinal fluid we used the method of Johnston and Gibson (1938), considering as normal 15 to 45 mg. per 100 c.cm.

The concentration of protein in cerebrospinal fluid was increased in twenty-one (42 per cent.) of our fifty cases. The increase was moderate in thirteen cases, ranging from 46 to 65 mg. per 100 c.cm., and notable in eight cases, ranging from 65 to 98 mg. per 100 c.cm.

Relationship to Blood Proteins.—The total blood proteins were normal (6 to 8 g. per 100 c.cm. serum) in forty-three of our cases, "borderline" in three, and somewhat raised in four. In only one of the last four cases was the total protein in the cerebrospinal fluid also increased.

There was no consistent relationship between concentration of total protein in cerebrospinal fluid and in blood, and the frequent increases in total protein of cerebrospinal fluid were apparently *not* the result of increased concentrations of proteins in blood serum.

Relation to the Duration of the Disease.—There was no constant relationship between the amount of protein in the cerebrospinal fluid and the duration of the disease *per se*.

Relationship to Severity of the Disease.—Of our fifty cases the disease was mild in twenty-five, moderately severe in twenty-one, and severe in four. The severity of the disease was gauged by the rate of its progression, the degree of disability present, the amount of constitutional reaction, and the type

of radiographic changes in sacro-iliac joints (Boland and Shebesta, 1946).

The spinal fluid proteins were increased in 40 per cent. of the twenty-five mild cases, in 33 per cent. of the twenty-one moderately severe cases, and in 100 per cent. of the four severe cases. The differences between the mild and moderately severe cases were not great: the total proteins averaged 44 mg. per 100 c.cm. in the mild cases, 43.9 mg. in the moderately severe group; but they averaged 77.9 mg. in the severe group. Although no definite conclusions can be drawn because of the small number of severe cases (only four), the figures suggest that the spinal fluid protein may be increased more often and in greater amounts in severe, rapidly progressive cases than in the less severe cases of rheumatoid spondylitis.

Relation to the Extension (Location of the Disease).—The following regions of the spine were affected: sacro-iliac joints alone in eleven cases; sacro-iliac joints and lumbar spine in twenty cases; sacro-iliacs, lumbar, and thoracic spine in fifteen cases; sacro-iliacs and entire spine in four cases. No apparent relationship existed between the concentrations of protein in spinal fluid and the degree of extension of the disease.

Relation to Associated Peripheral Rheumatoid Arthritis.—As stated previously, spondylitis alone affected thirty-three of our fifty patients, but in seventeen of the patients rheumatoid arthritis of peripheral joints was also present. The added presence of peripheral arthritis appeared to increase the chances for an increased spinal fluid protein. Increases were present in 59 per cent. of the seventeen patients with associated involvement of peripheral joints, but were present in only 33 per cent. of the thirty-three patients with spondylitis alone.

Relation to Sciatica.—Among our fifty patients, twelve complained of sciatica at the time of examination (nine others gave a past history of sciatica). Our results were contrary to the experience of Ludwig, Short, and Bauer, who found that alterations in cerebrospinal fluid occurred more often in spondylitic patients with severe pain or sciatica or both than in those without sciatica or severe pain. We found increased amounts of cerebrospinal fluid protein in 47 per cent. of the thirty-eight patients without sciatica but in only 25 per cent. of the twelve patients with sciatica.

Possible Causes for the Increased Cerebrospinal Fluid Protein in Rheumatoid Arthritis

Opinions of Previous Workers.—It was the opinion of Graber-Duvernay and Gerbay that the increased protein reflected "a more or less marked state of meningo-medullary or arachnoido-radicular

compression". But because the protein was increased in some of their fourteen patients with chronic polyarthritis without spondylitis, their assumption that a partial subarachnoid block was responsible is open to question.

Ludwig, Short, and Bauer considered the increased protein to result chiefly from "an increased permeability of the spinal cord membranes as a result of their proximity to acutely inflamed articular tissues", presumably in the spinal articulations. This assumption was based partly on the fact that in their spondylitics the protein content was found to be higher in lumbar than in dorsal or cisternal fluid. But an explanation based on such reasoning is not satisfactory because, according to Merrit and Fremont-Smith (1937), when there is an increase of protein in the cerebrospinal fluid in any condition it is greatest in the lumbar fluid; and even in patients with myxoedema, in whom there is an increase in the protein content of the lumbar fluid, there is also a definite but less evident increase in the protein contents of the cistern and ventricular fluid. Therefore neither an increased nor a relatively increased protein content of lumbar fluid in rheumatoid arthritis or spondylitis means necessarily that the protein comes from adjacent inflamed lumbar tissues.

Because Ludwig, Short, and Bauer did note increased values for total protein and globulin in the serum of some patients, they interpreted the abnormal colloidal gold curves in the spondylitics as resulting from alterations of serum protein, chiefly from increased serum globulin. Hence, according to these workers there were two probable sources of abnormal protein: (1) albumin and/or globulin originating locally from inflamed tissues adjacent to the lumbar spine, and (2) globulin from blood serum, introduced into spinal fluid, presumably through the choroid plexus.

Our Opinion.—It is conceivable that if a patient with peripheral or spinal rheumatoid arthritis had an increase of total protein or of globulin in serum, some of this excess protein might pass through the choroid plexus in abnormal amounts, whether the double-celled walls of the plexus were "normal", functionally disturbed, or actually damaged pathologically. But the present study yields no evidence that increases in spinal fluid protein are associated with increases in total blood proteins; therefore the increased cerebrospinal fluid protein in rheumatoid spondylitis cannot be attributed to increased blood proteins.

In rheumatoid arthritis or spondylitis is there a relative stasis or sluggish circulation in choroidal capillaries which might increase the permeability of the choroid plexus? We do know that in rheuma-

toid arthritis capillaries of nail-beds often show dilatation and stasis, and in this disease there are transient oedemas and other evidences of vascular and vasomotor abnormalities. But whether the capillaries of the choroid plexus participate in such disturbances and thus become more permeable is unknown.

In rheumatoid arthritis or spondylitis are the ependymal cells of the choroid plexus actually damaged, producing a "hole in the sieve" and an increased permeability of the barrier to the normal serum proteins? We do know that rheumatoid arthritis is a general disease with systemic involvement of many extra-articular tissues, such as lymph nodes, bone marrow, blood vessels, etc. It is therefore possible that in rheumatoid arthritis (with or without spondylitis), the choroid plexus may be functionally, perhaps even structurally, impaired. It might be profitable to examine choroid plexuses whenever necropsies on rheumatoid arthritics permit.

If the spinal fluid proteins were increased in some cases of rheumatoid spondylitis but were never increased in rheumatoid arthritis without spondylitis, we could suspect that the proteins came entirely from extra-ventricular spinal sources. But, since the proteins are increased in certain cases of rheumatoid arthritis with no clinical evidence of spondylitis, in such cases one must either ascribe the increased proteins largely to intraventricular sources or suspect that patients with peripheral rheumatoid arthritis may have some actual, but possibly sub-clinical, spinal involvement acting as a local (extra-ventricular) site of origin of the increased proteins.

In the presence of widespread inflammation and calcification of paravertebral tissues, is it possible that some meningeal veins might be partly occluded, producing stasis and subsequent local transudate of protein into the subarachnoid space? In rheumatoid spondylitis, how often, if ever, does a local spinal pachymeningitis or partial spinal subarachnoid block from meningeal adhesions exist? If such lesions did occur, they could account for increased protein in the lumbar fluid of spondylitics.

Our impressions relative to the increased cerebrospinal fluid protein which may be present in rheumatoid spondylitis may be stated as follows:

1. It is not necessary for the spine to be affected in order for an increased lumbar spinal fluid protein to be present: such may occur in rheumatoid arthritis without spondylitis. Therefore, the source of the increased protein in spondylitis need not necessarily be the inflamed spinal meningeal tissues.
2. In cases of rheumatoid spondylitis as well as in cases of rheumatoid arthritis without spondylitis some or even all of the increased spinal fluid protein

may enter the cerebrospinal fluid at the choroid plexus, probably as a result of increased permeability (lowered threshold) of the choroid plexus for proteins.

3. But since the presence of spinal involvement notably increases the chances that a patient with rheumatoid arthritis will have an increased protein content of his spinal fluid, the possibility cannot be dismissed that some of the increased protein in spinal fluid in spondylitis may enter the sub-arachnoid space, not via the choroid plexus, but via perivascular and perineural spaces as a result of local inflammation of the structures adjacent to the spine.

4. The presence of an increased protein content of cerebrospinal fluid depends more on the severity than on the duration of the disease, whether it be peripheral or spinal rheumatoid arthritis. The protein content of spinal fluid may be as high or even higher in the early months than in the later years of either condition. Therefore the mechanism whereby the spinal fluid protein is increased is related more to the stage of active inflammation than to the stage of residual pathology.

5. We are not prepared to state that when the spinal fluid protein is found to be increased in a case of peripheral rheumatoid arthritis one should suspect the additional presence of symptomless spondylitis, but certainly under such circumstances a careful review of the spinal situation is in order.

6. The finding of an increased protein content is alone of little value in differentiating rheumatoid spondylitis from other spinal conditions which result in chronic low-back disability with sciatica. Since increases in spondylitis are uniformly moderate in degree, if the protein is elevated notably above 100 mg. per 100 c.cm. some cause for the increase other than spondylitis should be sought, even though spondylitis is (also) present.

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Le Liquide Céphalo-rachidien dans la Spondylite Rhumatismale

RÉSUMÉ

Les auteurs ont étudié cinquante cas de spondylite rhumatismale. Tous les malades étaient des hommes jeunes. Trente-trois présentaient de la spondylite seule; chez dix-sept autres elle était accompagnée d'arthrite rhumatismale des articulations périphériques. Cette série ne comportait aucun cas d'arthrite rhumatismale périphérique non accompagnée de spondylite.

Au sujet de l'augmentation des protéines du liquide céphalo-ra-chidien qui peut accompagner la spondylite rhumatismale, les auteurs considèrent que:

1. L'augmentation des protéines dans le liquide céphalo-rachidien lombaire peut exister même si la colonne vertébrale n'est pas atteinte. L'excès de protéine dans la spondylite n'est donc pas nécessairement dû à l'inflammation des méninges médullaires.

2. Dans la spondylite rhumatismale comme dans l'arthrite rhumatismale sans spondylite une petite, ou même la totalité de l'excès de protéine présent dans le liquide céphalo-rachidien peut y entrer par la voie des plexus choroïdes, probablement par suite de l'augmentation de la perméabilité de ceux-ci aux protéines.

3. Puisque les chances d'une augmentation des protéines dans le liquide céphalo-rachidien d'un malade atteint d'arthrite rhumatismale sont augmentées par l'existence d'une atteinte du rachis, on ne peut rejeter la possibilité qu'une partie de l'excès de protéine présent dans le liquide céphalo-rachidien dans la spondylite ait pu passer dans l'espace sous-arachnoïdien le long des espaces périsvasculaires et périnerveux par suite de l'inflammation locale des tissus avoisinant la colonne vertébrale.

4. La présence d'un excès de protéine dans liquide céphalo-rachidien dépend d'avantage de la gravité de la maladie que de sa durée. Le taux de protéine dans le liquide céphalo-rachidien peut être aussi élevé ou même plus élevé pendant les premiers mois que pendant les années qui suivront. Par conséquent, le mécanisme produisant l'augmentation du contenu protéinique du liquide céphalo-rachidien est davantage en rapport avec le stade d'inflammation active qu'avec celui des lésions résiduelles.

5. Les auteurs ne prétendent pas affirmer que dans le cas d'une augmentation des protéines du liquide céphalo-rachidien dans un cas d'arthrite rhumatismale périphérique il y ait lieu de soupçonner que celle-ci est accompagnée de spondylite latente, néanmoins, dans un cas de ce genre, il est important de procéder à un examen minutieux de l'état de la colonne vertébrale.

6. La constatation d'une augmentation des protéines est en elle-même sans grande valeur pour la différenciation entre la spondylite rhumatismale et les autres affections de la colonne vertébrale qui aboutissent à une incapacité lombaire chronique avec sciatique. Mais dans la spondylite ces augmentations de protéines sont toujours modérées, et si le taux de protéines dépasse sensiblement 100 mg. pour 100 cc. il faut en chercher une autre cause que la spondylite, quand bien même la spondylite est également présente.