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THE CEREBROSPINAL FLUID IN 'ESSENTIAL' EPILEPSY*

By

W. G. LENNOX and H. H. MERRITT, BOSTON, MASS.

THE data in the literature dealing with the cerebrospinal fluid of patients with epilepsy are unsatisfactory. Most of the reports present the incomplete findings of a few cases. Also, many authors have made no attempt to separate the cases in which the convulsions are associated with inflammatory, expanding or other lesions of the brain from the cases in which there is no apparent cause for the seizures. Neel¹ examined the fluids of 381 cases with convulsive seizures. In 129 of these cases the cause of the convulsive seizures was unknown. In this group he found that 11 per cent. had more than six cells and 14 per cent. had an increased protein content. This is in marked contrast to the percentage of abnormalities in the group of cases with convulsive seizures of known cause. In this group 69 per cent. had an increase in the cell count of the fluids and 75 per cent. an increased protein content. Patterson and Levi,² in their 50 cases, measured pressure with patients in the unorthodox sitting position and their measurements of pressure cannot be used. Twenty-two per cent. of the fluids had five or more cells per c.mm.; 10 per cent. had a positive globulin test; the sugar and chloride concentration was normal in the 10 examined cases. Marchand and Courtois,³ in 100 cases of 'essential epilepsy,' measured the pressure (horizontal position) in 17 patients, in three of whom it was above 250 mm. of water. In 19 per cent. the protein was more than 30 mg. The highest cell count was 6 per c.mm. Kulkow,⁴ in 50 cases, found an increased pressure in half of the cases. The cell count was increased in four cases and the globulin in 22. The sugar content was determined in 15 cases and found to be normal. Fay⁵ reported the range of cerebrospinal fluid pressure readings

* From the Neurological Unit of the Boston City Hospital and Department of Neurology of Harvard Medical School. This is No. XXI. in a series entitled 'Studies in Epilepsy.' Aid was received from the Harvard Epilepsy Commission.

in 100 cases of epilepsy. Pressures were measured in both the horizontal and vertical positions. In the horizontal position his results varied between 3 and 20 mm. of mercury (40 to 270 mm. of water) with an average of 10.5 mm. of mercury (142 mm. of water).

PERSONAL RESULTS

We here report the results of lumbar puncture of 810 patients having recurrent seizures. The great majority of these were seen by us during the past 12 years as private or hospital patients. These patients had as a routine a carefully taken history, physical and neurological examinations, roentgen-ray films of the skull and examinations of the blood and the cerebrospinal fluid. Therefore, practically all patients with a presenting symptom of seizure had lumbar puncture, but this report deals only with that portion of the total group who, on discharge, did not receive a diagnosis of organic nervous disease. Patients with seizures associated with abscess or tumour of the brain, syphilis of the nervous system, meningitis, encephalitis, multiple sclerosis, cerebral trauma, birth injury, cerebral arteriosclerosis, cerebral vascular lesions, chronic nephritis, uræmia or acute infections are excluded. We realize that it is impossible on the basis of an examination short of the postmortem table to exclude with accuracy all such cases. This is especially true of cases with brain tumour, since convulsive seizures may precede the onset of the other symptoms of a brain tumour by several or even many years.

When we speak of the 'essential' epileptic, we use that term not as a diagnosis, but simply as a convenient means of indicating patients whose condition is as yet undiagnosed. This elimination of patients with organic nervous disease was based chiefly on the history and findings on examination and in part on the results of the spinal fluid examinations. In many instances an abnormal spinal fluid finding was the principal or only evidence that led to the establishment of the diagnosis of central nervous system pathology. This was particularly true with cases of syphilis of the nervous system or tumour of the brain. Hence, this report views a group of patients after a winnowing process and not before. This fact should not be forgotten by the physician who is considering whether his patient should have a lumbar puncture performed. The previous reports from this laboratory^{6, 7, 8, 9} dealing with a portion of the cases here reported did not attempt segregation of diagnosed and undiagnosed groups.

Pressure of the Cerebrospinal Fluid.—In considering the question of ætiology of seizures, abnormality in intracranial pressure is of considerable importance. Animal experiments have suggested that convulsant drugs more readily produce convulsions when intracranial pressure is high. Increase of pressure has been blamed for the convulsions associated with cerebral neoplasms, but against this is the fact that in these cases convulsions may occur early in the course of the disease before the intracranial

pressure is increased and also that seizures are relatively infrequent in patients with posterior fossa tumours, in which pressures are usually very high. Seizures which follow forcing of fluids and injection of pitressin are supposedly related to the retention of fluid and increased intracranial pressure. Fay⁵ has proposed a 'hydraulic' theory of epilepsy based on the idea of a defective absorption of cerebrospinal fluid and consequent increase in the volume and pressure of the fluid. His measurements of pressure (made with a mercury manometer) are remarkably similar to ours, but his standard for normal pressures is lower than that used by us. Our standard of normal is based on our own experience with the method used in our neurological service over a period of years.

Measurements of pressure were made by means of the Ayer manometer or the Fremont-Smith modification. Patients were punctured in the lumbar region while lying in the lateral recumbent position. Readings were delayed until the patient was relaxed and the spinal fluid in the manometer had reached a steady state. Pressures obtained by this method were considered normal if between 70 and 180 mm. of cerebrospinal fluid; questionable if between 180 and 200 mm., and definitely abnormal if above 200 mm.

We tabulated the pressure at the initial puncture of 735 patients. The highest pressure was 300 mm.; the lowest 35 mm., and the average 143 mm.

The percentage distribution of pressure readings in these 735 patients is shown in Table I.

TABLE I. THE RANGE OF THE CEREBROSPINAL FLUID PRESSURE IN 735 CASES OF 'ESSENTIAL' EPILEPSY

Cerebrospinal fluid pressure (mm. of C.S.F.)	Number of cases	Percentage
35 to 70	17	2
70 to 100	71	10
100 to 150	343	46
150 to 180	182	25
180 to 200	57	8
200 to 250	59	8
250 to 300	6	1
	735	100

Eighty-one per cent. of the patients had a normal pressure. Some of the pressures in the neighbourhood of 200 mm. might be explained by the fact that in the early years of this investigation the importance of not having the patient's head and legs in a flexed position was not realized. Only six patients—less than 1 per cent. of the total—had a pressure above 250 mm.

These measurements were made in a period between seizures. Pressure

readings just before a seizure are important with reference to theories regarding the immediate cause of a seizure. A preliminary fall of pressure would lend support to the theory of vascular spasm, whereas an elevation would be in favour of an acute cerebral œdema or hydrocephalus or a vascular dilatation.

The senior author has on numerous occasions observed the spinal fluid pressure during a petit mal seizure. Before the attack, there was never any significant change in pressure unless the seizure was precipitated by hyperpnœa, in which cases the resulting alkalosis caused a constriction of cerebral vessels and a fall of pressure. During the petit mal attack, also, there was no change unless respirations were suspended long enough to produce venous congestion and a rise. On several occasions, he has observed the changes in pressure preceding and during grand mal convulsions. Whether there was a preliminary change in pressure depended on the point in the respiratory cycle at which the patient's tonic spasm began. When the glottis was closed, if the patient attempted to inspire, the pressure fell; if to expire, it rose. Observations made on successive days in one patient are shown in fig. 1. The fact that during a convulsion the intracranial pressure becomes as great as 700 mm. may help to explain the dilated ventricles and the cortical atrophy which so many chronic cases exhibit.

These observations indicate that changes in intracranial pressure at the time of seizure are passive rather than active factors in seizures. They are in agreement with the observations recently reported by Denny-Brown and Robertson,¹⁰ who made graphic records of the cerebrospinal fluid pressures of six patients during convulsion.

White Corpuscles.—The white cells were counted in the fluids from 734 patients. The ordinary blood counting chamber was used, the cells being faintly stained with Unna's polychrome methylene blue. The number of cells varied between 0 and 21 per c.mm., with an average of 2 per c.mm. Only one patient had more than 10 cells per c.mm. and only 30 (4 per cent.) had more than five cells. As previously explained, cases believed to have any infection of the brain or meninges were excluded.

Protein Content.—The protein content of the fluid was measured in 793 cases. The Denis-Ayer¹¹ method was used and 45 mg. per 100 c.cm. was considered the upper limit of normal. The results varied between 7 and 200 mg., with an average of 31 mg. per 100 c.cm. The percentage distribution of these 793 values is shown in Table II.

Since there does not seem to be pathological significance in low values, 90 per cent. may be considered normal. In 10 per cent. the protein content was abnormally high, though in most instances the increase was moderate. The patient with the highest concentration of protein (200 mg.) one year later had 87 mg. and 10 years later 56 mg. per 100 c.cm. At autopsy 13 years after the first puncture there were several 'plaques jaunes' in the tips of the temporal lobes, probably the result of trauma received during some of his more than 10,000 convulsions.

CEREBROSPINAL FLUID PRESSURE DURING CONVULSIONS

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FIG. 1.—Changes in cerebrospinal fluid pressure accompanying grand mal (G.M.) convulsive seizures. The ordinate represents pressure in millimetres of spinal fluid; the abscissa, time in minutes. The dotted portion of the curve denotes pressures obtained after the draining of fluid. The second half of the chart shows the pressure changes in the same patient when repunctured 24 hours later.

TABLE II. THE PERCENTAGE DISTRIBUTION OF THE PROTEIN CONTENT IN 793 CASES OF 'ESSENTIAL' EPILEPSY

Protein content (mg. per 100 c.cm.)	No. of cases	Percentage
7 to 19	98	12.3
20 to 45	612	77.2
46 to 85	80	10.2
85 to 100	2	0.2
100 to 200	1	0.1
	793	100.0

Colloidal Gold Reactions.—The colloidal gold reaction was determined in 741 cases. The method of Lange as described by Cockrill¹² was used. Any change in the gold solution greater than a lilac colour '2' was considered abnormal. None of our cases gave an abnormal colloidal gold curve and in only 60 cases (8 per cent.) was there a change as great as lilac '2' in the colloidal gold solution.

Wassermann Reaction.—Cases which received a diagnosis of syphilis of the central nervous system are excluded from this report. Convulsive seizures occur in about 30 to 60 per cent. of patients with general paresis¹³ and about 17 per cent. of those with syphilitic meningitis.¹⁴ The proportion is less in meningovascular syphilis and is hardly above the level of that of the general population in tabes dorsalis.

Sugar Content.—The sugar content of the cerebrospinal fluid was measured in 229 cases. The Folin-Wu method, modified by Rothberg and Evans,¹⁵ was used. The results varied between 38 and 167 mg., with an average of 70 mg. per 100 c.cm. The percentage distribution of values is shown in Table III.

TABLE III. THE PERCENTAGE DISTRIBUTION OF THE CEREBROSPINAL FLUID SUGAR CONTENT IN 229 CASES OF 'ESSENTIAL' EPILEPSY

Sugar content (mg. per 100 c.cm.)	No. of cases	Percentage
38 to 50	7	3
50 to 60	35	15
60 to 80	154	67
80 to 100	24	11
100 to 167	9	4
	229	100

Eighty-two per cent. of the cases had values between 50 and 80 mg. per 100 c.cm. Of the 15 per cent. with values above 80 mg., some might be explained by the fact that in most instances the patients were not fasting at the time of the puncture. The absence of any very low concentrations speaks against hypoglycæmia as a significant finding in epilepsy.

Chloride Content.—The chloride content of the cerebrospinal fluid was determined in 209 cases. The Van Slyke ¹⁶ method or the Van Slyke method as modified by Wilson and Ball ¹⁷ was used and results expressed as milligrammes of sodium chloride. The greatest concentration was 794 mg. and the lowest 658 mg. per 100 c.cm. of fluid. The average was 723 mg. per 100 c.cm. The distribution of values is shown in Table IV.

TABLE IV. THE DISTRIBUTION OF THE CEREBROSPINAL FLUID CHLORIDE CONTENT IN 209 CASES OF 'ESSENTIAL' EPILEPSY

Chloride content (mg. per 100 c.cm.)	No. of cases	Percentage
658 to 675	2	1
675 to 700	9	4
700 to 760	194	93
760 to 794	4	2
	209	100

Only 3 per cent. of the values could be considered as definitely abnormal.

Calcium Content.—The calcium content was measured in 93 cases by the Clark ¹⁸ modification of the Kramer-Tisdall method. The values varied between 4.1 mg. and 5.8 mg., with an average of 5.0 mg. per 100 c.cm. Only seven cases had a value below 4.5 mg. and only one a value greater than 5.5 mg. per 100 c.cm.

Non-Protein Nitrogen.—The non-protein nitrogen content was determined in 10 cases by the Folin-Wu ¹⁹ method. The values varied between 11 and 26 with an average of 17 mg. per 100 c.cm.

SUMMARY OF INITIAL OBSERVATIONS.—The abnormalities in the cerebrospinal fluid in patients with epilepsy of undiagnosed ætiology were confined to a slight increase in pressure in 9 per cent., an increase of the cell count in 4 per cent., and a slight increase in protein content in about 10 per cent. of the cases. About one-fifth of the patients showed one or more abnormalities in the cerebrospinal fluid. Only six cases (one per cent.) had an increase in both pressure and the protein content.

Duration of Epilepsy and Cerebrospinal Fluid Abnormalities.—Tabulation was made of the cerebrospinal fluid pressures with relation to the age of the patient and also the duration of the history of seizures. The duration ranged from a few months to 45 years. The percentage of patients with

increased cerebrospinal fluid pressure was approximately the same for all age groups. Increased pressures were found in 8·3 per cent. of the 552 cases in which the duration of the disease was less than 10 years and in 10 per cent. of the 183 cases in which the duration was greater than 10 years. We therefore concluded that the age neither of the patient nor of the disease bears any significant relation to the pressure of the cerebrospinal fluid in these cases.

In tabulating the data with respect to any possible correlation between the increase in the protein content of the cerebrospinal fluid and age of the patient, we observed for each successive decade a slight progressive increase in the incidence of patients with an abnormal protein content. The proportion of patients with fluid abnormally high in protein content was 10 per cent. for those with a history of less than 10 years and 13 per cent. for those with a history longer than this.

Repeated Examinations.—This report deals only with the finding at the time of the patient's initial lumbar puncture at our hands. In comparison with other body fluids used for examination, the spinal fluid is relatively constant from one time to another. Even pressures, if made under standard conditions, are surprisingly alike. Examinations were repeated in many cases in order to check abnormal findings or apparent discrepancies. Checking was especially important in those cases with an abnormal pressure.

Of more interest are the examinations repeated at prolonged intervals. Twenty-eight patients had a second examination made from one year to as long as 11 years later. The number of cases in each of the first five years was successively five, six, two, four, and three. After seven years there were four, after 10 years one, and after 11 years two cases. The results of the second or third examination were with a few exceptions, as noted below, remarkably like the first.

Six of these 28 cases had a pressure of 200 mm. or greater at first puncture and all six had a normal pressure at the subsequent puncture one or more years later. In one case the pressure was 125 mm. at first puncture and 11 years later it was found to be increased to 220 mm.

The protein content was increased at first puncture in only one of the 28 patients. In this case already mentioned, a protein content of 200 mg. had fallen to 87 mg. after an interval of one year and to 56 mg. after 10 years. Two cases with original protein contents of 34 and 41 mg. had values of 47 and 52 mg. per 100 c.cm. respectively after a period of 11 years.

There was no significant change in the cell count or the colloidal gold reaction of any of the 28 cases.

SUMMARY

1. This report deals with the cerebrospinal fluid findings in 810 patients having seizures of undiagnosed origin.
2. The cerebrospinal fluid was entirely normal in approximately 80 per cent. of the cases.

3. An abnormal increase in pressure (between 200 and 300 mm.) occurred in 9 per cent. of the patients; only one per cent. had a pressure greater than 250 mm.

4. A slight pleocytosis (between 6 and 10 cells per c.mm.) occurred in about 4 per cent. of the cases.

5. The protein content was above normal in 10 per cent. of the cases; values greater than 85 mg. per 100 c.cm. were encountered in less than 0.5 per cent.

6. The colloidal gold and Wassermann reactions, the concentration of sugar, chloride, calcium and non-protein nitrogen content were normal in practically all cases.

CONCLUSIONS

The cerebrospinal fluid is normal in four-fifths of patients, the cause of whose seizures remains undetermined after clinical and laboratory examinations. A slight increase in pressure and in the protein content is the chief abnormality. Any marked abnormality in pressure or the contents of the fluid makes the diagnosis of 'essential' epilepsy hazardous.

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