TUMOURS OF THE BRAIN ASSOCIATED WITH MARKED PLEOCYTOSIS IN THE CEREBROSPINAL FLUID.*

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A SLIGHT or moderate pleocytosis in the cerebrospinal fluid is not rare in cases of tumour of the brain. Greenfield and Carmichael¹ state that a slight pleocytosis (5-10 cells) frequently occurs in cases of cerebral tumour. Alpers² examined the ventricular fluid in 102 cases and found a pleocytosis in nine instances; from 7 to 20 cells in seven fluids, 73 cells in one fluid, and 375 in another. Spurling and Maddox³ studied the cerebrospinal fluid from 108 patients and reported that the cell count was low, usually under 3. Moersch⁴ examined the cerebrospinal fluid obtained by lumbar puncture from 252 cases of cerebral tumours; he found more than 100 cells in two cases only. The finding of a large number of cells in the cerebrospinal fluid is rare, and for this reason we are reporting two such cases that have come under our observation.

PERSONAL CASES.

CASE 1.—E. C. The patient was a white Syrian merchant, aged 62; admitted to the Neurological Service of the Boston City Hospital, February 7, 1929, in a semicomatose condition. The following history was obtained from his daughter.

Until three weeks prior to entry the patient was perfectly well. At this time he developed a headache, just before or after sustaining a slight injury to his head. Ten days before entry he had a chill and was confined to bed for one day. He appeared to be confused, as he was playing with his fingers and had washed his face with an orange. For one week the daughter had noticed that the patient seemed sleepy, talked very slowly, complained of severe pain in both temples, and was incontinent of urine. Six days before entry he vomited, became very drowsy and slept continuously. On the day of admission the patient put his right hand to the right side of his head frequently. There was no record of fever while at home.

Physical examination showed a well developed but poorly nourished elderly male in a deep stupor. The skin was moist and the lips were slightly cyanotic. There was a mucopurulent discharge in the posterior nasopharynx. The ear drums appeared normal. There was moderate opisthotonus, slight stiffness of the neck, and bilateral Kernig's sign. The brachial and radial arteries showed a moderate degree of arteriosclerosis.

The right pupil was larger than the left; both reacted sluggishly to light. There was a mild choking (1-2 dipters) of the optic discs. Otherwise the cranial nerves

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were normal. The patient did not move the left arm or leg except on stimulation, whereas there were frequent spontaneous movements of the right limbs. The deep reflexes and the tonus of the muscles were increased on both sides but slightly more so on the left. There was bilateral ankle clonus which was more sustained on the left side. The left cremasteric reflex was absent. There was a positive Chaddock sign and a questionable Babinski reflex on the left.

The urine was normal. Examination of the blood showed 15,000 white blood cells and 5,500,000 red blood cells per c.mm. The blood Kahn test was negative and blood culture was sterile. The lumbar puncture showed an initial pressure of 450 mm. of water. The fluid was cloudy, xanthochromic and contained 2,106 white cells per c.mm., 90 per cent. of which were polymorphonuclear leucocytes. The total protein content was 216 mgm.; the sugar was 80 mgm. and the chloride content was 696 mgm. per 100 c.c. The Wassermann reaction of the fluid was negative.

These changes in the cerebrospinal fluid were interpreted as indicating that there was a suppurative process within the brain which had not as yet caused a meningitis. The left hemiparesis indicated that the lesion was in the right hemisphere, and from the history of mental disturbance it was thought that the lesion was probably frontal. Therefore, the diagnosis of abscess of the right frontal lobe was made, and the right frontal region was tapped by Dr. Donald Munro on the day of admission. No pus was found and culture of the bloody material obtained on aspiration was sterile. Dr. Munro thought that the brain tissue in the region explored seemed unusually soft.

The following noon lumbar puncture was again performed. The initial pressure was 300, the fluid was cloudy and slightly blood tinged. There was questionable evidence of spinal block. The fluid contained 3,000 white cells which were chiefly polymorphonuclear leucocytes and 45,000 red blood cells per c.mm. The sugar content was 75 mgm., chlorides 705 mgm., and total protein 426 mgm. per 100 c.c.

The patient became more stuporous with rapid respiration and died about twenty-four hours after admission.

TABLE 1.
THE CEREBROSPINAL FLUID FINDINGS IN CASE 1.

Date	Pressure	White blood cells	Total protein mgm./100 c.c.	Sugar mgm./100 c.c.	Colloidal gold	Comment
2/7/29	450 mm.	2106	216	80	000111C000	—
2/8/29	300 mm.	3000	426	75	0011110000	After operation

Necropsy.—At necropsy a large infiltrating tumour was found in the medial portion of the right frontal lobe (fig. 1) involving the corpus callosum and extending into the left frontal lobe. The anterior horns of both lateral ventricles were compressed by the tumour. The tumour appeared vascular, and there were numerous small hæmorrhagic areas. Microscopic examination showed the tumour to be a glioblastoma multiforme.

CASE 2.—E. B., a 54-year-old white, married, printer, was admitted to the Boston Psychopathic Hospital, October 23, 1931, in a depressed state. The following history was obtained from his brother.

With the exception of typhoid fever in 1900 the patient had always been in good health. For the past two years he had been worrying a great deal and was not feeling well. Eight weeks before admission he began to complain of nervousness and expressed fear that he was going to have a nervous breakdown.

He lost interest in his work and said that both of his legs felt weak. One month before entry he had an attack of muscular rigidity and a momentary loss of consciousness. He was driving his automobile at the time, but he regained possession of his faculties in time to prevent an accident. He continued to have transient attacks of general weakness and fell on several occasions. One week before admission he fell eight feet down the stairs, striking his head but not losing consciousness. Since then he complained of general weakness. He was in a depressed mental state and worried considerably about himself. He was seen in consultation by a local neurologist and was sent to the hospital with the diagnosis of 'hysteria.'

FIG. 1.—Case 1. Horizontal section of brain showing tumour mass in left frontal lobe, which has involved the corpus callosum and spread to the opposite frontal lobe.

Examination.—The general physical examination was negative. The blood pressure was 128/70. There was a marked slowing of all mental processes. He responded very slowly to questions. There was no disturbance of orientation, no delusions or hallucinations. He spoke of feeling depressed and wept easily.

On neurological examination the cranial nerves were normal. The fundi, visual acuity and visual fields were normal. On examination of the motor system the patient cooperated very poorly, but no definite weakness of any muscle groups could be found. The gait was very unsteady, he walked slowly, staggered from side to side, and required help in getting in and out of bed. In the performance of these tests the patient gave the impression that he was able to support himself and walk better than he was doing. No tremors or involuntary movements were noted. He spoke in a whisper, but on encouragement he could speak in a normal

tone. No psychomotor disturbance or apraxia could be demonstrated. A satisfactory sensory examination was not possible, but no gross disturbance was noted. The deep reflexes were all moderately hyperactive. On plantar stimulation there was a doubtful Babinski response on the left while the response on the right was definitely flexor in type.

The urine and blood were normal. The blood Wassermann was negative. X-rays of the skull showed a poorly defined shadow just above the lambdoid suture on both sides which was interpreted as a slight thickening of the inner table of the skull. The sella turcica was normal.

There was little change in the condition of the patient for the first six days of his stay in the hospital. The first lumbar puncture was performed three days after admission. Unfortunately no record of the pressure was made at this time. The fluid was clear and colourless and contained 8 white cells (lymphocytes) per c.mm., 82 mgm. of protein and 74 mgm. of sugar per 100 c.c. The colloidal gold curve was 0012300000, and the Wassermann reaction of the fluid was negative.

On the sixth day after entry, the patient sank into a semicomatose condition and could be aroused only for feeding. He was incontinent and his respirations were of the Cheyne-Stokes type. The temperature which had previously been normal rose to 101°. There was no stiffness of the neck or Kernig's sign. Lumbar puncture on October 29 (six days after entry) showed an initial pressure of 250 mm. of fluid with marked variations with the respirations (Cheyne-Stokes), and normal dynamics. The fluid was cloudy and contained 4,000 white cells, 70 per cent. of which were of the polymorphic neutrophilic type. Chemical examination showed 235 mgm. of protein and 43 mgm. of sugar per 100 c.c. Cultures of the blood and cerebrospinal fluid were sterile. In spite of the negative smears, cultures and only slightly reduced cerebrospinal fluid sugar content, the patient was treated with anti-meningococcus serum by the intraspinal and intravenous routes. He remained in a comatose condition for the next five days, during which he received numerous lumbar and cisternal punctures for the administration of serum. The lumbar puncture findings on the various punctures are shown in Table 2.

TABLE 2.
THE CEREBROSPINAL FLUID FINDINGS IN CASE 2.

Date	Source	Pres- sure	White blood cells	Total protein mgm./100 c.c.	Sugar mgm./100 c.c.	Colloidal gold	Comment
10/26/31	lumbar	—	8	82	74	001230C000	—
10/29/31	lumbar	250mm.	4090	235	43	0000121000	serum given
10/29/31	cistern	—	4800	145	62	0011232100	„
10/30/31	lumbar	75mm.	7200	1638	31	2223455555	„
10/30/31	lumbar	70mm.	600	468	78	3344354433	„
10/31/31	lumbar	—	200	216	63	2223345555	„
10/31/31	cistern	—	108	156	66	3344322100	„
11/1/31	lumbar	—	253	266	61	3445555431	—
11/1/31	cistern	170mm.	89	160	66	3455554311	—

The temperature was constantly elevated, varying from 98° to 103°. The patient died on November 2.

Necropsy.—The necropsy was performed four and one-half hours after death by Dr. Myrtelle Canavan. The abdominal and thoracic viscera showed nothing of significance. Externally the brain was of normal appearance, but when cut in frontal section a large infiltrating tumour was found in the mesial portion of the frontal lobes, involving the corpus callosum and the adjacent white matter of both hemispheres. The tumour extended from the level of the tip of the olfactory bulb anteriorly to the level of posterior portion of the optic chiasm posteriorly. The anterior horns of both lateral ventricles were compressed by the tumour mass.

FIG. 2.—Case 2. Frontal section at the region of the optic chiasm showing area involved by the tumour mass. Note relatively fresh hæmorrhage in the upper portion of the tumour in the right frontal lobe.

The tumour was very vascular in appearance, and in its posterior portion there was a fresh hæmorrhagic area about 2×2 cm. in diameter. No definite line between tumour tissue and brain could be found, but the greatest diameters of the tumour were approximately 3 cm. in the anteroposterior direction and 8 cm. in the transverse (fig. 2).

Microscopic sections of the tumour showed that it was composed chiefly of spongioblasts, and the microscopic diagnosis by Dr. Canavan was glioblastoma multiforme (fig. 3).

DISCUSSION.

In the first case the rapid onset of the symptoms and the finding in the cerebrospinal fluid of a marked pleocytosis with normal sugar content led to the diagnosis of cerebral abscess, although no primary focus was evident. The finding of a glioma at autopsy came as a surprise.

The second case was sent to the Boston Psychopathic Hospital by a competent neurologist with the diagnosis of hysteria. The behaviour of the patient in the wards tended to substantiate this diagnosis, but the minor

FIG. 3.—Case 2. Section from central portion of tumour showing the marked vascularity and the cellular nature (cresyl violet stain).

abnormalities found on examination pointed to an organic involvement of the central nervous system, as did also the changes in the cerebrospinal fluid found on the first puncture. Unfortunately the operator failed to record the intracranial pressure at the first puncture and a definite diagnosis could not be made. When the patient sank into a coma a few days later, however, a second puncture was performed. At this time the intracranial pressure was slightly elevated and the fluid was purulent. Although the sugar content of

the fluid was only slightly below normal and no organisms were seen on smear, it was thought wise to give the patient anti-meningococcus serum on the chance that he had developed a meningeal infection while in the wards. With further observation it was evident that the patient did not have an infection of his meninges, but that there was an intracerebral lesion, probably an abscess or possibly a tumour. The absence of any definite localizing signs and the extremely poor condition of the patient prevented any operative measures.

The cerebrospinal fluid in the second case was especially interesting in that the pleocytosis developed under observation, and that the patient lived for a sufficiently long interval to allow us to observe the further course of the changes in the fluid. On the first puncture the fluid had only 8 cells. Three days later the patient sank into coma and the fluid contained 4,000 cells. There was subsequent temporary increase in the cell count which can be attributed to the serum therapy. After this there was a steady decrease in the number of cells in the cerebrospinal fluid until there were only 80 white blood cells in the cisternal fluid on the day before death.

The findings of increased intracranial pressure, pleocytosis and normal sugar content in the cerebrospinal fluid usually indicate a septic focus (abscess) within the brain or in close relationship to the meninges. During life this seemed the best diagnosis in both of our cases. The necropsy showed, however, that a central tumour can cause a marked pleocytosis in the cerebrospinal fluid.

Similar cases have been reported by Parker⁵ and Moersch⁴. The case of Parker was that of a glioblastoma multiforme of the temporal lobe which had compressed the middle cerebral artery and produced an area of softening in the temporal lobe near the ventricle. The cerebrospinal fluid contained 1,707 cells. In those reported by Moersch⁴ the greatest pleocytosis was found in the case of a glioma involving the corpus callosum (anterior portion) and both frontal lobes. He reports three punctures in this case. The cell counts are reported as 'many,' 679 and 90 respectively. In the only other case in his series showing over 100 cells per c.mm. a glioma of the left temporal lobe was found. Only one puncture is reported in this case and the fluid contained 191 white blood cells, 50 per cent. of which were polymorphonuclear leucocytes.

It is interesting to note that our two cases and one of Moersch's involved the anterior portion of the corpus callosum. Ironsides and Guttmacher⁶ called attention to the frequency of increased protein and cells in the cerebrospinal fluid as the result of a tumour of the corpus callosum. None of their cases, however, had over 100 cells per c.mm. in the fluid.

The most satisfactory explanation of the occurrence of pleocytosis in the cerebrospinal fluid of cases of cerebral tumour is that it is due to the

release of cells into the ventricles or subarachnoid space from the symptomatic inflammation which occurs around an area of tissue degeneration. This hypothesis is supported by the work of Cone and Barrera⁷, in which they produced aseptic cerebral embolism in animals. They found that polymorphonuclear cells were poured out in the region of the infarcted area, and that these cells can reach the cerebrospinal fluid by way of the perivascular spaces, or by direct extension into the fluid when the softened area is in close relationship to the ventricles or the subarachnoid space.

Areas of softening occur in cerebral tumours as result of ischæmia or hæmorrhage, particularly in the rapid growing glioblastoma multiforme, and cells can find their way to the cerebrospinal fluid from the symptomatic inflammation which occurs around such necrotic areas, especially if they are near ventricles. In our second case it is most likely that the large hæmorrhage which was found in the tumour at necropsy was responsible for the onset of the coma and for the cells in the cerebrospinal fluid. In our first case, although the hæmorrhagic areas were smaller, they were probably responsible for the pleocytosis in the cerebrospinal fluid.

A further illustration of the occurrence of a pleocytosis in the cerebrospinal fluid as the result of a focus of necrosis near the ventricles is presented by the following case recently seen at the Boston City Hospital.

A white male (A. B.), 47 years of age, was admitted to the hospital in coma. The patient was known to have had a high blood pressure for several years, and on the day of admission he had had a 'stroke' characterized by a sudden onset of coma and the development of a left hemiplegia. On admission his systolic blood pressure was 200 mm. of mercury and the diastolic pressure was 140 mm. The cerebrospinal fluid was under a pressure of 180 mm. of water. The fluid was slightly turbid and contained 700 cells per c.mm., 42 per cent. of which were polymorphonuclear leucocytes. The protein content of the fluid was 56 mgm. and the sugar content 87 mgm. per 100 c.c. The patient died five days later and at necropsy a large hæmorrhage was found in the region of the right internal capsule and basal ganglia. There was no blood in the ventricles and the hæmorrhage was separated from the ventricles by a thin layer of necrotic brain tissue.

The rarity of cases of brain tumour with marked pleocytosis may be explained in part by the fact that lumbar punctures are usually not performed in cases with high-grade choked discs or when the diagnosis is evident. Even if such cases are punctured, cells would only be expected in those cases where a recent hæmorrhage or area of softening had occurred.

SUMMARY.

Two cases of glioma of the anterior portion of the corpus callosum and frontal lobes which showed a turbid cerebrospinal fluid are reported. The literature on this subject is discussed and the presence of the polymorphonuclear cells in the cerebrospinal fluid of cases of brain tumour is explained as being due to drainage of cells from the area of symptomatic inflammation occurring around foci of necrosis close to the ventricles.

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