Preoperative Hormonal Treatment in Cases of Cerebral Tumor

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Various authors have noticed the effects of cortico-adrenal therapy in certain cases of cerebral tumor. However, the results observed with delta-cortisone or dexamethasone were not satisfactory enough for their systematic use. It was necessary to establish with some precision a more complete understanding of the means and mechanisms of action of the cortico-adrenal hormones, in order that the cases could be selected and the appropriate therapy applied. For this purpose, we made use of the most recent knowledge concerning the central hypothalamopituitary control of the hydroelectrolytic metabolism and we were able to standardize an endocrinologic treatment which generally has a favorable effect on the clinical symptomatology of patients suffering from cerebral tumor. We have already dealt with the postoperative effects of this treatment. We should like also to show the advantages of this method in preparing patients for surgery, in cases other than of tumors of the pituitary in which classical corticotherapy has already proved its worthiness.

Choice of Patients

The use of this treatment has become almost routine in patients on whom we have operated, in particular those with meningiomas and glioblastomas, diagnosed by neuroradiological and gamma-encephalographic examinations. Cerebral metastatic tumors caused by a visceral cancer in male patients, and spontaneous intracranial hematomas also can be treated suitably by this method. Further on, we shall give statistical figures on 31 cases, and a detailed report of the observations in 4 cases in which a preoperative electroencephalographic study had been carried out.

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Technical Procedure

The treatment consisted of:

1) ACTH: 50 units (150 new units) via intravenous perfusions over 16 hours; every day up until the surgical operation.

2) Cortisol: 30 mg. orally, or hemisuccinate (25 mg. every 12 hours) if the patient was unable to take anything by mouth, every day up to the day of intervention.

3) Postpituitary extract: we used a total extract of posterior pituitary body (Post-hypophyse Polyvidone®), in a form that has a delayed action, in a dose of 3 units per day, by intramuscular injection. These injections were given 5 days out of 7 up to the day of operation.

If the patient was able to be fed orally, he was given a diet that included NaCl (2 gm. per day). If he was in a state of coma, we prescribed 1.5 liters of water per 24 hours together with 2 gm. of NaCl and 2–3 gm. of KCl.

In cases in which the patient had suffered from insufficient intake of water, it was necessary to correct this defect first until the osmolar condition of the plasma returned to normal. However, it was sometimes possible to start the hormonal treatment simultaneously. The reasons that led us to adopt the combination with the hormonal treatment are given further on.

Cases

Case 1. L.S., aged 33 years, was admitted on Dec. 16, 1961 with intracranial hypertension. During the previous 3 months the patient had complained of an increasing asthenia and headaches which lately were accompanied by vomiting. He was found to be in a state of stupor and semicoma, and on examination it was noted that, in addition to a paralysis of the right 6th cranial nerve, there was a right Babinski's sign. Also there was bilateral papilledema. Left carotid arteriography revealed the presence of a space-occupying lesion in the left frontal region.
A standard course of hormonal treatment was prescribed from December 16 to 26, and, after a few days, the state of consciousness was improved considerably. On the electroencephalogram of Dec. 19, 1961 a delta polymorphic activity was noted in the left frontal region, also considerable monomorphic activity spreading to this region, and a posterior bilateral delta rhythm. On December 23, the latter two types of activity had disappeared (Fig. 1).

A left frontal metastatic tumor (an epidermoid metastasis probably of pulmonary origin) was removed surgically on December 24, the brain tissue being edematous.

The patient left the Department in good condition on Jan. 19, 1962, his only symptom being slight aphasia.

Comment. Case 1 showed preoperative regression of intracranial hypertension (following 7 days of treatment) in a patient suffering from a frontal metastasis.

Case 2. E.S., aged 67 years, was admitted semi-comatose on Oct. 10, 1961. The onset of the disturbances had occurred 1 month previously, following which she had had a progressive right hemiplegia interrupted by Bravais-Jacksonian fits involving the same side. The state of somnolence became more pronounced although the patient tried to reply to loud verbal instigations.

The gamma-encephalogram showed the presence of a lower left rolandic focus resembling a glioma. Two electroencephalograms were taken, 1 before and 1 after two days of hormonal treatment and a definite clinical improvement in the state of consciousness was observed (Fig. 2: Oct. 12 and 14).

Surgical intervention was postponed in view of the doubtful postoperative prognosis, and the patient was transferred to a medical ward. She returned to the Department on Oct. 10, 1961 with marked deterioration in her condition, the rightsided hemiplegia being complete and the coma deeper. Once more the beneficial effect of the standard hormonal therapy was evident. On November 2, the coma had lessened sufficiently to enable the diagnosis of a distinct Wernicke's aphasia to be made; from the electroencephalographic point of view, the improvement was shown on the graph (Figs. 2 and 3). The treatment was stopped on November 4, and the patient again sank into a state of coma with total hemiplegia. Again revival was obtained when endocrinologic therapy was prescribed on November 10.

Operation on November 11 enabled the partial removal of a large rolandic tumor on the left side, which proved to be a glioblastoma.

The postoperative course was satisfactory and the patient left the Department in good condition, conscious, but with a hemiplegia.

Comment. Case 2 is an observation of experimental value. A patient suffering from a glioblastoma was revived from a state of coma by means of hormonal therapy, falling back into coma again as soon as the treatment was stopped on 3 different occasions.
Case 3. B.J., aged 58 years, was admitted on Feb. 14, 1961 with intracranial hypertension and aphasia. The disturbances had appeared 15 days previously. Here we were dealing with a patient who was confused, bewildered, disoriented, and with cephalgia.

Neurological examination revealed a slight right pyramidal syndrome, a bilateral "réflexe pollicio-mentonnier," and, of more significance, a state of aphasia: jargonaphasia, poor recognition of objects, incomprehension of complex orders and alexia. There was considerable papilledema and retinal hemorrhage. Left carotid arteriogram on February 7, and gamma-encephalogram on February 11 and 12 provided evidence of a malignant tumor of the left temporal region.

The patient's condition, however, improved because of the effect of the hormonal treatment prescribed from February 18 to 22. The patient was lucid and in particular the state of aphasia regressed considerably. Spontaneous speech improved, the vocabulary became good despite some hesitation; complex orders (the three-papers test) were carried out, and the patient was able to read and explain what he read. A comparison of the electroencephalograms of February 15 and 22 showed a regression of the delta focus of the left frontotemporal region (Fig. 4).

Surgical intervention was carried out on February 23 with removal of an anterior temporal tumor which proved to be a metastasis of an anaplastic epithelioma (probably of pulmonary origin).

The postoperative course was satisfactory and the patient left the Department on March 31, 1961.

Comment. In Case 3 the patient showed clinical improvement during the 9 days preceding operation for metastasis of the left temporal region.

Case 4. R.A., aged 38 years, was admitted on Jan. 1, 1963 with intracranial hypertension. The patient had complained of headaches during the previous 2 months and it was found that there was papilledema.

She had obnubilation, and neurological examination revealed only a hyperextensibility on the right side with Rossolimo's reflex on the same side. The electroencephalogram of January 1 showed diffuse anomalies most predominant in the left frontotemporal region.

The patient was submitted to hormonal treatment from January 1. Within a few days the state of obnubilation disappeared and a further electroencephalogram on January 10 was found to be considerably improved, the alpha rhythm and the diffuse anomalies not being so pronounced and a frontoprerolandic focus being identifiable on the left (Fig. 5). During this period, a gamma-encephalogram was carried out which gave evidence of a left frontal meningioma. Left carotid arteriogram on January 7 revealed the presence of a space-occupying lesion in the external frontal region.

On January 12, a meningioma, of the size of a tangerine, fixed to the left pterion was removed easily since the brain was not edematous.

The postoperative course was satisfactory and the patient left the Department in good condition on February 4.
Comment. In Case 4, a patient with a frontal meningioma showed clinical and electroencephalographic improvement during the 8 days of hormonal treatment prior to surgical intervention.

Discussion

The results obtained justify wider application of this method (Table 1). The use of this treatment, in our opinion, must modify the prognosis for cerebral tumors just as the effects of simple corticotherapy have done in cases of tumors of the pituitary body.

The therapeutic procedure we suggest has proved its value through experience. Theoretically, it is based on general considerations of the diencephalohypophysial regulation of the hydroelectriclyc metabolism. We have already set out these facts with regard to the "adrenopostpituitary imbalance in neurosurgery" and "the endocrinologic factors concerned in cerebral edema."

First of all it should be remembered that cerebral edema primarily is a cellular edema and that consequently a therapy that aims at eliminating water and K⁺ ions, the main elements of the cell medium, should have a favorable effect on cerebral edema.

In this respect, the study of the opposite effects produced by cortico-adrenal hormones and by the neuropostpituitary hormones on the hydroelectrolyc metabolism suggests different therapeutic possibilities (Fig. 6).

It is well known that cortisone or Doca causes a decrease in the amount of cellular K⁺ in vitro,10,12 and in vivo8 and experimental investigations confirm that this loss of K⁺ can be accompanied by cellular dehydration.28 The experiments of several investigators11,17,22 show this action particularly clearly in the region of the cerebral parenchyma. Cortico-adrenal hyperfunction would thus tend to redistribute the water within the organism, in favor of the extracellular areas at the expense of the cellular regions, but these effects are not always obvious in man when undergoing treatment with cortisone or with ACTH.26,31

The effects of postpituitary hormones on cellular metabolism are not well known. The experiments carried out by Friedman and S剧烈15 using vasopressin do not enable one to elucidate any typical specific action. Nevertheless, one of us (B-W.) together with Decourt et al.,2 has demonstrated that the total posterior pituitary extract increases the penetration of K⁺ in sections of the brain of the guinea pig. Hence, it is understandable why the administration of postpituitary hormones enables one to obtain experimental cerebral edema.27 Consequently, besides their better known antidiuretic effect, one of the main actions of the postpituitary hormones is
to increase the hydration and the K+ concentration of the cell medium.

Hence, one can consider that there is an adrenopostpituitary antagonism, at least antagonism between the physiological effects of these hormones.

But the practical application of these data for therapeutic purposes is impossible, or incomplete, if the problem of the regulation of these secretions is not taken into consideration.

It is well known that the release of neuropostpituitary hormones is, in normal subjects, under the variations of osmotic pressure of the plasma, just as the secretion of the adrenal mineralo-corticoids is controlled by the ratio between the intake of sodium and potassium by the organism.

Furthermore, it is very important to know the direct effects of one of these hormones on the secretion of the “antagonistic” or rival hormone from the point of view of its practical application to a therapeutic treatment.

On the one hand, it is known that the neuropostpituitary hormones contain a corticotrophic releasing factor. But even if the prescription of postpituitary extract supplies doses of the corticotrophic releasing factor that are in fact minute, it nevertheless produces a curious effect, the blocking or the decrease of the endogenous secretion of the neuropostpituitary hormones, for which Bas-tenié et al provided experimental evidence and which we have also tried to obtain from the therapeutic point of view. On the other hand, the effects of the cortico-adrenal hormones on neuropostpituitary secretion are debated. If, according to Dingman and Des-pointes, cortisol is able to inhibit the secretion of these hormones, there are other factors that prove, on the contrary, that this secretion can become increased under the same conditions: clinical facts provided by the observations of Decourt and Bernard-Weil, or histological data in the experimental investigations of Castor et al and Kovác.

Hence, it then becomes possible to understand the nature of the diencephalopituitary disturbances observed in a patient suffering from an intracranial lesion and particularly in the case of a cerebral tumor. The stress of the hypothalamus is one of the factors of cerebral edema, and consequently of the clinical aggravation of the encephalic neoformations: we define it as a neuropostpituitary...
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<td>Glioblastomas</td>
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<td>Metastasis (male patients)</td>
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hypersecretion that is not compensated for by an increase of the cortico-adrenal secretions. This definition is consistent with the findings of others\textsuperscript{12,14} who have shown that, in the case of neurological hyponatremic patients, there is “an inappropriate secretion of antidiuretic hormone.”

Thus the “neurogen hyponatremias” (or “hyperkalicytias”) by estimating the K⁺ of the blood corpuscles,\textsuperscript{4} contrast with the much less “neurogen hypernatremias” as reported by Cooper\textsuperscript{5} and Welt et al\textsuperscript{2} and which can be attributed to an inverted diencephalic disturbance, that of a postpituitary insufficiency associated with adipsia.\textsuperscript{2}

These ideas enabled us to establish the components of the hormonal treatment, the effects of which have already been specified, both for the preoperative phase and during the postoperative period, or even in certain clinical diseases of the encephalon and in head injury.\textsuperscript{24}

An attempt should be made to increase the actions of the anterior-hypophysial cortico-adrenal axis and block the neuropostpituitary function; consequently the use of ACTH and cortisol on the one hand, and weak so-called “blocking doses” of posterior pituitary extract on the other. In fact, cortisone, cortisol or deltacortisone were found by themselves to bring about improvements in similar cases.\textsuperscript{1,2} but the addition of ACTH is necessary to produce these results regularly. As for the third element of this therapy, the posterior pituitary extract, it appeared to us to be necessary in certain cases when the two other hormones proved to be inefficient.

In practice, this treatment can be applied in all cases of cerebral tumor in the preoperative period and should be continued during the first few days following the intervention: probable gliomas, meningiomas, metastatic tumor, except in the case of metastasis in women (in male patients, metastatic tumors

![Fig. 5.](image-url)
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are very infrequently not influenced by this treatment as shown in Table 1), and various types of space-occupying lesion, although the use of this treatment in the case of a hematoma or an abscess requires certain precautions. The duration of the treatment is about 7 days, but this time can be extended in the case of gliomas or meningiomas.

The advantages of systematic procedure are:

1) To be able to operate on a patient in better condition, with less tension of the brain, sometimes even without there being the slightest sign of peritumoral edema.

2) To be able to carry out all the additional examinations necessary for making a judicious decision regarding operation.

3) Especially to decrease the frequency of postoperative complications, in particular those caused by acute cerebral edema.

There are practically no contraindications except when there is a history of gastric ulcer, or possibly in cases of myocardial infarction (because of the posterior pituitary extract). The only true contraindication is the “neurogenic hypernatremia,” as distinct from hyperosmotic conditions caused by an insufficiency of intake of water during the preceding days: after correction of this defect, the hormonal treatment should be efficient.

Experimental investigations are now being carried out into longer-term hormonal therapy which might be useful in the treatment of certain cases of inoperable glioblastomas.

Summary

On the basis of the opposite physiological effects of the adreno-cortical hormones and the neuropostpituitary hormones the authors suggest a form of therapy, the aim of which is to deal with peritumoral cerebral edema. In the great majority of cases they obtained a considerable improvement of the preoperative electroencephalographic and clinical conditions, which seemed to facilitate a better postoperative course. A general understanding of the central hypothalampituitary regulation is necessary for the correct application of this method.

References


18. E. Bernard-Well and M. David


