CHANGES IN THE ELECTROENCEPHALOGRAM AND PLASMA ACTH LEVEL DURING VOLUNTARY HYPERVENTILATION IN PATIENTS WITH MALIGNANT NEOPLASMS

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Significant changes in the electroencephalogram (EEG) with signs of activation of diencephalic and hypothalamic structures are observed in patients with malignant neoplasms in various situations [1, 2]. It has recently been shown that the response of the EEG to hypocapnia, induced by voluntary hyperventilation, is reversed in patients with malignant neoplasms [3-5]: whereas in healthy subjects and patients with benign tumors the trend of the EEG parameters under the influence of hypocapnia is always negative, and activation of diencephalic structures occurs, in patients with malignant tumors, parallel with lowering of the partial pressure of carbon dioxide (pCO_2) in the blood, the initially changed EEG returns to normal and features of activation of hypothalamic structures are weakened.

It was accordingly decided to study the response of the hypothalamohypophyseo-adrenal system to hyperventilation in patients with malignant neoplasms and in healthy subjects.

EXPERIMENTAL METHOD

Altogether 14 patients with malignant neoplasms in various situations (six patients with carcinoma of the stomach, one with carcinoma of the esophagus, four with carcinoma of the breast, two with sarcoma of the soft tissues, and one patient with melanoma) and six normal individuals were investigated. None of the subjects had any diseases of the brain or respiratory organs. EEG of all the subjects was recorded during quiet breathing and voluntary hyperventilation on a portable eight-channel ink-writing electroencephalograph (Nihon Kohden, Japan), with bipolar and monopolar leads. In the hyperventilation test, both patients and healthy subjects breathed air with the maximal tidal volume (close to the vital capacity of the lungs), in response to a command, with an average frequency of 18.5 excursions per minute until they began to develop dizziness and other unpleasant sensations or a feeling of tiredness. Before the beginning and at the peak of hyperventilation (after 3-5 min of forced breathing) pCO_2 and the acid-base balance (ABB) of the capillary blood were determined and blood samples were taken from the cubital vein for determination of the plasma ACTH and cortisol levels by means of standard kits from CEA-Sorin (France).

During analysis of the EEG of patients with malignant tumors before hyperventilation, changes indicating disturbances in the diencephalic region were noted in 12 of the 14 patients: enhancement of the θ-rhythm in bipolar and, more especially, monopolar derivations from the precentral zones of the brain (Fig. 1a). In five of 12 patients, besides the θ-rhythm, a β-rhythm also was recorded against the background of a reduced α-rhythm; this type of EEG indicated activation of mesodiencephalic structures. Only in two patients were no signs of activation of the diencephalic region present on the EEG. In five of 12 patients diffuse background EEG changes indicating activation of diencephalic or mesodiencephalic structures were combined with local changes of cortical potentials. Local EEG changes (in the form of activity of greater amplitude and predominance of pointed waves and θ- and β-waves unilaterally) in two patients were observed in the anterior (mainly bipolar) derivations; in three patients they were observed in anterior and posterior derivations.

During the control tests on healthy subjects, monorhythmic traces were recorded in four of them with a dominant α-rhythm. Moderate signs of diencephalic activation were observed, not outside the limits of normal variability, on two subjects (in one combined with evidence

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TABLE 1. Changes in pH, pCO_2, BE, and Blood ACTH and Cortisol Levels in Patients with Malignant Neoplasms and Healthy Subjects

Group of subjects tested	During quiet breatching				
	pH	pCO_2, mm Hg	BE	ACTH, pg/ml	cortisol
Patients with malignant neoplasms (n = 14)	7,420±0,003	37,40±0,57	—1,80±0,21	45,54±19,81	176,1±17,8
Healthy subjects (n = 6)	7,40±0,097	37,8±0,5	—0,52±0,64	14,17±12,10	148,5±19,3

Group of usbjects tested	At peak of hyperventilation				
	pH	pCO_2, mm Hg	BE	ACTH, pg/ml	cortisol
Patients with malignant neoplasms (n = 14)	7,57±0,01*	22,6±1,4*	—0,70±0,84	109,6±16,8*	178,1±15,5
Healthy subjects (n = 6)	7,57±0,02*	22,3±1,4*	—0,46±0,50	184,8±82,1*	158,16±26,13

*$p < 0.05$ compared with initial value.

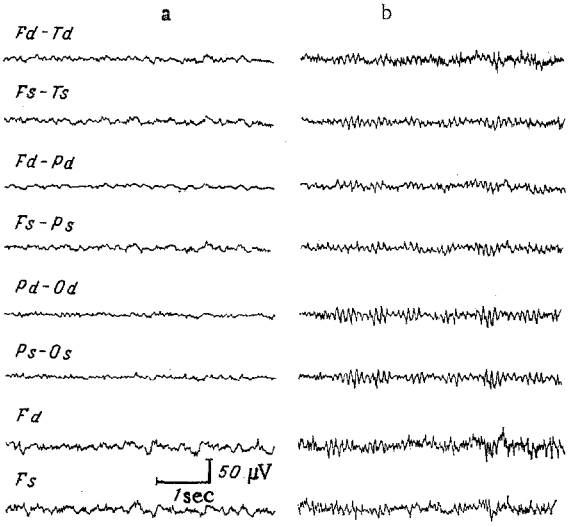

Fig. 1. EEG of patient K., a man aged 45 years, with diagnosis of carcinoma of the esophagus. a) Before hyperventilation, pH of capillary blood 7.41, pCO_2 38 mm Hg, venous blood ACTH level 22.0 pg/ml. Against the background of marked diffuse changes with signs of mesodiencephalic activation, the EEG showed moderate local pathology in derivations from the left fronto-temporal region; b) after 5 min of hyperventilation, pH 7.66, pCO_2 20 mm Hg, ACTH 16.5 pg/ml. Positive trend of diffuse and local EEG changes. Derivations: FT) fronto-temporal; FP) fronto-parietal; PO) parieto-occipital, F) frontal, with neutral ear electrode; d, s) right and left hemispheres.

of mesencephalic activation and with moderate asymmetry and asynchronous pointed waves of average voltage in the parieto-occipital derivation from the right hemisphere). The trend of the EEG in all six healthy subjects was negative under the influence of hyperventilation (Fig. 2), subjective sensations were negative, and ability to tolerate the hyperventilation was limited (to 3-4 min or, at most, 5 min of intensive hyperventilation).

Patients with malignant tumors subjectively tolerated hyperventilation much better (up to 10 min or more) than healthy subjects. Voluntary hyperventilation caused restoration of the normal EEG parameters in 12 of 14 patients with malignant tumors, i.e., the response of the EEG to hypocapnia was reversed (Fig. 1b). In one case hyperventilation led to a positive trend on the EEG during the first minute, but later, however, the pO_2 of this patient fell sharply (from 69 to 28 mm Hg) and transient loss of consciousness supervened.

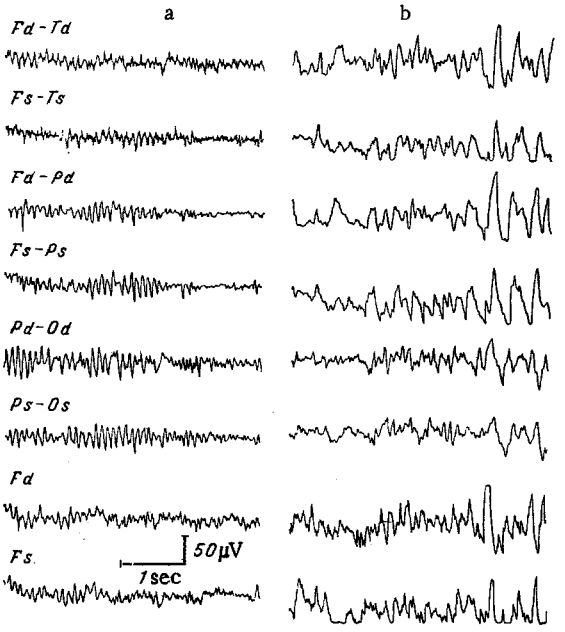

Fig. 2. EEG of healthy subject K., aged 32 years. a) Before hyperventilation, pH of capillary blood 7.44. pCO_2 37 mm Hg, ACTH in venous blood pg/ml.* EEG is dominated by α- rhythm with frequency of 11 waves/sec; b) after 4 min of hyperventilation pH 7.65, pCO_2 17 mm Hg, ACTH 170 pg/ml. Negative trend of EEG with marked effect of activation of hypothalamic structures, consisting of substitution of α-rhythm by θ- and Δ-rhythm (5-6 and 2.5-3 waves/sec). Derivations the same as to Fig. 1.

A general slowing of the principal rhythms and bilateral paroxysmal activity were recorded on the EEG under these circumstances. In one patient no significant changes in the EEG were observed in response to hyperventilation, and only in one of 14 patients was the trend of the EEG negative, despite better tolerance of deep hypocapnia (the initial EEG in both cases was on the borderline of normal).

Values of pCO_2, BE, and the blood ACTH and cortisol levels during quiet breathing and voluntary hyperventilation are given in Table 1. Clearly there was no difference between these parameters in cancer patients and healthy subjects either before or at the peak of the function test. Initial ACTH levels in patients with malignant neoplasms varied from 0 to 240 pg/ml, on average 45.5 ± 19.8 pg/ml. In healthy subjects the plasma ACTH concentration varied within lower limits (0-75 pg/ml, average 14.2 ± 12.1 pg/ml). The increase in the mean values of the initial ACTH levels in patients with malignant neoplasms compared with healthy subjects was not statistically significant. As a result of hyperventilation the ACTH concentration in healthy subjects increased on average to 185 ± 82 pg/ml, i.e., it was 13 times higher than initially. The plasma ACTH concentration in the patients increased as a result of hyperventilation on average to 110 ± 7 pg/ml, i.e., by only 2.4 times. Thus in patients with malignant neoplasms elevation of the ACTH level in response to hyperventilation was much less marked than in healthy subjects.

The blood cortisol level in the patients and healthy subjects was unchanged after hyperventilation. This was probably due to too short a time for the action of ACTH on the adrenal cortex to be exhibited.

A parallel study of the EEG and blood ACTH parameters thus revealed close correlation between the reversed response of the background EEG to voluntary hyperventilation and changes in pituitary corticotrophic function.

The data for the background EEG indicate an important role of disturbances in the diencephalic region in changes observed in the EEG of patients with malignant neoplasms.

*As in Russian original; the value is missing — Publisher.

The marked weakening of ACTH secretion in response to hyperventilation in patients with malignant neoplasms confirms the data of the background EEG regarding changes in the functional state of hypothalamic structures. In healthy individuals an increase (by 13 times) in ACTH secretion took place against the background of the negative trend of the EEG, with evidence of diencephalic activation. In patients with malignant tumors the increase (by 2.4 times) in ACTH secretion was combined with normalization of the EEG and inactivation of hypothalamic structures. Consequently, close correlation is found between the reversal of the response of the EEG to hypocapnia due to voluntary hyperventilation, and depression of hypothalamo-hypophyseal reactivity (possibly as a result of reduction of secretion of corticotrophin releasing factor by the hypothalamus).

We postulated that metabolic acidosis in brain cells is an essential factor causing background changes in the EEG and reversing the response of the EEG to hypocapnia. We know that in malignant disease increased glycolysis is observed, not only in the tumors, but also in intact tissues [6-8]. Gas alkalosis induced by hyperventilation can temporarily depress the degree of generalized acidosis in cancer patients, restore the normal state of brain function, and normalize reactivity of the hypothalamus and adrenal cortex.

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