CEREBROSPINAL FLUID AND PLASMA LACTATE LEVELS IN HUMAN BRAIN TUMOURS

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SUMMARY

Lactate is known to be formed from pyruvate in glycolysis in hypoxic conditions.

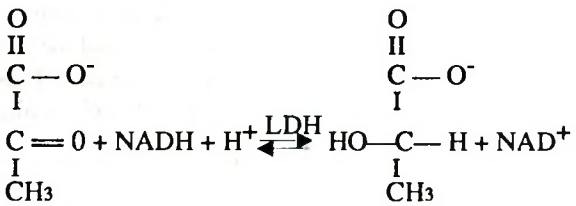
This study was carried out to investigate the possible change in lactate concentrations of cerebrospinal fluid and plasma in different types of brain tumours. Cerebrospinal fluid and plasma samples were obtained from patients admitted to Dokuz Eylül University Neurosurgery Department and diagnosed to have brain tumours of various types. Twenty eight cases were divided into two distinct categories, as malignant (n=14) and benign (n=14) tumour groups. The control group consisted of fifteen neurologically normal subjects. Cerebrospinal fluid and plasma lactate levels were determined using the enzymatic UV method of Bergmeyer, employing lactate dehydrogenase. The mean cerebrospinal fluid and plasma lactate concentrations were found to be statistically elevated in two distinct type of brain tumour groups, when compared with the controls ($p<0.05$ and $p<0.01$, respectively).

These findings may reflect a generalized, or localized hypoxy in the tumoural state.

Key words: Brain tumours; lactate.

INTRODUCTION

Characteristics of tumour cells generally is an increased glycolytic capacity and a high rate of lactate formation from glucose in the presence of oxygen (1). Early in this century, Otto Warburg observed this accumulation of lactate, as well as pyruvate, and a decreased respiratory rate, even in the presence of excess glucose and oxygen, in tumour tissue: He coined the term "aerobic glycolysis" for the production of pyruvate and lactate in the presence of adequate carbon sources and oxygen (2): Pyruvate is reduced by NADH to lactate, the reaction being catalyzed by lactate dehydrogenase (LDH, EC 1.1.1.27).



The reoxidation of NADH via lactate formation allows glycolysis to proceed in the absence of oxygen by regenerating sufficient NAD+ (3). Thus, tissues that function under hypoxic circumstances tend to produce lactate.

Lactate has been observed to accumulate in ischemic brain tissue and to play a role in the pathophysiology of cerebral ischemia and traumatic brain injury (4-11). Tumour growth has also been shown to be associated with an increase in the tissue lactate content (12-13). In fact, the elevated rate of aerobic glycolysis is one of the most consistent metabolic characteristics of tumours (14) Rapidly growing tumour cells especially those in ascitic form, present high rates of lactate production when compared to normal cells (15).

From the clinical point of view, it is interesting to elucidate the lactate levels in CSF as well as in plasma in the tumoral state. Reports in the literature of the lactate concentrations in the CSF and plasma of human brain tumors are not uniform, and a comparative study between benign and malignant tumours has not been done.

The present study was undertaken to elucidate any possible significant difference between malignant and benign tumours from the point of view of CSF and/or plasma lactate as well as the CSF/plasma lactate ratio.

MATERIALS AND METHODS

Subjects

Twenty - eight consecutive unselected patients (me-

an age ± standard deviation : 41.7 ± 18.2 years) with various brain tumours who were admitted to Dokuz Eylül University Faculty of Medicine, Neurosurgery Department between October 1987 and June 1989 were included in this study. Clinical and biological paramenters were obtained on all subjects including age, sex, duration of symptoms, serum glucose, urea and plasma fibrinogen levels, prothrombin time, partial thromboplastin time, platelet count, sedimentation rate, and histological diagnosis. Computerized tomography (CT) scans were also used to identify tumour volume. The tumour types studied and the clinical characteristics of the patients are shown in Table I. The control group consisted of 15 neurologically normal subjects.

specimen collection

The patients with histologically diagnosed various type of tumours underwent surgery for removal of tumour under general anesthesia. During this surgery, CSF was sampled through a spinal drainage needle inserted into the spinal lumbar sac. In the non-brain tumour group, the SCF was sampled by spinal tap. Most of the SCF samples from the control group were collected by lumbar puncture for general chemistry diagnostic workup.

The CSF specimens were collected in plastic containers, centrifuged for 5 min at 3000 x g at room temperature, and stored at + 4°C for 24 hours. No samples

TABLE I

Clinical characteristics of patients

Disease	No. Cases[1]	Sex (M / F)	Age (Mean ± SD)
Malignant brain tumour group	11	6/5	27.4 ± 16.7
Astrocytoma	8	4/4	25.0 ± 17.9
Medulloblastoma	1	1/0	21
Anaplastic oligodendroglioma	1	1/0	35
Anaplastic ependymoma	1	1/0	46
Metastasis to brain[a]	3	3/0	60.7 ± 4.9
Benign brain tumour group	14	9/5	48.8 ± 12.3
Meningioma	11	6/5	48.6 ± 12.8
Acoustic neurinoma	3	3/0	49.6 ± 10.4
Control group[b]	15	9/6	45.4 ± 6.1

a Epidermoid carcinoma and malign melanoma metastasis.

b Arterial - venous malformation in the brain, head trauma, headache, and lumbar disc herniation.

TABLE II

The ratios of cerebrospinal fluid lactate to plasma lactate values and mean ± SD concentrations of lactate (mg/dl) in CSF and plasma.

GROUPS	n	CSF	Plasma	CSF / Plasma
All of the tumour groups	28	16.6 ± 9.4*	30.4 ± 20.3*	0.69 ± 0.5
Malignant brain tumour group	14	15.5 ± 8.9*	28.2 ± 18.2**	0.66 ± 0.4
Benign brain tumour group	14	11.3 ± 5.7*	18.6 ± 10.3*	0.63 ± 0.3
Control Group	15	9.9 ± 3.3	11.2 ± 3.7	0.82 + 0.5

Statistical significance : *p < 0.05 and ** p< 0.01 compared with the control group.

containing visible amounts of blood were used in his study.

Before the surgical operation, 2 ml of blood sample were drawn into plastic tubes, admixed with 80 ml of fluoride / EDTA reagent as anticoagulant and immediately centrifuged (3000 x g for 5 min) at room temperature for separation of plasma. The supernatant plasma was then aliquoted and stored at + 4°C.

The analyses were performed within 24 hours.

Assay

CSF and plasma lactate levels were determined using the enzymatic UV - method of Bergmeyer (16), employing LDH and glutamic pyruvic transaminase (GPT) (Boehringer Mannheim GmbH, Cat. No. 149 993). The test principle is as follows:

$$\text{L - lactate} + NAD^+ \xrightleftharpoons{LDH} \text{pyruvate} + NADH + H^+$$

$$\text{pyruvate} + \text{L- glutamate} \xrightleftharpoons{GPT} \text{L -alanine} + \alpha\text{ - ketoglutarate}$$

The results were given in mg/dl.

Statistical Analysis

Our data were analyzed statistically by means of Student's test.

RESULTS

Table II lists mean ± SD values for the CSF and plasma lactate concentrations and the ratios of CSF lactate to plasma lactate levels as measured in the various study groups. Plasma lactate was on average significantly higher for all the tumour groups (30.4 ± 20.3 mg/dl. range: 7.8 - 83.2) compared with the control group (11.2 ± 3.7 mg/dl, range: 5.7 -22.0) $p<0.05$). However, there was considerable overlap among these groups; the distribution of plasma lactate levels, with fourteen of 28 (50 %) of the tumour patients having plasma lactate > 22 mg/dl was clearly different than the control group which had no values above 22 mg/dl. The mean lactate level in CSF for all the tumour groups (16.6 ± 9.4 mg/dl, range : 4.1 - 39.4) was found to be slightly higher when compared with he control group (9.9 ± 3.3 mg/dl, range : 5.5 - 13.6), this difference being statistically significant ($p<0.05$). On the other hand, sixteen of the 28 patients (57 %) in the group of all the brain tumours had CSF lactate levels over 13.6 mg/dl, which was the upper value in the control group.

The difference for CSF lactate concentration in malignant brain tumour group (15.5 ± 8.9 mg/dl, range: 5.9 - 39.4) was determined to be statistically significant ($p<0.05$). The mean plasma lactate (28.2± 18.2 mg/dl, range: 7.8-83.2)was also significant ($p<0.01$). Both of the mean CSF lactate (11.3 ± 5.7 mg/dl, range : 4.1 - 18.7) and plasma lactate (18.6 ± 10.3 mg/dl, range : 8.0 - 42.6) values were greater in benign brain tumour group than in the control ($p<0.05$ and $p<0.01$, respectively).

The ratio of CSF lactate to plasma lactate concentration was found not to be significantly different between all the diagnostic groups.

DISCUSSION

Lactate is formed from pyruvate in glycolysis under hypoxic conditions. This investigation was carried out to determine the possible change in lactate levels of the CSF and the plasma in human brain tumours.

Our lactate levels for the lumbar cerebrospinal fluid, as well as for the plasma in the control group consisting of healthy individuals, are in agreement with data in the literature (17, 18).

This investigation has clearly shown that lactate is significantly increased in the CSF for the tumoural group in comparison with the control group. Furthermore, both the malignant and the benign brain tumour groups, evaluated separately, have shown significant differences from the control group. Wood (19) has suggested that the lactate levels in CSF primarily reflect the brain tissue lactate content. In our cases of brain tumour, possibly, the glycolysis yielding lactate is augmented in the tumoural brain tissue, leading to an increase in lactate levels in the CSF. Unfortunately, we have not been able to compare our results with the data obtained by other investigators, since a systematic study of CSF and plasma lactate in malignant and benign human tissues, in parallel, has not been published.

Weber's work with hepatomas (20) states that aerobic glycolysis is not a necessary or invariant feature of all neoplastic cells, but is seen primarily in tumours with a rapid growth rate and high degree of dedifferentiation. However, in our study, the finding of elevated lactate in benign tumour group as well as in the malignant tumour group is in favor of the hypothesis that aerobic glycolysis is an invariant feature of all tumour cells. It has also been suggested that (21, 22) aero-

bic glycolysis is not a unique feature of neoplastic cells, since intestinal mucosa, renal medulla, and normal cells stimulated to proliferate by hormones also show it.

The findings of increased lactate in plasma in the brain tumour group in our investigation have given a new dimension to the interpretation of the situation. The lactate elevated in CSF, by itself, may reflect a localized hypoxia in the tumoural tissue. However, observed parallel increases in the plasma lactate levels tents to prove a more generalized hypoxia. This in turn, reflects close interaction of brain tumours with the vasculature of the central nervous system and its blood - brain barrier - a high degree of local infiltration and invasion.

Besides hypoxia, in our opinion, one also has to consider the possibility of the tumour deranging the intracellular metabolism, such as the machinery involved in the Krebs cycle - with or without hypoxia. In other words, continuous production of lactate from pyruvate may be also caused by the increased amount of pyruvate avaliable due to an impairment of the Krebs cycle.

In conclusion, it can be stated that, whatever the cause, increased lactate levels in CSF and in plasma are consistent findings in human brain tumours. We think that this subject is worthy of further investigation into the mechanism of this lactate overproduction.

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