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АМИНОКИСЛОТНЫЙ ПУЛ ПЛАЗМЫ КРОВИ БОЛЬНЫХ РАКОМ ГОРТАНИ*

Ю. Б. Бурлака, Н. В. Гринь, С. В. Веревка (Киев, Украина)

Возникновению и развитию злокачественных новообразований сопутствуют выраженные нарушения в промежуточном обмене и метаболизме аминокислот и их производных Информация, получаемая при анализе аминокислотного спектра физиологических жидкостей, имеет не только сугубо теоретическое, но и практическое значение. Это исследование было проведено с целью анализа аминокислотного спектра плазмы крови больных с раком гортани для установления информативности данного критерия для оценки степени тяжести и стадии заболевания. Были проанализированы 19 аминокислот у 15 пациентов с II и III стадией рака гортани, без метаболических нарушений или других сопутствующих заболеваний. По сравнению с контрольной группой, у пациентов с раком гортани наблюдалось достоверное увеличение уровней лизина, орнитина, аспарагиновой кислоты, серина, глицина, глутаминовой кислоты, цистеина, лейцина, тирозина и фенилаланина. Таким образом, изменения уровня аминокислот служат достоверными показателями метаболического дисбаланса как важнейшего биохимического критерия развития онкологического процесса.

Ключевые слова: *аминокислоты, плазма, рак гортани.*

Introduction

There is abundant literature concerning the plasma concentrations of amino acids (AAs) in various physiologic or pathologic conditions. However, it is frequently asserted that plasma levels of AAs are difficult or even impossible to interpret.

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The grounds for this assertion are that the plasma pool of free amino acids (PFAA) is very small compared with the intracellular pool of PFAA, which in turn is small compared with the protein-bound AA pool, all three being in equilibrium. In addition, AAs undergo various inter organ exchanges, which further hinder the interpretation of static plasma values. Also, there are a large number of cellular AA transport systems with overlapping properties and organ specificities [1].

As with most nutrients, plasma AA concentrations are subject to homeostasis. This means that, in physiologic situations, concentrations of each AA vary within fixed limits and are tightly regulated. The availability of plasma free amino acids is often reduced in cancer patients. The reduced availability is caused by the malnutrition in a tumor-bearing state and by an increase in the amino acid demand as a consequence of the presence of the tumor. Protein is a critical reservoir of metabolic fuel and may become seriously depleted during tumor growth. The severity of these disorders depends on the extent of the host cachetic response, which in turn is dependent on the stage and the type of the cancers [2].

Tumors in different organs can differ greatly, not only in their capacity for proliferation and metastasis, but also in the influence on the host metabolic status [3] and, consequently, in changes in the serum amino acid profile in relation to the type of tumor. Increased levels have been detected for amino acids that have certain specificities in relation to the specific type of tumor, like sarcomas [4], hepatomas [5], lung [6], breast [7], head and neck region [8], gastrointestinal [9], and bladder [10]. Other studies have shown that these amino acids return to their usual values after effective therapy, and in turn rise again when the disease relapses [11, 12].

The aim of our study was to analyze the serum amino acids in patients with oral cancer and in different stages of disease, not in the surgical period, with no nutritional alterations or other accompanying disorders, and to compare these levels with those of a healthy control group in order to try to detect specific patterns of amino acids in different stages of disease of tumors.

Material and methods

Patient selection

This prospective study included 15 patients with oral cancer, not in the surgical period, treated by Kolomiychenko Institute of Otolaryngology. The control group consisted of 10 healthy subjects without cancer or intercurrent diseases to determine the amino acid profile. The inclusion criteria were: age 18-70 years; weight loss less than 5%; advanced stage not in the surgical; no prior chemotherapy; no endocrinologic or metabolic disorders; no uncontrolled hypertension or infections; normal liver, heart and kidney function; and adequate bone marrow reserve. The inclusion criteria for the control group were: adults aged 18-70 years, good general state of health, normal nutritional and daily regimen, no intercurrent acute or chronic disease.

Laboratory measurements

The measurements consisted of the serum analysis of 19 different amino acids. The amino acids measured were: lysine, histidine, arginine, ornithine, aspartic acid, threonine, serine, glutamic acid, proline, glycine, alanine, cysteine, valine, methionine, isoleucine, leucine, tyrosine, phenylalanine, and glutamine. Measurements were made with a Beckman System 6300/7300 Amino Acid Analyzer (Pickering Laboratories) according to the manufacturer's instructions and protocols.

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Statistical analyses

The mean amino-acid concentrations ± standard deviations were calculated to determine summarized PFAA profiles for both patients and controls. Student's t-tests and Mann-Whitney U-test was used to assess significant differences of the plasma amino-acid concentrations between the patients and the controls.

Results and Discussion

The median age of the patients with II and III stage was 58 (range, 51-64). The median age of the controls, was 61 years (range, 47-67). Regarding tumor type, all patients had keratinizing squamous cell carcinoma. Tree patients with stage III had metastases in node of neck. All the patients were locally advanced, non resectable and no prior treatment. Concerning the comparative analysis of the serum amino acid levels in cancer patients and the control group, the concentration of amino acids in blood was determined in μM/L (Table I).

Analysis of the baseline serum amino acid levels between cancer patients and the healthy subjects showed significant differences in an important number of specific amino acids. In general, the mean serum concentration of the amino acids was higher in both stages of tumor studied in comparison with the normal population, except for the following amino acids: methionine, tyrosine, and glutamine. Significant increasing was seen in patients with II stage of cancer as compared with the control group in the following amino acids: lysine, ornithine, aspartic acid, serine, glutamic acid, cysteine, leucine, tyrosine, and phenylalanine. Significant differences were seen in the patients with III stage, as compared with the control group, in lysine, ornithine, aspartic acid, glutamic acid, glycine, cysteine, leucine, tyrosine, and phenylalanine content (Table I).

Free amino acids serve as a substrate for protein synthesis, glyconeogenesis, urea genesis and other anabolic processes. Accordingly, it is logical to suppose, as has been demonstrated, that in cancer and other diseases involving an imbalance in this metabolic order, alterations take place in serum levels of amino acids [13].

After it was learnt that the presence of a tumor resulted in increased protein metabolism, studies were undertaken on variations in serum levels of amino acids as possible indicators of the influence of the tumor on the host proteins, as well as which amino acids preferably require a neoplasm for protein synthesis. In our study, we found that in patients with oral cancer, the baseline serum levels of a series of amino acids were significantly different when compared with a healthy control group. Thus, the presence of a tumor may have a decisive influence on its general metabolism, and more specifically on its protein metabolism, which would affect the serum concentration of amino acids, which usually constitute about 0.5% of the whole pool of amino acids in a person weighting 70 kg [13].

Many recent studies have tried to find out whether cancer-specific amino acid exists. Alanine and glycine have been demonstrated to be released from Walker carcinoma 256 and glycine from hepatoma 7777 cells [14]. Glutamine has been declared to be an important respiratory fuel in breast cancers [15, 16] and prostate cancers [17]. However, the role of cancer-specific amino acid remains to be clarified.

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Table 1.
Baseline serum levels of amino acids in patients with oral cancer and healthy subjects and intergroup comparisons

Amino acid	Healthy subjects	Oral cancer II stage	Oral cancer III stage
Lysine	14,93±1,14	19,63±1,87*	18,50±0,89*
Histidine	7,12±0,50	7,55±0,64	7,78±0,62
Arginine	6,75±0,63	8,72±1,63	7,28±0,87
Ornithine	5,42±0,43	11,32±1,51***	10,50±0,53****
Aspartic acid	0,76±0,08	2,63±0,42****	2,37±0,25****
Threonine	10,12±0,92	12,39±1,05	10,45±0,69
Serine	8,86±0,89	11,99±1,15*	9,82±0,86
Glutamic acid	4,61±0,40	11,32±1,36****	10,97±1,59***
Proline	15,92±1,51	16,94±2,18	18,33±2,96
Glycine	19,76±1,47	26,05±3,42	27,92±3,23*
Alanine	37,27±3,52	43,37±4,07	42,63±5,97
Cysteine	6,83±0,66	10,89±1,61*	10,49±1,32*
Valine	16,96±1,24	18,58±1,20	19,77±1,69
Methionine	2,64±0,25	2,36±0,26	3,04±0,60
Isoleucine	5,46±0,40	6,11±0,69	6,74±1,12
Leucine	8,84±0,86	12,14±0,79**	12,69±1,01**
Tyrosine	8,45±0,53	5,72±0,80**	6,27±0,89*
Phenylalanine	4,19±0,23	6,40±0,43****	6,78±0,19****
Glutamine	58,28±5,69	48,17±5,11	44,40±7,47

Significant at t-test: * - $p<0,05$; ** - $p<0,02$; *** - $p<0,01$; **** - $p<0,001$*

In our study, we also found increased levels of arginine, threonine, alanine (with tendency to increase) and significant increasing of ornithine and glycine (only for the III stage). Glutamine levels have tendency to decreasing. It also consistent with Kubota et al. [18] who was found increased levels of alanine, arginine and threonine in breast cancer, alanine in female G-I cancer, and ornithine in female head and neck cancer patients.

Also it is well known that cancer growth requires glutamine, glycine and aspartate for purine and pyrimidine synthesis, and serine for membrane lipid component synthesis in addition to essential amino acids. Demand for certain amino acids may lead to a gradual loss of muscle mass, which causes the protein turnover in tissues [19] and results in a lower availability of amino acids, especially essential ones. In our series we also detect increasing ratio of those amino acids. As well as Cascino [20] we found a significant increase in glutamic acid compared with controls, suggesting that in this type of tumor may exist a certain situation of hypercatabolism preceding the cachexia.

Redistribution or translocation of peripheral protein is an essential feature of amino acid metabolism in cancer patients [21].

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Cancer patients without weight loss have a threefold higher rate; while with weight loss have a lower rate of hepatic protein synthesis when compared to non-cancer patients. It has, therefore, been suggested that both malignancy and nutritional status can affect on the rate of essential amino acids in patients with oral cancer.

Moreover in our study, we found changes in tyrosine and phenylalanine content. The conversion of phenylalanine into tyrosine involves irreversible oxidation by cytosolic phenylalanine hydroxylase with tetrahydropteridine as the immediate electron donor. The hydroxylation of phenylalanine represents the principal pathway for its catabolism, and during periods of dietary tyrosine deprivation provides adequate quantities of tyrosine to nitrogen equilibrium in man. Such a close interaction between a dietary indispensible amino acid and a semi-indispensible one suggests that the kinetics for the two amino acids would be strikingly different from those for other indispensible amino acids. First, because a component of tyrosine appearance is an irreversible step in the oxidation of phenylalanine, a greater fraction of tyrosine appearance is presumed to be catabolized than would be expected with an indispensible amino acid. Secondly, the proportion of phenylalanine appearance that would be oxidized entirely to CO_2 is also expected to be considerably less than with other dietary indispensible amino acids, since the principal fate of its oxidative metabolite, tyrosine is not further degradation but incorporation into whole body protein [22].

Another important finding is the significantly high level of cysteine. It is well known that changes of cysteine level are associated with oxidative damage and metabolic disorders, which may lead to carcinogenesis. A tissue level of cysteine is maintained at low level by tight regulation. Cysteine level may be elevated with the accumulation of homocysteine or when its catabolism is impaired due to low cysteine dioxygenase. Moreover cysteine has been considered to possess antioxidant properties through its rate-limiting role in biosynthesis of glutathione, the intracellular antioxidant and detoxifying agent. However, recent evidence from *in vivo* and *in vitro* studies have suggested that cysteine may act as a pro-oxidant agent that causes DNA oxidative damage as a result of the overproduction of free radicals and hydrogen peroxide, leading to gene mutation and subsequent cancer development [23].

Cancer cells are hypermutable [24] and may result in amino acid changes in certain protein sequences. Thus, the PFAA profile is considered valuable for diagnosis and for nutritional care in cancer patients. A large number of biological markers for cancers have been reported, including tumor-associated antigens, ectopic hormones, enzymes, and metabolic changes. Although certain cancers may metabolically differ from one another, they can induce similar derangements of the protein metabolism in the host [25]. The changes of protein metabolism, as reflected in the PFAA profiles, may be used as an additional tool for diagnosing cancer. The possibility of developing a cancer should be taken into consideration in a patient who shows abnormal PFAA levels. Meanwhile, the changes of either individual or group amino acids can be useful for the diagnosis of a specific cancer.

Summary and conclusion

Many reports have focused on the potential use of the PFAA profile as a tumor marker. These studies suggest that the metabolic alterations of various cancers can determine their own distinctive PFAA profiles. The results also

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show that the sensitivity of PFAA profile for cancer diagnosis is relatively high, but the specificity is low. This all suggests that further studies are required, with neoplasm in early stages, or more advanced stages of oral tumors, to define more precisely the deficit or excess of amino acids in this type of cancer.

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PLASMA FREE AMINO ACID PROFILE IN PATIENTS WITH ORAL CANCER

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Metabolic changes in patients with cancer lead to alterations in their amino-acid balances. Thus, amino acid profiles may be useful as biomarkers of cancers. This study was conducted to analyze amino-acid profiles in plasma in order to elucidate differences between cancer patients and controls. We analyzed the baseline serum levels of 19 amino acids in 15 patients with II and III stages of oral cancer with no metabolic alterations or other concomitant disorders and compared the results with a control group. Compared with the control group, patients with oral cancer had significant differences in lysine, ornithine, aspartic acid, serine, glycine, glutamic acid, cysteine, leucine, tyrosine, and phenylalanine. This study revealed significant differences in plasma amino acid profiles between cancer patients and controls. The development of a cancer alters plasma amino-acid profiles and the pattern of change differs between different stages of oral cancer. Plasma amino-acid profiling might therefore be useful for the early detection of cancer.

Keywords: *amino acid profiles, plasma, screening, cancer.*

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