Serotonin as a Marker to the Response of Patients with Advanced Stages of Cancer during Treatment with Chemotherapy and Radiotherapy

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Abstract

Serotonin is synthesized by conversion L-tryptophan into 5-hydroxytryptamine in the body by using two catalyze factors are tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase, it exhibits a growth stimulatory effect on several types of carcinoma, carcinoid and other tumor cells. In contrast, few data are available on serotonin involvement in cancer cell migration and metastatic processes. Serum serotonin level was found to be suitable for prognosis evaluation of urothelial carcinoma in the urinary bladder, adenocarcinoma of the prostate and renal cell carcinoma. Subjects: 201 patients with malignant tumors, 74 patients with different benign tumors and 83 healthy individuals were enrolled in the present study. Results: Outcomes show a significant increase (p=0.011 and 0.043) of serum serotonin levels in malignant tumors group when compared with those of benign tumors (as a pathological controls) group, and healthy individuals groups; respectively. No such results were shown when the two control (benign tumors and healthy individuals) groups were compared together. Conclusion: Increase of serotonin could be related to activation of the serotonergic receptors sensitivity.

Keywords: Serotonin; Cancer; Chemotherapy; Radiotherapy

Introduction

Malignant tumor (cancerous tumors) has the capability to invade neighboring tissue and moves to other sites in the body [1,2]. When it gets a change in the gene to normal cells due to mutations healthy cells become cancerous because of this situation produces a change in the construct and sequence of nitrogenous bases of DNA [1]. The DNA damaged is not repaired, the new cells don't have the same damaged DNA and do not people can inherit damaged DNA. As a result, the cell becomes a source of harm to the body [3-5]. Cancer takes a relative long time to develop because multiple genetic alterations are required to transform normal cells into malignant cells. A single change in one oncogene or tumor suppressor gene in an individual cell is not adequate for transformation, so that, cells accumulate multiple mutations through clonal expansion [6-9].

In mammals serotonin produced principally by enterochromaffin cells, it is found within the gut and stored within blood platelets. In the brain, serotonin is produced within axon terminals, where it is released in response to an action potential and then diffuses across the synapse to activate postsynaptic receptors. It specialized groups of cell bodies known as the raphe nuclei, located in the brainstem reticular formation [10]. Serotonin has an effect on the number of physiologic and behavioral function, it plays a number of very important roles in normal brain function, which include modulation of mood states, memory, emotion, anxiety, endocrine effects appetite, hunger, aggression, cognition, gastrointestinal function, emesis, endocrine function, motor function, perception, neurotrophism, sensory function, sex, sleep and vascular function, and many others [11,12]. Serotonin exhibits a growth stimulatory effect on several types of carcinoma, carcinoid and other tumor cells. In contrast few data are available on serotonin involvement in cancer cell migration and metastatic processes. Serum serotonin level was found to be suitable for prognosis evaluation of urothelial carcinoma in the urinary bladder, adenocarcinoma of the prostate and renal cell carcinoma. It actually used in oncology as tumor marker of gastrointestinal carcinoid, hepatic and ovarian carcinoid [13], in addition to, serotonin can be used as specific tumor marker for gastrointestinal tumors of the pancreatic islet cells and intestinal tract [12,14]. Serotonin is synthesized by conversion L-tryptophan into 5-hydroxytryptamine in the body by using two catalyze factors are tryptophan hydroxylase and 5-hydroxytryptophan decarboxylase [11,15]. In mammals, serotonin is biosynthetically derived by two enzymatic steps: (1) ring hydroxylation of the essential amino acid tryptophan by tryptophan hydroxylase, the rate-limiting step, and (2) side chain decarboxylation by aromatic amino acid decarboxylase [10-13].

This process occurs in number of systems body such as immune system cells and gastrointestinal tract (GIT), central and peripheral nervous system [12,16]. GI contains 90% of serotonin and it is synthesized basically in enterochromaffin cells and in enteric neurons of submucous and myenteric plexus layer [12]. When the serotonin levels fall in the brain leads to large number of the emergence of foul bad [17]. While, serotonin function increases in humans to strengthen the qualities of the positive behavior and the desired, whenever dropped the serotonin levels increased the emergence of aggressive behavior [18,19]. The serotonin receptors are located on the cell membrane of nerve cells and other cell types in animals, there are 14 know type of serotonin receptor and general varieties of serotonin receptor [20].

Serotonin receptor family is larger than any other family of G-protein coupled (GPCR) neurotransmitter receptors. These receptors are widely expressed throughout the brain and in many key structures responsible for cognition and basic brain functions. As one of the most ancient neurotransmitter systems, having appeared very early in

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evolution, its functions have been conserved and even expanded up through the various branches of the evolutionary tree [10].

**Materials and Methods**

During the period from the beginning of March 2016 to the end of September 2016; 358 individuals were enrolled in the present study and classified in three groups. The first group involved 201 patients with different malignant tumors, while the second group included 74 patients who underwent benign tumors and were used as a pathological control, and the last group included 83 healthy individuals. The enrolled patients (malignant and benign tumors), were collected from several public and private hospitals in addition to centers in Al-Najaf Al-Asraf governorate; involved: Al-Sadder Medical City, Al-Zahra Teaching Hospital, Al- Ameer Privet Hospital, Al-Ghadeer Hospital, Middle Euphrates Cancer Center, and Daily Specialized Najaf Clinic. Patients with malignant tumors were the basic group of the present study. Cancerous patients group were classified into six general subgroups (Breast, Lung, Brain, Bladder, Lymphoma, and Acute Lymphocytic Leukemia (ALL)) according to the cases that have been followed during treatment with chemotherapy or radiotherapy or together.

Five milliliters of venous blood samples were collected from the patients and healthy individuals, after fasting period more than eight hours. Samples were allowed to clot at lab temperature, centrifuged at 5000xg for 5 minutes. Sandwich-Enzyme-Linked Immune Sorbent Assay (Sandwich-ELISA) method was applied to evaluate of serotonin concentration.

**Results and Discussion**

Levels of serum Serotonin Concentration were measured in the three study groups; malignant and benign tumors' patients as well as healthy control individuals, at diagnosis and before treatment with chemotherapy or radiotherapy or the two types together. Table 1 shows a significant increase (p=0.011, and 0.043) of serum serotonin levels in malignant tumors group when compared with those of benign tumors (as a pathological controls) group, and healthy individuals groups; respectively. No such results were shown when the two control (benign tumors and healthy individuals) groups were compared together (Table 1).

Exactly 192 cases of 201 malignant tumors patients showed high serotonin levels comparison to average serotonin levels at healthy individuals, so the sensitivity of serum serotonin in detection of cancerous tumors group was 95.52%, while 65 cases of 74 patients with benign were recorded serotonin levels approximate or lower than average serotonin levels at healthy individuals, according to that the specificity of serum serotonin was 87.84%.

The highest sensitivity of serotonin was recorded at brain cancer patients when 100% of cases showed high serotonin concentrations, followed by those of breast cancer (Sensitivity 97%), while patients with bladder cancer recorded sensitivity of 93% in the detection malignant bladder tumors.

In general, serotonin has a participant role in several vital cell pathways when it is involved in the cell proliferation, apoptosis and platelet aggregation [14]. An elevation in the serotonin levels in the cancer cases may be explain through different hypothesis: During malignant transformation process, DNA translocation and amplification lead to an increased expression of oncogenes proteins and loss of tumor suppressor gene protein [20], out results of these phenomena are alteration in the cellular proteins amounts so as nature, according to that an increase in the concentration of serotonin synthesis enzymes system may be involved as result for activation of genes expression [21]. Previous studies have been recorded abnormal activation in the production of serotonin synthesis cintermediates [10,12-14,21-23], so as enzymes, e.g., tryptophan hydroxylase and indolamine 2,3-dioxygenase at prediction of cancers and directly arise at invasion stages [11,24]. Alterations in the expression of Serotonin Transporter (SERT) and Selective Serotonin Reuptake Inhibitors (SSRIs) may explained an observed increased in the serotonin concentration at malignant tumors patients. SERT is a glycoprotein belonging to the super-family of membrane bound NaCl-dependent neurotransmitter transporters, characterized by 12 putative membrane spanning domains: it promotes serotonin clearance from the extracellular milieu and modifies the sensitization state of serotonin receptors within the nervous system or non-neural districts (gut, platelets, lymphomocyttes) [10,21,25-27]. An activation of SERT and/or reduction of SSRIs as a results of mutations that caused malignancy occurred could be enhance serotonin production.

Increase of serotonin could be relate for activating of the serotonergic receptors sensitivity. Several studies highlighted on the probable role of alterations of the serotonin receptors action in enhancement of progressive loss of regulated cell proliferation, increased invasiveness, and increased metastatic potential of malignant cell [14,21,28-30]. Sleep disorder, anxiety, emotional disturbances, and appetite disorders are considered the most prominent features of the cancer development, from other side; many studies have been shown that these disorders are directly related to the alterations in levels of serotonin [12,31-33], so an elevation of serotonin concentration in the cancerous tumors groups may be reflex to the raise in the sleeping hours and decrease of food intake. Serotonin is stored in the intracellular vesicles and produced in response to many stimuli and factors [21], the present work suggests presence of overlap between the supposed factors to upgrade serotonin levels in the sera of malignant tumors patients.

Patients with malignant tumors undergoing to chemotherapy or radiotherapy in order to kill the greatest numbers of malignant cells and prevent recurrence of malignancy, on the other hand, patients with malignant tumors may receive chemotheraphy for the purpose of increase the survival rate; especially those of the end invasive stages, when the size of tumor to the extent that prevents the vital member from performing them role even at the lowest level and then known as a gentle treatment. In order to follow serotonin concentrations at cancerous patients group, their levels were measured after treatment with the chemotherapy or radiotherapy, these doses were arranged from one to five. The average dose among total was used for the present comparison.

Student’s t-test analysis of Serotonin concentration in the pre- and post- treatment with non-surgical strategies samples recorded significant decrease in the Serotonin concentration (p<0.05) as shown in Figure 1.

| Groups (n) | Serotonin Concentration (ng/ml) Mean ± SD | Range | p | Malignant vs Benign | Healthy vs Healthy |
|-----------|----------------------------------------|-------|---|-------------------|-------------------|
| Malignant 201 | 1.315 ± 0.622             | 0.203-2.721 | 0.011 | 0.043 | 0.858 |
| Benign 74     | 0.856 ± 0.594             | 0.152-2.496 |             |       |       |
| Healthy 83    | 0.895 ± 0.606             | 0.031-2.113 |             |       |       |

Table 1: Levels of serotonin concentration (ng/ml) in sera of tumoral patients and controls subjects (mean ± SD).
Decreased serotonin levels at cancerous patients group after treatment with chemotherapy or radiotherapy may explain as reflex to the decrease in the abnormal (cancerous) cells using toxic therapy. Consequently, the decrease in the serotonin concentration may decrease the vascularity of malignant cell then increase necrosis that finally leads to increase of cancer cell mortality.

Previously, several studies illustrated roles of different suggestiv e chemical compounds as chemotherapeutic agents [34,35]. In the 2002 team of researchers suggested 7-hydroxytryptophan as a highly specific chemotherapeutic compound against serotonin producing tumors that also interferes with the autocrine capabilities of serotonin synthesis, when they found that 7-hydroxytryptophan as analogue substrate specific tryptophan hydroxylase enzyme was capable of metabolizing in situ a harmless tryptophan analogue, to a potent toxin. The product of enzyme action (5,7-dihydroxytryptamine) which is a conversion blocked by the specific tryptophan hydroxylase inhibitor para-chlorophenylalanine. Chosen of tryptophan hydroxylase for testing was intelligent idea, because it is the rate-limiting enzyme of serotonin biosynthesis, which is expressed highly in malignancy, as a target for the induction of cellular suicide by chemotherapy [36].

Weight gain is consider one of the side effect to the chemotherapy treatment, this increase in the body mass index may be give explanation to the increase in the serotonin levels at cancerous patients during the treatment period through multi mechanisms based to the intake of food richly proteins, [37,38] alternative metabolic pathways of tryptophan [12], changes in the transport serotonin proteins, [39] reduction in the ability of different enzymes involved in the serotonin synthesis pathway, and serotonin receptors [31,40,41]. For monitoring the changes in the serum levels of serotonin with details; the cancer cases with the largest number of samples were selected, here the selected cases of the malignant patients group were subdivided into six different types (Breast, Lung, Brain, Bladder, Lymphoma, and Acute Lymphocytic Leukemia (ALL)) were enrolled in the present section. Levels of serotonin were evaluated in sera samples of selected cancers’ cases at pre- and post- at least two dosages of chemotherapy (or radiotherapy) treatment.

Highest serotonin concentrations were recorded at group of lung cancers, followed by bladder cancers, while the lowest serotonin concentrations were recorded at group of patients with malignant breast tumors. After treatment, serotonin levels were decreased in the total malignant tumors group as will show in the Figure 1, only bladder cancer and lymphoma groups showed significant increase in the serotonin levels comparison to their levels at diagnosis, as show in Figure 2.

Levels of serotonin in bladder cancer and lymphoma samples seem to need extensive study separately.

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