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Research Article

Determination of Ceruloplasmin Ferroxidase Activity, Iron & Transferrin in Patients with Brain Tumor

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ABSTRACT

Serum from healthy volunteers (n=30) was found to contain little ceruloplasmin (Cp) ferroxidase activity. Higher level of activity was found in the sera that obtained from patients (n=64) with benign and malignant brain tumors. The highest activity was measured in sera of malignant tumors patients. The differences were significant between Cp activity in sera of both type of patients in comparison to that of the control healthy group ($p<0.05$), and between benign patients with that with malignant brain tumors ($p<0.01$).

Also the results of the current work illustrated the presence of a significant increase in [iron] ($p<0.01$), as well as total iron binding capacity, in sera of the patients groups in comparison to that of healthy group. The increase in iron concentration was found to be accompanied with a significant decrease in transferrin concentration. This lead to an increase in the concentration of free iron, which is one of the pro oxidants that cause production of more free radicals.

Keywords

Brain tumors, Ceruloplasmin ferroxidase activity, Iron binding protein.

Introduction

Two important agents were reported to be responsible for the extracellular antioxidant activity: these are: ceruloplasmin the copper containing protein and transferrin: the iron binding protein [1-4].

Ceruloplasmin (Cp, ferroxidase, iron (II): oxygen oxidoreductase (EC.1.16.3.1) [5], a glycoprotein, which is mainly synthesized in hepatocytes with molecular mass of approximately of 132 KDa [6]. This protein is usually present in serum, and in cells, which release protein into various body fluid and secretions [7-9]. In addition, a 125 KDa truncated form has been identified in the liver and bile, and is thought to be the major biliary form [10]. A novel membrane bound form of ceruloplasmin was discovered to be expressed by astrocytes in the mammalian central nervous system [11-13]. Ceruloplasmin has been detected in leptomengeal cells (which cover the surface of the brain) and some fibroblast, this form is the major form of ceruloplasmin in the central nervous system since ceruloplasmin does not cross the blood – brain barrier [14,15].

This ceruloplasmin antioxidant protection capacity has derived from its binding to more than 90 % of copper [16,17]. It can also serve as a scavenger of superoxide radicals [18], moreover it is capable of oxidizing and detoxifying the catecholamine, neurotoxin 6-hydroxy dopamine [19]. Ceruloplasmin had been showed to be effective in inhibiting lipid per-oxidation stimulated by copper and iron [20,21]. The ferroxidase activity of ceruloplasmin plays an important role in preventing the formation of free radicals, through controlling the levels of highly toxic iron in the cells, in addition to binding the copper [22].

Transferrin is the primary iron transport protein in serum, since > 95% of serum nonheme iron is bound to this protein [23,24]. The antioxidant activity of transferrin depends on the number of available iron binding site present within this protein [2,25], since such binding decreases the involvement of this metal in oxygen radicals reactions [25,26]. Free iron presents as ferrous ion is very toxic, because of its ability to generate highly reactive superoxide and hydroxyl radicals, in addition to hydrogen peroxide in the presence of molecular oxygen [22].

$$O_2 + Fe(II) \rightarrow O_2^- + Fe(III)$$
$$2O_2^{\cdot} + 2H^+ \rightarrow O_2 + H_2O_2$$
$$Fe(II) + H_2O_2 \rightarrow Fe(III) + {}^{\cdot}OH + OH$$

Ceruloplasmin appears to play a key role in the oxidation of ferrous iron, and hence its release from cells and loading onto Apo transferrin [22,27]. Thus, it is necessary for iron incorporation into transferrin as this later protein binds largely the ferric form. This important physiological function of ceruloplasmin is mediated by its bound copper as follow:

$$4Fe(II) + 4\,Cu(II) \rightarrow 4Fe(III) + 4\,Cu$$
$$4H^+ + O_2 + 4\,Cu(I) \rightarrow 2H_2O + 4\,Cu(II)$$

This ferroxidase activity of ceruloplasmin was reported to play role in both iron release [28-31], and iron uptake by brain including nervous cells [6,32,33]. It was concluded out of many studies carried on diseases in the CNS regions, that many neurodegeneration is a consequence of oxidative stress that induced by iron deposition in brain [33].

The aim of present study was to follow the alteration in each of Cp ferroxidase activity, [iron], [transferrin] and UITC, TIBC in sera of patients with benign brain tumors and those with malignant brain tumors in comparison to that of healthy individuals.

Patients

Two groups of patients their aged ranged between 6-64 years, 31 of them with benign brain tumors, and 26 with malignant brain tumor with different types and stages attending Al-Gomla Al-Asabea/ Baghdad were chosen to be included in this study.

The diagnoses of the cases were confirmed by histological and cytological examination of biopsy specimens, which were carried in the laboratories of the above-mentioned hospital. The above patient groups were divided into subgroups: benign astrocytoma I-II (n=11), benign meningioma (n=15), low-grade glioma (n=5), malignant astrocytoma III-IV (n=7), malignant glioma (n=5) and high-grade glioma (n=14).

Methods

The ferroxidase activity of Ceruloplasmin was calculated, in term of decrease in the substrate concentration [ferrous ion] upon its incubation with the enzyme at pH 5.8 from the standard curve constructed as described by Erel [34].

The total protein concentration was determined using simple Lowry method [35]. The specific activity of ceruloplasmine is calculated by dividing the ferroxidase activity (U/L) by the protein concentration (g/L).

Serum iron concentration, TIBC and UIBC were determined using Randox Kit. Transferrin was estimated indirectly from the TIBC by the following equation [36]:
Transferrin (mg/dl) = 0.7 x TIBC (Mg/dl).

While the percentage of saturation of transferrin with iron was determined using the following equation [37]:
Saturation %= (Serum iron/ TIBC) x 100

Results

Results presented in Figure 1(a) indicate that the Cp ferroxidase activity increase significantly in sera of each benign and malignant patients group in comparison to that of the control ($p<0.05$). Also, there is a highly increase of ferroxidase activity in sera of malignant patients in comparison to that of the benign group ($p<0.05$).

A highly significant increase of specific ferroxidase activity was observed in sera of patients with benign and malignant brain tumors, in comparison to that of the control group ($p<0.01$) as shown in Figure 1(b).

The results in table 1 show that there are differences in sera Cp ferroxidase activity, and its specific activity among the studied subgroups, some of these results were found significant while the other were insignificant as indicated in the Table 1.

Iron concentration, total iron binding capacity (TIBC), unsaturated iron binding capacity (UIBC) and transferrin (Tf) level in the studied groups were determined. Table 2 shows presence of a significant increase in serum [iron] of the benign and malignant groups in comparison to that of control group ($p<0.001$), while no significant increase was observed between benign and malignant groups ($p>0.05$). On the other hand a significant decrease in TIBC, UIBC and Tf was observed in sera of patients with benign and malignant brain tumors in comparison to that of the control group ($p<0.01$). A significant decrease was also observed between these parameters upon their comparison in sera of malignant group, with that of their corresponding benign group ($p<0.001$).

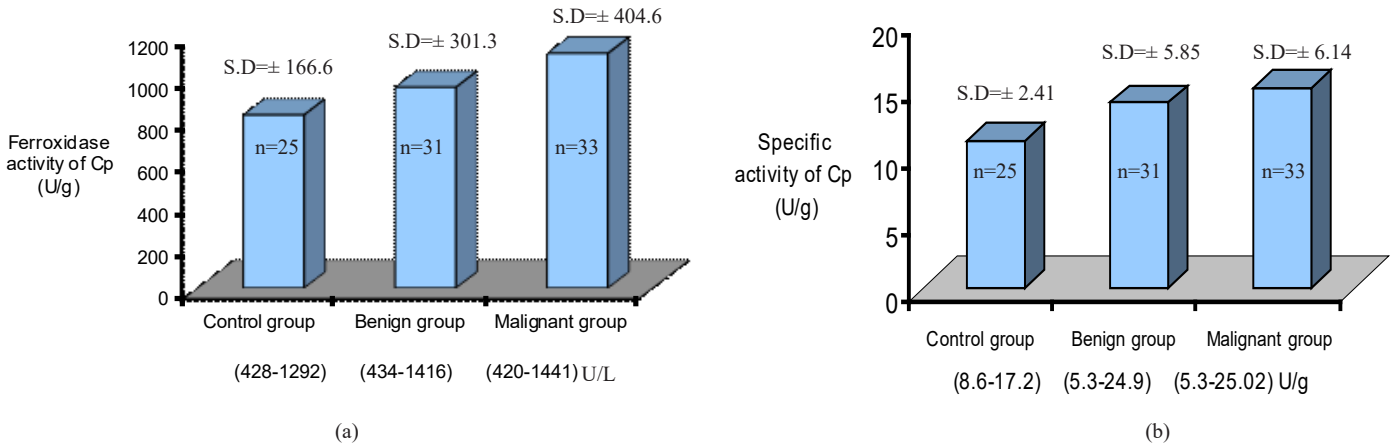

Figure 1: The mean value of ceruloplasmin ferroxidase: (a) activity of and (b) specific activity of the three studied groups, control, patients with benign brain tumors and those with malignant brain tumors

Table 1: Ferroxidase activity and specific activity of ceruloplasmin in control and subgroups of benign and malignant brain tumor patients.

		Ferroxidase activity			Specific activity		
Groups	**Sample Size (n)**	**Mean (U/L)**	**S.D**	**Range (U/L)**	**Mean (U/g)**	**S.D**	**Range (U/g)**
Control (A)	25	821.8	166.6	428-1292	11.09	2.41	8.6-17
Asrrocytoma I-II (B)	11	970.2	235.1	588-1393	13.45	7.81	5-2304
Benign meningioma (C)	15	1019.7	321.5	506-1416	11.9	5.97	5.5-24
Low grade glioma (D)	5	894.2	328.1	434-1005	11.16	6.23	6.2-21
Astrocytoma III-IV (E)	7	1061.1	535	420-1441	13.98	7.83	5.7-22
Malignant meningioma (F)	5	1031.8	305.8	529-1425	13.03	5.78	5.6-24
High grade glioma (G)	14	1063	448.4	585-1439	14.7	5.35	6.2-25

T-test of ferroxidase activity between: D/G significant ($p<0.05$)

Table 2: Mean values ± SD of the [iron], TIBC, UIBC, [Transferrin] and % saturation of transferrin in the normal, benign and malignant brain tumor groups.

Groups	**Iron conc. (µg/dL) (± S.D)**	**TIBC (µg/dL) (± S.D)**	**UIBC (µg/dL) (± S.D)**	**Transferrin (µg/dL) (± S.D)**	**%Saturation of transferrin (± S.D)**
Control	69.84 (20.7)	289.5 (56.21)	219.66 (38.5)	202.6 (21.4)	24.12 (15.3)
Benign	110.2 (26.91)	204.2 (46.65)	94 (33.91)	142.9 (30.1)	53.96 (12.7)
Malignant	119.5 (32.29)	166.05 (35.29)	46.5 (28.97)	116.2 (28.4)	71.96 (19.8)

The saturation percentage of transferrin with iron was highly significant elevated in benign and malignant groups compared to that of the control group ($p<0.001$). Meanwhile it was significant increase in malignant group in comparison to that of benign group ($p<0.01$).

Discussion

Generally, during the phagocytic activity of neutrophils, as well as certain other cells, superoxide radicals (O_2^{-}) and (H_2O_2) are generated [37]. In the presence of copper or iron these active oxygen species can form the highly reactive hydroxyl radical that attack and oxidative damage most biological molecules [38,39]. Generally the normal cells contain a defense mechanism in the form of enzymatic antioxidants such as catalase, glutathione peroxidase and superoxide dismutase, in addition to none enzymatic antioxidants such as vitamin C, vitamin E, vitamin D selenium, which protect them against these active oxygen species, while extracellular fluids are poor in these enzymes [40]. In the extracellular fluid Cp and Tf are important when iron is the catalyst [41]. During acute inflammation that result from different causes including tumor presence, ceruloplasmin was suggested to act as an antioxidant. This antioxidant activity came from its ability to oxidize iron thus help to incorporate iron into transferrin [42]. Iron in its ferrous state (Fe^{2+}) was reported to have cytotoxic activity that is considered to be of pathogenic significant, in certain brain degenerative disorders [43-45].

The elevation of ferroxidase activity in sera of brain tumors reported in the present study may aid in controlling the level of highly toxic iron within cells. This elevation in Cp ferroxidase may

result from increase in Cp synthesis in brain and liver, the GPI-anchored Cp reported to be the major form of Cp in the brain [22], and was reported to possess oxidase activity and has a function as a ferroxidase [46].

Ceruloplasmin was shown to be present on the surface on astrocytes [15] and on the surface on Schwann cells [46]. A study recognized that mutations in the Cp gene cause a neurodegenerative disorder that was characterized by a storage of iron by Cp and neurovascular, which further confirmed the biological significant of the ferroxidase activity of Cp [47-51]. The result of our study confirms the importance of Cp in brain tumor throughout its ferroxidase activity, in addition to its importance as an acute-phase reactant.

Iron level was determined previously in several studies dealing with different types of cancer. Some of these studies indicated that iron level was lower in serum of patients with lung cancer [52], and in those with head and neck cancer [53] while this level remained unaltered in sera of patients with carcinoma of the larynx [54], and decrease insignificantly in sera of patient with breast cancer [55,56].

Even-though the abnormally high levels of iron in the brain have been demonstrated in a number of neurodegenerative disorders [57-61], but Cp functions in brain iron metabolism are not well understood. But it was suggested that Cp through its ferroxidase activity, plays an important in iron efflux from brain cells as well as in iron influx into these cells, i.e. Cp play a vital role in brain iron homoeostasis [6], this copper binding protein seems to promote iron release rather than its uptake by brain, such role enables it to convert reduced iron released from storage sites (such as ferritin) to the oxidized form, by this way Cp allows iron to bind to its plasma transporter protein, transferrin. This dual role of Cp in brain's iron metabolism is depends on iron concentration in the cell i.e.: Cp enhances iron uptake where the intracellular concentration of iron is low and vice versa [61]. In this study, iron concentration as well as Cp ferroxidase activity was found to increase in the serum and this may occur as a result of the decrease that was detected in iron concentration in the brain cells.

The observed decrease in transferrin concentration was not significant. It is worth to mention that transferrin level was reported to decrease during acute-phase response, with infections and neoplastic disease [57].

The serum total iron- binding capacity (TIBC) represents the maximum concentration of iron that can be bound by serum protein, and TIBC is highly correlated with the level of serum transferrin, and usually only 30% of the available serum iron-binding sites of this protein are occupied, The changes in the ratio of serum iron to TIBC reflects the changes in the body iron stores. The total iron binding capacity of this protein was reported to decrease in chronic inflammatory disorders or malignancies [57].

The results reported here indicated that there was an iron overload in serum of the patients, so serum iron is high, while that in transferrin is low in the presence of high % saturation of TIBC. This Iron concentration as well as Cp ferroxidase activity was found to increase in the serum of the patients. These obtained results indicate that there is an elevation of the free iron in brain tumor patients, which was accompanied by a decrease in the iron binding protein transferrin leaving behind an increase in free iron concentration that produce oxygen free radical. The increase in free radical leads to lipid peroxidation that cause an increase in the viscosity of the membrane bilayer, changes the thermotropic phase behaviors and facilitates phospholipids exchange between the two monolayers. Upon lipid peroxidation membrane, proteins are cross- linked and their mobility decrease. Such changes may suggest that the alteration in oxidative stress cause cancer rather than it is one of its consequences.

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