Peripheral and Intracranial Compartment Serum Level of Selenium in Pediatric Patients with Intracranial Tumor in Department of Neurosurgery, Faculty of Medicine, Universitas Padjadjaran–Dr. Hasan Sadikin Hospital, Bandung, Indonesia: a Preliminary Study and Literature Review

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Abstract

Objective: To determine the level of Selenium (Se) in peripheral and intracranial serum in pediatric patients with intracranial tumor. Selenium has chemopreventive potentials and acts as neuromodulator.

Methods: This study was conducted on 13 pediatric patients with intracranial tumors who were treated in Dr. Hasan Sadikin Hospital, Bandung in the period of February 2014 to February 2015. Samples were taken from peripheral and intracranial serum. The results were analyzed with independent t-test and Pearson correlation test. Significance is defined as $p \leq 0.05$ with 95% confidence interval.

Results: The results showed that the average Se concentration in peripheral serum was significantly higher than the Se concentration in intracranial serum (95.92±20.95 µg/L and 66.62±22.37 µg/L, respectively). After classifying the subjects into groups based on sex, age, tumor location, and grades, the difference between Se concentrations were still statistically significant ($p \leq 0.05$), with the exception of the supratentorial group ($p=0.0053$). Pearson correlation test showed very-low to medium strength correlations between peripheral and intracranial serum Se concentration in all groups ($r=0.16$–0.59, $p>0.05$).

Conclusions: A significant difference is seen between the peripheral and intracranial serum Se concentration means in pediatric patients with intracranial tumors, with higher concentrations observed in the peripheral serum. Further studies are required to investigate the roles of Se in the management of pediatric patients with intracranial tumors.

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Introduction

Tumor is a dreaded diagnosis due to its high morbidity and mortality rates. The prevalence of intracranial tumor is 1.4% of all tumor cases, with a mortality rate of 2.4%.[1] In individuals below the age of 20, brain tumors are the most common solid tumor and the second leading cause of tumor-related deaths after leukemia.

In general, the management of tumor is emphasized on three modalities: radiotherapy, surgery, and chemotherapy. However, these modalities are less feasible for the pediatric patients due to their physiological condition, making this patient group more vulnerable.[2] Therefore, in order to improve the quality of the therapy, other modalities like the neoadjuvant therapy, are needed. One of the aspects approached by those modalities in tumor management is the microenvironment of the tumor. The use of antioxidants is one of the more commonly studied aspects of

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the modality aspects. Meanwhile, there are also tumor prevention methods available. In addition to the efforts to reduce the exposure to known risk factors, there are also efforts to increase protective factors and modify the DNA defense mechanism and repair, which is known as chemoprevention. Currently, chemoprevention studies are focused on finding pharmacologic agents or dietary factors that can be used as tumor preventive agents.[2]

Selenium (Se) is a micronutrient which plays an essential role in our diet, and is one of many agents that have been investigated as a chemopreventive agent. The role of Se as an anti-carcinogenic agent was first introduced in 1969 by Shamberger and Frost. They found that there was an inverse correlation between the rate of mortality caused by tumors and Se levels in the crops. Subsequent studies have strengthened the notion that Se has a chemopreventive potential. Additionally, in 1996, Clark found that there is a decrease in the incidence of prostate, lung, and colorectal cancers with Se supplementation in the elderly people.[2] Severral studies have shown that, in a concentration higher than the recommended daily intake, Se, both in its organic and anorganic form, has a chemopreventive potential. It has been shown to surpress cells' growth and stimulate cells' apoptosis in tumor cells model. Studies on Se are also focused on its potential as a selective eradicator of tumor cells and as an immunomodulator. Studies exploring the benefits of Se supplementation are not limited to its chemoprotective properties, but also include its benefits in heart diseases, hypertension, and inflammatory conditions.[2]

There were several studies that measured serum Se levels in normal and also pathological conditions, such as in tumors (i.e., prostate, lungs, and cervical) and abortion.[3–6] Studies had also been done to measure the trace elements in cerebrospinal fluid (CSF) of brain tumor patients.[7,8] Meanwhile, similar efforts to measure the peripheral Se serum in patients with cerebral and extracerebral tumor were also performed.[9,10] Currently, to the best of the authors' knowledge, there are no studies measuring the Se serum level, both in the peripheral and intracranial compartments of the same patients with pediatric intracranial tumor. Therefore, this study was conducted to determine the level of Se in peripheral and intracranial serum of pediatric patients with intracranial tumor. The results of this study will be used as preliminary data for further investigations on the role of Se in the course and management of pediatric brain tumors.

The concentration of Se in the body varies between tissues. The difference can partly be attributed to the differences in the ability of each tissue to store Se. In the brain tissue, the presence of the blood brain barrier, which limits the entry of some substances from the peripheral circulation might affect the Se concentration. The exclusiveness of the intracranial circulation also causes the lack of information on the levels of certain substances in intracranial circulation, including Se. Thus, data on the association between brain tumors and Se concentration in the vasculature surrounding the tumor tissue is still lacking. Consequently, this study was conducted to investigate the level of Se in pediatric patients with brain tumors, both in peripheral and intracranial tumors.

Methods

Subjects of this study were pediatric patients (World Health Organization/WHO criteria),

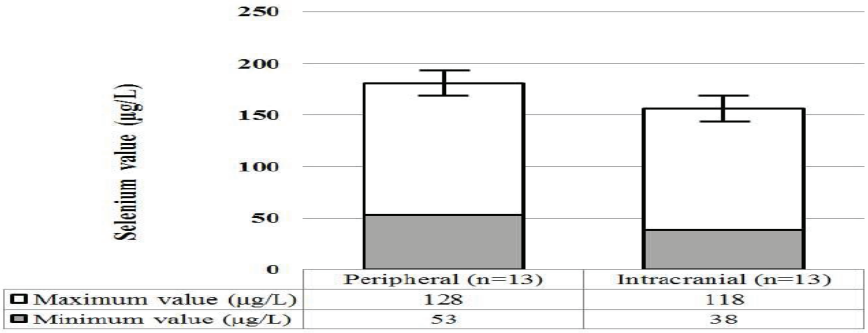

Fig. 1 Descriptive Statistics of Peripheral and Intracranial Serum Selenium Levels in Pediatric Patients with Intracranial Tumor

Table 1 Comparisons between Mean Values of Peripheral and Intracranial Serum Selenium Level in Pediatric Patients with Intracranial Tumor

Peripheral vs Intracranial Serum Selenium Level	Test	p Value	Conclusion
Overall	Unpaired t-test	0.002	Significant
Supratentorial		0.053	Not significant
Infratentorial		0.013	Significant
Boys		0.04	Significant
Girls		0.038	Significant
Age ≤ 9 years old		0.031	Significant
Age > 9 years old		0.022	Significant
Low-grade		0.031	Significant
High-grade		0.049	Significant

who were diagnosed with brain tumor at the age of ≤18 years old. Subjects were operated and hospitalized Department of Neurosurgery, Faculty of Medicine Universitas Padjadjaran, Dr. Hasan Sadikin Hospital, Bandung. Patients were excluded when they did not meet the above criteria and also when the histological tissue analysis proven that the patient did not have brain tumors. Patients were also excluded if the vein-blood samples from the peripheral and/or intracanial compartments were damaged or experienced lysis. This was a prospective descriptive study measuring Se concentrations in peripheral and intracranial serum. The samples were taken from both peripheral and intratumoral intracranial compartments of the same patients intra-operatively. These samples were then treated using centrifugation to separate the red blood cells (RBC) from serum. After that, serum samples were frozen at -80 °C for subsequent analysis of total Se concentration.

The calculation of selenium concentrations was peformed by fluorometric measurements at an excitation wavelength of 378 nm and an emission wavelength of 525 nm to determine the concentration of piazoselenol, which is produced by the reaction of selenite with 2,3-diaminonaphtalene.[3,6] The validity of the selenium analysis was confirmed through the measurement of a reference material (bovine liver, SRM 1577b, National Institute of Standards and Technology, USA).

Paired t-tests were performed to test the correlation between Se levels in peripheral and intracranial serum. This correlation was then extrapolated to groups based on age, sex, tumor location, as well as tumor grade. Pearson correlation tests were conducted to determine the correlation between peripheral and intracranial serum Se levels. Results with a p value of less than 0.05 were considered statistically significant.

This study protocol had been approved by the Health Research Ethics Committe of the Faculty of Medicine, Universitas Padjadjaran and informed consent was gained from all subjects. Hence, it is declared that all experiments in this study have been examined and approved by the appropriate ethics committee and have therefore been performed according to the ethical standards laid down in the 1964 Declaration of Helsinki.

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this study and accompanying images.

Results

The mean age of the subjects was 9.54±4.68 years old. Seven boys participated in this study. Out of 13 cases, 7 cases were supratentorial while 6 cases were infratentorial. Six cases were high grades while 7 were low grades. The total Se concentrations in the peripheral and intracranial serum are shown (Fig. 1). The mean of Se concentration in the peripheral serum (95.92±20.95 µg/L) was significantly higher ($p<0.05$) than that of the intracranial compartment (66.62±22.37 µg/L).

Table 2 Correlations between Peripheral and Intracranial Serum Selenium Levels in Pediatric Patients With Intracranial Tumor

Peripheral vs Intracranial Serum Selenium Level	Test	r	Conclusion	p Value
Overall	Pearson correlation test	0.37	Low	0.21
Supratentorial		0.45	Average	0.30
Infratentorial		0.58	Average	0.16
Boys		0.59	Average	0.16
Girls		0.16	Very low	0.76
Age ≤9 years old		0.12	Very low	0.81
Age >9 years old		0.35	Low	0.43
Low-grade		0.22	Low	0.62
High-grade		0.39	Low	0.44

In general and in groups, which were based on age, sex, tumor location, and tumor grade, the serum Se concentrations, both peripheral and intracranial were normally distributed ($p>0.05$) and, therefore, can be analyzed parametrically. The unpaired t-tests were performed to compare the means of Se concentrations. The results are presented (Table 1). Except for the supratentorial group ($p=0.053$), the differences between Se concentrations in all groups were statistically significant ($p<0.05$).

The range of the correlation value is -1 to 1. The values of the Se concentrations in this study were always positive, both in overall and in groups (Table 2). Therefore, there were no negative correlations observed. Further, based on their value, the strength of the correlations were grouped into very low (0–0.1999), low (0.200–0.399), moderate (0.400–0.599), high (0.600–0.799), and very high (0.800–1.000). It is apparent from the table above that the correlations between serum concentration of Se peripherally and intracranially, in overall and in groups, present positive coefficient values of between 0.16 to 0.59, which means that the correlation was either very low, low, or moderate. Moreover, the correlations were not statistically significant ($p>0.05$).

The degree of correlation found between the peripheral and intracranial serum Se levels for both overall and in groups were shown(Table 2). After being tested with the Pearson correlation test, several degrees of correlation strength were observed. Very low strength correlation was observed in girls and subjects aged ≤9 years old. While low strength correlations were observed in overall subjects, subjects aged <9 years old, and subjects with either high- or low-grade tumor. Moderate strength correlations were observed in boys and subjects with either supra- or infra-tentorial tumor location. All of those correlations, however, were not statistically significant ($p>0.05$).

The 13 patients included in this study were divided into two groups: (I) malignant brain tumor: six cases with a mean age of 10±4.4 years old (yo) and histologically diagnosed medulloblastoma (3 cases; 5±1 yo), primitive neuroectodermal tumors or PNET (2 cases; both were 12 yo), atypical teratoid/rhabdoid rumor or AT/RT (1 case in 13 yo boy) who were operated under general anesthesia for craniotomy removal of the tumors and (II) benign brain tumor: seven cases (10±5.4 yo) with histologically diagnosed pilomyxoid astrocytoma in a 3 yo girl, pilocytic astrocytoma (2 cases; 6.5±3.5 yo), meningotheliomatous meningioma (1 case; 10 yo boy), ependymoma (2 cases; 15.5±0.7 yo) or craniopharyngioma (1 case; 15 yo boy) who were operated upon and sample was collected from each sampling sites, both peripheral and intracranially (Fig. 2).

The mean and standard deviation (SD) for selenium level (µg/L) in the malignant brain tumor group were 108.9±14.9 (peripheral

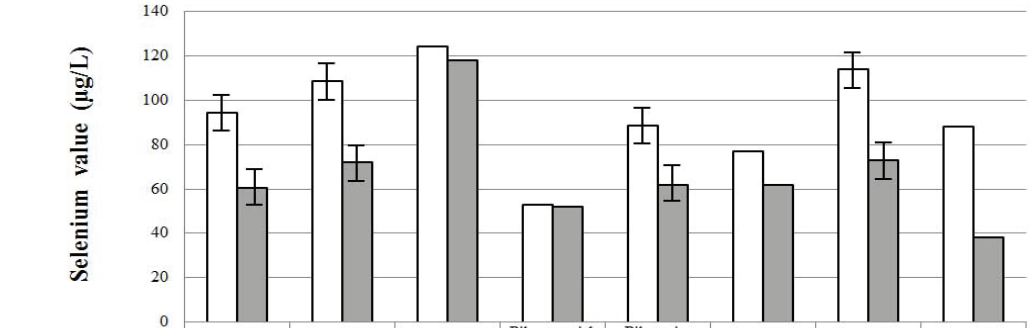

Fig. 2 Detail of Peripheral and Intracranial Serum Selenium Level in the Same Patients with Pediatrics Intracranial Tumor

serum) and 83.5±30.4 (intracranial serum): 94.3±16.6 (peripheral of medullablastoma) and 60.8±24.5 (intracranial of medullablastoma); 108.35±13.4 (peripheral of PNET) and 72±16.9 (intracranial of PNET); and 124 (peripheral of AT/RT) and 118 (intracranial of AT/RT).

The mean and standard deviation (SD) for Selenium concentrations (µg/L) in the benign brain tumor group were 84.1±22.1 (peripheral serum) and 57.4±13.2 (intracranial serum) with the following details: 53 (peripheral of pilomyxoid astrocytoma) and 52 (intracranial of the pilomyxoid astrocytoma); 88.5±2.1 (peripheral of the pilocytic astrocytoma) and 62±4.25 (intracranial of pilocytic astrocytoma); 77 (peripheral of the meningotheliomatous meningioma) and 62 (intra-cranial serum of the meningotheliomatous meningioma); 114±19.7 (peripheral of ependymoma) and 73±22.6 (intracranial of ependymoma), and 88 (peripheral of craniopharyngioma) and 38 (intracranial of craniopharyngioma).

Discussion

Intracranial tumors, particularly of the central nervous system (CNS) origin, account for 15–20% of all malignancies that occur during childhood and adolescence. Despite the fact that it is relatively common, with an incidence of 2,500–3,500 cases per year, diagnosis might be impeded due to a broad spectrum of clinical manifestations. The clinical manifestations are mainly influenced by the tumor growth rate, tumor location, and patient's age. Brain tumors in pediatric patients have distinct features if compared to brain tumors in adults. Although they can be found anywhere in the central nervous system, brain tumors in pediatric patients have a predilection to appear in the posterior fossa. In addition, they have more histologic variations, dissemination rate, and embryonal characteristics.[11,12]

As previously mentioned, one factor, which influence the clinical manifestations of the brain tumor, is its location. Around half of all brain tumors that occur in pediatric patients are located in the posterior fossa. Most of those patients usually present with focal neurologic deficits. However, when the tumor fills or compresses the fourth ventricle, and causes cerebrospinal fluid impediment, hydrocephalus may develop. It is common that those patients present with a classical triad that include increased intracranial pressure, headache, especially in the morning; nausea; and vomiting. Additionally, in infants, with dilatation of the third ventricle and tectum compression, a phenomenon called sunset eyes can be seen.[11,12]

Selenium is a nonmetal mineral located in VI A group in the periodic table. In its basic state, it has three main forms: elemental, organic, and anorganic. Se, which was initially thought as a contaminant in sulfuric acid, was discovered by Jons Jacob Berzelius in 1818. Around 140 years later, Schwarz and Foltz found that it

plays a role in preventing hepatocytes necrosis in mice with vitamin E deficiency. In the year 1960, its potential use in the medical field started to be explored. In the year 1973, Se was found to function as a cofactor for glutathione peroxides, a group of selenoprotein, which plays an important role in the human body, including tumor prevention.[13,14] There were several epidemiologic studies, which reported the correlation between Se supplementation and decrease in various tumors incidence. It is thought that because the majority of selenoprotein have antioxidant properties, increase in dietary intake of Se may increase the expression of selenoprotein, which in turn may confer protection on DNA against oxidative stress. However, the exact biomolecular mechanism is still a subject of research.[13,14]

Selenium is a micronutrient that has been widely studied in the medical field because of its many functions. Functions of Se that have garnered a lot of attention due to its chemopreventive and chemotherapy functions. Selenoprotein, which is an amino acid, which contain Se, is considered to have antioxidant properties that can prevent, or even eradicate tumor cells. There were some studies that showed a positive effect of Se supplementation in reducing incidence rate of tumor. Correspondingly, there were studies showing deficiency of Se in tumor patients. Those two findings clearly showed that there is a connection between Se level and the incidence of tumor, though there has been no consensus yet.[12,15,16]

El-Yazigi *et al*.[7] in 1984 measured nine trace elements in CSF of adult brain tumor patients. The Se concentration in LCS of non-brain tumor patients 19.1±13.3 µg/L, which was half the concentration in serum; while Haas *et al*.[8] in 1987 measured Se in CSF of pediatric brain tumor patients. Philipov and Tzatchev[9] in 1988 measuring the Se peripheral serum in 139 adult patients with tumor in cranium cavity vs 294 healthy adults individual and the Se concentration was significantly decreased in malignant tumor; Gromadzinska *et al*.[10] at the same year measuring the Glutathione peroxides (GPx) peripheral serum in pediatric patients with cancers. Recently, Al-Chalabi and Al-Chalabi[17] in 2007 measuring the Se peripheral serum in 93 adult patients (41 malignant cases, 52 bening cases) with brain tumor vs 65 healthy adults individual; the Se concentration in control group 0.93±0.02 µmol/L, 0.57±0.05 in benign tumor, 0.3±0.04 malignant tumor; the percent decrement was about (39% and 59%) respectively. No significant differences had been found on the Se level in serum of benign and malignant tumor patients.

In our study we found that serum Se concentrations in intracranial compartment of the pediatric tumor subjects were significantly lower than those of peripheral. The mechanism of the observed decreased concentrations of Se serum intracranial vs. peripheral with malignant cerebral tumors is unknown. The concentrations of these trace elements in serum intracranial in cases of brain neoplasms have not been previousy reported. Selenium is an essential trace element and has been shown to affect the function of selenoproteins by being a part of an active site in antioxidant enzymes, like GPx and thioredoxin reductase. Furthermore, Se also acts as an anticancer agent through plausible mechanisms, including the stimulation of the immune system and inhibition of cell proliferation.[16,18] Krehl *et al*.[19] stated that Se deficiancy is considered as a risk factor in cancer development. The protective effect of Se might be mediated by specific selenoprotein, such as GPx. As their mouse model experiment result showed that adequate Se supply provides the best protection against carcinogenesis, low Se status highlights the risk of cancer development. The sustainable persuasive evidence indicates that Se can certainly play an important role in cancer prevention.[12,20]

Several limitations are seen in this study: (I) the small patients sample size; (II) potential involvement of signaling pathways of other microenvironment in the development of malignancy; and (III) full explanation on the mechanism of selenium in clinical setting is still lacking. The phenomena of low-selenium concentration in intracranial compartment of the pediatric tumor, in this study, might be related to the complex mechanism, such as metabolisme of cancer cell itself or it might be related with protection of blood brain barrier (BBB), that remains to be elucidated. Understanding of selenium role both in normal and cancer cells might improve therapeutic strategies for patients with malignant diseases.

In conclusion, significant differences are found between the means of peripheral and intracranial serum Selenium concentration in pediatric patients with intracranial tumors, with the concentration on peripheral serums higher than intracranial ones. Further studies are currently performed to prove the roles and positions of Se in the management of pediatric patients with intracranial tumors.

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