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The Effect of Vitamin E Supplementation on Brain Tissue Element Levels in Epileptic Rats

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A B S T R A C T

The aim of this study was to investigate how the application of vitamin E affected the levels of chemical elements in the brain tissues of epilepsy-induced rats. 40 adult Wistar male rats were separated into 4 equal groups: Group 1: control, Group 2: vitamin E; Group 3: penicillin to induce epileptic form activity and Group 4: penicillin + vitamin E. After three months of treatment, an Atomic Absorption Spectrophotometer was used to analyze the presence of the elements in brain tissue sections (brain, brainstem, and cerebellum) of the decapitated animals.

The levels of magnesium in the groups that received vitamin E (G2 and 4) were significantly higher than in the control group (G1) and the first epilepsy group (G3) ($p<0.05$). Chrome and zinc levels in brain, brainstem, and cerebellum tissue of the two epilepsy groups (G3–4) decreased significantly compared to the control group (G1) and the vitamin E group (G2) ($p<0.05$). The levels of copper in the brainstem and lead in the cerebellum of the first epilepsy group (G3) were higher than in all other groups ($p<0.05$).

The results showed that the application of vitamin E in experimental epilepsy may have a limited effect on element metabolism in brain tissue. A decline in zinc levels in the brain, brainstem and cerebellum tissues in epilepsy groups constitutes another result of our study. This should be examined further to determine whether decreased levels of zinc play a role in epilepsy pathogenesis.

Key words

Epilepsy • Penicillin • Vitamin E • Brain • Element metabolism • Rat

Introduction

Epilepsy is a very common neurological disease that occurs equally in males and females, regardless of race. Epileptic seizures may occur at any age, but they mostly affect infants, children, and elder people (Brodie et al., 2012; Perucca and Gilliam, 2012). Constraints and the difficulty of conducting studies of epilepsy have lead researchers to use epileptic animal models, and the penicillin model is one of the most commonly used (Aygun et al., 2019; Fisher, 1989). An epileptic seizure is a clinical presentation caused by an over-discharge and electrophysiological anomaly of a neuron group in the brain. This clinical presentation covers sudden and temporary phenomena including motor, sensory, autonomic, and psychic incidents and changes in the level of consciousness. Epilepsy may occur without any known brain damage or risk factor, but it can also be prompted by other underlying neurological, systemic, metabolic, toxic or traumatic causes (Erbayat Altay et al., 2005).

Vitamin E is a bio-catalyzer that is regarded as essential for humans and animals (Putnam and Comben, 1987). It cannot be synthesized in the organism; it must be taken from outside through nutrition. Vitamin E is common in nature, and it is present in most vegeoils, seeds, and green plants (Singh et al., 1993). One of

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the most important known functions of vitamin E is that it is a free radical-scavenging anti-oxidant (Singh et al., 1993). Vitamin E is fat-soluble, and it includes 8 tocopherols, of which α-tocopherol has the highest anti-oxidant characteristics. Being a very strong anti-oxidant, α-Tocopherol forms the first line of defense protecting unsaturated fatty acids in the structure of membrane phospholipids against the effect of free radicals. It also eliminates lipid peroxyl radicals and ends the lipid peroxidation chain reactions. It is known as a chain-breaking anti-oxidant because of this characteristic (Niki, 2014). Vitamin E preserves membrane stability by using all radical-elimination, suppression, repair, and endogenous defense mechanisms, giving it a very fast and extensive anti-oxidant capacity (Niki, 2014). Chemical elements such as selenium, copper and zinc are known to have an important role in anti-oxidant activity (Baltaci et al., 2016; Baltaci et al., 2019), and these elements have been found at low levels in the blood of epileptic patients (Nazıroğlu and Yurekli, 2013). Some researchers consider that selenium and especially zinc may cause a decrease in epileptic seizures (Baraka et al., 2012; Pillai et al., 2014). Similarly, it has been reported that an imbalance of intra- and extra-cellular zinc in brain tissue increases the tendency toward convulsions in epileptic patients. Thus, zinc is critically important for brain function (Di Angelantonio et al., 2014). It has also been shown that a deficiency of manganese similarly increases the tendency for epileptic seizures o occur (Dedeurwaerdere et al., 2013).

Based on the evaluation of this information, it can be stated that there are significant relationships between epilepsy and vitamin E and between epilepsy and the levels of chemical elements in brain tissue. However, in med-line searches, no studies have been found that examined the relationship between vitamin E and the metabolism of elements together in epilepsy. Presenting how the application of vitamin E affects element levels in brain tissue in experimental epilepsy model may provide interesting findings for both vitamin E and epilepsy and how vitamin E is related to the metabolism of elements in epilepsy. The aim of this study was to investigate how the application of vitamin E affected element levels in brain tissue (brain, brain stem, and cerebellum) in epilepsy-induced rats.

Materials and Methods

This study was performed on Wistar-albino type adult male rats. Experimental stages of the study were made in 19 Mayis University Faculty of Medicine Physiology Department Laboratory. The study protocol was approved by the Selcuk University Experimental Medicine Research and Application Center Laboratory Animals Ethics Board (No: 2015/96). The laboratory animals were kept in private steel cages, which were washed every day. Feed was given in private steel cups and normal tap water was given in glass feeding bottles. The animals were given nearly 10 g feed per 100 g body weight every day, and they were kept at standard room temperature (21°C ±1°C) in 12 hours of dark and 12 hours of light.

A sample of 40 rats was divided into four groups based on their experimental applications:

- **Group 1, (n:10) the control group:** It was fed a normal diet for three months, but it did not receive any applications.
- **Group 2, (n:10) the vitamin E group:** It was fed a normal diet for three months and given a dose of 500 mg/kg of vitamin E with the gavage method every other day.
- **Group 3, (n:10) the penicillin group:** It was fed a normal diet for three months and given a 500 unit (IU) dose and 2.5 µl volume of penicillin intra-cortically (IC) to induce epileptic form activity.
- **Group 4, (n:10) the vitamin E + penicillin group:** It was fed a normal diet for three months and given a dose of 500 mg/kg of vitamin E with the gavage method every other day. It was given intramuscular 500 mg/kg vitamin E 30 minutes after epileptic form activity formation 24 hours after the last application of vitamin E.

After three months, the animals were decapitated so the related sections (brain, brainstem, and cerebellum) were separated for analysis.

Experimental Applications

Surgical Operations and Penicillin Application

The rats were not fed for 12 hours before the surgical operation. Anesthesia was provided through intraperitoneal (ip) application of 1.2 gr/kg urethane.

The rats were fastened on the operation after shaving their upper heads. A cut of an average length of 3 cm was opened on the scalp in rostro-caudal direction, and possible bleeding from soft tissue was prevented through electro cautery. The soft tissue on the left somatomotor cortex was removed, and the cranium was made thinner with an rpm motor; then the parietal bone was carefully lifted. Stainless-steel electrodes were placed on the duramater over the cortex: one in the frontal region (2 mm anterior and 3.5 mm lateral to bregma) and parietal region (6 mm posterior and 4 mm lateral to bregma) according to the atlas coordinates. Possible bleeding in bone tissue was prevented using bone wax. To prevent heating from friction, tamponade was made with serum physiological impregnated sponge on the skull when needed. After the parietal bone was completely removed, duramater was carefully lifted (Aygun et al., 2019). 1 million units of penicillin G potassium was used (solvent: distilled water). Penicillin with a dose of 500 units (IU) and a volume of 2.5 µl was applied intracerebroventriculer (IC) to induce epileptiform activity. The penicillin infusion rate was 0.5 µl/min (Aygun et al., 2019).

Sample Acquisition

Following the experimental applications lasting three months, the brain tissues of the decapitated animals were taken and the related sections (brain, brainstem, and cerebellum) were separated for tissue element analysis.

Tissue Element Analyses (Aluminum, Calcium, Chrome, Copper, Iron, Potassium, Magnesium, Manganese, Sodium, Lead, Zinc)

Brain tissue samples (brain, brainstem, and cerebellum) from the laboratory animals were put into polyethylene tubes washed with NHO_3 and deionizer water and covered to prevent contamination. The tissue samples were kept at –35˚C until the analysis day. An Atomic Absorption Spectrophotometer (AAS Varian AA240FS) was used to analyze the presence of the elements in the brain tissue, and the results were calculated as µg/gram tissue.

Statistical Evaluation

Statistics were conducted using the SPSS 21.0 computer package program; arithmetic means and standard deviations of all parameters were calculated. The "Shapiro–Wilk" test was conducted to determine data homogeneity. The data did not have a normal distribution. The Kruskal–Wallis H test was used to detect differences between groups, and the Mann–Whitney test was used to determine which group caused the difference. Considering all parameters, the relations of the groups among themselves were tested with correlation analysis. Differences at the level of $p<0.05$ were accepted as significant.

Results

Element levels in the brain tissue of the study groups

As noted earlier, three kinds of tissue sections were analyzed (brain, brainstem, and cerebellum). In the brain tissue, no difference was detected in the aluminum levels. However, the calcium levels in the vitamin E group (G2) and the vitamin E + penicillin group (G4) were significantly higher than the control group (G1) and the penicillin group (G3) ($p<0.05$). The levels of chrome were lower in the epilepsy groups (G3–4) than in the control group and the vitamin E group (G1–2) ($p<0.05$, Figure 1). Copper, iron, and potassium levels in the brain tissue were not different among the study groups. However, the magnesium levels were higher in the groups that received vitamin E (G2 and G4) than in the control group (G1) and epilepsy group (G3) ($p<0.05$, Figure 2).

No significant difference was detected among the groups in the levels of lead in the brain tissue. Manganese and sodium levels were significantly lower in the first epilepsy group (G3) than in the other groups ($p<0.05$). Zinc levels were found to decrease significantly in the epilepsy groups (G3–4) compared to the control group (G1) and the vitamin E group (G2) ($p<0.05$, Figure 3).

Element levels in the brainstems of the study groups

In the tissue taken from the brainstems, no difference was detected in the aluminum levels. Calcium levels were higher in the vitamin E + penicillin group (G4) than in the other groups ($p<0.05$). Levels of chrome were lower in the epilepsy groups (G3–4) than in the control group (G1) and the vitamin E group (G2) ($p<0.05$, Figure 4).

Iron and potassium values in the brainstem were not different among the study groups. The highest copper level in the brainstem tissue was detected in the first epilepsy group (G3) ($p<0.05$). Magnesium levels in the brainstem were higher in the vitamin E groups (G2 and 4) than in the control group (G1) and the first epilepsy group (G3) ($p<0.05$, Figure 5). No significant difference was detected among the groups in brainstem sodium levels. The levels of manganese and lead levels were significantly higher in the first epilepsy group (G3) than the other groups ($p<.05$). Zinc in the brainstems of the epilepsy groups (G3–4) declined significantly compared to the control group (G1) and the vitamin E group (G2) ($p<0.05$, Figure 6).

Element levels in the cerebellum tissue of the study groups

There was no difference in the aluminum levels in the cerebellum tissue of the study groups. Calcium levels were higher in the epilepsy groups (G3–4) than in the other groups ($p<0.05$), while chrome levels were lower in the epilepsy groups (G3–4) than in the control and vitamin E groups (G1–2) ($p<0.05$, Figure 7).

Iron and magnesium values in the cerebellum did not differ across the study groups. The highest copper levels in cerebellum tissue were detected in the first epilepsy group (G3) ($p<0.05$). Potassium levels were lower in the epilepsy groups (G3–4) than in the control group and the vitamin E group (G1–2) ($p<0.05$, Figure 8).

There was no significant difference in manganese levels in cerebellum tissue among the groups. Sodium and lead levels were significantly higher in the first epilepsy group (G3) than the other groups ($p<0.05$). Zinc in the cerebellum tissue declined significantly in the epilepsy groups (G3–4) compared to the control group (G1) and the vitamin E group (G2) ($p <0.05$, Figure 9).

Discussion

Calcium and magnesium levels in all three types of brain tissue were significantly higher for the groups that received vitamin E (G2–4) compared to the control group (G1) and the first epilepsy group (G3), while the levels of chrome and zinc declined significantly in the epilepsy groups (G3–4) compared to the other groups.

Temporal lobe epilepsy (TLE) is the most common epilepsy in adults. It is characterized by hippocampal sclerosis and neurodegeneration (Blumcke et al., 2012). Vitamin E and its family include strong anti-oxidants, which may protect cell membranes from oxidative damage (Ulatowski and Manor, 2013). Moreover, vitamin E has been shown to inhibit neurological stress seizures generated by iron chloride, hyperbaric oxygen, and penicillin (Kozan et al., 2007). Recovery from phenytoin-related hematotoxicity and oxidative stress from applying vitamin E supplements to rat brains was reported by Owoeye et al., (2014). It is already known that anti-oxidant activity and the production of free radicals are suppressed in epilepsy patients (Menon et al., 2014). This suggests that vitamin E and its family could be advantageous for epilepsy patients—at least their ability to prevent oxidative damage (Kiasalari et al., 2016).

Our aim in this study was not to investigate the anti-oxidant properties of vitamin E supplements in treating epilepsy, but how vitamin E affected the metabolism of elements that are changed by epilepsy. The levels of calcium and magnesium in the vitamin E groups (G2 and 4) were found significantly higher than in the first epilepsy group (G3) in the study. In our med-line searches, we did not find any study on the way that the application of vitamin E affects the metabolism of elements in epilepsy. Ulas and Cay (2011) showed that vitamin E supplements in ovariectomized rats restored calcium and magnesium levels. Patlar et al., (2011) showed that vitamin E supplements produce an increase in calcium and magnesium, and vitamin E may affect the metabolism of element in elite athletes. Interestingly, decreased bone mineral density and hypocalcemia, hypophosphatemia, and vitamin D deficiency – which are biochemical bone mechanism anomalies – were reported in adult epileptic patients (Razazizan et al., 2013). However, it has also been claimed that these conditions might be the side effect of the drugs used to treat epilepsy (Razazizan et al., 2013). Vitamin D deficiency was found to be common in a study on pediatric epilepsy patients, starting from the point that anti-epileptic drugs may cause complications in bone and vitamin D metabolism (Nakhaee Moghadam et al., 2018).

Although how epilepsy affects bone metabolism is not the subject of our study, reports that investigated the relationship between vitamin E, calcium, and bone metabolism showed that bone loss in epilepsy may be prevented by taking vitamin E supplements. We did not find any articles with which to perform a one-to-one comparison with the increased calcium levels we found in the vitamin E groups in our study. Based on our findings, however, we can at least state that applying vitamin E caused a change in calcium levels in the brain tissue sections (brain, brainstem, and cerebellum) in epileptic rats.

Yuen and Sander, (2012) emphasized the relationship between magnesium and the seizures that occur in epileptic patients, so low levels of magnesium have become a common method for forming spontaneous epileptic form discharges in hippocampal sections in rats. Thus, it is suggested that magnesium supplements may decrease epileptic seizures (Yuen and Sander, 2012). Parallel to this, Osborn et al., (2016) remarked that magnesium deficiency can be an important risk factor for epilepsy. Apart from its known anti-oxidant functions, it was claimed that vitamin E could play a direct role in the regulation of hippocampal neurogenesis (Cecchini et al., 2013). When considered together with the studies discussed above, the increased levels of magnesium we developed in brain tissue by applying vitamin E can be seen as an important and original result. It can be stated that the increased levels of magnesium in the brain tissue sections (brain, brainstem, cerebellum) from applying vitamin E constitutes the first finding of its kind on this subject.

Copper values in brain stems and lead values in cerebellum tissue in the first epilepsy group (G3) were found to be significantly higher compared to other groups in our study. It should be emphasized that high levels of copper may be a factor in epilepsy formation (Prasad et al., 2014). Superficial application of lead on the brain is an experimental epilepsy formation model (Sen et al., 2016). In this respect, this shows that the high levels of lead we found in cerebellum tissue of the first epilepsy group may be at least one factor in epilepsy formation.

Epilepsy is a common neurological disorder characterized by recurrent and spontaneous seizures. It affects 50 million people around the world (Brodie et al., 2012). Anti-epileptic drug (AED) treatment is the preferred approach. Nearly 70% of epilepsy patients can reach long-term remission using available anti-epileptic drugs (Brodie et al., 2012). This means that only 30% of patients are likely to have drug-resistant seizures (Brodie et al., 2012; Perucca and Gilliam, 2012). Moreover, AEDs have many side effects such as gastrointestinal diseases, lethargy, rashes, and rare but potentially fatal anti-convulsant hypersensitivity syndrome (Perucca and Gilliam, 2012). New treatments are still needed for epilepsy. Zinc seems to both inhibit and increase neuronal stimulability. This raises the possibility that zinc might have both pro- and anti-convulsant properties (Khan, 2016). Thus, zinc homeostasis in the brain can be important for seizure formation (Khan, 2016). In some studies, zinc demonstrated an anti-convulsant effect, but it has a pro-convulsant effect based on seizure type, animal types, and convulsant agents (Barry-Sterman, 1986). Systemic loads of zinc demonstrated an anti-convulsant character in some experimental models (Barry-Sterman, 1986). Deficiencies in the levels of plasma zinc were found to be related to human epileptic disorders (Kim et al., 2012). Moreover, studies of epilepsy representation models suggest that seizure activity might be controlled through zinc application (Kim et al., 2012). However, pathways binding synaptically released zinc to the regulation of seizure activity have not yet been understood enough (Khan, 2016). Many studies have shown that epileptic seizures increase hippocampal neurogenesis in adults (Khan, 2016). Zinc does not prevent neurodegeneration from metal ion bonding, but it decreases the proliferation of seizure-induced progenitor cells and neurogenesis. Zinc has an important role in modulating hippocampal neurogenesis following a seizure (Barry-Sterman et al., 1986; Khan, 2016; Kim et al., 2012).

In our study, the levels of chrome and zinc in brain tissue sections (brain, brainstem, cerebellum) significantly declined in the epilepsy groups (G3–4) compared to the other groups. Some trace elements are required for normal nervous system development. Changes in the serum levels of these elements may cause different diseases to develop, including epilepsy. In a study based on this point, it was stated that serum zinc of 200 epilepsy patients was found to be lower than in healthy controls (Prasad et al., 2014). Epilepsy patients were also separated into groups that were responsive and non-responsive

to anti-epileptic drugs. The serum zinc levels of the group that did not respond to anti-epileptic drugs were found to be significantly lower than in the responsive patients. That same study showed that patients with idiopathic intrac epilepsy (IIE) had lower zinc levels (Prasad et al., 2014). Based on the fact that serum zinc levels were significantly lower in epileptic patients with fever seizures compared to controls, it was suggested that restoring zinc levels could play a strategic role in planning the treatment of epilepsy patients (Saghazadeh et al., 2015). However, it is the dose-dependent effects of zinc in relation to epilepsy that should be considered here (Baraka et al., 2012). Baraka et al., (2012) found that seizures caused by pilocarpine were exacerbated in high-dose zinc pretreatment. Nevertheless, whether alone or in combination with valproic acid, one average dose of zinc decreased the severity of limbic seizures caused by pilocarpine. Moreover, alone or combined with valproic acid, zinc improved all the biochemical parameters examined (Baraka et al., 2012). As a result, given its clear neuromodulative effects, which are quite complicated, whether zinc becomes preventative or excitative may depend on circumstances (Baltaci et al., 2019; Elsas et al., 2009; Doboszewskaet al., 2019). Zinc treatment was reported to have a pro-convulsant activity during epileptic seizures and to increase the permeability of the blood-brain barrier. It is likely that it did this by changing the pro-oxidant/antioxidant balance and neuronal stimulability during seizures (Yorulmaz et al., 2013).

In a study of trace elements and oxidant stress conditions of intrac pediatric epilepsy patients compared to healthy controls, increased oxidant stress and decreased serum zinc levels were reported in the patient group. Based on this point, it was concluded that zinc could play a significant role in epilepsy pathogenesis (Saad et al., 2014). In a study on pediatric epilepsy patients, it was reported that epilepsy decreased zinc and chrome concentrations in all patients, including boys and girls. Starting from these findings in the same study, it was emphasized that the condition of trace elements should be observed in pediatric epileptic patients (Wojciak et al., 2013). In our study, the decreased levels of zinc and chrome found in the brain, brainstem, and cerebellum tissues of the epilepsy groups (G3–4) compared to the control group and the vitamin E group were compatible with the limited number of reports on the subject.

Conclusion

Findings from the study showed that experimental epilepsy changed the metabolism of elements in the brain tissue sections of rats. Application of Vitamin E in experimental epilepsy may have a limited regulatory effect on the metabolism of elements in brain tissues. Decreased zinc levels that we found in brain, brainstem, and cerebellum tissues in the epilepsy groups (G3–4), compared to the control group and the vitamin E group, constitute another result of our study which should be emphasized. Decreased zinc levels in these tissues may play a critical role in epilepsy pathogenesis.

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Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no potential conficts of interest to disclose.

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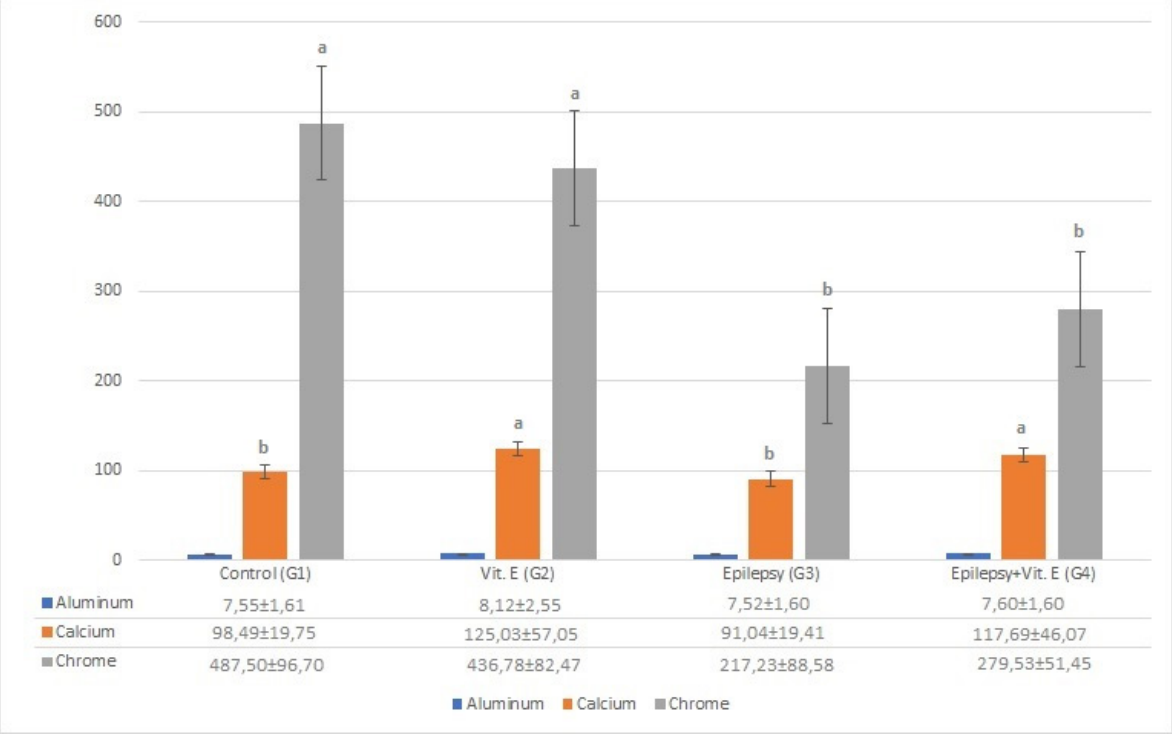

Fig. 1 - Comparison of Brain Aluminum, Calcium and Chrome Levels in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

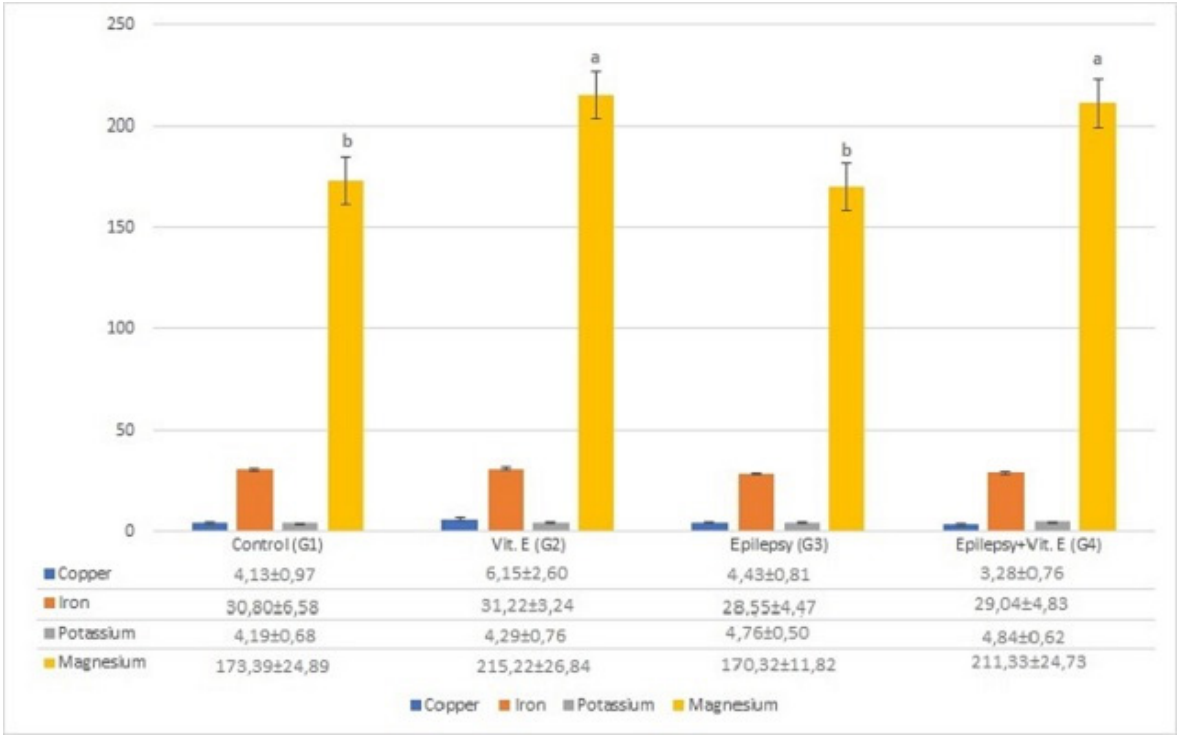

Fig. 2 - Comparison of Copper, Iron, Potassium and Magnesium Levels in Brain Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

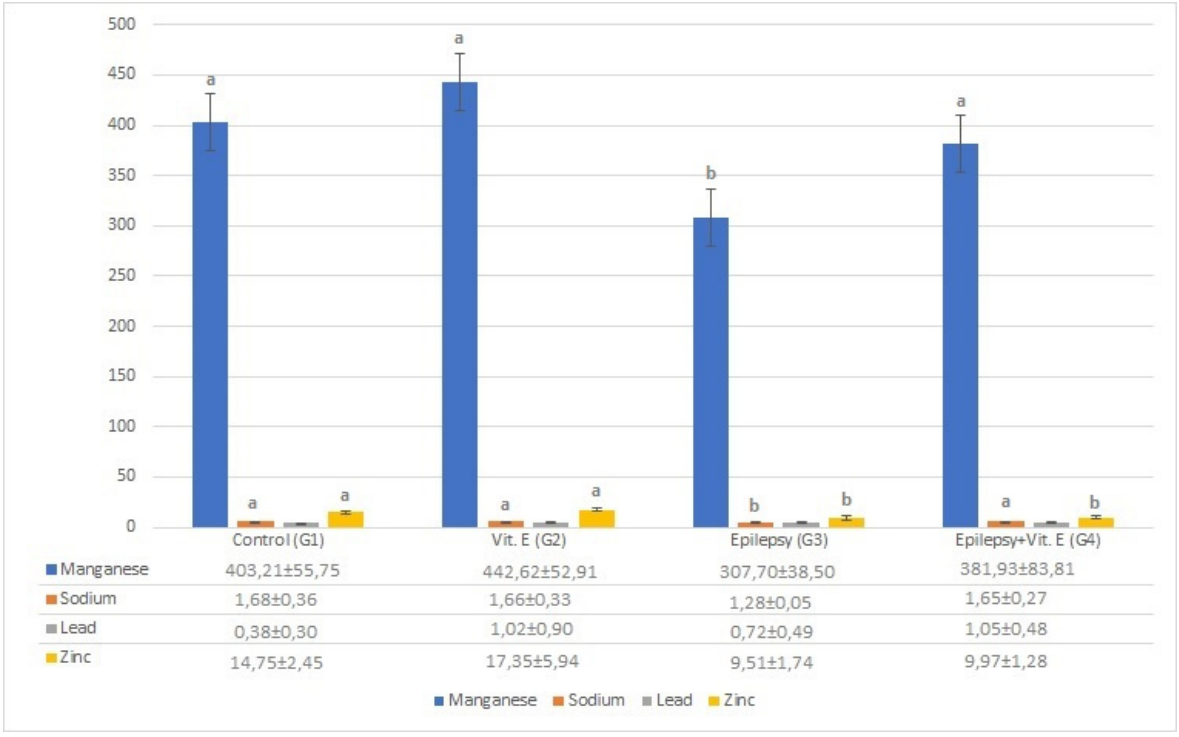

Fig. 3 - Comparison of Manganese, Sodium, Lead and Zinc Levels in Brain Tissue in Experimental Groups, (µg/gram tissue) a>b ($p<0.05$).

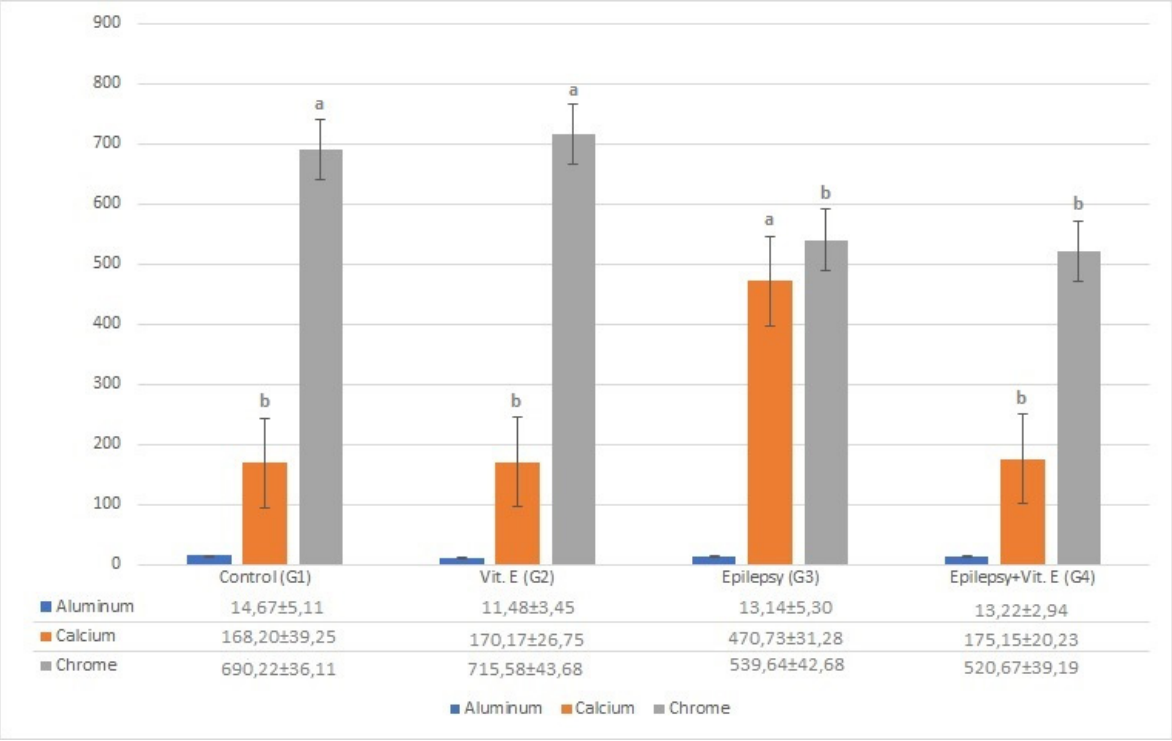

Fig. 4 - Comparison of Aluminum, Calcium and Chrome Levels in Brainstem Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

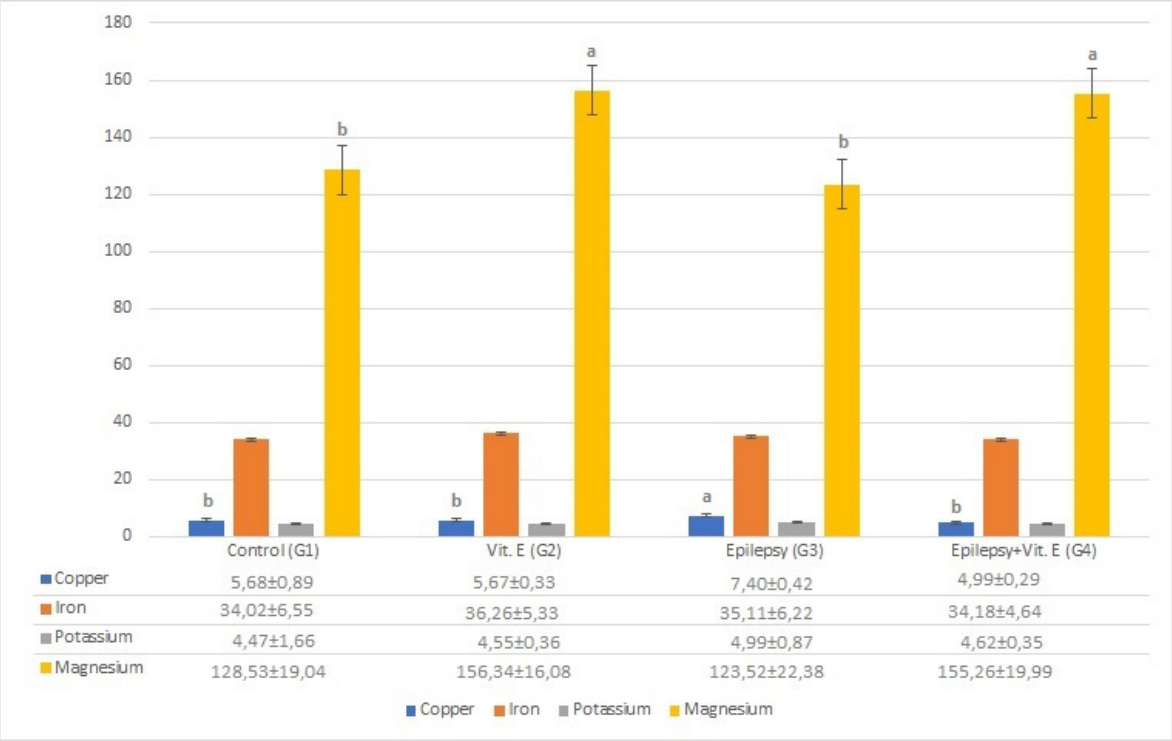

Fig. 5 - Comparison of Copper, Iron, Potassium and Magnesium Levels in Brainstem Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

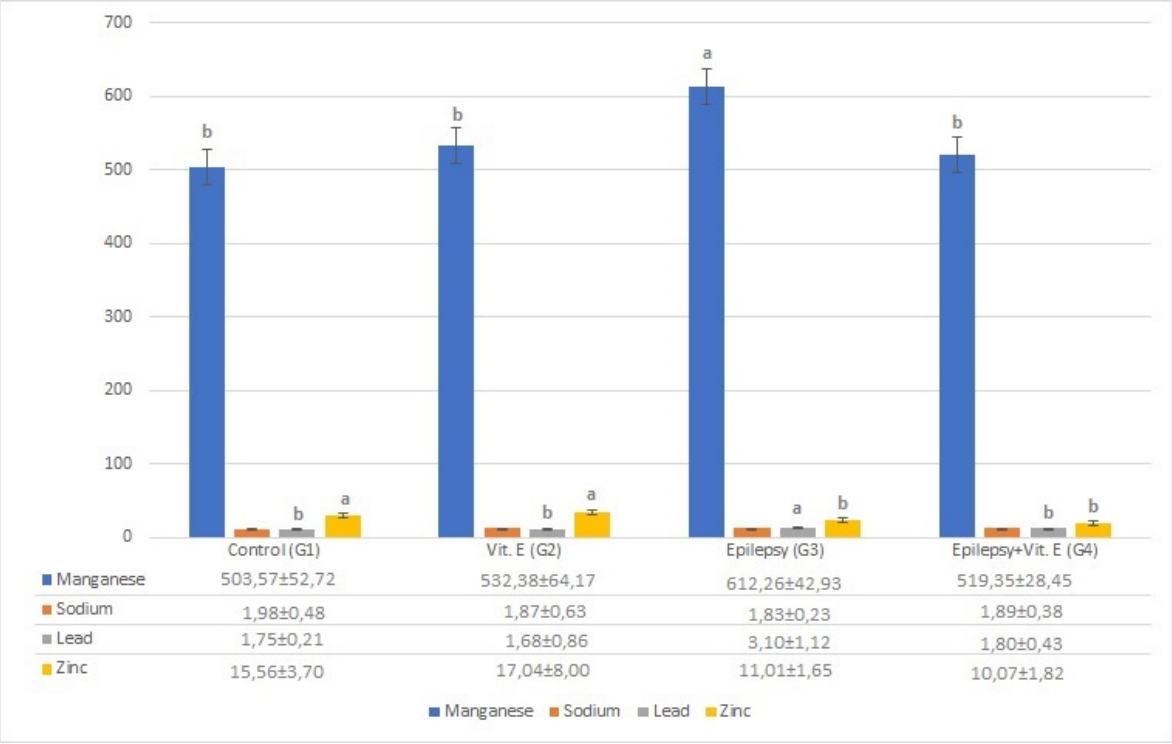

Fig. 6 - Comparison of Manganese, Sodium, Lead and Zinc Levels in Brainstem Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

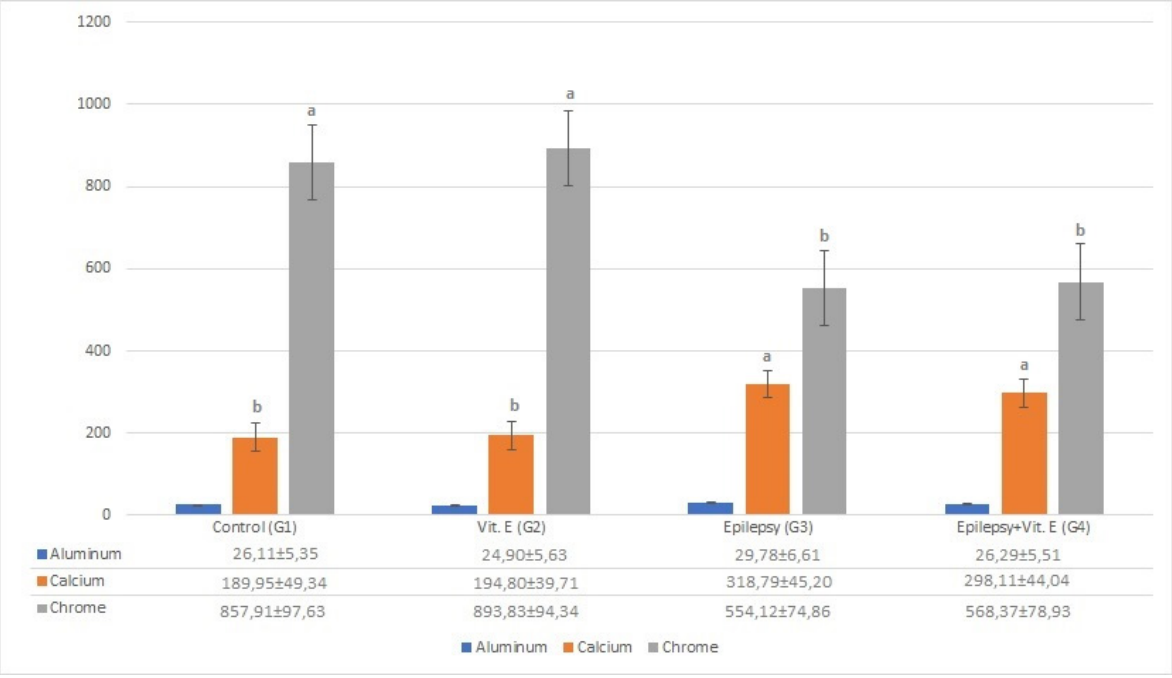

Fig. 7 - Comparison of Aluminum, Calcium and Chrome Levels in Cerebellum Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

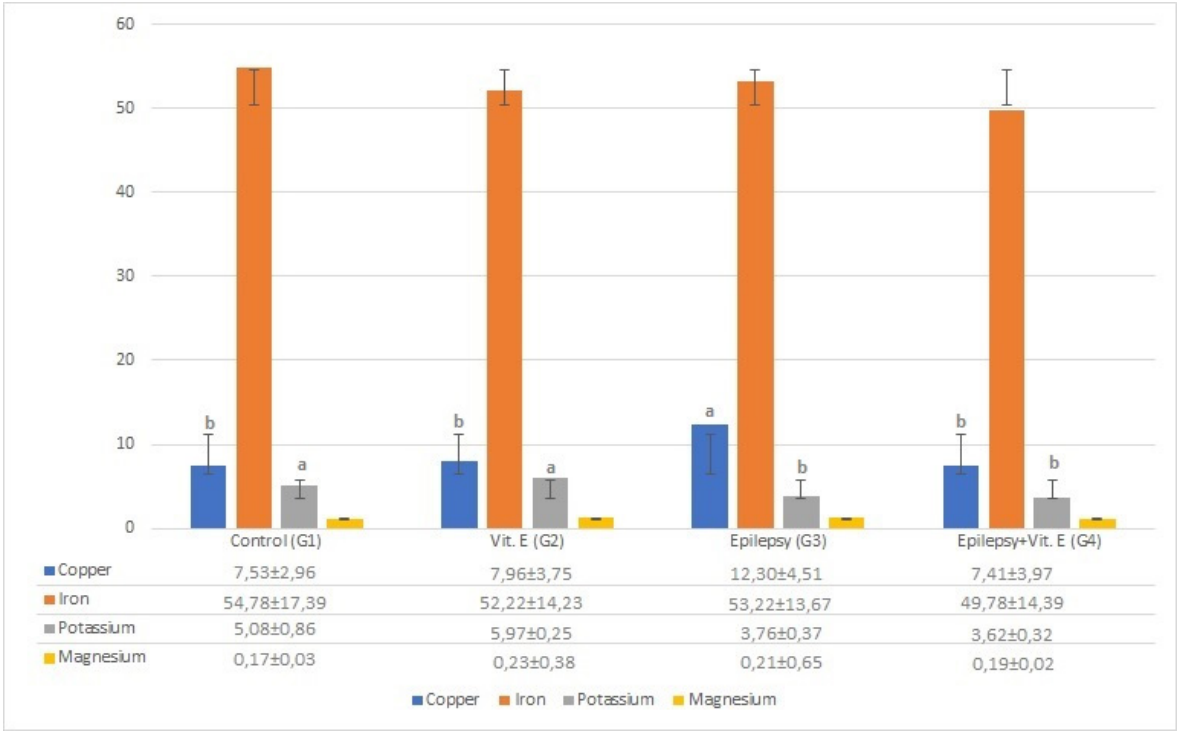

Fig. 8 - Comparison of Copper, Iron, Potassium and Magnesium Levels in Cerebellum Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).

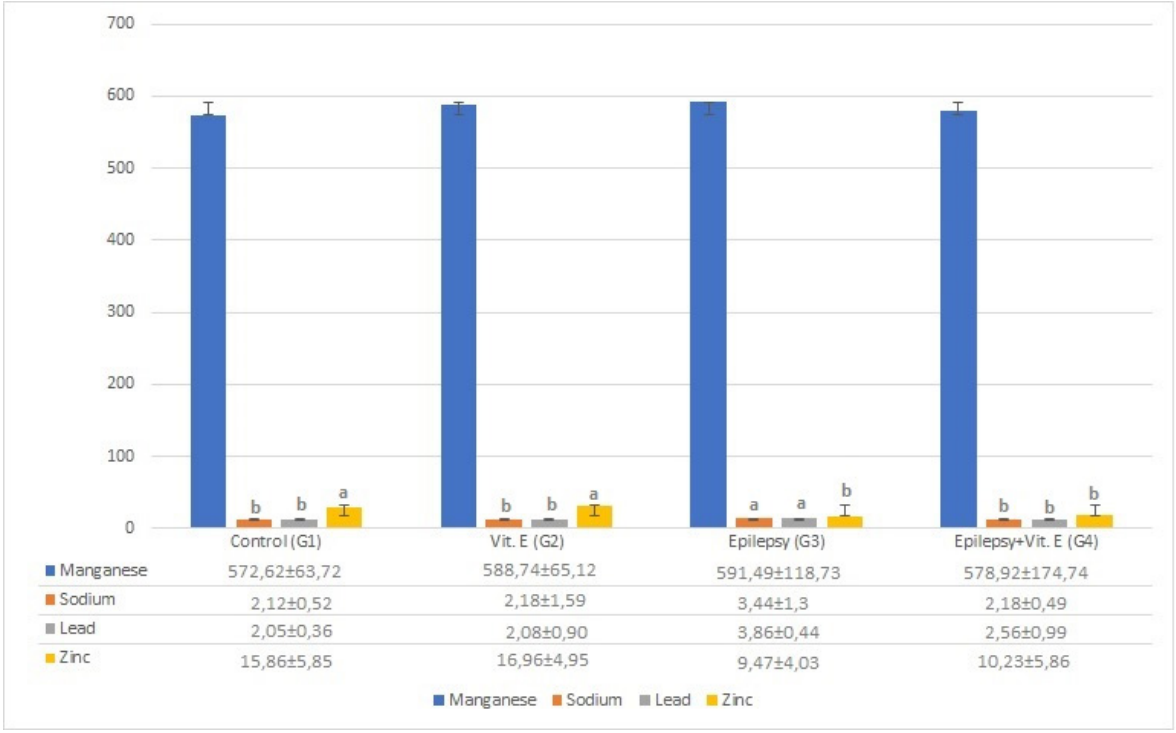

Fig. 9 - Comparison of Manganese, Sodium, Lead and Zinc Levels in Cerebellum Tissue in Experimental Groups (µg/gram tissue) a>b ($p<0.05$).