

Serum and urine boron and selenium levels in children with resistant epilepsy

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ABSTRACT

الأهداف: للبحث عن دور المصل، وسلينيوم البول، ومستويات البول في الأطفال الذين تم تشخيصهم بصرع مقاوم.

الطريقة: تم دراسة مستويات البول، وسلينيوم البول في 53 حالة (32 ذكور، 21 أنثى) تم تشخيصهم بصرع مقاوم خلال الفترة من أبريل 2006م حتى فبراير 2007م بقسم أعصاب الأطفال، جامعة إرجيس، قيصري، تركيا. تم تقسيم الاختلافات بين المجموعات باستخدام اختبار تي. عرفت البيانات الرقمية بنسب مئوية، والاختلافات داخل المجموعات تم قياسها باختبار كاي. وتم تقدير القيمة الإحصائية أقل 0.05 قيمة إحصائية مهمة إحصائية.

النتائج: حينما تم تقييم مستويات مصل السلينيوم، والسلينيوم البولي، ومستويات البول كمجموعة الشاهد، وجد أن هنالك اختلاف إحصائي في مصل السلينيوم، والسلينيوم البولي، ومستويات البول البولية $p < 0.05$ ، بينما لا يوجد أي اختلاف إحصائي في مستويات المصل البوري ($p > 0.05$).

خاتمة: أظهرت هذه الدراسة الحاجة إلى مكملات السلينيوم في علاج المرضى الذين يعانون من صرع مقاوم بينما لم يظهر أي دور سببي للبور.

Objectives: To determine the role of serum and urine selenium, and boron levels in children with resistant epilepsy.

Methods: Serum and urine boron and selenium levels were studied in 53 cases (32 boys and 21 girls) diagnosed with resistant epilepsy between April 2006 and February 2007 at the Department of Pediatric Neurology, Erciyes University, Kayseri, Turkey. Differences between groups were assessed using Student's t-test. Countable data were defined as percentage. Inter-group difference was assessed by Chi-square test. P-values less than 0.05 were considered significant.

Results: When serum and urine boron and selenium levels were evaluated and compare with controls, a statistically significant difference was found in serum selenium, urine selenium, and urine boron levels ($p < 0.05$). No significant difference was found in serum boron levels ($p > 0.05$).

Conclusion: It was observed that there is a need for selenium supplementation in treatment of patients with resistant epilepsy, while no etiologic role is observed for boron.

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Boron (B), which is essential for animals and humans, affects functions of cell membrane; thereby, activity of many metabolic enzymes.¹ It was found that B had several beneficial effects for human body.^{2,3} It was shown that it has important effects on metabolisms of steroid hormones, calcium, magnesium, and vitamin D, energy utilization, immune functions, and plasma lipid profiles.⁴ In addition, it was also found that it plays an important role on regulation of body minerals, including calcium and vitamin D, and protects bone texture by preventing calcium and magnesium depletion.^{4,6} Moreover, it also known that it contributes learning capacity and school skills and it is necessary for sportive performance and athletic physique in children.^{1,7,8} Selenium (Se), which behaves as a potent anti-oxidant and cytoprotective agent together with

vitamin E, is essential for normal brain development and functions.^{9,10} A low Se level is linked to senility and cognitive disorders in elder population.¹¹ Addition of Se to the treatment of resistant epilepsy reduces severity and number of epileptic seizures.¹²⁻¹⁴ In experimental studies, it was shown that Se administration to rats with induced epilepsy significantly reduced epileptic attacks.¹⁵ In the present study, it was aimed to determine whether B and Se play role in etiology of resistant epilepsy by measuring serum and urine B and Se levels in children with resistant epilepsy; and to determine whether or not epileptic seizure recover by replacement therapy in patients with low serum B and Se levels in further evaluations.

Methods. The study protocol was approved by the Medical Ethics Committee of Erciyes University Medical Faculty. Our medical research involving human subjects is according to the principles of Helsinki Declaration. The present study was conducted between April 2006 and February 2007 in 53 cases (32 boys and 21 girls) with ongoing convulsion, despite 2 or more anti-epileptic agent were followed and diagnosed as resistant epilepsy at the Pediatric Neurology Department, Erciyes University, Kayseri, Turkey and 32 healthy controls. Patients were divided into 2 groups according to the number and duration of medication and compared to control groups (Table 1). All parents were informed about the study and consent was obtained to take blood and urine samples.

Blood samples were drawn (5 cc) to heparinized syringes from children in resistant epilepsy group, then samples stored in Eppendorf tubes at -20°C following separation of plasma. Urine samples also stored in Eppendorf tubes at -20°C. A 500 µL serum sample was mixed with an oxidizing acid mixture containing 1 mL, nitric acid 0.7 ml, and hydrogen peroxide 0.3 mL.¹⁶⁻¹⁸ Concentrated nitric acid (65% HNO₃), suprapur quality (Merck, Darmstadt, Germany), hydrogen peroxide H₂O₂ (Merck) and water with purified to level 18.2 MΩ cm in a Milli-Q System 8 Millipore direct-Q3 UV, Bedford, MA, USA) were used. The serum and urine samples were prepared using microwave digestion (CEM MARS-5, CEM Corporation, Matthews, NC, USA). In the present study, measurement of B and Se elements were performed using Agilent 7500a-inductively coupled

plasma mass spectrometer (Agilent 7500a, UK).^{16,17} This calibration method was used for the measurements. Rates were obtained by dividing the counts of calibration and sample solutions to counts of internal standards were considered as analytic signal. The standard used to make calibration was Agilent-Multi Element Calibration Standard-2A-Part 8500-6940 (Agilent Technologies, New Castle, USA). Diluted serum and urine samples were taken into 10 ml sample container; then placed into auto-sampler with calibration and internal standard solutions and analysis were carried out. The obtained signals were put on their places in the calibration line and those concentrated samples were calculated using computer software (a computer program which control to the ICP-MS instrument and process the data for sample analysis). Figure 1 shows the calibration graphic.

Statistical analysis. Parameters measured in samples from study groups were assessed by using SPSS Version 10.0 for Windows. Normality of quantitative data was analyzed by Kolmogorov-Smirnov test; and abnormally distributed data were defined as median (min-max). Kruskal-Wallis variance analysis was applied to analyze the difference between the 3 groups. Difference was assessed by using Mann-Whitney U test with Bonferroni correction. Normally distributed data were defined as mean±SD. Differences between groups were assessed using Student's t-test. Countable data were defined as percentage. Inter-group difference was assessed by Chi-square test. P-values less than 0.05 were considered significant.

Results. Of the cases who were receiving anti-epileptic therapy, 26 cases older than 9 years, were classified as Group 1, while 27 cases younger than 9 years were considered as Group 2. Thirty-two healthy cases were also divided into 2 control groups as either older or younger than 9 years (Table 1). Thirty-five cases received 2 and 3 anti-epileptic agent, whereas 18 cases received 4 and 5 anti-epileptic agent. Anti-epileptic agents were carbamazepine (CBZ), valproic acid (VPA). Triple anti-epileptic regimes included CBZ, VPA, Topiramate (TPM), Lamotrigine (LTG), oxcarbazepine (OXZ), Levetiracetam (LVT), Clonazepam (CLN), Clobazam (CLB), Phenobarbital (FB) and Fenitoin (FE).

No low values of calcium and magnesium were detected in any of the cases in study groups. When serum and urine selenium and B levels were evaluated, as to controls, a statistically significant difference was found in serum selenium, urine selenium and urine B levels of group 1 and 2 ($p < 0.05$). No significant difference was found in serum B levels ($p > 0.05$) (Table 2).

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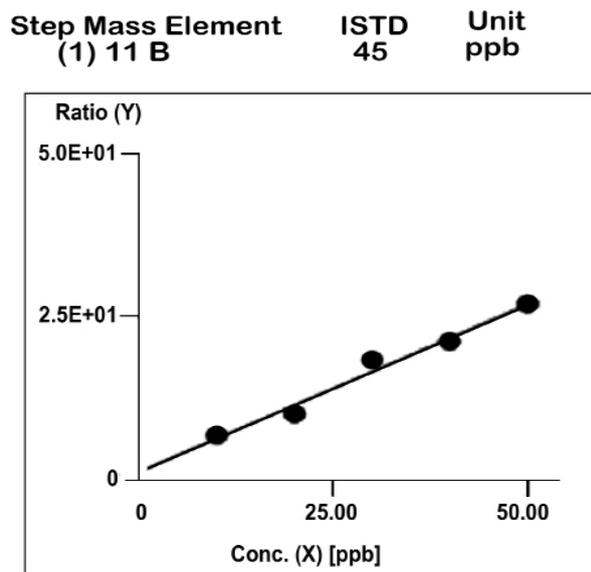


Figure 1 - The calibration graphic of ¹¹B isotope. Y scale of the graph is the ratio of ¹¹B counts and internal Standard counts. X scale of the graph is the concentration of ¹¹B in Standard solutions. Its unit is ppb (µg L⁻¹). ISTD - isotopic mass of internal standard. ⁴⁵Sc - Scandium

Discussion. Since the role for metabolism of essential elements are known in treatment and pathophysiology of epilepsy, studies regarding whether anti-epileptic agents impair metabolism of essential elements were performed for long. Controversial outcomes were found in these studies.^{9,19,20} Boron accumulates at bone tissue, but not soft tissues. We observed in the animal testing who received high dose or long term B: acute neurological disorders, diarrhea, anorexia, weight loss, testicular atrophy (in mice, rats and dogs), reduction at fetal body weight, increase in skeletal malformations and cardiovascular defects in pregnant females.^{21,22} However, there are limited human data in this issue.²³ In Japan, Usuda et al²⁴ measured serum B levels in 980 healthy cases by Inductively Coupled Plasma Optical Emission Spectrometer (ICPOES) and found reference intervals as 33.3-191.2 µg/L for men and 29.5-154.9 µg/L in women. It was observed that B levels are increasing, particularly in group below 49 years old and a plateau occurred at the age group 50-69 years. In America, Imbus et al²⁵ studied urine and serum B levels in healthy volunteers and found mean urine and serum B levels as 40-6600 µg/L 715 µg/L (40-6600 µg/L) and 98.5 µg/L (39-365 µg/L). Mauras et al²⁶ found serum B levels as 9.7-28.1 mg/L, Minoia et al²⁷ found mean serum B level as 1890 µg/L, and urine B level as 470-7800 µg/L, while Chao et al²⁸ found mean urine B levels as 798 µg/L and Usuda et al²⁹ found mean

Table 1 - Age and gender distribution according to groups among children with resistant epilepsy.

Groups	Age (year) mean±SD	Gender Male/Female	Number of participants
Group I	12.76 ± 2.76	14/12	26
Group II	5.89 ± 1.47	18/9	27
Group III	12.37 ± 2.27	9/7	16
Group IV	6.63 ± 1.31	9/7	16

Table 2 - The level of selenium and boron according to groups among children with resistant epilepsy.

Parameters	Group 1 n=26	Group 2 n=27	Group 3 n=16	Group 4 n=16	P-values
Serum Se (µg/L)	29.5 (23-39)	28 (24-42)	60 (40-93) ^{ab}	46 (34-84) ^{ab}	0.001
Urine Se (µg/L)	27.0 (21-45)	27 (23-37)	62.5 (36-84) ^{ab}	54 (44-78) ^{ab}	0.001
Serum B (µg/L)	37.5 (26-126)	45 (27-176)	56 (34-100)	50.5 (32-85)	0.18
Urine B (µg/L)	37.0 (23-482)	48 (24-105)	312 (150-435)	281 (93-466) ^{ab}	0.001

Date are expressed as as median (minimum - maximum). ^aindicates the group which is different from Group 1. ^bindicates the group which is different from Group 2. Se - Selenium, B - Boron

urine B levels as 798.0 µg/L (398-1600) in male adult electronic workers. In our study, we found serum B levels as 37.5 µg/L (26-126 µg/L) in Group 1 and 45 µg/L (27-176 µg/L) in Group 2, while 43 µg/L (32-100 µg/L) in the control group. We found urine B levels 37 µg/L (23-482 µg/L) in Group 1 and 48 µg/L (24-105 µg/L) in Group 2, while 334 µg/L (187-466 µg/L) in the control group. These findings were similar to others in terms of serum B levels, but urine B levels were found lower. This could be explained by absence of sufficient number of samples or by B levels have not been studied in children yet. Furthermore, no significant difference was observed between study and control groups in cases with resistant epilepsy. Similar B levels in cases with resistant epilepsy. It shows that B is not a factor in etiology of resistant epilepsy in the control group.

It was shown that B regulates steroid hormones; prevents calcium loss and bone demineralization; declines calcium and magnesium excretion; and increases calcium absorption. In experimental studies, it was found that B relieves characteristic findings of vitamin D deficiency. It would be more appropriate to assess B together with calcium, magnesium, and vitamin D. Plasma Se level varies by age.³⁰ It tends to decrease by the third day of life; which accepted as basal value. Plasma Se level continues to decrease until month 4 of life. It reaches 90% of adult level at age 10. Normal value is 40-100 ng/ml in newborns, while it varies between 50

and 150 ng/ml in adults.³¹ Coskun et al³² found mean Se level as 28.49±4.51 µg/L in newborns, Hincal et al^{31,33} found 45±10 µg/L in cord blood, 69±13 µg/L at 2-12 months; 77±12 µg/L between 12 months and 18 years of age, 74.16 µg/L between 18 and 48 years of age; and Yurdakok et al³⁴ found 43.73±4.7 ng/ml at 2-12 months of life. In Ankara, Hincal et al³³ found mean serum Se level as 74.2±15.6 µg/L in 71 healthy adults. Gurgoze et al³⁵ found serum Se level as 56.0±17.0 µg/L in healthy children. Mengubas et al³⁶ determined serum Se level as 44±2 µg/L in healthy children between 2 and 4 years old. Gurgoze et al³⁵ found Se level as 33.6±8.2 µg/L in children with iron deficiency anemia. In studies on healthy subjects, plasma Se level was found 58 ng/ml in Slovakia,³⁷ 62.10 ng/ml in healthy children of migrants between 2 and 5 years old in France³⁸ and 48-184 ng/ml at age 1-10 in the United States.³⁹ Serum Se measurements in various European countries revealed a mean level of 85 µg. Lowest Se levels were seen at China, New Zealand, Sweden, Finland, and North Germany, while highest levels at USA, Canada, and Venezuela.^{39,40} In those studies, the measured serum Se levels in the control group were 60 ng/ml in Group 3 and 46 ng/ml in Group 4. These values were similar to the studies in our country, but lower than the USA, Canada, France, and other European countries. Selenium status of Turkish children is found to be lower than that found in the literature; marginal Se deficiency could be important in the development of some Se deficiency; however, could be important in the development of some Se deficiency related diseases.³⁶ There is a need for extension of this study to healthy children from different regions in Turkey and to different disease states. In case reports, Weber et al¹² demonstrated that there is a severe reduction in serum and glutathione peroxidase levels in 4 children with resistant epilepsy and recurrent infections. Ramaekers et al¹³ showed a control on epilepsy by giving Se to 2 children younger than one year old with resistant epilepsy. They also found that convulsions reoccurred by cessation of Se and controlled by re-administration. An association was shown between Se and convulsions which occurred in patients receiving total parenteral nutrition. It was found that risk of convulsion was lower in formulations including Se. Selenium forms a defense mechanism by stopping neuronal damage and impaired oxidative stress.⁴¹ Some anti-epileptic drugs (AEDs) may alter trace element metabolism and free radical scavenging enzyme activities in humans and experimental animals. Recent studies suggest that membrane lipid peroxidation may be causally involved in some forms of epilepsies, and the decreased free

radical scavenging enzyme activity is believed to cause the increased risk of an idiosyncratic drug reaction encountered in the management of epilepsy. Two of the seleno-dependent enzymes glutathione peroxidase (GPX) and phospholipid hydroperoxide glutathione peroxidase (PHGPX) are speculated to play a key-role in the defence of neuronal cells against oxygen radical formation and peroxidative processes.¹³ Ashrafi et al¹⁴ detected serum Se levels as 68.88±17.58 ng/mL and 85.93±13.93 ng/mL in resistant epilepsy (with a mean age of 54 months) and control groups. Selenium levels were significantly low in the resistant epilepsy group. Ashrafi et al¹⁴ emphasized that serum Se levels should be measured in patients with resistant epilepsy; and if there is a deficiency, it should be replaced. Mahyar et al⁴² found a significant difference between patients with febrile convulsions and controls those having fever but not convulsion; thereby, proposed that selenium might have role in etiology of simple febrile convulsions. In our study, we found serum Se level as 29.5 µg/L (23-39 µg/L) in Group 1 and 28 µg/L (24-42 µg/L) in Group 2, while 42 µg/L (34-89 µg/L) in the control group. As in resistant epilepsy group of Ashrafi et al,¹⁴ our findings also showed lower levels in study group than control group. Navarco-Alarcon et al⁴³ studied serum and urine Se levels in patients with diabetes and found significantly lower levels than controls. Selenium levels were 64.9±22.8 µg/L in diabetic group, whereas 74.9±27.3 µg/L in the control group. In our study, we found urine Se levels as 27.0 µg/L (21-45 µg/L) in Group 1, 27 µg/L (23-37 µg/L) in Group 2 and 54 µg/L (36-82 µg/L) in control group. We found a significant difference in urine Se levels between study and control groups, whereas no significant difference between urine and serum Se levels. Although Se values were similar to those previously found in Turkey, control groups were detected at low range as to European countries. A lower level of serum Se in Groups 1 and 2 than controls suggests that Se can contribute to the development of resistant epilepsy. Lower Se levels than previous studies in controls could be explained by low Se levels by Kayseri.⁴⁴ Our study have similarities to the study of Ashrafi et al¹⁴ who evaluated same issue; and we detected a significant difference between study and control groups.

Study limitations. The factors limiting our study are unknown levels of nutrition and levels of B and Se before the anti-epileptic treatment. We did not evaluate the treatment of cases in low Se levels.

In conclusion, similar B levels in cases with resistant epilepsy and controls showed that B is not a factor in etiology of resistant epilepsy. It seems that further

prospective, double-blinded studies aiming to compare response to anti-epileptic agents, and convulsion frequency before and after Se supplementation are needed. If a relationship between resistant epilepsy and Se deficiency, Se supplementation should be a part of treatment in resistant epilepsy. Determining serum Se level can be helpful in diagnosis.

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