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# Serum Levels of Trace Elements and Heavy Metals in Patients with Acute Hemorrhagic Stroke

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**Abstract** Trace elements are essential components of biological structures, but alternatively, they can be toxic at concentrations beyond those necessary for their biological functions. Changes in the concentration of essential trace elements and heavy metals may affect acute hemorrhagic stroke. The aim of this study was to measure serum levels of essential trace elements [iron (Fe), zinc (Zn), manganese (Mn), copper (Cu), and magnesium (Mg)] and heavy metals [cobalt (Co), cadmium (Cd), and lead (Pb)] in patients with acute hemorrhagic stroke. Twenty-six patients with acute hemorrhagic stroke and 29 healthy controls were enrolled. Atomic absorption spectrophotometry (UNICAM-929) was used to measure serum Fe, Cu, Pb, Cd, Zn, Co, Mn and Mg concentrations. Serum Cd, Pb and Fe levels were significantly higher in patients with acute hemorrhagic stroke than controls ($p < 0.001$), while serum Cu, Zn, Mg and Mn levels were significantly lower (all $p < 0.001$). However, there was no significant difference between the groups with respect to serum Co levels ($p > 0.05$). We first demonstrate increased Cd, Pb, and Fe levels; and decreased Cu, Zn, Mg, and Mn levels in patients with acute hemorrhagic stroke. These findings may have diagnostic and prognostic value for acute hemorrhagic stroke. Further studies are required to elucidate the roles of trace elements and heavy metals in patients with acute hemorrhagic stroke.

**Keywords** Acute hemorrhagic stroke · Trace element · Heavy metals

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## Introduction

Stroke is recognized as a leading cause of death and severe neurological disability across the world (No authors listed 1990). Ischemic and hemorrhagic stroke are the two primary subtypes of stroke (Adams et al. 1993). A stroke occurs when blood vessels that deliver oxygen to the brain either rupture or become clogged, causing brain cells/neurons to die (Demirdogen et al. 2009). Acute stroke must be considered an emergency of the highest priority. Early brain imaging is essential to discriminate between ischemic and hemorrhagic stroke (Lichy and Hacke 2010). Several conventional risk factors, such as hypertension, diabetes, and genetic factors, have been identified in the etiopathogenesis of stroke (Benmoyal-Segal et al. 2005).

Trace elements at optimal levels are required for numerous metabolic and physiological processes in the human body (Mertz 1981). Moreover, trace metals have important influences on brain development and function (Hickenbottom and Grotta 1998). Zinc (Zn), copper (Cu), and manganese (Mn) are important cofactors for several enzymes that play a role in maintaining DNA integrity (Mahabir et al. 2007; Leach 1971). Cu, Zn, and Mn also act as antioxidants (Shenkin 1997). Moreover, Fe metabolism plays a key role in maintaining normal brain function. Fe is the most abundant transitional metal in the brain, and the brain has higher Fe content than most organs (Moos 2002). Fe is essential for normal neuronal function and activity. The synthesis of several neurotransmitters is Fe-dependent (Beard et al. 1993). On the other hand, magnesium (Mg) is the fourth most abundant cation in the body and plays a pivotal role as an enzyme cofactor in biosynthesis of proteins and mineral administration. Its metabolism is connected with bone health, as it is indispensable for osteogenesis and mineralization of bones (Rahnama and Marcınıak 2002).

The essential trace element cobalt (Co) is an integral part of vitamin $B_{12}$, which is essential for folate and fatty acid metabolism (Anderson et al. 1992). On the other hand, cadmium (Cd) is one of the most dangerous occupational and environmental toxins. It is found in drinking water, atmospheric air, and even food. Products of vegetable origin are the main carrier of Cd compounds in food (Klos 2001). Furthermore, lead (Pb) increases oxidative stress, affects endothelial function, promotes inflammation, downregulates nitric oxide production, and induces renal dysfunction (Sokolov et al. 2002).

Several studies have assessed trace elements such as Zn, Fe, and Cu in cerebral hemorrhage and stroke patients, but the results have been inconsistent (Munshi et al. 2010; Uza et al. 1995). However, to the best of our knowledge, serum levels of heavy metals have not previously been evaluated in patients with acute hemorrhagic stroke.

The aim of this study was to measure the serum levels of essential trace elements (Fe, Zn, Mn, Cu, and Mg) and heavy metals (Co, Cd, and Pb) in patients with acute hemorrhagic stroke.

## Materials and Methods

### Subjects

Twenty-six patients (12 females and 14 males) with acute hemorrhage stroke and 29 healthy volunteers (14 females and 15 males) were enrolled in this prospective study.

Patients admitted to the emergency department were examined neurologically, and they were assessed using the Glasgow Coma Scale (Teasdale and Jenett 1974). The diagnosis was also confirmed via brain computerized tomography.

Patients were examined neurologically. All hemorrhagic stroke patients were treated similarly in the emergency department. The treatment provided depended on the preservation of vital functions and the brain. The intracranial pressure was stabilized by administering intravenous mannitol or furosemide.

The control group was selected from 29 healthy volunteers (14 females and 15 males). All of the control subjects were asymptomatic with unremarkable medical histories and normal physical examinations. All of the control subjects were nonsmokers.

The study protocol was conducted in accordance with the Declaration of Helsinki as revised in 2000 and was approved by the local ethics committee. All of the subjects were informed about the study, and written consent was obtained from each one.

### Exclusion Criteria

Exclusion criteria included a history of alcohol abuse, habitual smoking, intravenous drug abuse, pregnancy, use of antioxidant supplements, hypertension, diabetes mellitus, liver or renal disease, rheumatoid arthritis, pulmonary disease, and coronary artery disease.

### Blood Samples

Blood samples were collected before treatment and were immediately stored at 4 °C. Serum samples were then separated from the blood cells by centrifugation at 3,000 rpm for 10 min. Serum samples prepared for measurement of trace element levels and heavy metals were maintained at −80 °C until they were used.

### Measurement of Trace Elements in Serum

Serum concentrations of Zn, Cu, Fe, Cd, Pb, and Mn were determined via atomic absorption spectrophotometry using a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK).

### Statistical Analysis

The results were expressed as the mean ± standard deviation. Parametric variables were compared using Student's $t$ test. Qualitative variables were assessed using Chi square tests. The results were considered to be statistically significant when the $p$ value was $<0.05$. The data were analyzed using SPSS® for Windows Version 11.0 software.

**Table 1** Demographic characteristics of the two groups in this study

| Parameters | Patients ($n = 26$) | Controls ($n = 29$) | $p$ |
|---|---|---|---|
| Age (years) | 44 ± 6 | 41 ± 3 | 0.211 |
| Sex (female/male) | 12/14 | 14/15 | 0.805 |

Values are mean ± SD

**Table 2** Serum iron, copper, lead, cadmium, zinc, cobalt, manganese, and magnesium levels of the two groups in this study

| Parameters | Patients ($n = 26$) | Controls ($n = 29$) | $p$ |
|---|---|---|---|
| Fe (μg/dl) | 0.63 ± 0.09 | 0.17 ± 0.06 | 0.001 |
| Mg (μg/dl) | 10.70 ± 0.97 | 24.56 ± 1.96 | 0.001 |
| Mn (μg/dl) | 0.11 ± 0.02 | 0.27 ± 0.04 | 0.001 |
| Zn (μg/dl) | 0.13 ± 0.02 | 3.17 ± 0.74 | 0.001 |
| Pb (μg/dl) | 0.98 ± 0.11 | 0.28 ± 0.10 | 0.001 |
| Cd (μg/dl) | 0.06 ± 0.02 | 0.01 ± 0.01 | 0.001 |
| Co (μg/dl) | 0.31 ± 0.22 | 0.36 ± 0.19 | 0.414 |
| Cu (μg/dl) | 2.82 ± 0.58 | 5.58 ± 1.57 | 0.001 |

Values are mean ± SD

*Fe* Iron; *Cu* Copper; *Pb* Lead; *Cd* Cadmium; *Zn* Zinc; *Co* Cobalt; *Mn* Manganese; and Mg Magnesium

## Results

The demographic characteristics of the patients with acute hemorrhagic stroke and the controls are shown in Table 1.

There were no significant differences between the groups with respect to age and gender ($p > 0.05$) (Table 1).

Serum Cd, Pb, and Fe levels were significantly higher in patients with acute hemorrhagic stroke than in controls ($p < 0.001$), while serum levels of Cu, Zn, Mg, and Mn were lower in patients with acute hemorrhagic stroke than in controls (all $p < 0.001$). However, there was no significant difference between the groups with respect to serum Co levels ($p > 0.05$) (Table 2).

## Discussion

The goal of this study was to investigate the serum levels of essential trace elements and heavy metals in patients with acute hemorrhagic stroke. To our knowledge, this is the first study to investigate serum levels of essential trace elements and heavy metals in patients with acute hemorrhagic stroke. We found that serum levels of Cd, Pb, and Fe were significantly higher, but that serum levels of Cu, Zn, Mg, and Mn were significantly lower in patients with acute hemorrhagic stroke than in controls. However, there was no significant difference between the groups with respect to serum Co levels.

Imbalance in the levels of trace elements increases the risk of cerebrovascular disease, particularly in patients with ischemic stroke. Moreover, certain trace elements are necessary for maintaining various aspects of neuronal and glial metabolism. Recently, Zangieva et al. (2013) demonstrated the importance of Mg, Zn, Mn, and Cu for the support of nervous tissue function.

To the best of our knowledge, very little is known about trace element concentrations in cerebral hemorrhage patients (Uza et al. 1995). Uza et al. (1995) reported that cerebral hemorrhage patients have lower levels of Zn than controls. In our study, we found that the decreased levels of Zn in patients with acute hemorrhagic stroke compared to healthy controls, which was consistent with the current literature (Uza et al. 1995).

Uza et al. (1995) also demonstrated that cerebral hemorrhage patients have higher serum Cu levels. In addition, Altamura et al. (2009) reported that Cu levels were elevated in the serum of patients with ischemic stroke. In contrast, we found that the decreased levels of Cu in patients with acute hemorrhagic stroke compared to healthy controls, which was inconsistent with current literature (Uza et al. 1995; Altamura et al. 2009).

Munshi et al. (2010) demonstrated that the serum Zn concentration was lower in stroke patients than in healthy subjects. We found that serum levels of Zn were significantly lower in patients with acute hemorrhagic stroke than in controls. In that study, however, Munshi et al. (2010) reported that no significant differences were detected in serum levels of Cu, or Fe of stroke patients compared to healthy controls (Munshi et al. 2010). In our study, we found that acute hemorrhagic stroke patients appear to have higher Fe levels and lower Cu levels than healthy controls.

Muir and Lees (1995) investigated those serum levels of Mg in patients with intracerebral hemorrhage, as well as patients with neurological diseases. We found that serum Mg levels were significantly lower in patients with acute hemorrhagic stroke than in controls.

Millan et al. (2007) reported that increased body Fe stores are associated with poor outcome after thrombolytic treatment of acute stroke. Pérez de la Ossa et al. (2010) investigated that whether high serum levels of ferritin are associated with poor outcome in patients with intracerebral hemorrhage.

Several investigators have measured the concentrations of some trace elements in patients with Parkinson's disease and Alzheimer disease (Dexter et al. 1989). Dexter et al. (1989) found increased Fe concentrations in the substantia nigra of patients with Parkinson's disease. On the other hand, Forte et al. (2004) reported that the serum level of Fe was normal in patients with Alzheimer disease.

Some studies suggested that serum Cu levels were normal in patients with Parkinson's or Alzheimer disease (Forte et al. 2004; Wenstrup et al. 1990). In addition, in another study of Dexter et al. (1992) reported an increase in

Zn levels in substantia nigra, lateral putamen, and caudate nucleus in Parkinson's disease patients.

In humans, Mn, Fe, Cu, and Zn fulfill decisive functions to maintain human health. Zn, Fe, Mn, and Cu are essential micronutrients incorporated into many metalloenzymes and proteins involved in cell metabolism, production of neurotransmitters, and regulatory pathways controlling oxidative stress (Tapiero et al. 2003). Excessive accumulation or depletion of trace elements may have significant clinical implications, including increased risk of cardiovascular disease, immune deficiency, cancer, and bone disease (Fraga 2005). To cause physiological or pathophysiological effects in the brain, the metals must either traverse the blood–brain barrier to act directly on the neurons or glial cells, or alternatively, they could have an indirect effect. Trace elements might also have indirect effects by influencing the transport or regulation of other substances at the blood–brain barrier. (Bradbury 1992)

Fe is an essential trace element for all organisms that is crucial for normal cell function, and its deficiency, or excess is associated with several disease states. It is known that excess Fe and Fe deficiency also lead to oxidative DNA damage (Dayani et al. 2004).

Mn is essential for normal physiologic function in humans and animals, but is toxic at higher levels of exposure (Bureau et al. 2002). Mn also plays a role in the free radical scavenging activity of superoxide dismutase (SOD).

Cd is a dangerous occupational and environmental toxin that accumulates in humans primarily in the liver and the kidneys (Kowalczyk et al. 2003).

Cu is an essential element that plays a role in the production of hemoglobin, myelin, collagen, and melanin (Aggett 1999). Recent evidence also suggests that adequate uptake of Cu is necessary for normal immune function (Ertekin et al. 2006). Cu deficiency affects various physiological functions that may be important in the immunological defense to pathogenic challenge (Stabel et al. 1993). Cu also functions as a cofactor of SOD and catalase in the antioxidant redox system. (Ozkaya et al. 2011; Kayan et al. 2010) However, Cu is also a highly toxic metal that has been associated with several neurodegenerative disorders (Levenson 2005). Moreover, high blood Cu concentration is thought to be an independent risk factor for cardiovascular disease (Kang 2011).

Zn is an essential nutrient that is a component of several metalloenzymes (Cartwright and Wintrobe 1964). In addition, Zn plays an important role in brain metabolism and has antioxidant and anti-inflammatory properties in the brain (Arslan et al. 2011), protecting cells from free radical injury. Moreover, Zn plays an anticarcinogenic role by stabilizing the structure of DNA, RNA, and ribosomes (Wu et al. 2004). Zn deficiency has been implicated as an explanation for the central nervous system (CNS) symptoms in liver cirrhosis, fetal alcohol syndrome, malabsorption, and acrodermatitis enteropathica. Low serum or plasma concentrations of Zn have been found in patients with multiple sclerosis and in chronic alcoholics with liver disease. High concentrations of Zn have been found in patients with multiple sclerosis and Pick's disease (Dexter et al. 1993).

Organisms have developed mechanisms to utilize vital trace elements such as zinc and copper, while minimizing the toxic influence of heavy metals such as Cd and Pb (Solioz et al. 1994).

Pb serves no useful function in the human body, and its presence in the body can lead to toxic effects. Recent research appears to indicate that even a low level of Pb exposure has a number of negative consequences on health. These consequences include impairment of renal tubular cell function, inhibition of sperm formation, fetal damage, slowing of motor nerve velocity, CNS dysfunction, hypertension, and other cardiovascular diseases (Meller et al. 1992). Pb is an indicator of oxidative stress and affects endothelial function, promotes inflammation, downregulates nitric oxide production, and induces renal dysfunction (Lustberg and Silbergeld 2002). Pb has been shown to permeate the blood–brain barrier. A high Pb level in the human body may lead to irreversible damage to the CNS (Donma and Donma 2002).

Physiological doses of Cd increase endothelial permeability via DNA damage-induced inhibition of endothelial proliferation and cell death induction (Messner et al. 2009). Cd is a ubiquitous toxic heavy metal and, unlike organic compounds, it is not biodegradable, and has a very long biological half-life (Donma and Donma 2002). Based on data from animals and humans, soon after Cd exposure, Cd in blood is present in plasma, whereas later, it becomes bound to erythrocytes (Nordberg 1978). Cd exposure may induce lipid peroxidation in the heart, the lungs, the liver, and the spleen (Manca et al. 1994), as well as increase oxidative stress in tissues (Kirchvink et al. 2006). Cd is an established toxic and carcinogenic heavy metal (Nawrot et al. 2002). Although Cd does not generate free radicals directly, it may contribute to the formation of reactive oxygen species indirectly. Cd has also a role in the inhibition of gene expression and signal transduction (Waisberg et al. 2003).

Co is a natural element found throughout the environment. Co is known to perform a vital role in hemoglobin biosynthesis and is an integral part of vitamin $B_{12}$, which is an essential for folate and fatty acid metabolism (Anderson et al. 1992). Excess Co in the body is characterized by polycythemia (Atasoy et al. 2011). Co may also induce DNA damage and mediate free radical generation (Jomova and Valko 2011).

There were several limitations in the present study. First, this study is cross-sectional in nature. Second, the number of patients with acute hemorrhagic stroke who were included in the study was relatively small, and a larger sample size would have increased the power to detect differences in serum levels of essential trace elements and heavy metals in patients with acute hemorrhagic stroke. Third, serum levels of essential trace elements and heavy metals levels were not measured after treatment in patients with acute hemorrhagic stroke.

In conclusion, we demonstrate that the increased serum levels of Cd, Pb, and Fe and decreased serum levels of Cu, Zn, Mg, and Mn in patients with acute hemorrhagic stroke. These findings may have diagnostic and prognostic value for acute hemorrhagic stroke. Further studies are needed to elucidate the roles of trace elements and heavy metals in patients with acute hemorrhagic stroke.

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## References

Adams H, Bendixen B, Kappelle L, Biller J, Love B, Gordon D, Marsh EE 3rd (1993) Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 24:35–41

Aggett PJ (1999) An overview of the metabolism of copper. Eur J Med Res 4:214–216

Altamura C, Squitti R, Pasqualetti P, Gaudino C, Palazzo P, Tibuzzi F, Lupoi D, Cortesi M, Rossini PM, Vernieri F (2009) Ceruloplasmin/Transferrin system is related to clinical status in acute stroke. Stroke 40:1282–1288

Anderson MB, Pedigo NG, Katz RP, George WJ (1992) Histopathology of testes from mice chronically treated with cobalt. Reprod Toxicol 6:41–50

Arslan M, Demir H, Arslan H, Gokalp AS, Demir C (2011) Trace elements, heavy metals and other biochemical parameters in malignant glioma patients. Asian Pac J Cancer Prev 12(2): 447–451

Atasoy N, Mercan U, Alacabey I, Kul AR (2011) Levels of heavy metals and certain macro elements in potable and tap water at Van City Center. Hacettepe J Biol Chem 39:391–396

Beard J, Connor J, Jones B (1993) Iron in the brain. Nutr Rev 51:157–170

Benmoyal-Segal L, Vander T, Shifman S, Bryk B, Ebstein RP, Marcus EL, Stessman J, Darvasi A, Herishanu Y, Friedman A, Soreq H (2005) Acetylcholinesterase/paraoxonase interactions increase the risk of insecticide-induced Parkinson's disease. FASEB J 19:452–454

Bradbury MW (1992) An approach to study of transport of trace metals at the blood-brain barrier. Prog Brain Res 91:133–138

Bureau I, Anderson RA, Arnaud J, Raysiguier Y, Favier AE, Roussel AM (2002) Trace mineral status in post menopausal women: impact of hormonal replacement therapy. J Trace Elem Med Biol 16:9–13

Cartwright GE, Wintrobe MM (1964) Copper metabolism in normal subjects. Am J Clin Nutr 14:224–232

Dayani PN, Bishop MC, Black K, Zeltzer PM (2004) Desferoxamine (DFO)-mediated iron chelation: rationale for a novel approach to therapy for brain cancer. J Neurooncol 67:367–377

Demirdogen BC, Demirkaya S, Türkanoglu A, Bek S, Arinc E, Adali O (2009) Analysis of paraoxonase 1 (PON1) genetic polymorphisms and activities as risk factors for ischemic stroke in Turkish population. Cell Biochem Funct 27(8):558–567

Dexter DT, Wells FR, Lees AJ, Agid F, Agid Y, Jenner P, Marsden CD (1989) Increased nigral iron content and alterations in other metal ions occuring in brain in Parkinson's disease. J Neurochem 52:1830–1836

Dexter DT, Jenner P, Schapira AH, Marsden CD (1992) Alterations in levels of ıron, ferritin, and other trace metals in neurodegeneretive diseases affecting the basal ganglia. Ann Neurol 32: 94–100

Dexter DT, Sian J, Jenner P, Marsden CD (1993) Implications of alterations in trace element levels in brain in Parkinson's disease and other neurological disorders affecting the basal ganglia. Adv Neurol 60:273–281

Donma O, Donma MM (2002) Association of headaches and the metals. Biol Trace Elem Res 90:1–14

Ertekin A, DeGer Y, Mert H, Mert N, Yur F, Dede S, Demir H (2006) An investigation of the effects of alpha-tocopherol on the levels Fe, Cu, Zn, Mn and carbonic anhydrase in rats with bleomycin-induced pulmonary fibrosis. Biol Trace Elem Res 114:1–12

Forte G, Bocca B, Senofonte O, Petrucci F, Brusa L, Stanzione P, Zannino S, Violante N, Alimonti A, Sancesario G (2004) Trace and major elements in whole blood, serum, cerebrospinal fluid and urine of patients with Parkinson's disease. J Neural Transm 111:1031–1040

Fraga Cesar G (2005) Relevance, essentiality and toxicity of trace elements in human health. Mol Aspect Med 26:235–244

Hickenbottom SL, Grotta J (1998) Neuroprotective therapy. Sem Neurol 18:485–492

Jomova K, Valko M (2011) Advances in metal-induced oxidative stress and human disease. Toxicology 283:65–87

Kang YJ (2011) Copper and homocysteine in cardiovascular diseases. Pharmacol Ther 129(3):321–331

Kayan M, Nazıroglu M, Barak C (2010) Effects of vitamin C and E combination on trace element levels in blood of smokers and nonsmokers radiology X-ray technicians. Biol Trace Elem Res 136:140–148

Kirchvink N, Martin N, Fievez L, Smith N, Marlin D, Gustin P (2006) Airway inflammation in cadmium-exposed rats is associated with pulmonary oxidative stress and emphysema. Free Radic Res 40:241–250

Klos A (2001) Lead, cadmium and mercury content in meals planned for consumption in selected kindergartens in Warsaw: IV International Scientific-Technical Conference, Warsaw, p 4–5

Kowalczyk E, Kopff A, Fijalkowski P, Kopff M, Niedworok J, Blaszczyk J, Kêdziora J, Tyoelerowicz P (2003) Effect of anthocyanins on selected biochemical parameters in rats exposed to cadmium. Acta Bio Pol 50:543–548

Leach RM Jr (1971) Role of manganese in mucopolysaccharide metabolism. Fed Proc 30:991–994

Levenson CW (2005) Trace metal regulation of neuronal apoptosis: from genes to behavior. Physiol Behav 15:399–406

Lichy C, Hacke W (2010) Stroke. Internist (Berl) 51(8):1003–1011

Lustberg M, Silbergeld E (2002) Blood lead levels and mortality. Arch Intern Med 162:2443–2449

Mahabir S, Spitz MR, Barrera SL, Beaver SH, Etzel C, Forman MR (2007) Dietary zinc, copper and selenium, and risk of lung cancer. Int J Cancer 120:1108–1115

Manca D, Ricard AC, Tra HV, Chevalier G (1994) Relation between lipid peroxidation and inflammation in the pulmonary toxicity of cadmium. Arch Toxicol 68:364–369

Meller L, Tage S, Kristensen TS (1992) Blood lead as a cardiovascular risk factor. Am J Epidemiol 136:1091–1100

Mertz W (1981) The essential trace elements. Science 213:1332–1338

Messner B, Knoflach M, Seubert A, Ritsch A, Pfaller K, Henderson B, Shen YH, Zeller I, Willeit J, Laufer G, Wick G, Kiechl S, Bernhard D (2009) Cadmium is a novel and independent risk factor for early atherosclerosis mechanisms and in vivo relevance. Arterioscler Thromb Vasc Biol 29:1392–1394

Millan M, Sobrino T, Castellanos M, Nombela F, Arenillas JF, Riva E, Cristobo I, García MM, Vivancos J, Serena J, Moro MA, Castillo J, Dávalos A (2007) Increased body iron stores are associated with poor outcome after thrombolytic treatment in acute stroke. Stroke 38(1):90–95

Moos T (2002) Brain iron homeostasis. Dan Med Bull 49:279–301

Muir KW, Lees KR (1995) A randomized, double-blind, placebo-controlled pilot trial of ıntravenous magnesium sulfate in acute stroke. Stroke 26:1183–1188

Munshi A, Babu S, Kaul S, Shafi G, Rajeshwar K, Alladi S, Jyothy A (2010) Depletion of serum zinc in ischemic stroke patients. Methods Find Exp Clin Pharmacol 32(6):433–436

Nawrot TS, Thijs L, Den Hond EM, Roels HA, Staessen JA (2002) An epidemiological re-appraisal of the association between blood pressure and blood lead: a meta-analysis. J Hum Hypertens 16:123–131

No authors listed (1990) Special report From The National Institute of Neurological Disorders and Stroke. Classification of cerebrovascular diseases III. Stroke 21:637–676

Nordberg M (1978) Studies on metallothionein and cadmium. Environ Res 15:381–404

Ozkaya MO, Nazıroğlu M, Barak C, Berkkanoğlu M (2011) Effects of multivitamin/mineral supplementation on trace element levels in serum and follicular fluid of women undergoing in vitrofertilization (IVF). Biol Trace Elem Res 139:1–9

Pérez de la Ossa N, Sobrino T, Silva Y, Blanco M, Millán M, Gomis M, Agulla J, Araya P, Reverté S, Serena J, Dávalos A (2010) Iron-related brain damage in patients with intracerebral hemorrhage. Stroke 41(4):810–813

Rahnama M, Marcınıak A (2002) Influence of Estrogen Deficiency on the level of magnesium in rat mandible and teeth. Bull Vet Inst Pulawy 46:267–271

Shenkin A (1997) Micronutrients and outcome. Nutrition 13:825–828

Sokolov DL, Bailey MR, Crum LA, Blomgren PM, Connors BA, Evan AP (2002) Prefocal alignment improves stone comminution in shockwave lithotripsy. J Endourol 16:709–715

Solioz M, Odermatt A, Krapf R (1994) Copper pumping ATPases: common concept in bacteria and man. FEBS Lett 346:44–47

Stabel JR, Spears JW, Brown TT (1993) Effect of copper deficiency on tissue, blood characteristics and immune function of calves challenged with infectious bovine rhinotracheitis virus and Pasteurella hemolytica. J Anim Sci 71:1247–1255

Tapiero H, Townsend DM, Tew KD (2003) Trace elements in human physiology and pathology. Biomed Pharmacother 57:399–411

Teasdale G, Jenett B (1974) Assessment of coma and impaired consciousness: a practical scale. Lancet 2:81–83

Uza G, Comes L, Uza D, Pop O (1995) Serum zinc and copper in patients with cerebral vascular disease. Rom J Intern Med 33:19–26

Waisberg M, Joseph P, Hale B, Beyersmann D (2003) Molecular and cellular mechanisms of cadmium carcinogenesis. Toxicology 192:95–117

Wenstrup D, Ehmann WD, Markesbery WR (1990) Trace element imbalances in isolated subcellular fractions of Alzheimer's disease brains. Brain Res 533:125–131

Wu T, Sempos CT, Freudenheim JL, Muti P, Smit E (2004) Serum iron, copper and zinc concentrations and risk of cancer mortality in US adults. Ann Epidemiol 14:195–201

Zangieva ZK, Torshin IIu, Gromova OA, Nikonov AA (2013) Trace elements in the nervous tissue and ischemic stroke. Zh Nevrol Psikhiatr Im S S Korsakova 113:30–36