



## Levels of serum trace elements in ischemic stroke patients

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### ABSTRACT

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The mortality and morbidity of ischemic stroke (IS) can be decreased by early diagnosis and proper treatment of these patients in the emergency department. The levels of trace elements in the human body are important in maintaining the balance in the various biological components. In this study, we examined the impact of imbalance in levels of trace elements in patients with acute IS. In this prospective study, serum copper (Cu), lead (Pb), cadmium (Cd), zinc (Zn), cobalt (Co), manganese (Mn), and magnesium (Mg) levels were investigated in 25 healthy participants (control group) and 24 IS patients. The Cd, Pb, Co, and Cu levels were significantly higher in the patients compared to control groups ( $P<0.05$ ), while the levels of Zn, Mg, Mn were lower. The results of our study show that an increase in the levels of Cd, Pb, Co and Cu may be important in the occurrence of IS.

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### 1. Introduction

Ischemic stroke (IS) is a common neurological condition resulting in high mortality and disability. A patient recovering from a stroke has increased risk of recurrence, permanent physical and cognitive inability, and can require long-term hospitalization (Yaşın et al., 2008). The incidence of IS increases with age and is affected by genetic and environmental factors (Öztürk et al., 2013). In addition, the main risk factors for ischemic stroke are diabetes mellitus (DM), hypertension, hypercholesterolemia, atrial fibrillation, cigarette smoking, carotid stenosis, coronary artery disease, and valvular heart disease (Hankey, 2006).

The lack of specific biological markers constitutes a problem for treatment and diagnosis of stroke. Trace elements which are important components of biological structures may also be toxic at levels above the amounts required for biological function (Pirincci et al., 2013). Currently, some

trace elements have begun to gain attention in terms of the treatment and diagnosis of stroke since they are essential for sustaining metabolism of neurons and glia (Zangieva et al., 2013). For instance, the role of magnesium is seen to be important in the pathogenesis of a stroke and recovery of brain cells (Akarachkova et al., 2012). Zn is a necessary component of many metalloenzymes which are recognized to be of importance for the function of the central nervous system (CNS). In the literature there are reports that an imbalance of trace elements increases the risk of IS (Zangieva et al., 2013).

The purpose of this study was to examine serum concentration of the trace elements, copper (Cu), lead (Pb), cadmium (Cd), zinc (Zn), cobalt (Co), manganese (Mn), and magnesium (Mg) in patients with acute IS, and the possible relationship between the levels of these elements and the occurrence of IS.

## 2. Materials and methods

### Subjects

In this prospective study, 24 (13 females, 11 males) patients with acute IS (Group I) were enrolled. In the emergency department of the hospital all IS patients are examined neurologically and blood samples are taken before treatment. Then, treatment is based on the preservation of vital functions and brain activity. Intracranial pressure was reduced with intravenous mannitol or furosemide.

The control group was comprised of 25 (12 females, 13 males) healthy volunteers. Physical examination of control subjects was normal. They were nonsmokers with unremarkable medical histories.

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

### Exclusion criteria

The exclusion criteria consisted of any of the following history of alcohol abuse, smoking, intravenous drug abuse, pregnancy, antioxidant supplements, hypertension, DM, liver or renal disease, rheumatoid arthritis, and pulmonary or coronary artery disease.

### Blood samples

Blood samples were collected, from all the participants, placed into empty tubes and immediately stored at 4°C. The serum samples were then separated from the cells by centrifugation at 3.000 rpm for 10 min. The serum samples were stored in plastic tubes at -80 °C.

### Trace Elements

The determination of serum concentrations of Mg, Mn, Zn, Pb, Co, Cd, and Cu was performed by Atomic Absorption Spectrophotometer measurements, in which a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK) was used.

### Descriptive Statistical analysis

The results were expressed as a mean  $\pm$  standard deviation and parametric variables were compared using an independent t-test. The results were considered to be statistically significant when the p value was less than 0.05. The data was analyzed using SPSS for Windows (version: 13).

## 3. Results

In our study there were 24 (mean age of 66.95 $\pm$ 11.94) patients with IS consisted of 11 (45.8%) males. In the control group, there were 25 (mean age 52.96 $\pm$ 9.080) healthy volunteer consisted of 13 (52%) male. There were no significant differences in age or gender between the patient and healthy control groups.

Serum Cu, Co, Pb, Cd levels were determined to be higher in the patients with IS compared to the control group (p<0.0001) (Table 1). Mn, Mg, Zn levels were significantly higher in the control group compared to the patients with IS (p<0.0001) (Table 1).

**Table 1.** Descriptive statistics and comparison results for studied characteristics

Parameters ( $\mu\text{g/dl}$ )	Patient Group (n= 24)	Control Group (n= 25)	P value
Mg	27.4912 $\pm$ 5.1571	63.0842 $\pm$ 3.6941	<0.0001
Mn	0.0133 $\pm$ 0.0065	0.6941 $\pm$ 0.1775	<0.0001
Zn	0.8565 $\pm$ 0.1969	3.1192 $\pm$ 0.5955	<0.0001
Pb	0.0347 $\pm$ 0.0074	0.0015 $\pm$ 0.0003	<0.0001
Cd	0.0033 $\pm$ 0.0009	0.0011 $\pm$ 0.0001	<0.0001
Co	0.0024 $\pm$ 0.00121	0.0010 $\pm$ 0.0001	<0.0001
Cu	1.4146 $\pm$ 0.24093	0.7273 $\pm$ 0.1271	<0.0001

The results were expressed as mean  $\pm$  standard deviation (SD).

Denotes a significant difference (P<0.001) between the IS patients and control group

## 4. Discussion

Acute stroke is a neurological emergency needing urgent management. The development of imaging techniques has allowed the easier diagnosis of stroke (Emre et al., 2007). Many studies have been conducted on concerning the effect of biochemical markers in cerebrovascular diseases that indicated glial activation and neuronal damage but, these markers have not been considered to be clinically important in the diagnosis and treatment of stroke (Herrmann et al., 2000; Napoli et al., 2001) Therefore, we analyzed the levels of trace elements in patients with acute IS and found increased levels of Pb, Cd, Co and Cu.

To have a direct physiological or pathophysiological effect on the brain, the element must traverse the blood-brain barrier to act upon the neurones or glial cells. The trace elements might also have an indirect impact by influencing the transport or organization of another substance at the blood-brain barrier (Bradbury, 1992).

The levels of trace elements may be important indicators in different neurological diseases. Various studies have shown increased Zn, decreased Cu and normal Mn concentrations in the substantia nigra of Parkinson diseases (Larsen et al., 1981; Dexter et al., 1989; Uitti et al., 1989). Zangieva et al. (2013) reported that magnesium, Zn, Mn, Cu and selenium are important for function of the nerve tissue. Some authors have suggested that decreased Zn levels have a role in pathogenesis of Alzheimer patients (Burnet, 1981; Wenstrup et al., 1990). Also it is considered that magnesium has useful neuroprotective and neurotrophic features in the treatment and prevention of cerebrovascular disease (Akarachkova et al., 2012). In the present study the levels of Mn, Mg and Zn was determined to be low in IS patients group. From this finding it is inferred that these elements are important in ethiology of IS and may be critical for nerve tissue.

A close relationship of stroke with magnesium has been described in the literature (Pirincci et al., 2013). Magnesium is known to block glutamatergic N-methyl-D-aspartate receptors in the central nervous system during instances of glutamate neurotoxicity such as acute IS (Yu et al., 2002). Increased serum levels of Mg may contribute to an improved outcome after IS since magnesium has an significant role in mitochondrial energy production (Donma and Donma, 2002; Yu et al., 2002). Goldman and Finkbeiner (1988) have stated that Mg treatment offers a therapeutic benefit following a

stroke. Data from our study shows that the Mg levels in the IS patients were low and this may illustrate the role of Mg in the ethiology of IS.

Copper is a necessary trace metal found in all living organisms in oxidized and reduced forms. It is required for survival and serves as an important catalytic cofactor for proteins that are needed for the growth and development of body. However, increasing Cu levels in cells may be cytotoxic (Tapiero et al., 2003). Altamura et al., (2009) reported that Cu levels were elevated in the serum of patients with IS in their study however, in another study it was found that the Cu levels did not change in IS patients (Munshi et al., 2010). The findings of our study were compatible those of the study by Altamura et al., (2009) with Cu levels being high in the patient group.

Some authors claimed that an increase in the levels of Zn can protect against oxidative stress. Other authors did not find changes in Zn levels in the brains of people with Parkinson's disease. However, a possible role of Zn deficiency in the pathogenesis of Alzheimer diseases has been proposed and some researchers found decreased Zn concentrations in the brains of Alzheimer patients (Burnet, 1981; Wenstrup et al., 1990). Similar to our study, Munshi et al., (2010) reported that Zn levels were decreased in patients with IS.

Manganese regulates numerous enzymes and is important for normal development and body function (Donma and Donma, 2002). In their study Imai and Okabe (2011) found that Mn-Superoxide dismutase activity was lower in the stroke group than the control group. We found that the Mn levels in the serum of patients with IS was lower than that of the control group.

Cadmium is known to be one of the most toxic carcino-

genic metals found in environmental and industrial pollutants (Messner et al., 2009). Cebi et al., (2011) analyzed the serum Cd levels in patients with coronary artery diseases but determined no significant differences between them and a healthy control group. However, no study has been found in the literature that evaluates Cd levels in IS patients. In the current study Cd levels were found to be high in the IS patients group.

Cobalt plays an important role in hemoglobin biosynthesis. An excess of Co in the body is characterized by polycythemia (Atasoy et al., 2011). The literature contains only a few cases of severe adverse effects on nervous system associated with Co (Schirmacher, 1967). In the present study, the level of Co was only minimally higher in the IS patients in comparison to the healthy controls.

Lead is an indicator of oxidative stress (Stohs and Bagchi 1995) and one study, proposed a link between occupational exposure to Pb and brain tumor (Cocco et al., 1988). However, in the literature there is no certain association between Pb exposure and IS. Continuous exposure to Pb has led to increased Pb levels and results in headaches (Uitti et al., 1989) furthermore, smoking has an effect on blood Pb levels. A high Pb level in the human body may lead to irreversible damage to the central nervous system (Donma and Donma, 2002). In our study, the serum Pb level was higher in the IS patient group.

In this study, low number of cases was the most important limiting factor. It seems that Zn, Mg, Mn may be considered to be an independent risk factor for IS. This information may contribute to the diagnosis, treatment and prevention of IS. Further studies are needed to examine the role of trace elements in the pathogenesis of IS and this study will light on the more comprehensive trials.

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