

RESEARCH COMMUNICATION

Altered Serum Levels of Elements in Acute Leukemia Cases in Turkey

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Abstract

Objective: The purpose of the study was to compare serum concentrations of some elements [zinc (Zn), copper (Cu), manganese (Mn), magnesium (Mg), lead (Pb), iron (Fe), cadmium (Cd) and cobalt (Co)] in acute leukemia patients with those of healthy subjects. **Methods:** The study group consisted of newly diagnosed acute leukemia patients and the controls were matched for socioeconomic status and eating habits. The elements levels in the patient group were measured before treatment with an atomic absorption spectrophotometer. The selection criteria for the patients and controls were the lack of recent blood transfusion history and taking any medication with mineral supplement. **Results:** The acute leukemia group composed of 42 patients and there were 40 persons in the control group. There was no difference between the age of the two groups ($p=0.239$). Serum levels of Zn, Mg and Mn were significantly lower with acute leukemia than in controls ($p<0.001$, $p=0.011$, $p<0.001$, respectively), while Cu, Pb and Cd were significantly elevated ($p=0.003$, $p<0.001$, $p<0.001$, respectively). There were no significant differences regarding Co and Fe ($p=0.323$ and $p=0.508$, respectively). **Conclusion:** In this study, we found levels of Zn, Mg and Mn to be lowered and of Cu, Pb and Cd to be elevated in patients with leukemia. Further studies are needed to clarify the role of these elements in pathogenesis of acute leukemia.

Keywords: Element - acute leukemia - serum levels - Van, Turkey

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Introduction

Acute leukaemia is a clonal malignant disorder affecting all age groups. It is characterised by the accumulation of immature blast cells in the bone marrow. This results in bone marrow failure, reflected by peripheral blood cytopenias and circulating blast cells. In most cases the etiology is not obvious, but internal and external factors associated with damage to DNA can predispose to acute leukaemia (Everington et al., 2003).

Trace elements at optimum levels are required for numerous metabolic and physiological processes in the human body (Mertz, 1981). 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). In addition, they are involved in membrane transport, nerve conduction and muscle contraction and also in the function of sub-cellular systems such as mitochondria. Cu, Zn, Mn and selenium also act as antioxidants (Shenkin, 1997). Therefore, imbalances in the optimum levels of these trace elements may adversely affect biological processes and are associated with many fatal diseases, such as cancer. There are several reports on serum trace element

levels in malignant diseases including leukemia and lymphomas (Tessmer et al., 1972; Ilicin, 1971). But, there are contradictory data between the previous studies, done related to the trace elements state in acute leukemia.

In this study we made in order to determine serum Zn, Cu, Mn, cadmium (Cd), cobalt (Co), lead (Pb), iron (Fe) and magnesium (Mg) levels of our patients with leukemia.

Materials and Methods

Study Subjects

The study group consisted of 42 newly diagnosed acute leukemia patients (28 males and 14 females). The diagnosis was made by means of cytochemical stains and bone marrow smears. All the patients were enrolled in the study before receiving the first course of chemotherapy. The patients were recruited from Medical Faculty of Hematology Department of Yuzuncu Yil University, Turkey. The control group consisted of 40 healthy subjects (25 males and 15 females). Both two groups were of the similar socioeconomic status and similar food habits.

The study subjects were briefed about the purpose of the study, and written consent was taken from each of them. Ethical approval was obtained from the local ethics

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committee. The selection criteria for the patients and controls were the lack of recent blood transfusion history and taking any medication with mineral supplement. The control subjects were selected from healthy individuals. All subjects had to go through clinical examination to determine existence of other diseases such as liver disease that might alter trace elements level. Some tests such as complete blood count, thyroid function test, renal impairment test and liver function test were also performed for each subject.

Blood Collection

Venous blood sample (5 ml) was collected from the antecubital vein of each of the acute leukemia patients and healthy group in a metal-free sterile tube, in the morning. Samples with signs of hemolysis were discarded. The blood was then allowed to clot and centrifuged for 15 minutes at 3000 rpm to extract the serum. The serum was aliquoted into deionised polyethylenetubes and stored at -80°C in a deepfreeze (without thawing) until the day of study.

Biochemical Analysis

Serum concentrations of Cu, Zn, Mg, Mn, Fe, Pb, Cd and Co in both patients and controls were determined by using atomic absorption spectrophotometry, in which a Unicam-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK).

Statistical Analysis

One-way ANOVA was used for the comparison of mean values of the groups. Then, Student-t test was used to determine the difference between groups. A "p" value <0.05 was considered statistically significant. Statistical analyses were carried out using the SPSS® statistical software package (SPSS for Windows version 13.0, SPSS Inc., Chicago, Illinois, USA). All results are expressed as mean and standard deviation (mean ± SD).

Results

Acute leukemia group composed of 42 person (AML: 38; ALL: 4), 14 of them were females and the other 28 person were males. The average age of patients was 38.08±11.22 years (range 24-56). There were 40 persons in control group, 15 of them were females and the rest 25 person were males, and the average age of control group was 33.10±7.10 years (range 24-45). There was no statistically difference between the ages of both groups (p=0.239).

Serum levels of Cd, Mg, Mn, Fe, Zn, Co, Cu, and Pb of the acute leukemia and healthy human were shown in (Table 1). Serum levels of Zn, Mg and Mn were significantly lower in with acute leukemia patients than in the controls (p<0.001, p=0.011, p<0.001, respectively). Serum levels of Cu, Pb and Cd were significantly higher in with acute leukemia patients than in the controls (p=0.003, p<0.001, p<0.001, respectively). Both groups were not different in terms of levels of Co and Fe (p=0.323 and p=0.508, respectively).

The data of studied other parameters of the patient and

Table 1. Serum Zn, Co, Cu, Fe, Mg, Mn, Pb and Cd Levels of the Participants

| Parameter | Leukemia cases (n=42) | Controls (n=40) | p |
|------------|-----------------------|-----------------|---------|
| Zn (µg/dL) | 49.4 ± 0.04 | 110.8 ± 0.20 | p<0.001 |
| Cu (µg/dL) | 122.6 ± 0.18 | 104.7 ± 0.16 | p=0.003 |
| Co (µg/dL) | 0.20±0.17 | 0.11 ± 0.06 | p=0.323 |
| Fe (µg/dL) | 93.3 ± 19.9 | 96.1 ± 24.7 | p=0.508 |
| Mg (µg/dL) | 1.10 ± 0.50 | 2.80 ± 0.90 | p=0.011 |
| Mn (µg/dL) | 0,003 ± 0,001 | 0,027 ±0,014 | p<0.001 |
| Pb (µg/dL) | 0,079 ± 0,055 | 0,003 ± 0,001 | p<0.001 |
| Cd (µg/dL) | 0,015 ±0,004 | 0,004± 0,003 | p<0.001 |

Zn, Zinc; Cu, Copper; Co, cobalt; Fe, Iron; Mg, Magnesium; Mn, Manganese; Pb, Lead; Cd, Cadmium; All results are expressed as mean and standard deviation (mean ± SD); P value < 0.05 was considered statistically significant

Table 2. Some Hematological and Biochemical Parameters of the Participants

| Parameter | Leukemia cases n=42 | Controls n=40 | p |
|--------------------------|---------------------|---------------|---------|
| WBC (10 ⁹ /L) | 51.5±35.1 | 7.21±2.02 | p=0.001 |
| Hb (g/dL) | 8.93±0.91 | 13.7±1.16 | p<0.001 |
| Plt (10 ⁹ /L) | 36.4±11.7 | 231.7±55.2 | p<0.001 |
| AST (IU/L) | 34.6±9.58 | 28.7±6.68 | p=0.118 |
| ALT (IU/L) | 45.0±23.6 | 33.2±11.4 | p=0.165 |
| Cre (mg/dL) | 0.85±0.32 | 0.68±0.17 | p=0.150 |

WBC, White blood cell; Hb, Hemoglobin; Plt, Platelet; AST, Aspartate transaminase; ALT, Alanine transaminase; Cre, Creatinine; All results are expressed as mean and standard deviation (mean ± SD); P value < 0.05 was considered statistically significant

the control groups [White blood cell (WBC), hemoglobin (Hb), Platelet (Plt), Aspartate transaminase (AST), Alanine transaminase (ALT) and Creatinin (Cre)] were given in (Table 2). The Hb and Plt values of the patient group were found significantly lower compared with the control group (p<0.001). The WBC values were higher in patients than in controls (p=0.001). There was no difference between the two groups in terms of liver and kidney functions (AST, ALT, Cre) that dysfunctions of these two organs may influence levels of the trace elements (p=0.118, p=0.165, p=0.150, respectively).

Discussion

Some elements have been studied by different authors to establish a relationship between trace elements and malignant diseases. For instance, changes in blood zinc and copper have been found in lymphoproliferative disorders, as well as in breast, lung and gastrointestinal tumors (Jayadeep et al., 1997; Rosas et al., 1995).

Zinc is the element having essential roles in immune functions and regulation of cell growth. There are some data suggesting an association between the deficiency of Zn and the development of malignant disorders (Schwartz, 1975). Zinc levels-related data is variable in patients with cancer. Experimental results support towards slightly decreased zinc concentrations in malignant diseases (Brown et al., 1980). Variations of zinc levels have been shown in leukemia (Tessmer et al., 1972; Andronikashvili and Mosulishvili, 1980). The present study showed decreases in Zn levels in patients with acute leukemia

as compared with control subjects. Our serum findings of Zn levels are in agreement with that of another study (Sahin et al., 2000).

Copper is an essential nutrient that is a component of several metalloenzymes that are required for oxidative metabolism (Cartwright and Wintrobe, 1964). In the studies performed on leukemic patients, serum Cu levels have been found to be higher than those of controls (Tessmer et al., 1972; Carpentieri et al., 1986; Osman et al., 1983; Akkus et al., 1998). These studies have shown that serum copper levels in cases of malignant disease increase with increasing disease activity. Remission is usually associated with the return of Cu levels to normal ranges. It has been suggested that serum copper would be a useful indicator for the extent of leukemia and malignant lymphoma, and might be a predictor for chemotherapy response (Tessmer et al., 1972; Ilicin, 1971). We found that the levels of Cu were high according to control group in leukemic patients. However, further studies are necessary to interpret this finding better.

Although Fe is an essential nutritional element, it is known that excess iron also lead to oxidative DNA damage (Ames, 2001). Excessive intake of iron may predispose to mammary tumorigenesis due to the fact that free iron works as a catalyst for the generation of reactive oxygen species and the suppression of host defense cells (Liehr and Jones, 2001). Hercberg et al (2005) reported that serum ferritin concentration >160 ng / mL is an increased risk of developing cancer in women but not in men. In this study, Fe levels in the cancerous stomach tissue samples were significantly higher than those in the non-cancerous tissue samples. On the other hand, it was reported that iron levels are significantly decreased in cancerous stomach tissue in comparison with normal stomach tissue (Reddy et al., 2003). In investigators iron concentrations have been measured in lymphocytes from patients with acute lymphoblastic leukemia, acute myeloid leukemia. Decrease in iron concentrations have been demonstrated in leukemia patients (Tessmer et al., 1972; Sahin et al., 2000). In contrast to these studies, in our study, both groups were not different in terms of levels of Fe.

Magnesium deficiency has caused lymphopoietic neoplasms in young rats. Extension of the studies showed that 20% of 92 rats of two strains, which rarely have spontaneous lympholeukemia, had thymic lymphosarcoma after 65 days of Mg deficiency (Bois et al., 1976). In literature, Mg concentrations have been measured in lymphocytes from patients with acute lymphoblastic leukemia and acute myeloid leukemia and magnesium concentrations have been significantly low in the patient groups, compared with control values (Rzymowska, 1996). The findings about serum Mg levels of patients under treatment were found to be higher after treatment than before treatment. This was explained by the amount of Mg arised from cells destroyed as a result of chemotherapy (Ilicin, 1971; Osman et al., 1983) . It has been highlighted that magnezium also may be an index for the activity of leukemia. Serum Mg level may be used as an index for the activity of leukemia in literature (Ilicin, 1971). We found that the levels of Mg were low according to control group in leukemic patients. When it is considered

together with findings of other studies, the low level of Mg may be important in the leukemia.

Lead serves no useful purpose in the human body, and its presence in the body can lead to toxic effects. Literature data about Pb are more controversial. Over the past decade, it has become increasingly evident that contact with lead, even at very low levels, can produce serious adverse health effects, especially in young children (Rosen, 1995). The main targets of Pb toxicity are the hematopoietic system and nervous system (Moore et al., 1986; Claeys-Thoreau et al., 1987). It is classified as a Group B2 carcinogen (possible human carcinogen) by the International Agency for Research on Cancer (IARC Monographs, 1987). There is no study evaluating Pb metal levels in acute leukemia in the literature. In our study, we found the levels of Pb were high in serum of acute leukemia compared to the control group.

The serum level of Mn changes in various cancerous diseases (Mulay et al., 1971). Kanabrocki et al (1967) found the high serum concentration of Mn in some diseases except for of patients with leukemia and carcinoma of the prostate. Our analysis of serum trace elements indicated a significant decrease in the serum concentration of Mn in with leukemia patients. Sadat et al (2008) found significant decrease in the serum concentration of Mn in lung cancer patients compared with those of the control subjects. Diez et al (1989) found a higher level of Mn in lung cancer patients than those found in control samples.

Little research on Co with cancer has been published, but the few studies that do exist are suggestive. Simultaneous exposure to Co has converted human osteoblast-like cells into the tumorigenic phenotype, and it has activated the expression of genes related to cancer (Miller et al., 2001). There are limited data regarding the level of Co in leukemia. Sheppard et al (2007) suggested that the "results in Fallon [Nevada] suggest a temporal correspondence between the onset of excessive childhood leukemia and elevated levels of tungsten and cobalt. In our study both groups were not different in terms of levels of cobalt.

Data related with carcinogenic effects of Cd are available from the literature (Waisberg et al., 2003). Cd can generate free-radical tissue damage because it may be a catalyst to oxidation reactions (Waalke, 2003). Cd is poorly mutagenic and probably acts through indirect mechanisms, although the precise mechanisms remain unknown (Waalke, 2000). Cd inhalation in rats results in pulmonary adenocarcinomas, supporting a role in human lung cancer. Prostate tumors and preneoplastic proliferative lesions can be induced in rats after cadmium ingestion or injection (Verougstraete et al., 2003; Nordberg, 2006). Other targets of Cd are testes, adrenals and hematopoietic system. We did not find a study that examined the association between acute leukemia and cadmium. In our study, Cd levels were higher in patients with leukemia compared to healthy group.

As a result, element studies have been made more in solid organ cancers. As for acute leukemia a few studies have been carried out in child population. It is important that this study has been performed in adult leukemia cases. In this study, we found that levels of Zn, Mg and

Mn were lower and levels of Cu, Pb and Cd were higher in patients with leukemia compared to healthy group. Both groups had no significant difference between the Co and Fe levels. More comprehensive studies are needed if this situation is important to clarify in the pathogenesis of the acute leukemia.

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