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Report

Evaluation of trace elements, calcium, and magnesium levels in the plasma and erythrocytes of patients with essential hyperhidrosis

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Abstract

Background Essential hyperhidrosis is a disease that expresses itself with excessive sweating in palmar, plantar, axillary, and craniofacial regions. The etiopathogenesis of the disease, which has particular importance because of leading to psychosocial morbidity, could have not been completely elucidated. In previous studies, it has been shown that oxidative stress might play a role in the pathogenesis.

Aims Assessing the levels of trace elements such as Se, Zn, Cu, Fe, and Mg that have an important role in oxidative stress, as well as Ca and Mg that have an important role in membrane physiology, in patients with essential hyperhidrosis.

Materials and methods Blood samples taken from the patient group with essential hyperhidrosis (42) and the control group (37) were separated into plasma and erythrocytes, and the levels of the bioelements were measured by use of ICP-OES device.

Results Erythrocyte levels of Se, Fe, Cu, Zn, Ca, and Mg were detected significantly higher in patients with essential hyperhidrosis. Furthermore, plasma levels of Cu, Ca, and Mg were significantly lower in patients with essential hyperhidrosis. Plasma levels of Se, Fe, and Zn showed no statistical difference between two groups.

Dicussion It was thought that the high levels of Cu and Fe in erythrocytes may play a role in increased intracellular oxidative stress, whereas the increase in Se and Zn levels may be secondary to increased oxidative stress. Low extracellular concentrations of Ca and Mg raise the thought that they play a role either enhancing the membrane excitability of eccrine sweat glands or influencing the autonomic nerve system.

Conclusion The levels of trace elements, which were determined to be different from the control group, may play a role in the pathogenesis of essential hyperhidrosis either in direct relation with or without oxidative mechanisms.

Introduction

Essential hyperhidrosis is thought to be associated with complex dysfunction of the autonomic nervous system.[1] In particular, decreased parasympathetic activity and/or increased sympathetic activity have been demonstrated.[2] Because no structural defect of the sweat glands has been observed in such patients, a neurohumoral or metabolic secretory cell abnormality has been postulated.[3,4] In addition, family history of essential hyperhidrosis has been reported in 5–50% in patients, providing evidence that genetic factors may play a role in this disorder.[5]

Because reactive oxygen species (ROS) may directly activate the central and peripheral sympathetic nervous systems, an etiologic role for ROS has been proposed. In patients with essential hyperhidrosis, superoxide dismutase activity and malondialdehyde levels are significantly high, whereas glutathione peroxidase and catalase activities are significantly low, as compared with the control groups. We confirmed that the oxidative stress resulting from increased ROS due to insufficient antioxidant capacity might play a role in the pathogenesis of essential hyperhidrosis.[6]

Trace elements play important roles in oxidative stress and a number of physiological events, as pro-oxidants and antioxidants. In addition, Ca^{2+} and Mg^{2+} contribute to membrane physiology. We postulated that variations in levels of trace elements Ca^{2+} and Mg^{2+} in the plasma and erythrocytes of patients with essential hyperhidrosis might play a role in the pathogenesis of this disease.

Materials and methods

Our study was conducted in collaboration with the Dermatology Department, School of Medicine, and the Chemistry Department, Faculty of Science and Letters (Afyon Kocatepe University, Afyonkarahisar, Turkey). Approval of the Ethical Committee of the Afyon Kocatepe University School of Medicine was obtained.

Forty-two self-referred patients with essential hyperhidrosis evaluated in the outpatient clinic (Dermatology Department) and 37 subjects without any dermatological complaint were included in the study. Complete blood count, biochemistry, and thyroid function tests were performed in all patients.

The diagnosis of essential hyperhidrosis was based on history of focal, excessive idiopathic sweating for at least six months and at least two of the following criteria: bilateral and relatively symmetric, affected daily activities, at least one episode weekly, onset before age 25 years, familial history of essential hyperhidrosis, and/or absence of nocturnal sweating.[1]

Blood samples were obtained from the cubital veins and placed in heparinized tubes. Erythrocyte sediment was prepared (4000 cycles, five minutes), and the plasma was transferred into Eppendorf tubes. Equal amounts of normal saline (0.9% NaCl%) were added to the sediment, and the erythrocytes were washed and then centrifuged at 1000 g for three minutes. This erythrocyte washing process was repeated three times. Samples were kept in a freezer at –80 °C until the day of analysis.

Decomposition of the organic matrix in the samples was performed by using a microwave oven. A Milestone Start D (Italy) microwave oven with a Pro 24 high throughput rotor and temperature control program was used to simultaneously digest 24 samples of tissue per cycle. Samples (0.1 g by weight) were put in high-pressure Teflon vessels and the following were added: 3 ml concentrated HNO_3, 1 ml H_2O_2, and 0.5 ml $HClO_4$ (Merck KGaA, Darmstadt, Germany). Teflon vessels, with Teflon lids, were placed in steel bombs and heated at 90 °C for 15 minutes, 120 °C for 15 minutes, 140 °C for 60 minutes, and 150 °C for 60 minutes. After cooling to room temperature, the solution was transferred, and final volume was adjusted to 10 ml with ultrawater (Milipore DirectQ UV, 2-15-1 Kounan, Minato-ku, Tokyo, Japan). Trace and major element concentrations in the digest were determined by inductively coupled plasma-optical emission spectroscopy (Milipore DirectQ UV, 2-15-1 Kounan, Minato-ku, Tokyo, Japan).

Table 1 Essential hyperhidrosis: demographic features

	Patients	Controls	*P* value*
Group size (*n*)	42	37	< 0.05
Age	26.3	26.6	< 0.05
Gender (female/male)	27./15	23./14	< 0.05

*Independent samples *T*-test.

Table 2 Essential hyperhidrosis: age at onset and duration

Years	Number	Minimum	Maximum	Mean ± SD
Duration	42	5	28	14.5 ± 6.2
Age at onset	42	4	28	11.8 ± 6.2

Table 3 Erythrocyte bioelement levels

Element	Patient group	Control group	
(mg/l)	Mean ± SD	Mean ± SD	*P* value*
Ca^{2+}	38.16 ± 16.02	30.02 ±10.51	< 0.01
Cu^{2+}	0.54 ± 0.09	0.49 ± 0.10	< 0.05
Fe^{2+}	984.81 ± 98.39	895.35 ± 130.22	< 0.01
Mg^{2+}	49.55 ± 7.11	43.22 ± 6.87	< 0.01
Mn^{2+}	0.000	0.000	
Se^{2+}	0.16 ± 0.03	0.15 ± 0.007	< 0.01
Zn^{2+}	11.26 ± 2.40	9.46 ± 1.7	< 0.01

*Independent samples *T*-test.
In the analyses, concentrations below 0.001 mg/l were presented as 0.000.

Table 4 Plasma bioelement levels

Element	Patient group	Control group	
(mg/l)	Mean ± SD	Mean ± SD	*P* value*
Ca^{2+}	124.49 ± 27.94	144.83 ± 15.83	< 0.01
Cu^{2+}	0.76 ± 0.22	0.98 ± 0.18	< 0.01
Fe^{2+}	1.36 ± 0.74	1.48 ± 0.39	> 0.05
Mg^{2+}	18.91 ± 3.71	22.66 ± 1.51	< 0.01
Mn^{2+}	0.000	0.000	
Se^{2+}	0.13 ± 0.007	0.13 ± 0.01	> 0.05
Zn^{2+}	2.24 ± 1.13	2.23 ± 0.73	> 0.05

*Independent samples *T*-test.
In the analyses, concentrations below 0.001 mg/l were presented as 0.000.

Statistical analysis

Statistical calculation was performed by the SPSS 10.0 package (IBM). Data were presented as mean ± SD. Statistical correlations between the groups were determined using *t*-test. $P < 0.05$ was considered statistically significant.

Results

The group of 42 patients with essential hyperhidrosis consisted of 27 females (64%) and 15 males (36%), age range 14–53 years (mean age was 26 years). The control group consisted of 23 women (62%) and 14 men (38%), age range 18–57 years (mean age 27 years). There was no statistical difference in age between the groups ($P > 0.05$). The demographic characteristics of patients and control groups are shown in Table 1. The mean duration of hyperhidrosis duration was 14.5 years, and average age of onset was 11.8 years (Table 2).

All patients complained of palmoplantar sweating, and 50% had axillary sweating. Seventeen of 21 patients with axillary hyperhidrosis reported that their axillary sweating was less intense than their palmoplantar sweating. Most patients (35 of 42) noted daily excessive sweating, while the remaining seven patients complained that excessive sweating occurred at least three times a week.

Mean erythrocyte Ca^{2+}, Cu^{2+}, Fe^{2+}, Mg^{2+}, Mn^{2+}, Se^{2+}, and Zn^{2+} levels were significantly higher in the patient group than in the control group ($P < 0.01$ for all except $P < 0.05$ for Cu^{2+}, Table 3). Plasma Ca^{2+}, Cu^{2+}, and Mg^{2+} levels were significantly lower in the study group as compared with the control group ($P < 0.01$, Table 4) There was no significant difference between the controls and patients with regard to plasma Fe^{2+}, Se^{2+}, and Zn^{2+} levels ($P > 0.05$).

Discussion

Essential hyperhidrosis may have a profound impact on daily activities and quality of life. Patients avoid shaking hands and touching and may develop shyness and social anxiety. The disorder is chronic but sometimes spontaneously improves after age 35 years.[2] Average age of onset has been reported to be 25 years in the United States but 12 years in China.[7–9] Our patient group was similar to the Chinese, with mean onset at age 12 years. There was a family history of hyperhidrosis in 35.7% of our patients, in line with reported rates of 15.3–47.9%.[8–10]

Because of their contributions to physiological processes, changes in erythrocyte and/or plasma levels of trace elements, calcium and magnesium may play a role in essential hyperhidrosis. Intracellular oxidative stress is increased in patients with essential hyperhidrosis.[6] Selenium is a trace element found in the antioxidant enzyme glutathione peroxidase and participates in cellular defense against oxidative stress.[11] Zinc protects biological structures from free radical damage by maintaining tissue levels of metallothioneins, which remove free radicals and indirectly provide cell membrane stabilization. In addition, zinc antagonizes catalytic properties of Fe^{2+} and Cu^{2+}, which are red-ox active transition metals.[12] Malondialdehyde levels, which are indicators of lipid peroxidation, may be elevated in patients with essential hyperhidrosis.[6] Cu^{2+} and Fe^{2+} are involved in lipid peroxidation in membranes and in direct oxidation of proteins.[13] Fe^{2+} may be a co-factor in enhancing oxidative stress. Iron is an important factor in cellular oxygenation and oxygen transport to tissues.[11] In addition to acting as a membrane stabilizer, calcium affects permeability and excitability. Low serum free Ca^{2+} levels result in increased neuromuscular excitability and tetany, while high Ca^{2+} lowers neuromuscular excitability.[11] Decrease in extracellular Mg^{2+} enhances membrane excitability in tissues. Impairment in neuromuscular functions is good evidence of Mg^{2+} deficiency and is expressed as hyperirritability, tetany, convulsion, and electrocardiographic abnormalities.[11] Mg^{2+} loss due to sweating in sportsmen may account for 10–15% of total Mg^{2+} excretion.[14] Reduced serum Mg^{2+} concentration may contribute to decrease in parasympathetic tonus.[15] Adjusted duration of QT interval is reported to be increased in patients with essential hyperhidrosis,[16] and hypocalcemia is an important cause of prolonged QT interval. Low Mg^{2+} levels also contribute to prolongation of the QT interval.[17]

Thus, increased levels of Cu^{2+}, Fe^{2+}, Se^{2+}, and Zn^{2+} in erythrocytes may play a role in essential hyperhidrosis by affecting oxidative mechanisms. Changes in plasma Ca^{2+} and Mg^{2+} levels may indirectly affect the autonomic nervous system and directly influence eccrine sweat glands by enhancing membrane excitability.

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