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Serum Iron, Zinc, and Copper Concentration in Premature Graying of Hair

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Abstract Premature graying of hair with unclear etiology, which is known as premature canities, is a common cause of referrals to the dermatologists. We assessed the relationship between serum iron, copper, and zinc concentrations with premature canities. This study was conducted on patients under 20 years old suffering from premature canities, having a minimum of ten gray hair fibers, and referring to university hospitals of Isfahan (Iran). The results were compared with age–sex-matched controls. Demographic data and disease characteristics were recorded for two groups. We studied serum iron, copper, and zinc concentrations of 66 patients and 66 controls using atomic absorption and Ferrozine methods. The mean age of studied cases was 17.8±2.0 years, and the mean age of the onset of canities was 15.5±3.2 years with no significant difference between males and females ($P>0.05$). Serum copper concentration was significantly lower in patients compared with controls (90.7±37.4 vs. 105.3±50.2 μg/dL, $P=0.048$), but serum iron concentration was significantly lower in controls compared to patients (88.8±39.5 vs. 108.3±48.4 μg/dL, $P=0.008$). Also, there was no significant difference between patients and controls in serum zinc concentration (114.8±67.8 vs. 108.2±49.9 μg/dL, $P=0.285$). According to these results, among copper, zinc, and iron, a low serum copper concentration may play a role in premature graying of hairs in our society. Further studies are needed to find the underlying mechanism of this relationship.

Keywords Serum mineral concentration · Nutrition · Premature graying of hair · Canities · Zinc · Iron · Copper

Introduction

Canities, a term which refers to the depigmentation of hairs, is a genetically determined phenomenon that is usually age-related and can be accelerated by some exogenous factors

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[1]. The average gray-free life span is 45 years, in which each scalp hair follicle undergoes fewer than 15 melanocyte seeding cycles. Three processes are involved in the pathogenesis of canities including gradual decline in the pigmentation of hairs during several cycles, loss of pigment within the anagen phase of the same hair cycle, and the emersion of the fully depigmented hair from the surface of the epidermis. Some evidences have confirmed a marked diminution of melanogenically active melanocytes located in the basal layer of the infundibulum and the hair bulb in aging process. Moreover, it has been revealed that a specific defect develops in the melanocyte/keratinocyte interaction of the graying hair follicles that finally results in the failure of keratinocytes to obtain melanin granules [2–4].

Although there is no precise definition for the premature canities, it is defined as the occurrence of the hair graying before the age of 20 in whites, 25 in Asians, and 30 in Africans. Premature canities has been shown to be associated with a cluster of autoimmune disorders such as vitiligo, pernicious anemia, autoimmune thyroid diseases, and some rare premature aging syndromes like Werner's syndrome. Also, studies have shown a role for environmental factors such as UV light, climate, smoking, drugs, trace elements, and some other nutritional deficiencies in the pathogenesis of premature canities [1, 5–10].

Trace element deficiencies lead to a spectrum of clinical manifestations especially in skin. Xerosis, erythematous scaly papules and plaques, cheilitis, vesiculobullous eruption, sparse light-colored hair, and hair loss are these manifestations [5, 7, 11]. While Bertazzo et al. [12] reported lower concentrations of Cu in white hairs in comparison to black ones and they observed no significant difference in Zn concentrations of different hair colors, Allergi et al. [13] demonstrated lower concentrations of both Zn and Cu in white hairs [12, 13]. However, no study has been done on the correlation of serum mineral content and the premature graying of hair. The aim of this study was to find whether there is any correlation between iron, zinc, copper serum concentrations and premature canities.

Methods

This cross-sectional study was performed in university hospitals of Isfahan (Iran) between September and November 2009. Premature canities was defined as having a minimum of ten gray hair fibers in a person under 20 years old, and the patients were chosen among the patients of dermatology clinics, while sex–age-matched controls who had no premature canities were selected randomly from the patients of other specialties. Also, public announcements were distributed in two university hospitals in order to collect enough cases and controls. However, those who had used supplementary drugs with a known effect on canities (e.g., B12 and minerals) within the past 3 months or the patients who had comorbid diseases with known relationship with premature canities like thyroid diseases, vitiligo, or pernicious anemia were not included. Ethical approval was obtained from the Isfahan University of Medical Sciences Ethics Committee, and a written informed consent was taken from each of the subjects.

The subjects were interviewed by a physician, and data including age, gender, age of onset, drug history, comorbid diseases, family history of canities, educational level, and job were collected. After overnight fasting, 10 ml of venous blood was taken from the arm veins. The blood samples were collected without adding the anticoagulants. Also, the plasma and serum were separated by centrifugation at 3,500 rpm for 15 min. Five milliliters of each blood sample was used for the measurement of copper and zinc concentrations by atomic absorption spectrophotometric method and the remaining amounts were used to measure serum iron concentrations by automatic analyzer.

A PerkinElmer Zeeman 5100 PC atomic absorption spectrophotometer, an AS-10 autosampler, and autostation 3600 (PerkinElmer, Norwalk, CT, USA) were used to determine the concentration of trace elements in serum. The concentrations of Cu and Zn were measured by flame atomic absorption spectroscopy. Also, quality control was strictly carried out using standard reference materials (SRM 1598, NIST). Ferrozine method with commercial kits (Boehringer, Mannheim) was used for measurement of serum iron concentrations, and the assays were carried out by an automatic analyzer (Hitachi 911).

Moreover, data were analyzed with SPSS software version 14 (SPSS® Inc.) using Chi-square test for comparison of categorical data and independent sample *t* test for comparing serum concentrations of mentioned trace elements between cases and controls. Moreover, one-sample *t* test was done to compare the results with normal concentrations. The normal mean concentration of iron was considered as 90±37 μg/dL [14]. We considered the normal concentrations of zinc as 89.0±18.0 μg/dL, and copper, 95.0±24.0 μg/dL, which is reported as normal concentrations for people of 12–30 years old, living in Tehran, Iran [15]. $P \leq 0.05$ and a difference of at least 0.8 μg/dL in the concentration of Zn between case and control groups were considered as significant differences. The minimum sample size in each group was 50, and the serum mineral concentrations were reported as micrograms per deciliter±standard deviation. The study was performed on a total of 132 participants divided into two groups.

Table 1 Comparison of demographic characteristic and serum mineral concentrations between the two groups

	Case, n=66	Control, n=66	P
Age, years	17.8±2.0	18.3±1.5	0.58
Female/male	45/21	45/21	–
Positive family history	43.9%	28.8%	0.07
Zn (μg/dL)	114.8±67.8	108.2±49.9	0.285
Cu (μg/dL)	90.7±37.4	105.3±50.2	0.048
Fe (μg/dL)	108.3±48.4	88.8±39.5	0.0085

Results

The characteristics of the 132 participants are summarized in Table 1. There were no significant differences between cases and controls in age, gender, comorbid diseases, or family history ($P>0.05$). However, cases had higher levels of education compared with controls ($P<0.05$). Also, the mean age of onset of premature canities was 15.5±3.2 years. It was 16.7±2.5 years in males and 14.5±3.5 years in females with no significant gender differences ($P>0.05$).

As presented in Table 1, the mean serum copper concentration was significantly lower in the case compared to control group (90.7±37.4 vs. 105.3±50.2 μg/dL, $P<0.05$), but no difference was found in the mean serum zinc concentrations of the two groups (114.8±67.8 vs. 108.2±49.9 μg/dL, $P>0.05$). Moreover, the mean serum iron concentration was significantly higher in the case group compared to the control group (108.3±48.4 vs. 88.8±39.5 μg/dL, $P<0.05$).

Although there was no significant difference between the normal mean serum concentration of copper (95.0±24.0 μg/dL) and the concentrations of this trace element in case or control groups ($P>0.05$), the serum zinc concentrations were significantly higher in both case and control groups compared to the normal mean serum zinc concentration reported in Iran (114.8±67.8 and 108.2±49.9, respectively, vs. 89.0±18.0 μg/dL, $P<0.05$).

A comparison of serum mineral concentrations between female and male in the case group is presented in Table 2. There was no significant difference in the different trace element concentrations of different groups ($P>0.05$), except for the mean serum iron concentration which was higher in males than in females (126.6±49.4 vs. 99.3±45.8 μg/dL, P=0.017).

Table 2 Comparison of serum mineral concentrations between female and male in the case group

	Females, n=45	Males, n=21	P
Zn (μg/dL)	113.2±67.3	118.3±70.8	0.402
Cu (μg/dL)	93.3±37.5	85.2±37.7	0.2395
Fe (μg/dL)	99.3±45.8	126.6±49.4	0.017

Discussion

Canities is a phenomenon usually caused by aging process. Also, it is affected by some environmental and genetic factors. Although in most cases canities is inherited in an autosomal dominant manner, some environmental factors accelerate this process [1, 2]. The results of this study show that there was a relationship between premature canities and low serum copper concentration. However, there was no significant difference between the mean serum copper concentrations in the case group compared to the normal one. In addition, serum iron concentration was significantly higher in the case group. No relationship between serum zinc concentration and premature canities was found.

The reason we investigated the relationship between serum iron, copper, and zinc concentrations and premature canities was the role of these trace elements in melanogenesis. Two types of pigments, eumelanin and pheomelanin, are synthesized within the melanosomes. In a series of oxidative reactions, tyrosine turns into 3,4-dihydroxyphenylalanine (DOPA), in which both pigments are derived from. One of the most important enzymes in these reactions is tyrosinase. This glycoprotein, which is located in the melanosomal membrane, is composed of three domains: the inner melanosomal domain that contains the catalytic region, the short transmembrane domain, and the cytoplasmic domain. Copper ions, which are required for tyrosinase activity, bind to the inner portion of tyrosinase. Furthermore, two tyrosinase-related proteins, TRP-1 and TRP-2, span the melanosomal membrane. TRP-1 is necessary for tyrosinase activation and/or stabilization, while TRP-2, which is needed for the conversion of DOPAchrome to the carboxylated derivative dehydroxyindole-2-carboxylic acid (DHICA), complexes with tyrosinase and TRP-1. The enzymatic activity of TRP-2 needs metal ions such as zinc [16]. In addition, iron and zinc were shown to affect the melanogenesis, for example in the rearrangement of dopachrome to 5,6-dihydroxyindoles and the oxidative polymerization of the 5,6-dihydroxyindoles to melanin pigments. Moreover, studies provided evidence for a role of iron in the modulation of the activity of tyrosinase [17]. Ashok et al. reported that in a tautomerization reaction by dopachrome tautomerase, which is one of the later stages of melanin biosynthesis, the isomerization of dopachrome to DHICA occurs. As they confirmed, this enzyme is a metalloenzyme with ferrous ion at its active site [18]. Additionally, the role of other metal ions such as Ni, Co, Mn, Ca, Al, and Cd in some steps of the melanogenesis pathway has been shown by other studies [18–20].

Many studies investigated hair metal ions' contents in different hair colors. However, there were controversial results in different studies [12, 13, 21–24]. Previous studies assessed the contents of hair minerals rather than the serum ones. Now, the question is whether there is any relationship between the contents of the hair trace elements and their concentrations in the body. The concentrations of trace elements in a hair are at least ten times higher than those present in serum and urine samples [25]. In addition, many factors affect the mineral contents of a hair including environmental exposure, season, race, hair color and thickness, age, cosmetic treatment of the hair, and body location of the hair (due to differences in surface contamination, hair growth cycles, and texture of the hair) [25, 26]. Also, the certainty of hair analysis for the nutritional status is suspected since there is no agreement between laboratorians on the standardization of methods and materials of hair analysis. Therefore, there is diversity in reference ranges and different interpretations of "normalcy" [25–33]. In the study of Shamberger, an attempt was made to show the validity of hair analysis, but finally, it was concluded that the use of hair analysis for nutritional evaluation had some limitations. It was stated that hair analysis for nutritional purposes had some use for chromium, selenium, and zinc; however, zinc and copper concentrations are altered by age, sex, place of residency, and some physiologic and pathologic conditions [34]. Finally, while other specimen types such as the serum and urine are more reliable, it is not reasonable to use hair analysis for the assessment of nutritional status.

On the other hand, this study had some limitations. Since the controls were selected among people referring to other specialty clinics, the serum mineral concentrations may had been affected by the conditions which brought them to these places, such as low financial status and the consequent nutritional deficiency, other diseases or conditions with known or unknown effect on mineral concentrations, etc. Although the comparison of the mean serum mineral concentrations with normal ones decreased the possibility of this bias, it could not eliminate the limitation completely. In addition, there is not any information about the normal concentrations of these trace elements in Isfahan for more precise comparison. Therefore, other studies with a more appropriate control group are suggested.

Conclusion

In conclusion, the present study shows a relationship between low serum copper concentration and premature canities, while such association was not found with serum iron and zinc concentrations. However, further studies with a more appropriate control group concerning the causes of premature graying of the hair in low serum copper concentration and whether there is any relationship between the serum copper level and the number of gray hair fibers are suggested.

Conflict of interest The authors have no conflicts of interest.

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