THE NEW METHODOLOGICAL APPROACH TO DETERMINATION OF NORMAL RANGE OF MACRO- AND TRACE ELEMENTS IN DIAGNOSTIC BIOSUBSTRATES

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KEYWORDS: hair, normal levels, chemical elements

ABSTRACT: The estimation of macro- and trace elements' normal levels in human scalp hair using statistically significant changes in health conditions (on the basis of clinically suggested morbidity data according to International Classification of Diseases rev.10) was carried out. The upper and lower physiological levels for essential elements (Ca, Mg, Fe, Zn, Cu, Mn, Se and Cr) in investigated population and only the upper or biologically allowable levels for Pb, Cd, As, Ni were established.

Introduction

It is well known, that majority of diseases have polyetiologic origin. This is why the estimation of a single factor influence on the disease's appearance is very difficult task. It can be done only if the investigators use the real normal ranges of indicators, reflecting the factor's action on the functioning of the organism, first of all. In the field of trace element research in man and animals there is lot of discussions, concerning the estimation of normal levels, especially in case of human hair (Barrett, 1985; Bass et al, 2001; Drasch, Roider, 2002; Skalny, 2002; Skalnaya et al., 2004). Described methodological approaches are mainly mechanistic, based on statistical but not physiological or medical points of view (see, for example, IAEA, CDC reports; Iyengar, Woittiez, 1987; Pangborn, 1994; Skalny, 2002 etc.). Formerly, the numerous associations and significant correlations between human scalp hair elemental content and a lot of diseases, metabolic disorders, occupational or environmental exposures, nutritional status were found (Anke, Risch, 1979; Passwater, Cranton, 1983; Haaranalyze…, 1987; Skalny, Bykov, 2003; Skalnaya, 2005 etc.). As hair elemental analysis recently becomes one of widely used diagnostic tools for estimation of macro- and TE chronic deficiencies or excesses in humans, the determination of their normal ranges is very important, but not easily solvable task. Hair elemental content varies widely in different age-, sex-, environmental and occupational groups of population, also it depends on washing, digestion and analytical procedures. It causes lot of difficulties in interpretation of obtained data and sometimes even leads to controversial conclusions (Drasch, Roider, 2003; Bass et al., 2001 etc.).

As it was supposed (Skalny, 2000) that hair mineral content is an integral indicator of health condition, we decided to compare the hair multielement analyses data of individuals suffering from different diseases. The aim of this study was to reveal the upper and lower normal hair levels for essential elements such as Ca, Mg, Fe, Zn, Cu, Mn, Cr, Se and only upper normal levels or so called biologically allowable hair Ni, As, Pb and Cd levels on the basis of simultaneous individuals' diseases histories and hair elemental profiles investigation.

Materials and methods

Totally, 2831 adults of 16-60 y.o. and 1757 children of 3-14 y.o. (all living in Moscow permanently) were investigated. Adults were occupationally non-exposed to metals. All of the investigated persons were examined and interviewed by physicians, in each case the hair multielement analysis was carried out in independent non-governmental Center for Biotic Medicine (Moscow). They have had 1 to 4 clinically verified diagnoses of chronic diseases. No acute or subacute ill persons were among them. For the classes of diseases recognition the 10th revision of International Classification of Diseases (ICD-10) was used.

All ranges of obtained analytical data were divided in 3, 5, 10, 15, 20, 25, etc. percentiles. The hair element's percentile level with observed simultaneous statistically significant increase of morbidity in any of disease classes in comparison with average morbidity rate in the investigated population was determined as upper or lower normal level.

Analytical determination of hair elemental content has been carried out by atomic emission spectrometry with inductively coupled argon plasma (ICP-AES) method using ICAP-9000 (Thermo Jarrell Ash, USA) and Optima 2000 DV (Perkin Elmer, USA) spectrometers. Hair analyses were carried out in accordance with IAEA recommendations and methodical guidelines of Ministry of Health of Russian Federation. For the check-up our laboratory data the certified reference material of human hair GBW09101, obtained from Shanghai Institute of Nuclear Research, was used (Skalnaya et al., 2004).

Statistical calculations were made using Microsoft Excel XP application package.

Results and discussion

According to proposed methodological approach there were obtained a lot of interesting data. Firstly, it was revealed, that Pb, Cd, Cr increase in adults' hair

was appeared to be associated with endocrine (ICD-10 class IV), Cd – with neurological (class VI), Ni – with bronchopulmonary (class X) diseases (Skalnaya, 2005). Elevated hair Se correlated with increased rates of infectious (class I), oncological diseases (class II), traumas and poisonings (class XIX). At skin (class XII) diseases increase of Zn, Cu, Mn levels was observed. As it was found, humans are more sensitive to elemental deficiencies, especially to Mg (IV, V, VI, IX, XI, XIII classes of diseases), Zn (IV, VI, IX, XI, XIII) and Mn (II, V, IX, XIII, XVII). Less frequent were the correlations between decreased hair Fe and morbidity rates (III, V, XIV classes), Cu (I, X, XIII), Ca (IV, XIX), Se (XI, XIX) and Cr (III). So, in general, in adults the increase of morbidity rate corresponds to elevated hair toxic metals Pb, Cd, and also Se, and, on the other hand, to deficient hair essential elements Mg, Zn, Mn, Fe, Cu content.

In children the maximal occurrence of elevated hair elements (Pb, As, Ni, Cu) was in the traumas and poisonings group (class XIX). Decreased hair Mg and especially Zn in the birth defects group (class XVII) suggest the role of their deficiencies in intrauterine developmental derangements, described in literature. Possibly, Ni, Fe, Cr accumulation during the intrauterine development or further secondary changes in their metabolism can be very important in birth defects pathogenesis. Heavy metals presumably also play a role in appearance of behavioral and mental disturbances (Pb), neurological (Pb, Cd, Cr) and bronchopulmonary (Cd) diseases in childhood. According to the obtained data, elevated hair Ca, Mg, Zn levels reflect the importance of these elements for regulation of endocrine system and skin functioning. The most susceptible to lack of elements are children, suffering from diseases of blood (ICD-10 class III) (Ca, Mg, Zn, Mn), infections (class I) (Mg, Mn, Se), diseases of urinary tract (class XIV). Low hair Fe is the most frequent indicator of children's diseases (classes V, IX, X, XIII, XIV), than Mg (classes I, III, VI, XVII) or Mn (classes I, III, X, XIII).

Almost all of the presented data are well corresponding to modern knowledge in medical elementology (Ermidou-Pollet, Pollet, 2000; Biesalski et al., 2001; Skalny, Rudakov, 2004; Elements and their Compounds… 2004 etc.).

Adults, occupationally not exposed to metals, are the "carriers" or "eliminators" of Pb, Cd, Cr in cases of endocrine diseases, of Cd and Ni at the neurological and bronchopulmonary ones, respectively; also they lose Mg and Se in cases of oncological diseases, Zn, Cu, Mn in cases of skin diseases, Se in cases of both traumas, poisonings and infectious illnesses; these facts reflect the involvement of elements' metabolism disorders (sometimes even minimal) in pathogenesis of observed classes of diseases (ICD-10).

So, adults are relatively more susceptible to deficiencies of elements as compared to children, but it is necessary to emphasize that lacks of Mg and Mn in hair are most associated with indicators of disease rates increasing in both groups. Additionally, low hair Zn in adults and low hair Fe in children are also very informative indicators of illness existence or, possibly, predisposition. It is interesting, that the evaluated connection between cancer diseases and low hair Mn and elevated Se confirms our previous data (Skalnaya, Semikopenko, 2003). Presumably, hair Mn level can be sufficiently specific indicator of predisposition to neoplasms, for example, breast cancer.

Obtained normal limits for essential elements in investigated groups of population are presented in Table 1.

As shown above, in children the normal values for majority of elements are found between the 25 and 75 percentiles. This agrees with our previous proposals for determin normal ranges (Skalny, 2003, 2004). Only for Mn, Se and Cr the lower normal levels reached 5, 5 and 10 percentiles, and for Fe and Se the upper levels

Table 1. Normal limits for hair element contents (essential elements)

Element	Adults				Children			
	Lower limit		Upper limit		Lower limit		Upper limit	
	mcg/g	percentile	mcg/g	percentile	mcg/g	percentile	mcg/g	percentile
Ca	450	25	–	–	220	25	480	75
Mg	41	25	480	98	16	25	43	75
Fe	11	25	–	–	12	25	35	90
Zn	165	25	220	75	90	25	190	75
Cu	10	25	25	90	9.0	25	14	75
Mn	0.15	5	2.5	95	0.15	5	–	–
Se	0.05	5	3.0	90	0.05	5	2.6	90
Cr	0.15	5	1.4	95	0.2	10	0.7	75

equal to 90 percentile. The upper normal limit for hair Mn in children was not revealed. Also, in adults lower normal levels were equal to 25 percentiles (Ca, Mg, Fe, Zn, Cu) and 5 percentiles (Mn, Se, Cr). But the upper levels of hair Ca and Fe were not estimated, and only for Zn it was equal to 75 percentile. In another cases they were higher than in children (90-98 percentiles). These facts reflect more wide normal range in adults in contrary to children and, possibly, better adaptation of adults to elimination of essential elements from the body. So, we can generalize that deficiencies of essential elements are more typical for children and this is why less dramatic or dangerous for them. On the other hand, the metabolic disturbances, causing the increased losses of elements, are more characteristic for adults, those are finally less sensitive to them, but very susceptible to lacks of essential elements.

The established upper normal levels for toxic elements are demonstrated in Table 2.

In general, we can assume, that young organisms are more sensitive to toxic effects of Ni and especially of Cd, As, but matured organisms are more susceptible to Pb. Also, another explanation can be assumed: the mechanisms of detoxification or elimination of As, Ni and Cd, but not of Pb in adult persons are more developed or efficient as compared to children.

Conclusions

- there is a significant difference in "sensitivity" to macro- and trace element excesses and deficiencies in growing peoples vs. adults;
- in the same classes of diseases (ICD-10) there are the different hair elemental profiles in child and adult ages; a trace element's relation to disease's "origin and existence" is different in different stages of ontogenesis?;
- presumably, children are more susceptible to element-related metabolic disturbances (increased elimination of elements due to increased metabolism or lack of ligands?), but not to element deficiencies, which are typical of childhood, in contrast to adults; adults are more susceptible to lack of elements, especially to their combinations;
- the proposed methodological approach for determination of normal limits of hair elemental content in population can be useful for evaluation of normal values in another diagnostic biosubstrates (blood, urine, saliva, nails, bones etc.) in any species, not only in humans.

Table 2. Normal limits for hair elemental content (toxic elements)

Element	Adults		Children	
	mcg/g	percentile	mcg/g	percentile
Pb	2.0	90	5.0	95
Cd	0.25	95	0.15	75
As	–	–	1.4	95
Ni	4,0	> 98	0.75	90

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