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Lithium and Other Elements in Scalp Hair of Residents of Tokyo Prefecture as Investigational Predictors of Suicide Risk

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Abstract The high suicide rates in Japan and several reports of inverse associations of suicide rates with the levels of lithium (Li) in drinking water prompted determinations of Li along with other elements in samples of scalp hair of 100 male and 100 female residents of Tokyo Prefecture. In more than half of the samples of both genders, Li levels were below the instrumental detection limit or below or the lower limit of the laboratory reference ranges. Among other elements, the concentrations namely of cobalt were also frequently below the laboratory reference range, suggesting that low circulating levels of vitamin B_{12} were common in this study population. As vitamin B_{12} deficiency is associated with depression and other psychiatric conditions, and there is evidence of interactions between Li and vitamin B_{12}, Li deficiency as well as suboptimal vitamin B_{12} status must be considered as potential suicide risk factors. In view of its established positive effects on mood and brain function, an adequate supply of selenium (Se) is important as well. Although the analytical results suggested that the Se status of the subjects was generally adequate, as seafood was a major dietary source of Se, much of it was actually sequestered by mercury and only a fraction was bio-available. In addition, the hair samples were found to contain not insignificant levels of As, Cd, Ni, and Pb, arising from the adventitious presence of these elements in foods and the environment. As these elements also interact with Se in vivo and are known to adversely affect mood and behavior, in investigational studies, subjects at risk need to be evaluated also with respect to these elements.

Keywords Tokyo Prefecture · Suicide risk · Hair trace elements · Lithium · Mercury · Selenium · Vitamin B_{12}

All other authors have read the manuscript and have agreed to submit it in its current form for consideration for publication in the journal.

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Introduction

The suicide incidence in Japan is among the highest in the world. It was 22,000 per year in 1988–1997 and has since risen to over 30,000 per year. This increase has been associated with the worsening of the economic situation [1], but as similar increases have not occurred in other economically challenged countries, other contributing factors must be considered. Lithium (Li), a newly recognized nutritionally essential trace element [2], is of interest within this context in view of the existence of statistically significant inverse associations of the drinking water Li with the suicide rates in Texas counties [3]. Since drinking water Li levels have since been also shown to be inversely associated with the suicide rates in municipalities of Oita Prefecture, Japan [4, 5], supplementing the population with low levels of Li was recommended to prevent suicide in the general population [6]. To test the hypothesis that Li deficiency might be widespread in Japan, the levels of Li were determined in a collection of scalp hair samples of male and female residents of Tokyo Prefecture. Hair was chosen as the indicator matrix as it reflects the average Li intake during the past 1–3 months. In addition to Li, the levels of other elements that are known or suspected to affect mood and behavior were determined and will be reported as well.

Materials and Methods

Scalp hair samples from 100 males and 100 females consecutively collected at a Tokyo clinic of preventive medicine and were placed into contaminant-free plastic bags. It was ascertained that none of the samples were from acutely ill patients or from subjects on prescription medications. The analyses were performed by Doctor's Data, Inc. St. Charles, IL, 60174–2420, a certified commercial laboratory, by ICPS-MS. The validity of the values was checked by comparisons with a certified hair reference sample, spiked hair samples, and other in-house controls. The hair samples were washed four times with a 1:200(*v*/*v*) solution of Triton X-100 and then rinsed three times with ultrapure deionized water and twice with acetone. The dried samples were weighed and subjected to nitric acid/microwave digestion as described by Puchyr et al. [7]. The mean age of the male subjects was 38.0±22.9 years, range 1–84 years, and of the female subjects 47.9± 19.4 years, range 1–87 years.

Results

Medians and means of the elements measured are given in Table 1. Table 2 lists the observed percentages of elements below the detection limit, below the lower limit of the reference ranges, as well as the percentages within and above the laboratory reference ranges, for males and females.

Individual Elements

Lithium

Li was below the instrumental detection limit in 31% of the samples of males, 19% of the samples of females, below the lower limit of the reference range in 32% and 29%, and

Table 1 Observed means and medians in the scalp hair samples of males and females

Element	Median, μg/g		Mean (±SD)	
	Males	Females	Males	Females
Li	0.0110	0.017	0.019 (0.025)	0.0275 (0.029)
Na	184.5	175.5	243.3 (204.2)	224.2 (202.4)
K	114.0	76.0	199.7 (278.8)	115.5 (128.1)
Ca	488.0	629.0	588.4 (377.2)	1,017 (923.6)
Mg	39.0	52.5	45.5 (29.86)	82.64 (84.45)
Fe	8.00	9.0	8.83 (4.17)	13.41 (19.12)
Co	0.031	0.024	0.125 (0.146)	0.130 (0.146)
Cu	12.00	17.50	16.32 (10.33)	30.13 (42.03)
Zn	162.0	155.5	156.7 (35.49)	155.5 (45.29)
Ni	0.37	0.37	0.491 (0.565)	1.067 (1.976)
Mn	0.186	0.14	0.298 (0.319)	0.125 (0.087)
Al	6.00	6.000	7.28 (6.35)	8.527 (11.81)
As	0.321	0.1950	0.536 (0.33)	0.431 (0.443)
Cd	0.060	0.0550	0.114 (0.147)	0.086 (0.0882)
Pb	1.700	1.400	1.879 (1.547)	1.926 (2.001)
Ni	0.370	0.400	0.491 (0.061)	1.067 (0.2330)
Cr	0.610	0.660	0.672 (0.245)	0.767 (0.601)
V	0.084	0.0645	0.203 (0.218)	0.228 (0.273)
Hg	3.100	2.965	3.891 (3.781)	3.193 (2.529)
Se	1.813	1.892	1.720 (1.001)	1.697 (1.104)
I	0.650	0.610	0.672 (0.244)	0.630 (0.525)

above the reference range in just 5% of the samples of males and 8% of the samples of females, respectively (see Table 2). Based on these results, more than one half of the subjects would have to be classified as Li deficient. Figure 1 shows that undetectably low hair Li values occurred at all ages, and that there was a declining trend of the hair Li levels with age in men, and especially in women above 50 years.

The mean hair Li levels were higher in females than in males, but the difference was statistically not significant. The hair Li levels in subjects with low to moderate hair levels of Na were directly correlated with those of Na, in males with $P=0.0125$ and in females with $P=0.0023$. However, in subjects with the highest Na levels, the association with Li was inverse, suggesting that the excretion of Li is promoted by high Na intakes. Noteworthy among associations of hair Li with other elements is the direct association with iodine, statistically equally significant in males and females with $P<0.0001$.

Sodium and Potassium

The levels of sodium (Na) and potassium (K) were directly correlated ($P<0.0001$), showed no consistent age dependence, and were higher in men than in women, as is commonly observed in Asian as well as in non-Asian subjects.

Observed hair Na and K concentrations				
	Means±SE		Medians	
	Men	Women	Men	Women
Na	243.3±20.42	202.3±2	84.51	157.5
K	199.7±29.55	124.9±14.86	114.0	79.5

Whereas the levels of K of both genders were mostly within the laboratory reference ranges, those of Na were substantially higher than the laboratory reference ranges (see Table 2). Since these reference ranges were derived from data mostly of American subjects, these results seem to reflect the generally higher dietary salt consumption in Japan compared to the USA.

Magnesium and Calcium

The observed concentrations of magnesium (Mg) and calcium (Ca) were higher in women than in men, the differences were statistically significant with $P<0.0001$.

Observed hair Mg and Ca concentrations				
	Means±SE		Medians	
	Men	Women	Men	Women
Mg	45.48±3.24	72.27±7.56	39.00	51.50
Ca	588.4±40.9	932±98.6	488.0	579.4

The Ca levels showed a statistically significant increase with age in men, with $P=0.025$, and in women, with $P=0.0070$. Whereas the highest hair Ca concentration among men reached 1,760 μg/g, Ca reached 3,760 μg/g in the hair sample of a 56-year-old woman, consistent with the higher incidence of bone demineralization processes in postmenopausal women.

Other Elements

Iron In women, the hair iron (Fe) concentrations were directly correlated with age, with $P=0.034$. In men, no clear association of the Fe levels with age was observed. The hair Fe concentrations of both genders were directly correlated with the cobalt levels, with $P=0.002$, a result consistent with the role of vitamin B_{12} in erythropoiesis (see section below for further discussion). Other statistically significant direct associations were seen between Fe with Al ($P=0.0004$), Fe and Ni ($P=0.04$), Fe and Cr ($P<0.001$), and Mn ($P=0.012$). These associations presumably reflect the nonspecific binding of these metals to serum iron transport proteins.

Iodine The levels of iodine (I) in hair were directly associated with those of Li in males with $P<0.0001$. In females, this association was also direct, but significant only with $P=0.029$. However, the lower statistical significance was traced to the presence of three high-iodine outliers; after the elimination of these outliers, the statistical significance of this

Table 2 Percent of samples of males (M) and females (F) with values below the detection limits, below, within, or above the reference ranges (RefR) of essential elements, and within and above the reference means (RefM) of nonessential and/or toxic elements

Essential elements								
	Below detection		Below RefR		Within RefR		Above RefR	
Element (RefR)	M	F	M	F	M	F	M	F
Li (0.05–0.12)	31	19	32	29	32	40	5	8
Co (0.009–0.045)	9	0	56	36	28	61	5	0
Ca (280–600)	0	0	17	26	48	43	34	31
Mg (30–75)	0	0	32	21	53	47	15	32
Na (20–90)	0	0	3	0	22	30	75	70
K (9–40)	0	0	20	25	67	68	13	7
Fe (5–14)	0	0	16	24	73	54	11	22
Cr (0.80–1.25)	0	0	2	2	71	69	27	29
V (0.009–0.080)	4	1	5	6	35	41	49	52
Se (0.95–1.7)	0	0	41	29	11	7	41	64
I (0.25–1.3)	0	0	18	23	69	72	13	5
Nonessential and/or toxic elements								
	Below detection		Below RefM		At and above RefM			
Element (RefM)	M	F	M	F	M	F		
Al (7)	0	2	68	70	32	28		
As (0.15)	4	5	28	32	68	63		
Cd (0.25)	17	17	69	76	14	7		
Hg (1.5)	0	0	41	35	59	35		
Ni (0.20)	1	12	34	32	65	56		
Pb (0.80)	0	0	30	23	70	77		

association became as significant ($P<0.0001$) as that in the males. There is evidence of interactions between Li and I, affecting thyroid function [8], causing, for example, hypothyroidism to develop in bipolar patients treated with therapeutic levels of Li [9]. On the other hand, hair I levels were lower in the subjects of the present study with undetectably low hair Li, suggesting that Li deficiency diminishes iodine retention.

Cobalt The mean levels of cobalt (Co) of the males and of the females were identical within statistical error ($P=0.468$). Figure 2 shows that hair Co increases with age in about 25% of the samples of our male and female subjects. In the remainder of the subjects, Co values were below the reference range, suggesting that in these subjects the dietary supply, transport, and/or the uptake of vitamin B_{12} were compromised. Since there is evidence of interactions between vitamin B_{12} and Li and vitamin B_{12} deficiency is associated with a variety of psychiatric conditions [10, 11], attention needs to be given also to the vitamin B_{12} status in evaluating subjects at risk.

Selenium and Se-Antagonistic Elements Table 2 shows that the hair selenium (Se) levels were above the upper limit of the reference range in 41% of the men and 64% of the

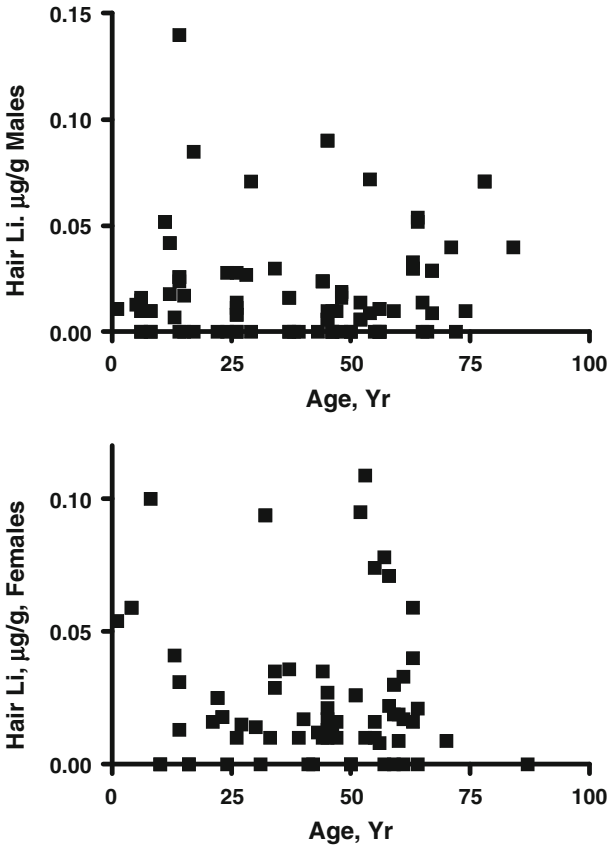

Fig. 1 Distribution of hair lithium levels in Japanese males and females as a function of age

women, attesting the generally higher dietary Se intakes of Japanese compared to American subjects. However, as ocean fish provide a significant percentage of the Se in the Japanese diet, much of the Se in these foods is present in the form of complexes with mercury (Hg), causing the hair Se values of the present subjects to be directly and significantly correlated with those of Hg, with $P<0.0001$. The mean hair Hg level of 3.891±0.415 µg/g of the men was higher than that of the women of 2.905±0.294 µg/g. From the observed Hg/Se slope of the least squares fitted line of 2,105 in the males, it is estimated that 82% hair Se is bound to Hg. In the females, the corresponding percentage was estimated to 45%, suggesting that the women obtained more of their dietary Se from food sources with lower mercury contents than the men.

Contrary to the direct association of Se with Hg, the hair Se levels of males were *inversely* correlated with those of arsenic (As), $P=0.02$; cadmium (Cd), $P=0.002$; nickel (Ni), $P=0.0025$; and with lead (Pb), $P=0.03$. The opposing behavior compared to Hg arises because these elements, once ingested, will react with Se in vivo to form selenide complexes that are either excreted or deposited in storage organs such as the kidneys or the liver and give rise to the observed inverse associations. These interactions are parts of physiological metal-detoxification processes, but also cause the physiological inactivation of Se. Comparing the atomic equivalents of Se with the sums of the atomic equivalents of

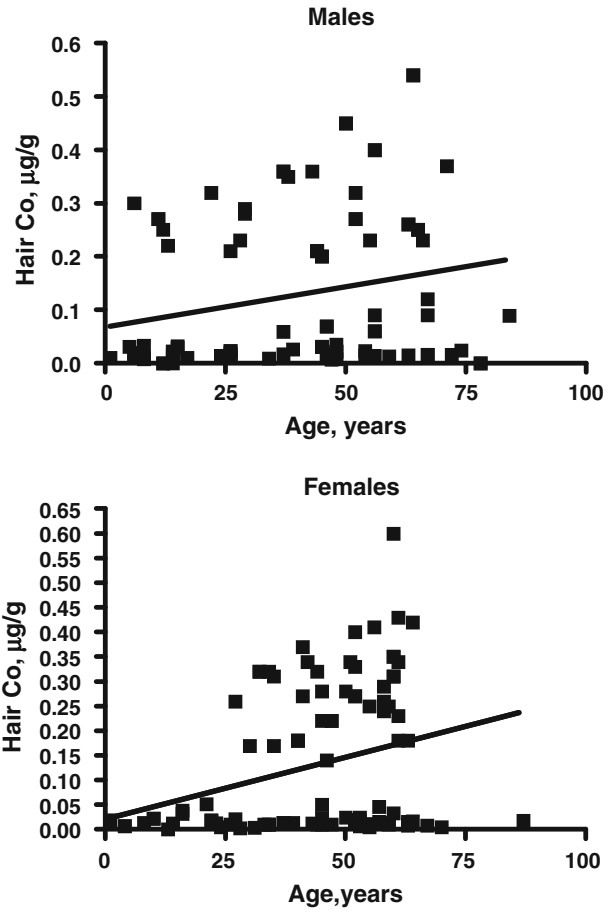

Fig. 2 Hair cobalt levels vs. age in males and females

Hg, Cd, As, Ni, and Pb reveal that these elements are deposited into the hair follicles largely as the selenides.

Summary and Conclusions

While the high suicide incidence in Japan is undoubtedly determined by a complex interplay of cultural and socioeconomic influences, Li deficiency could be an important factor in view of the observed absence of detectable levels of Li in a significant percentage of the hair samples analyzed. To lower suicide risk, the addition of small amounts of Li to the drinking water supplies has been recommended [3, 7]. Among other elements, the levels of cobalt were also found to be frequently low, suggesting that the vitamin B_{12} status of a substantial percentage of the study subjects was suboptimal. The same is true for selenium, an element also recognized as essential for optimal brain function. Although the observed hair Se levels of both genders were close to the upper limit of the laboratory reference ranges, much of the Se was sequestered by Hg, As, Cd, Ni, and Pb. Thus, the presence of these toxic and Se-antagonistic elements must be considered if hair is used for assessments of Se status.

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