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ORIGINAL PAPER

HAIR TOXIC METAL AND METALLOID LEVELS IN CHILDREN WITH CHRONIC SINUSITIS*

Svetlana I. Alekseenko[1,2], Alexey A. Tinkov[3,4], Anatoly V. Skalny[3,4,5]

[1] Raukhfus Children's City Hospital №19, St. Petersburg, Russia
[2] Mechnikov North-West State Medical University, St Petersburg, Russia
[3] Yaroslavl State University, Yaroslavl, Russia
[4] I.M. Sechenov First Moscow State Medical University, Moscow, Russia
[5] Federal Research Centre of Biological Systems and Agro-technologies of the Russian Academy of Sciences, Orenburg, Russia

Abstract

The objective of the present study was to assess hair toxic metal and metalloid levels in 150 children with chronic sinusitis and 150 controls, using inductively-coupled plasma mass-spectrometry (ICP-DRC-MS) on a NexION 300D (Perkin Elemer, USA). The data demonstrate that hair As and Be levels in children with chronic sinusitis were 24% and 125% higher than those in healthy children, with no significant group difference in hair levels of Al, Cd, Hg, Ni, Pb. In the group of younger children (2-9 years old) hair As and Be levels were higher than in the controls, whereas older children (10-18 years old) were characterized by increased levels of As, Be, and Hg. Hair Al, As, Cd, and Pb levels in healthy children from the older group were significantly lower in comparison with the first age group, by 39%, 22%, 35%, and 46%, respectively. At the same time, an age-related decrease in children with chronic sinusitis was observed only for hair Al, Cd, and Pb. The correlation between hair metal(loid) levels and age in the chronic sinusitis group was weaker than in the control one. It is proposed that reduced mucociliary clearance in chronic sinusitis is associated with impaired metal particle removal from the upper airways and their absorption. The latter in turn aggravate chronic inflammation and mucociliary dysfunction. Further studies are required for assessment of the mechanisms underlying the observed relationship.

Keywords: chronic sinusitis; beryllium; arsenic; mercury.

prof. Anatoly V. Skalny, MD, PhD, DSc., Laboratory of Biotechnology and Applied Bioelementology, Yaroslavl State University, Sovetskaya st., 14, Yaroslavl, 150000, Russia; e-mail: skalny3@microelements.ru

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INTRODUCTION

Chronic sinusitis is a disease with a high socioeconomic burden (HALAWI et al. 2013), being characterized by the prevalence varying from 2 to 16% in the USA (HALAWI et al. 2013), and 5 to 10% in China (SHI et al. 2015). Both local (allergic rhinitis, anatomic abnormalities, polyposis, trauma, etc.) and systemic (immune deficiency, cystic fibrosis, ciliary dysfunction) predispose to chronic sinusitis development (BADR et al. 2016). It has been demonstrated that chronic rhinosinusitis significantly decreases quality of life of the patients due to its symptoms as well as complications including depression, sleep disturbances, fatigue, olfactory dysfunction (RUDMIK, SMITH 2011). Particularly, both untreated chronic sinusitis (recurrent) and acute sinusitis may result in intracranial complications with long-term neurologic deficits like hemiparesis, aphasia, epilepsy, hydrocephalus, and visual deficits. Orbital complications include preseptal cellulitis, orbital cellulitis, abscesses (subperiosteal, orbital), as well as cavernous sinus thrombosis (BADR et al. 2016). It also increases the risk of nasopharyngeal cancer (TSOU et al. 2014), as well as extranasal diseases including ischemic stroke (KANG et al. 2013).

Environmental factors play a significant role in chronic rhinosinusitis (MIN, TAN 2015). The association between atmospheric pollution and chronic sinusitis is especially pronounced in urban environments (KHANNA, GHARPURE 2012). In particular, pollutant exposure was associated with ciliary dyskinesia and altered tight junctions (CALDERON-GARCIDUENAS et al. 2001).

The existing data demonstrate some association between metal exposure and nasal pathology (SUNDERMAN 2001). Particularly, nasal polyp tissue was characterized by an increased arsenic (As), cadmium (Cd), and nickel (Ni) content compared with healthy tissues (KHLIFI et al. 2015*b*). Certain metals, including chromium (Cr), As, and Ni, are capable of induction of rhinitis (SRIVASTAVA et al. 2018). At the same time, data on the association between toxic metal exposure and chronic sinusitis are insufficient.

Although environmental metal levels may partially originate from natural geochemical sources, extreme metal pollution is associated with their wide use in industry, pharmacy, agriculture, and the resulting emissions (JAISHANKAR et al. 2014). Metal pollution poses a significant health hazard for humans, especially for children, who are more prone to metal toxicity. Metal toxicity may result in impaired growth and development, neurotoxicity, respiratory diseases including asthma, as well as carcinogenicity (TCHOUNWOU et al. 2012). It has also been demonstrated that the upper respiratory tract may bea target of metal toxicity. Correspondingly, certain studies have shown that prenatal As exposure may increase the risk of respiratory infections (FARZAN et al. 2013).

Generally, the existing studies propose that environmental factors have a direct effect on the development of chronic rhinosinusitis. Therefore, the primary objective of the present study was to assess hair toxic metal and metalloid levels in children with chronic sinusitis using ICP-DRC-MS.

MATERIALS AND METHODS

The protocol of the present study was approved by the Local Ethics Committee. All procedures performed were in agreement with the principles of the Declaration of Helsinki (1964) and later amendments. The parents of the examined children signed informed consent forms prior the inclusion into the study.

A total of 300 children (gender ratio – 1:1) aged from 2 to 18 years, including 150 children with chronic sinusitis (J32.0 – ICD-10) and age-, gender-, and BMI-matched controls, were enrolled in the present study. Children were additionally divided into two age-groups: group 1 – aged 2-9 years old, and group 2 – children aged 10-18 years old, in order to assess age-related changes in hair trace element content. No significant group difference in age of the studied case-control groups was observed.

Only patients and controls living in St. Petersburg for the whole their lives or more than the last 5 years were included in the study in order to avoid the impact of environmental factors. The following exclusion criteria were used in order to prevent the influence of other side factors on hair trace element content: the presence of other chronic or acute processes in nasal cavity; prior nasal surgery; acute or chronic inflammatory processes of other localizations; acute traumas or posttraumatic period; vegetarianism and other disorders of food behaviour; endocrine disorders (obesity, diabetes); metallic implants (including dental amalgam fillings); dyed hair; the use of mineral-enriched shampoos and hair care products.

The hair was washed at the day of sampling using regular shampoos. Proximal parts (1-2 cm) of occipital scalp hair strands were collected using ethanol-precleaned stainless steel scissors (0.05-0.1 g). The hair samples were washed with acetone, rinsed three times with double distilled water. Subsequently, 0.05 g of cleaned hair samples were digested (20 min - 170-180°C) in Teflon tubes containing 5 ml of concentrated (65%) HNO_3 (Sigma-Aldrich Co., St. Louis, MO, USA) in a microwave Berghof SW-4 DAP-40 (Berghof Products & Instruments, Eningen, Germany) system. The digests were added double distilled water to a total volume of 15 ml and used for analysis. The levels of aluminium (Al), arsenic (As), beryllium (Be), cadmium (Cd), mercury (Hg), nickel (Ni), and lead (Pb) were assessed using inductively-coupled plasma mass spectrometry on a NexION 300D (PerkinElmer Inc., Shelton, CT 06484, USA) equipped with an ESI SC-2 DX4 autosampler (Elemental Scientific Inc., Omaha, NE 68122, USA). The system was calibrated using standard solutions (0.5, 5, 10 and 50 μg L^{-1}) of trace elements prepared from Universal Data Acquisition Standards Kits (PerkinElmer Inc., Shelton, CT 06484, USA). Internal online standardization was performed using Yttrium (Y) and Rhodium (Rh) solutions (10 μg L^{-1}) Pure Single-Element Standard (PerkinElmer Inc., Shelton, CT 06484, USA). Laboratory quality control was regularly performed using the certified reference material (CRM) of human hair GBW09101 (Shanghai Institute of Nuclear Research, Shanghai, China) with the recovery rates for all elements of 92% - 106%.

The data obtained were processed using Statistica 10.0 (Statsoft, Tulsa, Ok, USA) software. As the distribution of data was not Gaussian, descriptive statistics of hair elements content included median and the respective 25 and 75 percentile boundaries (interquartile range). The non-parametric Mann-Whitney *U*-test was used for group comparisons. Correlation analysis included assessment of the Spearman rank order correlation coefficient (*r*) and particular *p* values. The level of significance was set as $p < 0.05$ for all analyses.

RESULTS AND DISCUSSION

The data demonstrate that hair toxic metal levels in the total cohort of children were associated with chronic sinusitis (Figure 1). In particular, hair As levels in the examined patients were 24% higher than those in healthy children. At the same time, hair Be content in patients with chronic sinusitis exceeded the respective control values by a factor of more than two. At the same time, no significant group difference in hair levels of Al, Cd, Hg, Ni, and Pb was observed (Table 1).

Further analysis demonstrated that the age of children modulates the association between hair toxic metal and metalloid levels and chronic sinusitis (Table 2). In particular, the hair As and Be levels in the group

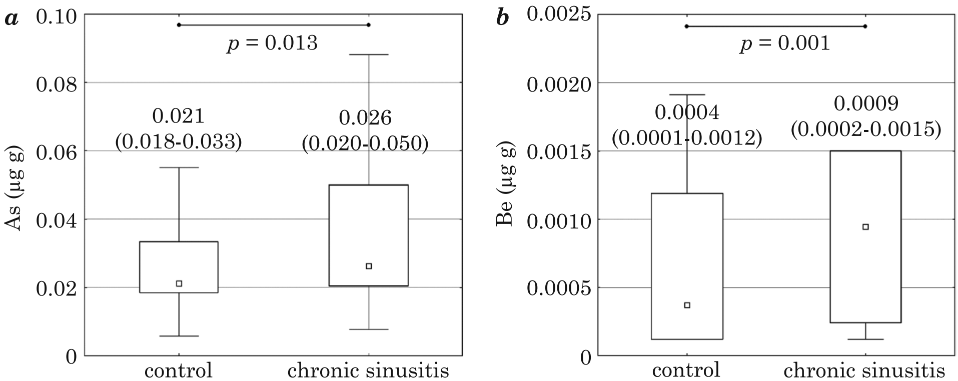

Fig. 1. Hair arsenic (*a*) and beryllium (*b*) content in children with chronic sinusitis and age-matched controls

Table 1

Hair metal levels in children with chronic sinusitis (μg g^{-1})

Element	Control	Chronic sinusitis	*P* value
Al	5.146 (3.301-8.375)	4.919 (3.001-8.155)	0.566
Cd	0.013 (0.009-0.024)	0.014 (0.007-0.026)	0.886
Hg	0.175 (0.071-0.339)	0.184 (0.105-0.392)	0.220
Ni	0.169 (0.106-0.262)	0.153 (0.106-0.232)	0.291
Pb	0.378 (0.190-0.637)	0.327 (0.168-0.594)	0.342

Data expressed as median (25-75 percentiles); no significant group difference was detected.

Table 2

Hair metal and metalloid levels (μg g^{-1}) in children with chronic sinusitis in relation to age

Element	Control	Chronic sinusitis	*P* value
2-9 years old			
Al	6.743 (4.451-10.85)	5.033 (3.367-9.525)	0.122
As	0.027 (0.021-0.04)	0.034 (0.021-0.058)	0.047 *
Be	0.0004 (0.0001-0.001)	0.0008 (0.0003-0.0015)	0.004 *
Cd	0.017 (0.010-0.03)	0.021 (0.011-0.039)	0.387
Hg	0.221 (0.077-0.33)	0.179 (0.105-0.325)	0.680
Ni	0.164 (0.101-0.26)	0.138 (0.103-0.220)	0.298
Pb	0.477 (0.284-0.70)	0.416 (0.268-0.687)	0.445
10-18 years old			
Al	4.090 (2.759-6.447) †	4.857 (2.840-7.278)	0.346
As	0.021 (0.016-0.026) †	0.021 (0.018-0.042) †	0.039 *
Be	0.0004 (0.0001-0.0015)	0.0013 (0.0001-0.0015)	0.006 *
Cd	0.011 (0.007-0.018) †	0.011 (0.006-0.020) †	0.848
Hg	0.137 (0.066-0.339)	0.216 (0.109-0.420)	0.050 *
Ni	0.175 (0.108-0.266)	0.163 (0.106-0.259)	0.598
Pb	0.256 (0.136-0.514) †	0.252 (0.146-0.491) †	0.871

Data expressed as median (25-75 percentiles); * significant group difference at $p < 0.05$;
† significant difference in comparison to the values of younger children (2-9 y.o.)

of younger children were 26% and 100% higher than in the controls. At the same time, the hair Be content in children aged 10-18 years exceeded the respective control values by a factor of more than three. Although no difference in medians of hair As were observed between the groups, the Mann-Whitney U test revealed a significantly higher level of As in children with chronic sinusitis. In addition, older children are also characterized by a significant 58% increase in hair mercury relative to the control values.

Age-related changes in hair metal and metalloid levels were also associated with chronic sinusitis. In particular, the hair Al, As, Cd, and Pb levels in healthy children of the older group were significantly lower than in the first age group: by 39% ($p < 0.001$), 22% ($p < 0.001$), 35% ($p = 0.004$), and 46% ($p < 0.001$), respectively. At the same time, an age-related decrease in children with chronic sinusitis was observed only for hair Al (38%; $p = 0.001$), Cd (52%; $p < 0.001$), and Pb (40%; $p = 0.002$), but not for Al.

The correlation analysis also demonstrated a statistical effect of chronic sinusitis on age-related changes in hair metal and metalloid levels (Table 3).

Table 3

Correlation between hair metal and metalloid levels and age in patients with chronic sinusitis and healthy controls.

Element	Control		Chronic sinusitis	
	r	*p*	*r*	*p*
Al	-0.307	< 0.001 *	-0.237	0.004 *
As	-0.222	0.007 *	-0.161	0.049 *
Be	-0.049	0.558	0.054	0.514
Cd	-0.187	0.023 *	-0.243	0.003 *
Hg	0.015	0.853	0.029	0.721
Ni	-0.067	0.420	0.043	0.600
Pb	-0.262	0.001 *	-0.189	0.021 *

Data presented as correlation coefficients (r) and particular p values; * correlation is significant at $p < 0.05$

Particularly, an age-related decrease in hair toxic metal and metalloid levels was more profound in the control group, whereas the association in the chronic sinusitis group was characterized by lower correlation coefficients and significance, with the exception of cadmium. At the same time, no age--related change in hair Be, Hg, and Ni was revealed, neither in the control nor in the patient groups.

The present findings are generally in agreement with data on nasal effects of arsenic exposure including rhinitis (Saha et al. 1999, Chen et al. 2010). It has also been demonstrated that As exposure is associated with a higher incidence of nasal polyposis in Tunisia. In particular, blood As levels in patients with nasal polyposis were 75% higher than the control (Khlifi et al. 2015*a*). Correspondingly, higher levels of As, Cd, and Ni were revealed in the nasal polyp tissue when compared with the baseline levels of healthy tissues (Khlifi et al. 2015b). An association with sinonasal cancer has also been reported (Shusterman 2011).

Taking into account the role of mucociliary clearance in the pathogenesis of sinusitis (Cohen et al. 2006), the association between metal exposure and chronic sinusitis may be mediated via alteration of mucociliary clearance.

In particular, prenatal As exposure was shown to affect the ciliary function via alteration of the responsible genes (Ramsey et al. 2013) and ATP--dependent Ca^{2+} Signaling (Sherwood et al. 2011). As also affects the barrier function of the airway epithelium (Sherwood et al. 2013). As-induced up-regulation of matrix metalloproteinase-9 (MMP-9) also results in altered reparation in the airway epithelium (Olsen et al. 2008).

The most significant elevation was detected for hair Be in children with chronic sinusitis. Although certain indications of the link between Be exposure and rhinitis exist (Cooper, Harrison 2009), no data demonstrated the association between Be and chronic sinusitis. At the same time, Be exposure was shown to up-regulate airway the epithelial intercellular adhesion molecule-1 (ICAM-1) (Rodriguez et al. 2008), which is known to play a role in chronic sinusitis (Kramer et al. 2000). Be is also capable of the induction of airway inflammation with overproduction of tumor necrosis factor α (TNFα), interleukin-12 (IL-12), and interferon γ (IFNγ) (Salehi et al. 2009). It is also notable that mucociliary clearance plays a significant role in beryllium removal from lungs (Maier 2002).

Similarly, inhaled Al (Exley et al. 2013), Cd (Nawrot et al. 2010), and Pb (Hu et al. 2007) particles are excreted from the lungs and nose by mucociliary clearance.

Cd was also shown to inhibit the ciliary activity in the upper airways (Lag et al. 1986). In addition, Cd exposure is also associated with impaired tight junction integrity in the airway epithelial cells (Cao et al. 2015). These data correspond to the finding of the role of heavy metal exposure (Cr, Cd, Ni) in nasal epithelium dystrophy (Sunderman et al. 2001). High blood levels of Cd were also associated with a more than twofold increase in the incidence of nasal polyposis (Khlifi et al. 2015*c*).

An additional mechanism of ciliary dysfunction induced by heavy metals may include their antagonism with essential trace elements like zinc and selenium (Rahman et al. 2019), which are known to play a significant role in mucociliary clearance (Jaspers et al. 2007, Woodworth et al. 2010).

Environmental sources of arsenic exposure may include contaminated drinking water and foods, smoking, industrial (wood and leather preservatives, pharmaceutic and glass industry, etc.) emissions (Chung et al. 2014). Significant beryllium emissions may occur from the electronic and aerospace industry (Taylor et al. 2003). However, taking into account the lack of significant group differences in hair metal levels between the sinusitis and control groups living in the same locations, as well as the role of the ciliary apparatus in metal removal, it can be suggested that, rather than dealing with greater metal exposure in children with chronic sinusitis, altered mucociliary clearance may result in reduced airway beryllium and arsenic clearance and higher retention.

CONCLUSIONS

The data demonstrate that children with chronic sinusitis have significantly elevated hair As and Be, being more pronounced in older children. Hypothetically, reduced mucociliary clearance in chronic sinusitis is associated with impaired metal particle removal from the upper airways, thus increasing the body's burden of these metals. The latter in turn aggravate chronic inflammation and mucociliary dysfunction. However, further studies are required to explore the inherent mechanisms of the revealed relationship.

Conflict of interest

The authors state no conflict of interest

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