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Research article

# ENVIRONMENTAL CONTAMINATION WITH METALS AS A RISK FACTOR CAUSING DEVELOPING AUTOIMMUNE THYROIDITIS IN CHILDREN IN ZONES INFLUENCED BY EMISSIONS FROM METALLURGIC ENTERPRISES

**I.E. Shtina, S.L. Valina, K.P. Luzhetskiy, M.T. Zenina, O.Yu. Ustinova**

Federal Scientific Center for Medical and Preventive Health Risk Management Technologies,
82 Monastyrskaya Str., Perm, 614045, Russian Federation

*Chemical environmental factors trophic for the endocrine system and its organs produce negative influence on it that becomes apparent through growing incidence and pathomorphism of endocrine diseases.*

*Our test group was made up of 102 children with diagnosed autoimmune thyroiditis (AIT) who were chronically exposed to metals (lead, manganese, nickel, chromium, and zinc) being components in emissions from metallurgic enterprises in Perm region. Our reference group included 46 children with AIT who lived beyond zones influenced by the aforementioned enterprises in areas with the sanitary-hygienic situation being relatively favorable. We comparatively analyzed the results of clinical and ultrasound examinations that focused on evaluating children's thyroidal and immune state.*

*A growth in incidence with thyroiditis amounted to 63.6 % on the test territory over 10 years and it was 1.6 times higher than on average in the region (40.8 %); there was no growth in the indicator detected on the reference territory. Concentrations of chromium, nickel, lead, zinc, and manganese higher than regional background level were 1.7–5.5 times more frequently detected in blood of children from the test group against the reference one. A number of AIT cases was higher among exposed boys (by 2.0 times, p = 0.070); exposed children also had higher Ig A, M, and G contents in blood serum (by up to 2.9 times, p = 0.015–0.056), higher TSH levels (by 2.0 times, p = 0.096), and lower free T4 contents (by 5.4 times, p = 0.057). Diffuse damage to the thyroid gland was by 1.3 times more frequent under exposure to adverse factors created by metallurgic production; AIT combined with other diseases was also more frequent (p = 0.041).*

*Rates and growth in incidence of thyroid gland diseases and thyroiditis are by 1.3–2.3 times higher among children and teenagers living on territories where metallurgic enterprises are located against the same indicators on territories where sanitary-hygienic situation is relatively favorable. We detected less apparent gender-related differences in AIT frequency, a greater number of improper thyroidal state, elevated risks of diffuse changes in the thyroid gland and activation of humoral immune response that was by 2.2–3.4 times more frequent together with concomitant damage to other systems under elevated contents of metals in blood.*

***Key words:*** *incidence, autoimmune thyroiditis, children and teenagers, metals, less apparent gender-related differentiation, cause–effect relations, diffuse structural changes, hypothyroidism.*

According to federal statistical data provided by the Public Healthcare Ministry of the Russian Federation, diseases of the thyroid gland hold the second rank place among endocrine pathologies following obesity and their prevalence amounts to 10.6 cases per 1,000 children. Analysis of statistical data in dynamics has revealed that there hasn't been any drop in this prevalence since 2015 [1, 2].

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**Irina E. Shtina** – Candidate of Medical Sciences, Head of the Laboratory for Complex Issues of Children's Health (e-mail: shtina_irina@mail.ru; tel.: +7 (342) 237-27-92; ORCID: http://orcid.org/0000-0002-5017-8232).

**Svetlana L. Valina** – Candidate of Medical Sciences, Head of the Department for Children and Teenagers Hygiene (e-mail: valina@fcrisk.ru; tel.: +7 (342) 237-27-92; ORCID: https://orcid.org/0000-0003-1719-1598).

**Konstantin P. Luzhetskiy** – Doctor of Medical Sciences, Deputy Director for Organizational and Methodical Work (e-mail: nemo@fcrisk.ru; tel.: +7 (342) 236-30-12; ORCID: http://orcid.org/0000-0003-0998-7465).

**Mariya T. Zenina** – doctor of ultrasound diagnostics at Department of Radiation Diagnostics (e-mail: shtina_irina@mail.ru; tel.: +7 (342) 237-27-92; ORCID: https://orcid.org/0000-0001-6623-3075).

**Olga Yu. Ustinova** – Doctor of Medical Sciences, Deputy Director responsible for clinical work; Professor at the Department for Human Ecology and Life Safety (e-mail: ustinova@fcrisk.ru; tel.: +7 (342) 236-32-64; ORCID: http://orcid.org/0000-0002-9916-5491).

Reversible risk factors taken into account, early detection and treatments of diseases of the thyroid gland in children and teenagers are vital for preventing compensatory hyperplasia of the thyroid gland tissue, hormonal imbalance and associated delays in sexual, physical, and mental development. Efficient diagnostics of the pathology is provided by detecting risk factors, early clinical signs and symptoms [3–6].

Autoimmune thyroiditis (AIT) is a multifactorial disease with complicated etiopathogenesis when genetically determined peculiarities of immune responses are realized under exposure to environmental factors including technogenic chemicals and iodine deficiency [1, 7–9].

Metals are widely spread in environmental objects and are able to seriously damage the body when penetrating it from the environment. Research results described by L.N. Palagina indicate that thyroid gland pathologies become much more frequent when blood is contaminated with chromium and lead [10].

Autoimmune processes play a significant role among various immune pathologic impacts exerted by metals. B.A, Rozhko reviewed the current situation with autoimmune thyroiditis and highlighted that environmental factors induced an autoimmune process in people who were genetically predisposed to AIT; these factors accounted for 31.8 % among cause-effect relations regarding development of autoimmune diseases of the thyroid gland [11].

A child’s body is the most vulnerable to technogenic environmental factors with their contribution to health disorders reaching 30 % [12][1]. Excessive introduction of metals into children’s bodies in cities where metallurgic enterprises are located produces direct thyreocytotoxic effect; they can make for developing chronic inflammatory diseases of the thyroid gland that have autoimmune genesis or aggravate their clinical course in case they are already present. These diseases are often combined with other autoimmune pathologies [13, 14].

**Our research aim** was to establish clinical, laboratory and ultrasound peculiarities of autoimmune thyroiditis in children who were chronically exposed to metals in the environment.

**Materials and methods.** Our test group was made up of 102 children with previously diagnosed autoimmune damage to the thyroid gland; they lived on territories where metallurgic plants were located. Our reference group included 46 children with diagnosed AIT who lived on a territory where sanitary-hygienic situation was relatively favorable.

To reveal AIT peculiarities in exposed children, we comparatively analyzed average group results of clinical, laboratory and ultrasound examinations and frequency of their deviations from physiological standards. Both groups were comparable as per age (13.79 ± 12.63 in the test group and 13.10 ± 7.95 in the reference one, $p = 0.688$) and social status ($p > 0.05$).

Incidence of thyroid gland diseases and thyroiditis among children depending on a territory where they lived was comparatively analyzed based on statistical data collected in 2010–2019 and provided by the Perm Regional Medical Information and Analytical Center.

We examined contents of several metals in blood (lead, manganese, nickel, chromium, and zinc) according to the Methodical guidelines[2] on *Agilent 7500cx* mass spectrometer

[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2019 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2019: The State report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2020, 299 p. (in Russian).

[2] MUK 4.1.3230–14. Izmerenie massovykh kontsentratsii khimicheskikh elementov v biosredakh (krov', mocha) metodom mass-spektrometrii s induktivno svyazannoi plazmoi: utv. rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 19 dekabrya 2014 g. [Methodical guidelines MUK 4.1.3230–14. Measuring mass concentrations of chemicals in biological media (blood and urine) by mass spectrometry with inductively coupled plasma: approved by A. Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and the RF Chief Sanitary Inspector on December 19, 2014]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/495856222 (September 18, 2021) (in Russian).

("Agilent Technologies Inc."). All the results were compared with background regional levels that amounted to 0.0144 ± 0.0067 mg/dm$^3$ for lead; 0.013 ± 0.00397 mg/dm$^3$, manganese; 0.00225 ± 0.00202 mg/dm$^3$, nickel; 0.0027 ± ± 0.00199 mg/dm$^3$, chromium$^{6+}$; 4.77705 ± ± 0.7517 mg/dm$^3$, zinc.

Thyroidal state was evaluated based on determining levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), and antibodies to thyroperoxidase (AB-TPO) in blood. Levels of immunoglobulins Ig G, M and A were analyzed in blood serum with radial immunodiffusion (Manchini method) to determine the current state of humoral immune response.

Ultrasound examination of the thyroid gland (morphometry and volumetry) was accomplished as per conventional procedures on *"VividE9"* (Vingmed Ultrasound AS) and *"AplioXG"* (Toshiba AplioXGSSA-790A) expert devices and the results were interpreted in comparison with conventional reference values [15].

All the examinations were accomplished in accordance with ethical principles stipulated by the Helsinki Declaration (2013) and the RF National standard GOST-R "Good clinical practice" (ICHE6 GCP).

Statistical and mathematical analysis was performed with conventional parametric statistic procedures. Intergroup differences were analyzed based on comparing mean values of the indicators (*M*) and standard deviation (*SD*) ($M \pm SD$). Pearson's chi-square ($\chi^2$) was used to compare qualitative features. Odds ratio (*OR*) was used to quantitatively measure an effect when relative indicators were compared; a significance of a correlation between an outcome and a factor was considered to be proven in case the confidence interval was beyond the boundary of an area where no effects were detected and this boundary was considered to be equal to 1. Pearson's correlation coefficient (*r*) was calculated to quantitatively assess correlations between the indicators and correlation intensity was evaluated as per the Chaddock scale. "Metal concentration in blood – incidence with AIT, morphological and functional disorders in the thyroid gland" dependence was analyzed by building up one-factor regression models with included values of regression coefficient (*b1*) and calculated determination coefficient ($R^2$). The results were considered statistically significant at $p \leq 0.05$.

**Results.** The environment in Perm region where all the examined children live has moderate and mild natural iodine deficiency. Incidence of thyroid gland diseases in the region grew by 1.5 times over 10 years and reached 6.91 ‰. Official statistical data were analyzed in detail to establish that overall incidence of thyroid gland diseases grew by 1.65 time among children who lived in a zone exposed to metallurgic production (from 6.16 to 10.17 ‰) whereas it grew only by 1.3 times on territories where the sanitary-hygienic situation was relatively favorable (from 2.1 to 2.62 ‰). Average regional growth in incidence of thyroiditis amounted to 40.8 % (from 0.49 to 0.69 ‰); it was 63.6 % on the test territory but the incidence rates were stable on the reference territory (Table 1).

Table 1

Incidence of thyroid gland diseases and thyroiditis among children in 2010 and 2019, ‰

| Year of research | Perm region | Test territory | Reference territory |
|---|---|---|---|
| Incidence of thyroid gland diseases | | | |
| 2010 | 4.69 | 6.16 | 2.1 |
| 2019 | 6.91 | 10.17 | 2.62 |
| Incidence of thyroiditis | | | |
| 2010 | 0.49 | 0.55 | 0.40 |
| 2019 | 0.69 | 0.90 | 0.35 |

Metal contents in blood were analyzed using chemical-analytical procedures; the examination revealed that a share of children with lead contents in blood being higher than background levels was by 2.3 times higher in the test group against the reference one ($p < 0.001$); elevated lead contents, by 5.5 times ($p < 0.001$); elevated nickel contents, by 2.0 times ($p = 0.027$); elevated chromium contents, by 1.7 times ($p < 0.001$); elevated zinc contents, by 2.7 times ($p < 0.001$) (Table 2).

Table 2

A share of samples with elevated metal contents in children's blood, %

| Metals | Test group, *n* = 102 | | Reference group, *n* = 46 | | $\chi^2$ | *p* |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | | |
| Chrome[6+] | 96 | 94.1 | 26 | 56.5 | 23.85 | < 0.001 |
| Zinc | 95 | 93.1 | 16 | 34.8 | 57.58 | < 0.001 |
| Lead | 61 | 59.8 | 12 | 26.0 | 14.42 | < 0.001 |
| Manganese | 61 | 59.8 | 5 | 10.8 | 30.73 | < 0.001 |
| Nickel | 36 | 35.3 | 8 | 17.4 | 9.44 | 0.003 |

Table 3

Results obtained through examining hormone and immunological status in children, *M* ± *SD*

| Indicator | Test group, *n* = 102 | Reference group, *n* = 46 | *p* |
|---|---|---|---|
| TSH, μIU/cm$^3$ | 2.41 ± 3.87 | 1.87 ± 2.56 | 0.317 |
| Free T4, pmol/dm$^3$ | 13.8 ± 6.62 | 14.6 ± 4.07 | 0.369 |
| Antibodies to TPO, IU/cm$^3$ | 189.91 ± 658.59 | 79.56 ± 164.94 | 0.115 |
| IgG, g/dm$^3$ | 12.42 ± 3.77 | 11.32 ± 2.73 | 0.047 |
| IgM, g/dm$^3$ | 1.49 ± 0.66 | 1.36 ± 0.40 | 0.144 |
| IgA, g/dm$^3$ | 1.81 ± 0.92 | 1.66 ± 0.64 | 0.254 |

We established a statistically significant correlation between growing incidence of AIT and elevated contents of lead ($R^2$ = 0.68; *b1* = 125.6; $p \leq 0.0001$), manganese ($R^2$ = 0.17; *b1* = 83.9; $p \leq 0.05$), nickel ($R^2$ = 0.32; *b1* = 98.9; *p* = 0.02) and zinc ($R^2$ = 0.70; *b1* = 18.1; *p* = 0.04) in blood.

We didn't reveal any authentic differences between the groups regarding age structure of patients with AIT since pre-adolescent children (aged 7–13) accounted for 26–27.4 % in both groups and adolescent children (older than 13) accounted for 72.6–74 % ($p > 0.1$).

Having examined sex structure in two groups, we revealed that males tended to have AIT 2 times more frequently than females in the test group in comparison with the reference one (26.4 against 13 %, *p* = 0.070).

Average group levels of hormones in blood (TSH and free T4) didn't have any statistically significant differences in both groups (*p* = 0.31–0.23) (Table 3). However, there was an ascending trend in a number of children with signs of sub-clinical and manifest hypothyroidism detected in the test group as it was indicated by 2.2–5.4 times greater share of samples with elevated TSH contents (20 (19.6 %) against 4 (8.7 %); $\chi^2$ = 2.78; *p* = 0.096) and lower free T4 contents (12 (11.8 %) against 1 (2.2 %); $\chi^2$ = 3.64; *p* = 0.057) in blood. We established a statistically significant correlation between growing TSH contents and elevated nickel and zinc contents in blood (*b1* = 2.99–3.2; $R^2$ = 0.49–0.51; $p < 0.001$).

Average group contents of antibodies to thyroidal peroxidase were by 2.4 times higher among children from the test group against those from the reference one but this difference was not statistically significant (*p* = 0.11) (Table 3).

Having evaluated humoral immunity, we established that children with metal contents in their blood exceeding background levels had elevated contents of immunoglobulins in their blood serum by 1.8–2.9 times more frequently; it was true for IgG (30 (29.4 %) against 5 (10.9 %); $\chi^2$ = 6.04; *p* = 0.015; *OR* = 3.42, *CI* = 1.23–9.49); IgM (19 (18.6 %) against 3 (6.5 %); $\chi^2$ = 3.67; *p* = 0.056; *OR* = 3.28, *CI* = 0.92–11.71); IgA (37 (36.3 %) against 9 (19.6 %); $\chi^2$ = 4.13; *p* = 0.043; *OR* = 2.34, *CI* = 1.02–5.38).

Ultrasound examination of the thyroid gland and surrounding tissues revealed certain changes; their frequency is given in Table 4. Children who were chronically exposed to adverse chemical factors had diffuse changes in thyroidal tissues revealed by ultrasound examination of the thyroid gland; these changes were typical for AIT and were registered in such children by 1.3 times more frequently than in children from the reference group (74 (72.5 %) against 25 (54.3 %); $\chi^2$ = 4.74, *p* = 0.030) who mostly tended to have only minimal changes in the organ and tissues (28 (27.5 %) against 21 (45.7 %); $\chi^2$ = 4.74, *p* = 0.03). A probability of diffuse changes in the thyroid gland was by 2.2 times higher for children with AIT who were exposed to metals against children with the same pathology who lived on a territory where the sanitary-hygienic situation was relatively favorable (*OR* = 2.22, *CI* = 1.08–4.58).

Table 4

A share of children with changed indicators revealed through ultrasound scanning of the thyroid gland, %

| Ultrasound scanning results | Test group, $n$ = 102 | | Reference group, $n$ = 46 | | $\chi^2$ | $p$ |
|---|---|---|---|---|---|---|
| | $n$ | % | $n$ | % | | |
| Increased volume of the thyroid gland | 65 | 63.7 | 24 | 52.2 | 1.76 | 0.185 |
| Diffuse structural changes | 74 | 72.5 | 25 | 54.3 | 4.74 | 0.030 |
| Minimal structural changes | 28 | 27.5 | 21 | 45.7 | 4.74 | 0.030 |
| Enhanced vascularization of the gland | 77 | 75.4 | 33 | 71.7 | 0.23 | 0.629 |
| Increased linear blood flow velocity | 35 | 34.3 | 16 | 34.8 | 0.003 | 0.956 |
| Decrease in peripheral resistance indices | 38 | 37.2 | 19 | 41.3 | 0.22 | 0.640 |
| Reactive hyperplasia of regional lymph nodes | 58 | 56.8 | 26 | 56.5 | 0.002 | 0.970 |

Growing volume of the thyroid gland, enhanced vascularization, and reactive changes in regional lymph nodes as per hyperplasia type were detected with similar frequency regardless of a territory where examined children lived ($p$ = 0.185–0.97) (Table 4).

Correlation analysis confirmed a moderate inverse correlation between lead contents in blood and values of peripheral resistance indices ($r$ = -0.35, $p$ = 0.045); a significant direct correlation between nickel contents in blood and volume of the thyroid gland ($r$ = 0.58, $p$ = 0.027).

Having analyzed concomitant pathologies, we revealed that children who were exposed to adverse chemical factors due to metallurgic production tended to have alopecia areata (L63) more frequently than children from the reference group (15 (14.7 %) against 2 (4.3 %); $\chi^2$ = 3.34; $p$ = 0.068). Although diseases that occur due to immunologic reactivity disorders, such as dermatitis (L20–30) (15 and 16 %), bronchial asthma (J45) (12 and 18 %), and other disorders involving the immune mechanism (D89.8; D89.9) (25 and 25 %) as well as such endocrine pathologies as obesity and other hyperalimentation (E65–E68) (24.5 and 17.4 %) were detected with similar frequency, overall burden of concomitant diseases was by 1.3 times higher for children who lived in a zone influence by emissions form metallurgic production than for children from the reference group (4.2 ± 4.07 against 3.1 ± ± 2.36 diseases, $p$ = 0.041).

**Results and discussion.** Our study on incidence of thyroiditis in Perm region revealed that average regional incidence rates were similar to those in the country in general (0.69 ‰ in 2019 in Perm region and 0.81 ‰ in the RF in 2018) [1, 8]. Our data on higher incidence of thyroid gland diseases and thyroiditis among children living on territories where certain industries are located against their counterparts living on territories where the sanitary-hygienic situation is relatively favorable are well in line with data obtained by other authors in previous studies [16, 17].

We established that children who lived on a territory where metallurgic production was located tended to have hormonal disorders by 2.0–4.5 times more frequently. Although most examined children (80.0–88.0 %) didn't have any functional disorders in the thyroid gland in spite of the disease, we should bear in mind that untimely detection of hypofunction has negative consequences for children's development. This substantiates the necessity to perform control over thyroidal status in children with AIT [17–19].

A greater burden of AIT and concomitant diseases in children who are chronically exposed to adverse chemical factors determines deteriorating forecasts for the disease development and creates additional difficulties in diagnosing and treating it. This increased burden is probably due to common risk factors and common involvement of different sections in pathogenetic mechanisms of the disease development [13, 14, 20, 21].

Results obtained by ultrasound scanning of the thyroid gland indicate that more significant changes in the thyroid gland structure are a cardinal sign of developing AIT associated with chemical environmental factors. This confirmed that ultrasound scanning remains a valuable diagnostic instrument. Absence of any apparent differences between results of hormonal and ultrasound scanning might be due to Perm region being somewhere in between territories with mild and moderate iodine deficiency [22–24].

Created mathematical models and revealed correlations prove negative effects produced by lead, manganese, nickel, and zinc and leading to adverse changes in the structure and functioning of the thyroid gland.

**Conclusions:**

1. In Perm region rates and growth in incidence of thyroid gland diseases is by 1.7 times higher among children living on territories with developed metallurgic production than on average in the region and by 2.6 times higher than on a territory where the sanitary-hygienic situation is relatively favorable.

2. Gender-related differences in frequency of detecting AIT tend to decrease among children with nickel, lead, zinc, and manganese contents in blood being higher than background regional levels; such children also tend to have sub-clinical and manifest hypothyroidism by 2.2–4.5 times higher than their counterparts from the reference group.

3. A probability of diffuse changes in the thyroid gland structure and activation of humoral immune response is by 2.2–3.4 times higher under exposure to chemical environmental factors that are tropic for the endocrine system and its organs.

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