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ENVIRONMENTAL DETERMINANTS OF THYROID PATHOLOGY

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Ключевые слова: *щитовидная железа, экологически обусловленная патология, гипотиреоз, тяжелые металлы, тиреодизрапторы, радиационно-индуцированная патология, электромагнитно-индуцированная патология*

Abstract. Environmental determinants of thyroid pathology. Ryabukha O.I., Fedorenko V.I. *Ecological situation of many countries, including Ukraine, is characterized by progressive anthropogenic and technogenic pollution, which causes growth in thyroid pathology, the share of which is significant in the structure of endocrine diseases. The main causes of thyroid disorders include iodine deficiency in the environment, exposure to a number of widely used chemicals (thyrodisruptors), heavy metal ions. A variety of physical environmental factors are important. A significant increase in thyroid cancer is frequently associated with local or general exposure to ionizing radiation. Prolonged exposure to electromagnetic fields can lead to disorders in the gland's homeostasis. The functional capacity of the gland is also impaired by unsanitary living conditions, some bacteria and viruses, and improper nutrition. High sensitivity of the gland to external impacts and high social significance of thyroid pathology give grounds to consider the morphofunctional condition of the thyroid gland as a marker of ecological well-being of the environment.*

Реферат. Екологічні передумови виникнення тиреоїдної патології. Рябуха О.І., Федоренко В.І. *Екологічній ситуації багатьох країн, зокрема й України, притаманне прогресуюче антропо- та техногенне забруднення, що спричиняє зростання тиреоїдної патології, частка якої в структурі ендокринних захворювань є вагомою. До основних причин розладів діяльності щитоподібної залози відносять дефіцит йоду в об'єктах довкілля, вплив низки широковживаних хімічних речовин (тиреодизрапторів), іонів важких металів. Важливими є різноманітні фізичні фактори навколишнього середовища. Значне зростання онкологічної патології щитоподібної залози часто пов'язують із локальним чи загальним впливом іонізуючого випромінювання. До порушень гомеостазу залози може призводити тривалий вплив електромагнітних полів. Функціональну спроможність залози також погіршують антисанітарні умови проживання, деякі бактерії та віруси, нераціональне харчування. Велика чутливість залози до зовнішніх впливів та висока соціальна значущість тиреоїдної патології дають підстави вважати морфофункціональний стан щитоподібної залози маркером екологічного благополуччя довкілля.*

Throughout life, an organism is constantly exposed to various environmental impacts that transform the activities of its organs and systems, which can pose a serious threat to health. One of the components in the unified system of maintaining homeostasis, regulation of vital functions, control over metabolic, physiological and adaptive processes is the thyroid gland, which hormones play an important role in the body's adaptation to existence in changing environmental conditions [37]. At the same time, this makes the thyroid gland one of the most vulnerable organs involved in the environment. The growth of anthropogenic and technogenic pollution causes the syndrome of ecological maladaptation, which negatively affects the population health, leads to a chain reaction of changes in the

work of various organs and activities of the body as an integral biological system [12].

The purpose of the work is to single out, characterize the main determinants of ecologically caused thyroid gland pathology and to generalize information about environmental factors that may be its cause, according to the literature.

The study of the thyroid gland drew attention not only to the high level of thyroid pathology in the overall structure of the disease and the acceleration of its spread [3], but also permitted to identify the anatomical and physiological features of the body [13] that make it sensitive to various external impacts [1, 2] and lead to activity disorders and structural problems, autoimmune and proliferative processes. A review of the scientific literature permitted [47] to note that thyroid gland damage can occur due to both natural (bioactive food substances) and artificial (exogenous chemicals) impacts, and to emphasize that the action of these factors can be aimed at any link of the hypothalamus-pituitary-thyroid gland axis, to disrupt the synthesis and secretion of thyroid hormones, their transport through the bloodstream, to impede transmembrane transport or to block the local action of hormones. The key to the normal functioning of the organism is the stability of its chemical composition. Biometal imbalance, including that mediated by the environment, is the cause of various health disorders. At the same time, as it is noted [7], this problem ranks first among the pressing and unresolved issues of preventive medicine, reaching the national scale in some cases. Prerequisite for the thyroid gland's effective activity is a sufficient supply of exogenous iodine as a substrate for biosynthesis of its hormones. However, 2 billion people in the planet live in areas with iodine deficiency, of which about 1.6 billion are at risk of developing iodine deficiency diseases [41], the most common of which is hypothyroidism. The result of iodine deficiency is thyroid failure as an organ and development of secondary alimentary hypothyroidism, which is accompanied by a number of interrelated disorders of the thyroid gland and the body.

A characteristic feature of hypothyroidism caused by alimentary iodine deficiency is goiter, which morphological basis is diffuse growth of thyroid tissue. According to the WHO (2000), 655 million people had endemic goiter, and 43 million had brain dysfunction and mental retardation due to iodine deficiency. In regions where severe iodine deficiency is endemic (for example, in some highlands of the Andes or the Himalayas), according to the WHO (2011) from 5 to 15% of the population may be affected by endemic cretinism; endemic goiter is also often associated with a large number of genetic disorders [40]. Although iodine deficiency in the environment of Ukraine does not reach a critical level, a decrease in the thyroid gland's functional activity and in levels of thyroid hormones may be accompanied by a negative impact on population health. There is evidence that iodine-deficient conditions, even in the absence of clinical manifestations of decreased thyroid functional activity, may increase the risk of thyroid cancer [44].

At the same time, goiter can be induced by many environmental factors. It is the improper feeding is a cause of hypothyroidism, as it is emphasized by the researchers who believe that in the poor population development of goiter with clinical signs of hypothyroidism is often due to the predominance of products with goitrogenic properties in their diet, such as cabbage, turnips, radishes, soybeans, millet, maize, cassava and others. The study of mechanisms of influence of plant strumogenic agents has shown that their action is due to the presence of thiocyanates, which inhibit the transport of iodide into the thyroid gland; it is believed that the consumption of large amounts of goitrogenic products reduces absorption of thyroxine (T4), which is a leading factor in the development of hypothyroidism and goiter [20]. Important data have been obtained [19], which suggest that excessive consumption of foods with goitrogenic properties may be a trigger for autoimmune thyroid disease. The above thyroid gland's pathology can be caused by biological environmental factors, such as bacteria and viruses. It is most commonly associated with *Coxsackie A virus*, *Escherichia coli* and *Yersinia enterocolitica*, which can cause autoimmune thyroiditis, Graves' disease, and other immune disorders, including the production of antibodies to thyroid-stimulating hormone (TSH) receptors.

When within one region, several factors are combined, characterized by a negative impact on the thyroid gland, thyroid pathology increases progressively [5, 8]. Thus, the combination of iodine deficiency with anthropogenic pollution potentiates inhibition of thyroid synthesis and leads to thyroid hyperplasia. According to the study results [14], the iodine supply of the body in pregnant women deteriorated with increasing concentrations of carbon monoxide, nitrogen dioxide and sulfur oxide in the air of Samara (Russian Federation). Using the possibilities of mathematical analysis, the authors established the presence of direct correlations between the registered thyroid pathology and soil contamination in residential areas with salts of heavy metals (lead, cadmium, manganese). These data are consistent with the results of research [6], which

studied the state of the pituitary-thyroid system in children living in the iodine deficiency area in conditions of its contamination by oil and gas products – methane, nitrogen compounds, carbon dioxide, salts of heavy metals. The authors found that persons living in iodine-deficient environmentally contaminated environment had a significantly increased incidence of goiter, with reduced levels of T4 and triiodothyronine (T3) in their blood, while TSH levels were elevated. As a feature of Ukraine is the mosaic location of iodine deficiency areas and technogenic pollution, the obtained results significantly deepen the view of the problem of the thyroid disease polyetiology and permit to associate its occurrence with the environment status.

According to [4], technogenic pollution with various chemicals is becoming a leading risk factor for population health. Getting into the body with food, drinking water, air (atmospheric, in working or living areas), heavy metal ions accumulate in the thyroid gland and further lead to eco-dependent pathology; an extremely adverse effect of exposure to heavy metals is thyroid cancer [11]. Toxic effects of heavy metal ions on the thyroid gland are realized through direct and indirect mechanisms. Although the degree of damage may vary, the points of their application in the body are intrathyroid nucleic acids and proteins, hormone receptors, enzyme systems of hormonal synthesis and antioxidant orientation. In particular, it is believed that the action of mercury and lead can be a trigger for production of antibodies and cause autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis. Cadmium can disrupt thyroid function even at small concentrations. At chronic poisonings by cadmium compounds there is hypersecretion of thyroglobulin, hyperplasia of parafollicular epithelium cells, the morbidity incidence of multinodular goiter, autoimmune thyroid gland pathology grow; in [39] its carcinogenic effect is reported. Manganese is also able to change the level of TH. Analysis results on determining the content of manganese, copper, cobalt, nickel and chromium ions in the thyroid tissue under the conditions of its proliferative pathology (malignant and benign tumors, goiter, autoimmune diseases) showed that in such processes as papillary, follicular and undifferentiated cancer, the content of cobalt and nickel ions increase, while the content of manganese ions decreases. In recent years, data have been obtained on the presence of carcinogenic effect of lead [22] and vanadium [48] compounds.

The intense and rapid increase in environmental chemical pollution causes a legitimate concern. This is reflected by WHO experts and in the UN Environment Program in the press release "State of the science of endocrine disrupting chemicals 2012"; researchers have not only pointed out to the existence of this problem, but also emphasized its importance. The increase in the producing large groups of substances in household and industrial chemistry against the background of constant expansion of their scope and range of their applications poses urgent challenges to researchers to determine hazard or safety of these substances for human health [31]. Generalization of the accumulated experience permitted a large international group of scientists in early 2020 to publish a consensus on 10 key characteristics that are inherent in chemicals with dangerous endocrine disruptor properties [21]. The category of thyrodisruptors includes endocrine disruptors (EDs), in which the thyrotoxic action is established. Most of them can cross the placenta and the blood-brain barrier and affect the brain; their ability to be excreted in breast milk poses a potential risk to the thyroid gland of infants. Analysis of EDs mechanisms influence on the thyroid gland, performed by [24], permitted to establish that these substances have different fields of action on the hypothalamic-pituitary-thyroid axis. At the same time, according to the author, most of them inhibit the transmembrane protein responsible for iodine uptake by thyrocytes (sodium-iodine symporter - NIS) and TH synthesis, and their metabolites can bind to transporter proteins of thyroid hormones, including transthyretin. Though substances with antithyroid properties belong to different chemical classes, their persistence in the environment potentiates their harmful effects. Because EDs are constantly present in the environment, they have the ability to accumulate in the body. In this connection, we consider very alarming the notification [23] about the ability of EDs to inhibit development of the fetal brain against the background of the simultaneous destruction of its thyroid gland. For a total, the consequences of disorders in vital systems can be a homeostatic disruption in individual organs or the body as an integrative system as a whole, and the end exogenous chemicals' effects on the thyroid gland can be various deviations in the thyroid gland itself, functionally related organs and systems, general disorders of the body, including autoimmune and proliferative processes.

Of the large number of xenobiotics that are classified as persistent organic pollutants (POPs), the greatest danger to humans and the environment are dioxins and polychlorinated biphenyls (PCBs) [16]. According to the US Department of Veterans Affairs (2018), in the blood serum of American Vietnam War veterans who came into contact with a dioxin-like substance in Agent Orange, there is a steady

increase in TSH levels with decreased levels of T3 and T4, which can be considered a sign of hypothyroidism [49]. Until recently, PCBs were used worldwide in the manufacture of transformers, electrical wire sheaths, hydraulic fluids, etc., but according to the Stockholm Convention on POPs (2001), most European countries have committed to neutralize all sources of PCBs by 2028. Polybrominated diphenyl ethers (PBDEs) are used as fireproof substances in the production of building materials, furniture, plastics; they are widely represented in household items. Up to 1.5 million tons of these chemicals are used annually in the world. Polychlorinated dibenzodioxins, PCBs, and PBDEs can bind to thyroid hormone transporting proteins. Having the ability to both antagonistic and agonistic effects on protein receptors, these substances displace T4 and disrupt the thyroid gland's function; the inherent ability of PCBs to act as thyroid pseudohormones allows them to reduce the levels of circulating T4, to stimulate pituitary gland, to impair thyroid hormones metabolism in the liver and to inhibit deiodinase activity. In addition, PCBs can lead to abnormal brain development, similar to that observed in clinical hypothyroidism, and can act as thyroid hormones agonists. In addition, there are reasons to believe that PCBs and PBDEs may be important risk factors for thyroid cancer [45].

Thyroid disruptor properties are inherent in a wide range of plasticizers, including bisphenols and phthalates. Bisphenol A (BPA) is used in the production of food packaging, including canned food, plastics, dental sealants, etc. The extent of BPA use is indicated by the fact that according to the United States Environmental Protection Agency it is detected in the urine of more than 90% of the US population. At the same time, in the scientific literature [17] there is evidence that BPA can provoke hypothyroidism. The authors believe that the mechanism of this phenomenon is the ability of BPA to bind to thyroid hormones receptors, which inhibits the effect of T4 on them. Phthalates, chemicals used as plasticizers in the manufacture of adhesives, cosmetics and detergents, can also suppress thyroid function. A significant decrease in T4 levels under the action of phthalates was found [25] in pregnant women, which can lead to impaired neurodevelopment of the fetus. Another class of thyrodisruptors are perfluorinated chemicals (PFC), which are used in the manufacture of furniture, textiles, utensils. The influence of PFC on the physiology of thyroid hormones is multiple and complex. In particular, they are responsible for increasing the conjugation of total T4 in the liver and the conversion of T4 to T3 in the thyroid gland. In general, PFC reduces the levels of thyroid hormones, which may affect the neurodevelopment of the fetus and requires further in-depth research [29].

Thyroid disruptor effect is inherent in different classes of pesticides [36]. Though in developed countries organochlorine pesticides such as DDT and hexachlorane have not been officially used for a long time, due to their resistance to degradation in the environment, lipotropy and prevalence in the food chain, these compounds continue to enter the body and adversely affect the thyroid gland. At the same time, the growing incidence of malaria and the general severe epidemiological situation currently observed in many countries of the African continent have led to the resumption of DDT use for antiparasitic purposes. Carbamates, which are used as insecticides, herbicides and fungicides, have a complex mechanism of action on the thyroid gland. They can disrupt the coherence of the hypothalamic-pituitary-thyroid axis. In addition, thiourea, which is a metabolite of some carbamates, inhibits thyroperoxidase, which is required for thyroid hormones synthesis. Pyrethroids are mainly used as insecticides. Because their chemical structure is somewhat similar to T3 and T4, they act as pseudothyroid hormones; there is evidence that pyrethroids are able to destroy thyroid hormones [18].

Nitrates are components of fertilizers; they inhibit NIS and can provoke development of proliferative processes in the thyroid gland, especially against the background of ionizing radiation [46]. Some fertilizers may contain perchlorates; when they get into drinking water and food, thyroid hormonopoiesis is blocked, iodine transport is reduced and T4 is converted into T3 [30]. Thiocyanates, which enter the body in various ways, including tobacco smoke, have a similar mechanism of action; it is important to note that adolescents are a particularly sensitive population category to the effects of these substances [33].

A large number of cosmetics (soaps, lotions, toothpastes) contain triclosan, an antibacterial agent, which can exhibit thyroid-stimulating properties, disrupting the development of the thyroid gland [32]. Some halogen-containing compounds, in particular chlorides and fluorides, can damage the thyroid gland. It was found that fluorides even at an acceptable concentration of less than 0.5 mg/l affect TSH and T3 [34]; the mechanism of their action is aimed at blocking NIS [50].

It is necessary to indicate separately such sources of environmental pollution, which are landfills for solid waste. Toxic substances from landfills get into the soil and water, which leads to persistent pollution of the surrounding areas and deteriorating the

population's health. In addition, these mostly unauthorized landfills are periodically incinerated to dispose accumulated waste. At the same time, according to the data of recent years, PCBs, dioxins, heavy metals, solvents, pesticides, etc. have been identified in the products of household waste incineration and the environment of the studied areas [35]. This permits to include the territories of solid waste accumulation into the anthropogenically determined neo-anomalous zones.

Radiation-induced thyroid lesions are another manifestation of ecologically determined pathology and one of the most significant consequences of the Chornobyl disaster [15]. The basis for the formation and persistence of disorders in the activity and condition of the thyroid gland was a combination of thyrocytes hypersensitivity to this complex of damaging effects: in this case the gland has increased "readiness" to capture iodine, and its iodine accumulation capacity increases significantly. Because the thyroid gland is abundantly vascularized, radioisotopes of iodine quickly enter it and accumulate in significant amounts: the thyroid gland absorbed up to 30% of radioiodine, which entered the general blood circulation. It is believed that this formed the preconditions for the emergence of radiation-induced oncological pathology of the thyroid gland and supported the tendency to its growth. In addition, in iodine-deficient areas, prolonged hyperstimulation of the TSH organ was a major risk factor for increasing the incidence of thyroid cancer. Currently, thyroid cancer among the population of these regions of Ukraine, which has been exposed to radiation, is registered 10-15 times more frequently than among the population of iodine-rich areas. This was one of the reasons for including Ukraine in the program of UNICEF and the WHO International Committee for Control of Iodine Deficiency Regions. In the occurrence of thyroid cancer, in addition to purely radioisotope pollution, certain "modifying" factors were important: the main ones are the age at which the person received a radiation injury, and the nature of the victims' diet. It is believed that in infants this phenomenon is associated with intense blood supply to the thyroid gland with its small volume, which causes active absorption and accumulation of radioiodine, and in adolescents – with a disorder of the initial balance in the system "hypothalamus – pituitary – thyroid gland" due to intense hormonal restructuring. The accident at the Fukushima-1 nuclear power plant raised legitimate concerns about its possible negative consequences for the population's health, including the impact on the thyroid gland and the resulting morbidity. At the same time, the results obtained by the researchers are to some extent contradictory and do not contain unambiguous conclusions about the dependence of the detected thyroid gland's oncological pathology on the fact of irradiation and its dose. Despite reports [43] of an association between the air levels of radioactive I^{131} and thyroid cancer in Fukushima prefecture, [38] it is believed that there is currently no convincing evidence of cause-effect relations between radiation exposure and thyroid cancer. The authors attribute this not only to the small dose received, but also to the traditional Japanese diet, which is rich in seaweed. The dependence of radiation and the use of iodine-containing substances, including and seafood, is indicated in the study [9].

The consequence of scientific and technological progress is an increase in the impact of non-ionizing radiation. This applies in particular to electromagnetic radiation (EMR), the main sources of which are power lines, telecommunications and radio and television antennas, electric motors for railway and urban transport, household appliances, computers and duplicating equipment etc. The growth of EMR background radiation indices by thousands of times is due to the almost comprehensive use of their anthropogenic sources for the needs of professional activity and household; low-intensity EMRs have become an inevitable component of urbanization, the body's response to which is mediated through the thyroid gland [10]. This raises a number of questions about its safety or probable danger to the human body. At the same time, the results of the studying the effects of EMR on the body are often contradictory, and some of its aspects remain unclear. In particular, studies [27] have established the ability of EMR to disrupt the functional activity of the thyroid gland, as indicated by an increase of T4 levels in blood serum with simultaneous reduction of T3 levels. In addition, the results of surveys in people living near high-voltage power lines or exposed to electromagnetic fields (EMF) during their professional activities, gave grounds [26] to recognize their impact harmful to the thyroid gland.

The reason for this was an increase in the size of the gland against the background of a decrease in the level of free T4, which according to the authors indicates an impairment of thyroid metabolism due to prolonged exposure to EMF.

Intensive use of cell phones for professional activities and in everyday life, increasing the duration of contact with the radiation source, reduction in the age of users necessitated an in-depth study of their impact on the thyroid gland. The results obtained by the researchers are not unambiguous. The mechanisms of EMR impact on the

thyroid gland are presented in the review [42]. The authors note that EMR causes oxidative stress and generates the formation of large amount of free radicals, in particular the hydroxyl radical of ozone, nitric oxide, hydrogen peroxide etc. Since the above substances are chemically unstable, they actively affect thyroid cells - free radicals bind to other macromolecules and destabilize the morphological status of thyrocytes. Though oxidative processes are necessary for the functioning of the thyroid gland as an organ, it is very sensitive to oxidative stress: excess free radicals damage macromolecules, leading to morphological and functional changes that can have various manifestations, including hypothyroidism and accelerated apoptosis [28].

Thus, the state of the thyroid gland is largely due to environmental impacts, which gives grounds for the isolation of anthropogenically caused thyroid pathology. Therefore, it is only possible to radically influence the occurrence of thyroid diseases by realizing all the dangers posed by an unfavorable environmental situation.

CONCLUSION

Disorders of the thyroid gland are polyetiological in nature, as they can be caused by various factors of natural or artificial origin, of chemical, physical or biological nature. Particularly unfavorable is the summation of the action of several damaging factors, which leads to significant thyroid dysfunction, and thus to multiorgan pathology. In the conditions of environmental pollution, the thyroid gland is a target organ, and its morphofunctional state is a marker of environmental well-being/problem, which puts the issue of thyroid pathology in the category of important medical and social problems of today.

Conflict of interests. The authors declare no conflict of interest.

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