Article

Pathogenetic Mechanisms of the Influence of SARS-COV-2 on the Pathology of the Thyroid Gland (Clinical And Experimental Study)

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Abstract:

Abstract: In 2022-2024, the study of the pathogenesis of thyroid diseases is most relevant due to the increased level of stress and the emergence of various early and late consequences of the past COVID-19 pandemic.The purpose of the study is to study the pathogenetic mechanisms of the influence of SARS-COV-2 on the pathology of the thyroid gland in a model experiment on laboratory animals and in statistical studies of the structure of morbidity during the COVID-19 pandemic.

In a model experiment on two species of laboratory rodents sensitive to the SARS-COV-2 virus, the morphology and molecular biology of thyroid tissue was studied using histological and immunohistochemical methods. In the clinical part of the work, a retrospective analysis of the structure of the incidence of surgical pathology of the thyroid gland was performed based on diagnostic results at the preoperative and postoperative stages over 4 years (2019-2023). All quantitative data are processed by statistical methods.Results were obtained indicating that, based on the pathophysiology of SARS-CoV-2 infection, patients with COVID-19 often experience symptoms of thyroid dysfunction, thyroiditis associated with antigenic mimicry of the virus and activation of a three-level regulatory axis, cytokine storm, autosensitization leading to damage to thyrocytes and initiating thyroiditis. These patterns were also revealed in a model experiment on humanized B6.Cg-Tg (K18-ACE2) 2 Prlmn Ifnar1- mice (Stock No. 035041, The Jackson Laboratory, USA) and Syrian hamsters sensitive to the virus. A retrospective analysis over a period of 4 years showed an increase in the number of patients with autoimmune thyroiditis and toxic goiter, an increase in the percentage of nodular formations requiring surgical intervention, with suspected atypia or with reliable signs of cancer (III-VI categories according to Bethesda) from 8.8% to 16 .6%, an increase in the incidence of papillary cancer by 10.3%.

Thus, against the background of immunosuppressive therapy and the general negative impact on the body of severe acute respiratory syndrome caused by this type of coronavirus, it is important to pay close attention to the thyroid gland of patients, an appropriate assessment of low-grade fever and cardiovascular disorders is important, and further fundamental research is advisable to study the long-term consequences of the pandemic on carcinogenesis.

Keywords: thyroid gland, pathological physiology, SARS-CoV-2 virus, autoimmune thyroiditis

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1. Introduction

At present, the study of pathogenetic mechanisms of thyroid gland (thyroid) pathology development has acquired special relevance. In addition to the main risks, such as: man-made disasters and destabilisation of the nuclear power industry, iodine deficiency, the action of stressors in the period of aggravation of geopolitical conflicts, a new factor of pathogenic action has appeared. High incidence of surgical pathology of the thyroid, progressing in 2020-2023 in connection with the pandemic COVID-19 [1]. At the same time, the high incidence of thyroid cancer, including among young people and children, the first place among malignant tumours of the endocrine system, as well as the highest rate of increase in the incidence of thyroid cancer among other types of carcinomas draws attention [2, 3]. The COVID-19 pandemic affected more than 670 million people and its minuscule consequences are still relevant after subsiding. The infection affects the endocrine system, whose dysfunction is caused by: direct damage by the virus to the gland or mediated effects on the regulatory axis, through the effects of systemic inflammation, circulatory disorders, autoimmune reactions due to antigenic mimicry associated with cross-reactivity with thyroperoxidase, sensitisation by adjuvants in vaccination [4]. There are correlations between thyroid dysfunction detected in 15-64% of patients and the clinical severity of COVID-19 [5, 6]. Inflammation of the thyroid and its damage are cytokine-mediated and are accompanied by either an increase in thyroxine production or thyrocyte death [5, 6].

The aim of the study was to investigate the pathogenetic mechanisms of the effect of SARS-COV-2 on thyroid pathology in laboratory animal experiments and in studies of morbidity patterns during the COVID-19 pandemic.

2. Patients and Methods

Morphology and molecular biology of the thyroid tissue were studied in a model experiment on two species of laboratory rodents sensitive to SARS-COV-2 virus (Syrian hamsters and mice of B6.Cg-Tg (K18-ACE2) 2 Prlmn Ifnar1- line (Stock No. 035041, The Jackson Laboratory, USA) using light microsocopy and immunohistochemical method (IHC). The structure of the gland was studied at 5, 10 and 30 days after infection. IHC was performed in a Bond-MAX processor with label detection by Bond Polymer Refine Detection System (Leica, UK). Preparations were scanned on Aperio CS2 (Leica, USA), using Aperio Image Scope at 40x in 5 fields. Lymphocyte differentiation markers CD4, CD8, CD68, CD20, CD138, CD30 as well as cKit, iNOS, Cyclin D1, p16, p63 and MMP3, CD95, Tie2, VEGF were studied. Digital data were processed in STATISTICA 10.0. Me[Q1;Q3] were determined. Differences were determined by Mann-Whintney method by comparison with the intact group. In the clinical part of the work, a retrospective analysis of the structure of morbidity of surgical pathology of the thyroid according to the results of diagnostics at the preoperative and postoperative stages for 4 years (2019-2023) was performed with comparison by chi-square criterion, with $P \leq 5\%$.

3. Results

After intranasal infection of laboratory rodents with virus obtained from a sick person, respiratory infection develops in animals on 2-3 days, for mice high severity of respiratory dysfunction is more characteristic. Clinical recovery occurs on 10-15 days. Morphological and molecular changes in the thyroid tissue develop by the end of the first and beginning of the second week after infection, there is activation of the cell cycle in thyrocytes (increased expression of

markers of mitosis and apoptosis, angiogenesis and extracellular matrix modelling). Signs of inflammation in the tissue - increased expression of macrophages, T-helpers and B-lymphocytes - were also detected. In the recovered animals on the 30th day of the experiment there is still an increase in the number of T- and B- cells compared to the control group (Table 1). These changes are more characteristic for females.

Table 1. Expression level of lymphocyte differentiation markers in control and experimental animals (number of cells in the field of view at 40x magnification, Me[Q1;Q3]).

Group	Intact	Females, 5 days	Males, 5 days old	Females 10 days	Males 10 days old	Females 30 days	Males 30 days old
CD4	2 [1;3]	1 [0;2]#	3 [1;4]	5 [4;5]^	2 [2;3]	5 [4;5]^ *	1 [1;1]
CD138	3 [3;4]	1 [1;2]^	4 [3;4]	1 [1;2]	3 [2;3]	5 [2;3] ^*	3 [2;3]
CD163	4 [1;3]	3 [2;5]	5 [5;6]	7 [6;7]	4 [2;5]	6 [3;3]*	3 [2;3]

* - differences from intact animals

^ - differences between males and females at the same experiment term

\# - differences between experiment terms within the same sex.

Retrospective analysis over a period of 4 years showed an increase in the number of patients with autoimmune thyroiditis and toxic goitre, an increase in the percentage of nodules requiring surgical intervention, with suspected atypia or with reliable signs of cancer (Bethesda categories III-VI) from 8.8% to 16.6%, an increase in the incidence of papillary cancer by 10.3% and the detection of tumours at earlier stages of growth compared to the period of 2019 (Table 2).

Table 2. Results of cytology of aspiration biopsy putunctates and histology of thyroid nodules during different periods of the pandemic.

Group	Distribution (in %) according to Bethesda Thyroid Classification		Proportion of cancer (in %) among all nosologies according to post-pore histology data			Proportion of papillary cancer (in %) among all nosologies according to post-pore histology data
	I-II	III- VI	all patients	men	women	gender-neutral
Before the pandemic.	91,2	8,8	38,7	55,6	36,9	22,6
During the pandemic.	85,9	14,1*	31,0	25,0*	30,6	21,4
After the pandemic.	83,4	16,6*	40,8**	20,0*	42,4**	32,9 *, **

Note: * - significant relative to the group before the pandemic, ** - to the group during the pandemic

4. Discussion

We obtained results indicating that, based on the pathophysiology of SARS-CoV-2 infection in COVID-19 patients, the phenomena of thyroid dysfunction, thyroiditis associated with antigenic mimicry of the virus and activation of the three-level regulatory axis, cytokine storm, and autosensitisation leading to thyrocyte damage and initiating thyroiditis are frequently observed. These patterns were also revealed in a model experiment on humanised B6.Cg-Tg (K18-ACE2) 2 Prlmn Ifnar1- mice and Syrian hamsters susceptible to the virus, and are comparable to the results obtained by other authors [5, 6]. The pandemic is characterised by an increase in patient referrals with primary manifestation of thyroid disease, which is somewhat paradoxical in the context of limited routine interventions. During the pandemic a reversible increase in the number of

operations for toxic goiter and adenomas on the background of gland hyperfunction and irreversible increase in the proportion of malignant tumours was established; predominance of more differentiated forms of cancer with low risk prognosis, as well as tumours at earlier stages, frequent detection of prognostically more favourable forms after the pandemic.

5. Conclusions

Thus, against the background of immunosuppressive therapy and the general negative effect on the organism of severe acute respiratory syndrome caused by coronavirus, it is important to focus on the thyroid of patients, the appropriate assessment of subfebrile and functional disorders is important, and further basic research to study the long-term effects of the pandemic on carcinogenesis in the thyroid tissue is appropriate.

Application of artificial intelligence:

The article is written without the use of artificial intelligence technologies.

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Conflicts of interest. The authors declare that there are no conflicts of interest.

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