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Popular co-occurrence of thyroid autoimmune disorders and specific gastrointestinal tract diseases

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ABSTRACT

Introduction: Thyroid gland, despite of its small average size, is a crucial organ of human body. Hormones produced by the thyroid i.e. thyroxine (T4) and triiodothyronine (T3) are necessary for proper functioning the whole organism. Excess or deficiency of these hormones manifest as multiple symptoms of different organs or systems. In this review we focused on special complaints of gastrointestinal tract. Worth to notice is that some thyroid disorders are present in particular gastrointestinal disorders more frequently.

Purpose: The aim of this review is to indicate co-occurrence disorders of the thyroid gland, especially autoimmune thyroiditis with disorders of some organs of gastrointestinal tract.

State of knowledge: By this time we can enumerate series of thyroid diseases, i.e. hypothyroidism, hyperthyroidism, thyroid nodular goiter, neoplasms or multiple forms of thyroiditis. Generally chronic autoimmune thyroiditis is the most frequent disorders of the gland. That's the reason why we focused on coexisting this state with gastritis, chronic inflammatory bowel diseases, steatosis of the liver or with neoplasms of gastrointestinal tract. We aim to prove the necessary of constitute diagnosis towards other autoimmune diseases, when the one has bed diagnosed.

Thyroid disorders may result in abnormalities of functioning particular organs of the human body. This fact may have an impact on blood tests results – for example elevation of transaminases evaluating function of the liver is often noted in thyroid diseases, what should sensitize clinicians towards performing diagnostics of thyroid function during treatment of liver or intestines or stomach dysfunction.

Summary: Diseases of the thyroid gland may coexist with particular diseases of gastrointestinal tract. They may alter the course of these disorders and constitute unfavorable factor of the treatment.

Key words: thyroid; thyroiditis; gastrointestinal tract; liver; gastritis; microbiome

Introduction

Thyroid is a quite small endocrinology gland located in front of the neck, with the average volume about 15-20ml. Despite small size of the organ, thyroid hormones i.e. thyroxine (T4) and triiodothyronine (T3) are necessary for normal functioning all of the body systems, for example cardiovascular or bronchopulmonary. The aim of this paper is to indicate the diversity of possible diseases that can affect gastrointestinal tract and their co-occurrence with chronic thyroid diseases, especially thyroiditis.

Generally we can distinguish several types of thyroid illness, such as hypothyroidism and hyperthyroidism, a number of inflammatory diseases, goiter and tumors.
Hypothyroidism is the metabolic state, when thyroid hormones levels are in suboptimal range. Due to the level of thyro-pituitary axis failure, there may be primary and secondary hypothyroidism featured. Primary disease is related with disorder firstly concerning the thyroid gland and the secondary refers to dysfunction of pituitary gland or hypothalamus. We can indicate subclinical hypothyroidism – when levels of T4 and T3 are in optimal range yet with the thyrotropin hormone (TSH) elevation above upper norm and overt deficiency, when levels of T4 and T3 are decreased, and the thyrotropin hormone (TSH) is elevated. Actually the most common cause of this state is chronic autoimmune thyroiditis or Hashimoto's disease.
Analogical situation takes place with hyperthyroidism: subclinical hyperthyroidism is diagnosed when T4 and T3 levels are elevated and TSH is decelerated.
When primary hypothyroidism may be diagnosed due to thyroid gland hypoplasia or inflammation – predominantly due to chronic thyroid inflammation (Hashimoto's thyroiditis), primary hyperthyroidism is most commonly recognized due to Graves-Basedow disease or secernent adenoma.

Hashimoto's thyroiditis, as well as Graves-Basedow disease, are genetically conditioned disorders– in individuals with specific HLA alleles and/or CTLA-4 polymorphisms recognition is more often; frequently these disorders are reported in different members of the same family. Not without significance remains lifestyle and environmental factors, for example iodine intake, probably also stress and diet.
Common feature of multiple autoimmune diseases is lymphocytic infiltration of particular organ. Due to this state, autoantibodies which are directed against autoantigens are produced, what results in organ destruction or overactivation – as we may notice in Hashimoto's thyroiditis and Graves-Basedow disease. Autoantibodies detected in Hashimoto's disease, i.e. anti-thyroglobulin (a-Tg) and anti-thyroperoxidase (a-TPO) antibodies correlate with the presence of a thyroid lymphocytic infiltrate (Weetman, 2004). Because of anti- TSH-receptor antibodies (widely known as reported in Graves-Basedow disorder) specifity and laboratory detection method, their measurement is quite more complicated. Majority of autoimmune disorders have probably similar etiology as written above. As genetically conditioned disorders, they may arrange in specific groups of diseases, known as polyglandular autoimmune syndromes (PAS). We are able to distinguish several type of these autoimmune syndromes (see Table 1). Table 1 was created according to references: (Cellini et al., 2017), (Eira, Mota, …, & 2017, n.d.).

Name of PAS	Disorders reported in particular type of PAS - two or more autoimmune endocrine diseases needed for diagnosis
PAS I = APECED (autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy) or MEDAC (multiple endocrine deficiency autoimmune candidiasis syndrome)	Mucocutaneous candidiasis (70–80%) Hypoparathyroidism (80–85%) Addison's disease (60–70%) Type 1 diabetes (<20%) Hypogonadism (12%) Thyroid disease (10%) Hypopituitarism (0–2%) Vitiligo, Alopecia areata, Autoimmune gastritis, Pernicious anemia, Autoimmune hepatitis, Malabsorption, Sjögren's syndrome, Myasthenia gravis
PAS II	Thyroid disease (70–75%) + Type 1 diabetes (50–60%) = Schmidt's syndrome an/or Addison's disease (40–50%) = Carpenter's syndrome Hypoparathyroidism (0–5%) Immunogastritis, Pernicious anemia, Alopecia areata
PAS III	Autoimmune thyroid disease (ATD) associated with other autoimmune diseases, excluding the involvement of the adrenal gland

More frequent co-occurrence of particular autoimmune disorders should prompt doctors for careful clinical assessment of symptoms of the patient and - if necessary – to implement adequate diagnosis and treatment.

State of knowledge:
STOMACH & THE THYROID
Stomach, as very active muscular and secernent organ is responsible mainly for proper digestion and for protection organism from multiple external microorganisms, that are able to enter the human body at the time of eating. What is interesting, but not widely known, is that stomach and thyroid gland originate from the same type of embryogenic tissue. They contain similar intracellular enzymes and electrolytes symporters that have ability to concentrate iodine - they also can suffer together. Chronic lymphocytic thyroiditis or Hashimoto's thyroidits is the most popular among autoimmune disorders. Chronic autoimmune atrophic gastritis is quite rare and it requires differentiation with chronic *Helicobacter pylori* (Hp) infection. Anyway, Hashimoto's thyroiditis has been reported to be associated with gastric disorders in 10–40% of patients while about 40% of patients with autoimmune gastritis also present chronic lymphocytic thyroiditis (Cellini et al., 2017). Chronic gastritis due to its possible metabolic result, such as iron deficiency anemia in progress of hypochlorchydria and following pernicious anemia, require patient awareness from clinicians – especially due to the higher risk of development gastric adenocarcinoma or neuroendocrine tumors and likely impairment of L- thyroxine absorption.
Summarizing, co-occurrence of stomach and the thyroid disorders are quite common. State described above, not without a reason was named ,,thyrogastric syndrome" .

LIVER & THE THYROID
Liver is a multifunctional organ located in right upper part of the abdomen. As the thyroid gland, it is crucial for proper metabolism functioning. Malfunction of one of above organs often results in impairment of the second one. Hypothyroidism may result in abnormal liver function tests or lipids.

Elevated aspartate aminotransferase (AST), as well as serum creatine kinase (CK) and lactate dehydrogenase (LD) may be connected with underlying myopathy in progress of hypothyroidism (Burnett, Crooke, Delahunt, & Feek, 1994). It's well known that thyroid hormones have important effect on hepatic fatty acid and cholesterol synthesis and metabolism (Sinha, Singh, & Yen, 2018). Generally at the time of thyroid hormones deficiency, we may notice increase in total level of cholesterole. Quite dealing reports inform, that increased level of alanine aminotransferase
(ALT) may be associated with total cholesterol and abdominal circumference (Silva et al., 2016), what may be linked with hypothyroidism and thyroid hormones action. Continuing, decreased level of thyroid hormones may serve as a predictors of NASH and advanced fibrosis and may have a pathogenic role in modulating NAFLD outcomes (Manka et al., 2019). From the other hand also hyperthyroidism may result in serum elevation of liver enzymes, as well as newly examined fibroblast growth factor 21 (FGF21) (Xiao et al., 2019).
In literature we can find some articles presenting infrequent cases of coincidence autoimmune hepatitis and Graves' Disease (Rana, Ahmed, Salgia, & Bhan, 2019) or severe cholestatic jaundice and Graves' Disease (Abebe, Eck, & Holyoak, 2018).
Undeniably tiamazole, metimazole or propylthiouracil - medicines used in treatment of thyrotoxicosis, may result in liver enzymes elevation (Zeng, Zhan, CLINICAL, & 2018, n.d.).
From the other side, also disorders primarily concern the liver, such as hepatitis, hepatocellular carcinoma, cirrhosis or even alcoholic liver disease, ay seriously affect thyroid function (Dauth, Vermehren, & Bojunga, 2017).

INTESTINES & THE THYROID

It's scientifically and statistically proved, that multiple autoimmune disorders may coexist quite often – as Hashimoto's thyroiditis and chronic autoimmune gastritis mentioned above. It's the reason why diagnostic procedure towards chronic autoimmune thyroiditis in patient with newly diagnosed insulin-dependent diabetes mellitus or in patient with newly detected Hasimoto's thyroiditis toward celiac disease should be implemented. Due to Fallahi, the prevalence of autoimmune disorders in autoimmune thyroiditis patients is greater in chronic autoimmune gastritis, celiac disease, diabetes, vitiligo and several rheumatoid disorders (Fallahi et al., 2016). And what about Crohn'disease or ulcerative colitis and its co-occurence with Hashimoto thyroiditis? Analyzing available medical literature, we found divergent opinions. For example, due to mentioned above Fallahi and his publication, statistical analysis converting data interpreting coincidence of presence Hashimoto's disease, with other autoimmune diseases, reached near the significance for ulcerative colitis (Fallahi et al., 2016). Analyzing the work of Szczeblowska, we are able to accept the theory of more frequent occurence of chronic autoimmune thyroiditis with Crohn's disease (Szczeblowska & Wojtuń, 2013).
Microscopic colitis is a primary disease of the colon, that mainly affects women. It appears as diarrhea with macroscopically normal or near to normal colonic mucosa with characteristic histopathological changes. Thyroid disorders seem to be more frequent in patients with microscopic colitis, however not subclinical thyroid disorders (Gustafsson et al., 2013).
As we can see, thyroid disorders, especially Hashimoto's thyroiditis, may coexist with inflammatory bowel disorders. Worth to notice are cases of developing diseases of the colon as effect of thyroid gland disorder. Very entertaing case was written by Laterza. He presented the patient with ulcerative colitis developed due to metabolic stress induced by hyperthyreosis in progress of Graves' disease (Laterza, Piscaglia, …, & 2016, n.d.)

NEOPLASMS OF GASTROINTESTINAL TRACT & THE THYROID

We are obligated to mention about co-occurrence of neoplasms of gastrointestinal tract and thyroid disorders. For example Kirkegard J. observed increased risk of all gastrointestinal cancers within

the first year after thyroid disease diagnosis in Danish population (Kirkegård, Farkas, Jørgensen, & Cronin-Fenton, 2018). What is also interesting, the thyroid cancer is more probable due to diagnosis of Crohn's disease, not ulcerative colitis (Wadhwa, Lopez, & Shen, 2016).

MICROBIOME & THE THYROID

Nowadays, more popular become experiments in the field of microbiome and its connections to multiple disorders, especially autoimmune ones, such as celiac disease, inflammatory bowel diseases, chronic thyroiditis (Virili, Fallahi, Antonelli, Benvenga, & Centanni, 2018) or thyroid cancer and nodules (Zhang et al., 2019).

Billions of microbes that colonize human body, are called microbiome. They may affect human body in different ways – especially modifying special metabolic function, for example production of vitamins or short-chain fatty acids. Any kind of abnormality in the structure or functioning microbiome is called dysbiosis. This state seems to have a huge impact on immune system of the host . Recently observed ,,leaky gut syndrome'' probably participate in development number of autoimmune disorders. Very interesting review paper was published in 2019 in ,,Trends in Endocrinology & Metabolism'' - ,,Microbiota and Thyroid Interaction in Health and Disease''. Authors in transparent way has presented the role of human microbiome affecting organism in different ways (Fröhlich & Wahl, 2019).

Concludes, Thyroid disorders are very common, especially chronic inflammatory thyroiditis. We hope that our short review turned out interesting for readers and encouraged for further exploration and following the topic of co-occurrence autoimmune thyroid disorders with diseases of gastrointestinal tract.

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