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THE IMPACT OF CHRONIC STIMULATION ON THYROID GLAND NODOSUM

Sažetak: Uvod: Nodozna struma je klinički prepoznatljiva ograničena promena građe štitaste žlezde. FNA je prva linija dijagnostičkih testova kod uvećane štitaste žlezde. TSH je poznat kao tiroidni faktor rasta, ali patogena uloga ovog hormona u tiroidnoj onkogenezi je nerazjašnjena.

Cilj: Cilj rada je da se analizira veza između povišenih vrednosti TSH i tireoidnog maligniteta kod osoba sa nodozno izmenjenom štitastom žlezdom.

Materijal i metode: Retrospektivno je pregledano 637 tiroidnih FNA citoloških izveštaja uzoraka, dobijenih punkcijom pacijenata sa tiroidnom nodoznom bolešću Odeljenja za štitastu žlezdu, Klinike za endokrinologiju, dijabetes i bolesti metabolizma, Kliničkog centra Srbije u Beogradu, u periodu od oktobra 2007. do januara 2010. godine. Analiziran je odnos između dijagnostičkih kategorija citopatoloških nalaza i serumske koncentracije TSH. Podaci su statistički testirani Kruskal Wallis testom razlike pomoću kompjuterskog programa SPSS 12.0 softverskog paketa.

Rezultati: Od ukupno 637 pacijenata 3,45% (22/637) je imalo maligni, a 4,87% pacijenta (31/637) neodređeni citopatološki nalaz. 91,52% (583/637) pacijenata je bilo sa benignim nalazom, i samo jedna neuspela punkcija. Prosečna vrednost TSH u grupi pacijenata sa malignom dijagnozom iznosila je 9,83±17,48 mmol/l sa medijanom 3,31 mmol/l. U sve tri dijagnostičke kategorije (benigno, maligno i neodređeno) najviše je pacijenata sa referentnim vrednostima TSH, ali postoji relativno veća proporcija, 27,3% (6/22) pacijenata, sa malignim citopatološkim nalazom

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kod grupe pacijenata sa povišenim vrednostima TSH. Postoji statistički značajna razlika između dijagnostičkih kategorija po grupama vrednosti TSH (χ^2=8,136, p=0,017).

Zaključak: Zaključuje se da rizik za razvoj tiroidnog maligniteta raste kod pacijenata sa povišenim serumskim koncentracijama TSH. TSH treba koristiti kao pomoćno dijagnostičko sredstvo u identifikaciji visokorizičnih pacijenata koji zahtevaju dalja ispitivanja i/ili hirurški tretman.

Ključne reči: nodozna struma, tireotropin, aspiracija tankom iglom

Abstract: Introduction: Nodular goiter is a clinically recognizable restricted structure change of the thyroid gland. FNA is the first line diagnostic test for an enlarged thyroid gland. TSH is known as a thyroid growth factor, but the pathogenic role of this hormone in thyroid oncogenesis is unclear.

Objective: The aim of this study is to analyze the relationship between elevated serum TSH concentrations and thyroid malignancies in patients with nodular thyroid goiter.

Material and Methods: We retrospectively reviewed the 637 reports of thyroid FNA cytology of samples obtained by puncture of patients with nodular thyroid goiter, at the Department of thyroid gland, Department of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia in the period from October 2007 to January 2010. We analyzed the relationship between findings of cytopathological diagnostic categories and serum concentrations of TSH. The data were statistically tested by means of Kruskal Wallis test of differences using the computer program SPSS 12.0 software package.

Results: Of total 637 patients, 3.45% (22/637) had malignant, and 4.87% patients (31/637) cytopathological indeterminate findings. 91.52% (583/637) patients were with benign findings, and only one puncture failed. The average value of TSH in the group of patients with the diagnosis of malignancy was 9.83 ± 17.48 mmol/l with a median 3.31mmol/l. In all three diagnostic categories (benign, malignant and unspecified) most patients are with the normal concentrations of serum TSH , but there is a relatively large proportion of 27.3% (6/22) of patients with malignant cytopathological findings in the group of patients with elevated TSH concentration. There is a statistically significant difference between diagnostic categories by group TSH values(χ^2=8.136,p=0.017).

Conclusion: It is concluded that the risk of developing thyroid malignancy increases in patients with elevated serum TSH concentrations. TSH should be used as an additional diagnostic tool in identifying high-risk patients who require further investigation and / or surgical treatment.

Key words: nodular goiter, thyrotropin, fine needle aspiration

Introduction

Nodular goiter is a clinically recognisable and restricted change in the structure of the thyroid gland. Nodular thyroid disease is frequent and occurs in 2-6% of cases diagnosed by palpation (5% in women and around 1% in men who live in iodine-sufficient areas), in as many as 19-35% cases in which it is diagnosed by sensitive procedures such as ultrasound and in autopsy, and in nearly 8-65% cases among general population. The prevalence increases in a linear way with age, exposure to radiation and iodine deficiency. There could also be the endemic type in the areas with iodine deficiency, when the prevalence of nodular disease in children aged 6-12 is higher than 5%, and sporadically, when the prevalence is lower than 5%. It is more common in women than in men. Thyroid nodosums can be solitary or individual, and multiple, and they can be functionally active or inactive. Solitary thyroid nodosums exist in a dimensionally and morphologically unchanged gland, whereas the dominant nodosum occurs in diffuse and multinodular goiter (1). In the absence of thyroid dysfunction, autoimmune thyroid diseases of thyreoiditis and thyroid malignancy form an entity described as a non-toxic nodular goiter. Apart from non-toxic nodular goiter, clinical forms include multinodular toxic goiter and toxic thyroid adenoma (Plummer disease).

The most common causes of thyroid nodular disease are benign: colloid nodule, Hashimoto thyroiditis, plain or hemmorhagic cyst, follicular adenoma, subacute thyreoditis; and the malignant ones are: primary (originating from follicular cells – papillary, follicular and anaplastic carcinoma, originating from C-cell thyreoidea – medullary thyroid carcinoma, and lymphoma) and secondary metastatic carcinoma.

Clinical importance of the thyroid nodular disease apart from the aesthetic changes such as thickening of the neck, local compressive syndromes and thyroid dysfunction is the possibility of malignancy development in 5% of cases. Annual incidence of thyroid carcinoma is 1-2 per 100,000 people, which makes 90% of all malignancies of the endocrinological system, 1% of all malignancies in people and 0.5% of morbidity caused by malignancy (2,3). Relevant anamnestic and clinical data which indicate a potential malignant nature of the nodule are: family anamnesis of thyroid carcinoma, previous radiation of the head and the neck and/or the whole body, rapid growth of the nodule, hard and solid nodule, hoarseness or vocal cord paralysis, ipsilateral cervical lymphadenopathia and fixation of the nodule to the surrounding tissue.

The disease is diagnosed on the basis of physical examination, laboratory analyses, fine needle aspiration (FNA) and visualisation method (scyntygraphy, ultrasound and ultrasound elastography, CT, MR and PET).

Since many clinical findings in the solitary nodule do not make a distinction between a benign and a malignant process, more efficient methods are needed for the selection of patients who should have surgery. The number and range of operations are reduced in this way.

Fine needle aspiration (FNA) was applied for the first time by Martin and Ellis at the *Memorial Hospital for Cancer and Allied Diseases* in New York in 1930, although, due to its restrictions, it was rarely used, only to become popular

in the last four decades when, in Scandinavia, it was introduced as one of the primary diagnostic tests in thyroid nodular disease (4). It is the main method of preoperative diagnosis in children and adults. It is superior to clinical, radionuclide and ultrasound methods. In the last few years, it has proved itself as the key diagnostic procedure and it has drastically changed the approach in thyroid nodular disease treatment. It is among the primary diagnostic tests in cases of an enlarged thyroid. FNA application reduces the number of throidectomies by 50% and total medical expanses of over 25% of patients.

The key to the success of this method is an adequate and representative cell sample and expertise in thyroid cytology. Classification of diagnostic categories of the thyroid FNA usually involves the following categories: 'malignant', 'benign', 'indeterminate' and 'unsuccessful'. The term 'indeterminate' refers to lesions which could not be definitely categorised as benign or malignant on the basis of their cytological picture, and they include follicular, oxyphyllic lesions (Hurthle cell) and suspicious findings. The category of 'unsuccessful' refers to the samples which do not provide sufficent material or the material is not adequate for a diagnosis.

The therapy is usually surgery or radioiodine ablation, whereas recently, in the cases indicated for them, recombinant human thyreotropin therapy, percutaneous ethanol injection, laser thermal ablation and radiofrequency ablation have been used.

Thyreotropin (TSH) is a hormone of the frontal lobe of the hypofise which causes an increased secretion of the thyroid gland hormones. It is also known as the factor of growth of thyroid nodules. The suppression of TSH by exogenous hormones of the thyroid prevents the further enlargement of the existing nodules and the development of the new ones. The suppressive thyroxin therapy shows positive effects in patients with differentiated thyroid carcinoma. It is well-known that chronic iodine deficiency, which causes a decrease in the serum concentrations of thyroid hormones with a consequential increase in concentrations of TS, is a factor of goiter development and follicular thyroid carcinoma. Considering all of the above-mentioned facts, it is believed that TSH serum concentration is an independent indicator of thyroid malignancy in patients with a nodular thyroid. It is assumed that chronic thyreotropin stimulation of the nodular thyroid causes neoplasia and carcinogenesis. Given that TSH concentration is higher in patients with aggressive tumors, it is believed that this hormone also causes tumor progression. Consequently, patients with higher TSH concentrations need to be examined more elaborately and treated more aggressively.

Study objective

Study objective is to analyse the relationship between increased TSH values and thyroid malignancy in people with nodullary thyroid.

Material and methods

The study was conducted at the Clinic for endocrinology, diabetes and metabolism diseases, Clinical Centre of Serbia, Belgrade. Retrospectively, 637 thyroid FNA cytology report samples were examined, obtained by performing puncture inpatients with nodular thyroid disease at the Thyroid Department in the period from October 2007 to January 2010.

The patients were examined at the dispensary, anamnesis was taken as well as all the laboratory anayses (biochemistry, blood sample and hormone status), ECG and ultrasound were made, and thyroid scintigraphy was done in some patients. Afterwards, fine needle aspiration puncture (FNA) was performed, and the obtained results were analysed at the Institute for pathology at the Clinical Centre of Serbia in Belgrade.

Cytological findings of the FNA samples were classified according to the scheme of diagnostic categories of thyroid FNA as: benign, malignant, indeterminate and unsuccessful (6).

The relationship between diagnostic categories and TSH serum concentrations was analysed.

The data were statistically tested by means of Kruskal Wallis test of differences using the computer program SPSS 12.0 software package.

Results

The relationship between diagnostic categories and TSH was analysed. All the patients were divided into three categories on the basis of TSH values: TSH values lower than (up 0.5 mU/l), normal, referential TSH values (0.51-4.5 mU/l) and TSH values above the normal range (over 4.51 mU/l). Table 1. shows the distribution of diagnostic categories in relation to TSH values.

Table 1. Diagnostic categories in relation to TSH values

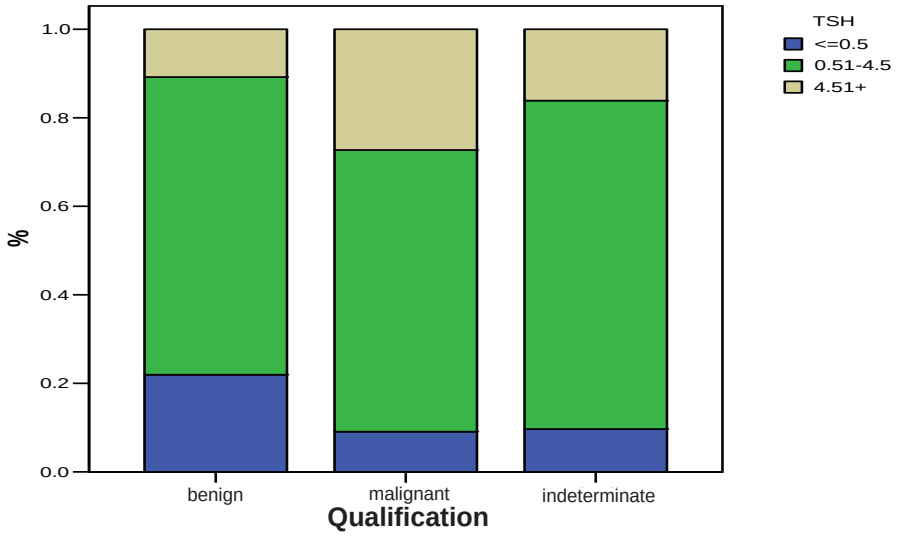
			TSH			Total
			<=0.5	0.51-4.5	4.51+	
Diagnostic category	*Benign*	N	128	392	63	583
		%	22.0%	67.2%	10.8%	100.0%
	Malignant	N	2	14	6	22
		%	9.1%	63.6%	27.3%	100.0%
	Indeterminate	N	3	23	5	31
		%	9.7%	74.2%	16.1%	100.0%
	Unsuccessful	N	1	0	0	1
		%	100.0%	.0%	.0%	100.0%
	Total	*N*	*134*	*429*	*74*	*637*
		%	*21.0%*	*67.3%*	*11.6%*	*100.0%*

The average TSH value in the benign group was 3.12±12.70 with the median of 1.15, the average TSH value in the group of patients with the diagnosis of malignancy was 9.83±17.48 with the median of 3.31, whereas the average TSH value in patients with indeterminate diagnosis was 3.16±3.80 with the median of 2.

Analysing these data by means of Kruskal Wallis test, it was established that there was a statistically relevant difference between these four categories within TSH groups (χ^2=8.136, p=0.017).

The results are shown in Graph 1.

Graph 1. Diagnostic categories in relation to TSH values



Discussion

TSH is known as the thyroid growth factor, but the pathogenous role of this hormone in thyroid oncogenesis is still unresolved.

The results show that there is a statistically relevant difference between diagnostic categories in terms of group TSH values (χ^2=8.136, p=0.017) (7). Of the total 637 patients in our study, 22 (3.45%) of them had malignant, and 31 (4.87%) of them had indeterminate cytopathological findings, which also called for a surgical treatment. The largest number of them, 583 (91.52%) patients had benign findings and only one puncture failed. The average TSH value in the group of patients with the malignant diagnosis was 9.83±17.48 with the median of 3.31. The obtained results show that in all three diagnostic categories (benign, malignant and indeterminate), the largest

number of patients are with referential TSH values, but there is a relatively larger proportion (27.3%) of patients with malignant cytopathological findings in the group of patients with higher TSH values (6 out of 22 patients). Available citations from literature concord with our results.

On the basis of this, it can be concluded that the risk of the development of thyroid malignancy is higher in patients with increased TSH serum concentrations or with TSH concentrations in the upper part of referential values. The second explanation might be that in patients with low TSH concentrations, an autonomous function is developed, which is connected with the low risk of developing thyroid malignancy.

Namely, Fiore and associates analysed the connection between serim TSH and the diagnosis of papillary thyroid carcinoma in 10,178 patients with a nodular disease and found out that patients with thyroid carcinoma had a much higher concentration of TSH. At the same time, they came to the conclusion that the development of the autonomous thyroid function (TSH < 0.4 μU/ml) was related to the reduction in the risk of developing papillary thyroid carcinoma.

The study of Ichikawa and associates showed the expression of TSH receptors at the cell membrane of benign and malignant tumors, and Carayan and associates concluded that TSH increased the production of adenylate cyclase, which lead to the cAMP production and cell growth through the stimulation of these receptors. It was later established that the lower incidence of carcinoma in hyperfunctional nodules was related to the constituent activating mutations of TSH receptors by activating cAMP pathway via Gsα subunit, whereas RAS-dependent MAPK pathway activated via Gβγ subunit and phosphatidylinositol-3 kinase were more important for carcinogenesis.

Haymart and associates also showed the connection between the serum TSH and advanced stages of carcinoma, i.e. extrathyroid spread of carcinoma (5).

In the study involving 1,500 patients, Boelaert and associates showed that higher TSH serum concentrations (> 0.9 mIU/l) were related to the risk of a thyroid malignancy diagnosis. The lowest risk of malignancy existed in patients with subclinical hyperthyreosis (TSH < 0.4 mIU/l), and the highest was in patients with subclinical hyperthyreosis (TSH > 5.5 mIU/l). These results were later confirmed by other authors in their research.

Haymart and associates examined 843 patients who needed surgery and their preoperative TSH serum concentrations. Malignancy probability was 16% when TSH was < 0.06 mU/l, 25% for TSH between 0.4 and 1.39 mU/l, 35% for TSH between 1.40 and 4.99 mU/l and 52% in the group with TSH over 5 mU/l and more. Polyzos and associates pointed at the high frequency of malignancy when TSH was between 1.5 and 4 mIU/l , i.e. when it was near the upper limit of the normal range (5).

Given that TSH concentration is higher in patients with more aggressive tumors, it is believed that this hormone also affects malignancy progression.

Contrary to these facts, there is a large number of arguments against its role in the development and progression of thyroid cancer.

Matsuo and associates suggested that in thyroid carcinoma TSH receptor mutations related to the increase in signal transport were very rare.

Then, in their vitro studies, Derwahl and associates showed that some other factors, such as insulin-like growth factor IGF-1, were important in the stimulation of growth of thyroid cancer, and Kimura and associates suggested that TSH needed to act together with insulin and IGF-1 in order to show its proliferative effects.

Shi and associates established that there was an inversive relationship between the level of mRNA TSH receptors and cancer aggressiveness.

Citations from literature confirm that thyroid cancer very often appears in contralateral lobe in relation to hyperfunctional nodule, where TSH is supremed.

Numerous studies dealing with the genome showed that serum TSH concentrations were lower in patients who carried one or two alleles related to the increase in the risk of developing papillary and follicular carcinoma.

Conclusion

On the basis of the results, it is concluded that the risk of developing thyroid malignancy is higher in patients with increased TSH serum concentrations. Consequently, the assessment of risk of developing malignancy in patients with a nodular thyroid, apart from clinical, biochemical parameters and FNA findings, demands the determination of TSH serum concentration as an auxiliary tool in the identification of high-risk patients who need further examination and/or surgery.

The role of TSH in malignancy development has not been confirmed. It is still unclear whether high values of this hormone cause carcinogenesis or whether they are the consequence of thyroid malignancy.

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