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Clinical picture versus concentration of triiodothyronine in patients with hypothyroidism

Obraz kliniczny a stężenie trójjodotyroniny u pacjentów z niedoczynnością tarczycy

INTRODUCTION

Hypothyroidism is a condition caused by a deficiency or lack of thyroxine (T4) and/or, rarely, triiodothyronine (T3), which can lead to insufficient expression of T3 in cells. Sometimes dysfunctions of T4 peripheral metabolism as well as intracellular production of T3 are present despite normal production of T4 in thyroid. T4 and T3 are produced by the thyroid gland. T4 is produced only by the thyroid, whereas T3 is produced by the thyroid and through the process of T4 deiodination. These hormones are secreted into the bloodstream in response to thyroid-stimulating hormone (TSH), which is regulated by the negative feedback loop. Hypothyroidism is classified by association with a particular organ dysfunction. The primary hypothyroidism is caused by thyroid gland damage, the secondary or tertiary hypothyroidism result from hypothalamus or pituitary impairment. Secondary types of hypothyroidism are characterized by a mild course of disease usually with no goiter [7]. Hypothyroidism is present in 2% of the world population being diagnosed 5–10 times more frequently in women than in men with the frequency rising with age – 5% of people over 60 suffer from hypothyroidism. On the other hand, the subclinical type (SHypo), defined as a pathology connected with normal T4 and T3 concentrations and increased TSH, is reported more frequently, i.e. in 8%–10% of women and 2%–3% of men [4, 12].

It is believed that T3 deficiency is responsible for the clinical and biochemical manifestations of hypothyroidism. Thus, basic intracellular functions such as oxygen consumption by the mitochondria and calorigenesis are slowed down. The decrease in energy metabolism and heat production are manifested by the low basal metabolic rate, decreased appetite, cold intolerance, and slightly low basal body temperature. Other symptoms appear: weight gain, water binding in glycosaminoglycans of the connective tissue, drowsiness, psychomotor impairment, constipation, dry skin, increased hair

fragility, puffy eyes and bradycardia. Hypothyroidism disturbs the lipid balance, which is reflected in an increased total cholesterol (TC) concentration and low-density and very-low-density lipoproteins, which favours intensification of oxidative stress and atherogenesis. That is why a frequent complication is ischaemic heart disease aggravation [5]. However, the analysis of available literature points to difficulties in diagnosing this endocrinopathy basing only on clinical manifestations which are often unspecific or poorly expressed. It was M.T. McDermott and E.C. Ridgway's studies which showed that euthyroid subjects reported similar constellations of clinical symptoms as compared to patients suffering from SHypo or overt hypothyroidism [10]. It should be added that hypothyroidism may be asymptomatic, especially when subclinical, because typical symptoms of hypothyroidism are manifested in patients with a lower concentration of free triiodothyronine (fT3), whereas they are rare or may not be manifested in patients with a normal fT3 concentration but with a lower concentration of free thyroxine [14].

T3 (3,5,3'-L-triiodothyronine) is a hormone synthesized and secreted by the thyroid or it is produced during peripheral deiodination of T4 in extrathyroidal tissues. T4, which is the main product of the thyroid, is converted to T3, T4 being in many respects considered as a prohormone for the more potent T3. This is performed in the cytoplasm and the nuclei of target tissue cells by three specific deiodinases with the subtraction of a molecule of iodine from the peripheral ring of T4 [12]. It is believed that the effect of T3 on target tissues is mediated genomically by T3 binding to one of the T3 receptor isoforms [13].

In bloodstream as many as 99.7% of T3 is bound with transport protein mainly with thyroxine-binding globulin (TBG) and, to a lower extent, with albumin and prealbumin. The remaining T3 remains free in bloodstream as free triiodothyronine (fT3) which is an active metabolic fraction. FT3 concentrations are dependent on secretion of total T3 and its metabolism. In thyroid dysfunction the concentration of fT3 changes along with total T3. These changes also result from alternations in proteins binding T3, mainly TBG [7].

The aim of the study was a retrospective analysis of symptomatology of hypothyroidism and search for a correlation with fT3 concentration in blood serum.

MATERIAL AND METHODS

In 2009 medical records of 241 patients, including 188 women and 53 men, suffering from hypothyroidism were analysed in the Endocrinology Outpatient Clinic of the Autonomous Public Clinical Hospital no. 4 in Lublin. The patients were divided into two groups depending on fT3 concentration in blood serum at diagnosis: group I with normal fT3, which was recognised as a control group, and group II with a lower fT3 concentration as compared to the normal one, which was recognised as the study group. Additionally, the age of the patients at diagnosis of hypothyroidism was assessed as well as the current age. While analysing the medical history a lot of attention was drawn to subjective clinical manifestations which were reported by the patients at diagnosis. The incidence of coexisting diseases was also accounted for, especially the cardiovascular ones.

The parameter applied while dividing the subjects into groups was the fT3 concentration measured at diagnosis by carrying out an immunodiagnostic test using direct chemiluminescence. Lipid disorders were assessed however, they were limited to tagging the TC concentration only because there were no data on particular fractions. An enzymatic method was employed for quantitative determination of cholesterol.

Statistical analysis. Statistical analysis of the acquired data was carried out with STATISTICA ver. 8.0 software. Qualitative data were assessed by cross tabulation $\chi 2$ analysis. Student's t-test for dependent and independent variables was employed for the comparison of normal distribution variables. In the case of the distribution different from the standard one, the Mann-Whitney U test was applied. The differences were recognized as statistically significant with $p<0.05$.

RESULTS

Table 1 shows the characteristics of the studied population. Analysing the clinical picture of patients with hypothyroidism, more frequent incidence of typical symptoms was observed in group II, however; it was of no significance. On the verge of significance were: weight gain (group I vs. group II) 16.56% vs. 26.67%, psychomotor impairment 3.31% vs. 8.89% while statistically significant were non-specific headaches 0.00% vs. 5.56%. The most frequently reported symptoms in group II were: weight gain 26.67%, drowsiness 24.44%, weakness 15.56% and dry skin 11.11%, respectively. The most frequently reported symptom was hipercholesterolemia (group I vs. group II) 43.71% vs. 42.22%. Moreover, in both groups non-typical symptoms of hypothyroidism, i.e. those connected with the circulatory system were manifested to a comparable extent: hypertension 32.45% vs. 31.11%, ischaemic heart disease 18.5% vs. 15.6% as well as arrhythmia 11.8% vs. 7.8%. The frequency of symptoms in both groups is compared in tables 2 and 3.

Table 1. Phenotypic characteristics of groups

Group	I / control	II / studied
Size	151	90
Number of women	121	67
Number of men	30	23
Age (years) ± SD	55.2 ±16.1	55.55± 14.9
Age at which the disease was diagnosed	50.0 ±15.7	49.8 ±14.7

Table 2. The frequency of subjective clinical symptoms in both groups

Group	I / control (%)	II / studied (%)
Weight gain	16.6%	26.7%
Constipation	2.0	5.6
Cold intolerance	7.3	8.9
Drowsiness	16.6	24.4
Dry skin	5.3	11.1
Psychomotor impairment	3.3	8.9
Weakness	13.2	15.6
Puffy eyes	7.8	6.7
Peripheral oedema	0.7	1.1
Hair loss	2.0	1.1
Palpitation	1.32	0.0
Headaches	0.0	5.6
Joint pain	5.3	3.3

Table 3. The frequency of coexisting diseases

Group	I / control (%)	II / studied (%)
Hypertension	32.5	31.1
Ischaemic heart disease	18.5	15.6
Arrhythmia	11.9	7.8
Hipercholesterolemia	43.7	42.2

DISCUSSION

The clinical picture of hypothyroidism in adults is controversial as the course of the disease may be typical and symptomatic or it may manifest itself as subclinical, in which case the clinical symptomatology depends on the phase of the disease as well as the patient's age. Subclinical types of hypothyroidism lack typical clinical symptoms that is why they remain undiagnosed for a long time or the diagnosis is coincidental. Many scientists have tried to propose an objective score of hypothyroidism symptoms which were to help to establish an unequivocal diagnosis [2,14]. However, they are not recommended as nowadays routine thyroid function testing is the best and most reliable way to identify patients with thyroid failure. The frequency of typical symptoms of hypothyroidism cited in available literature is high; however, in our study it concerned less than 20% of the patients, especially in the control group, i.e. the group with fT3 within the normal range [6]. In the group with lower fT3, the frequency above 20% concerned only two symptoms i.e. weight gain and drowsiness. According to Kostoglou-Athanassiou I and Ntalles K, only 30% of hypothyroid patients had some of the symptoms, most frequently fatigue, dry skin and cold intolerance but 17% of euthyroid patients had at least one [9]. Among the most frequently reported symptoms in hypothyroid women before menopause Górowski mentions weakness, drowsiness and permanent cold intolerance [6]. Most of the typical symptoms of overt hypothyroidism was reported by our patients regardless of their fT3 concentration, which differs from the results of Zulewski et al. [14]. Nonetheless, it should be noted that hipercholesterolemia was the most frequent secondary metabolic disorder reported by the studied group as a result of peripheral deficiency of thyroid hormones. It happens so as hypothyroidism has an adverse effect on lipoprotein metabolism, increasing the concentrations of TC in blood serum, low-density and very-low-density lipoproteins and triglycerides. These disorders may lead to premature atherogenesis and, in consequence, to the development of cardiovascular disease (CVD). Thus, hypothyroidism becomes an independent risk factor of atherosclerosis and cardiac infarction, which seems obvious after the publication of results of the Rotterdam study. Hak et al. Reported a 2.3 times higher risk of cardiac infarction and a 1.9 times higher risk of abdominal aorta atherosclerosis in menopausal women not only with overt but also subclinical hypothyroidism [8]. In the light of the above, quick and accurate diagnosis as well as adequate treatment seems of great importance. However, literature from the last few years has shown no watertight evidence of an increased risk of ischaemic heart disease and death of patients with SHypo [11]. Most clinicians treat SHypo patients who have a serum TSH concentration above 10 mIU/L, whereas opinions differ about the management of mild disease in which TSH ranges between 4.5 and 10 mIU/L, especially in elderly asymptomatic patients. Some endocrinologists support the idea that treatment is indicated in patients with SHypo, even those with a mild TSH increase, in the presence of risk factors, whereas others believe that treatment is rarely necessary [3].

CONCLUSIONS

At diagnosis of hypothyroidism, the clinical picture does not correlate with the fT3 concentration in the studied group. Routine thyroid function testing remains the most reliable way to identify patients with thyroid failure.

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SUMMARY

Hypothyroidism may be asymptomatic, especially when subclinical, because typical symptoms of hypothyroidism are manifested in patients with a lower concentration of free triiodothyronine (fT3), whereas they are rare or may not be manifested in patients with a normal fT3 concentration but with a lower concentration of free thyroxine. The aim of the study was a retrospective analysis of symptomatology of hypothyroidism and search for a correlation with fT3 concentration of in blood serum. A total of 241 outpatients with hypothyroidism treated in 2009 (188 women, 53 men), mean age 55.4±15.6, were divided into two groups: group I: 151 patients with a normal fT3 concentration and group II: 90 patients with a lower fT3 concentration in blood serum at diagnosis. During a retrospective evaluation of patients' medical documentation, we searched for correlations between the clinical symptoms of hypothyroidism and fT3 concentration. The clinical picture of patients with hypothyroidism showed that typical symptoms appeared more frequently in group II, which, however, was of no statistical importance. The most commonly reported symptoms in this group were: weight gain 26.67%, drowsiness 24.44%, weakness 15.56% and dry skin 11.11%, whereas in group I non-typical hypothyroidism symptoms dominated – connected with circulatory system, i.e. symptoms of ischaemic heart disease 15.54% and arrhythmia 11.92%. In both groups similar values of the following manifestations were found (group I vs. group II): lipid disorders 43.71% vs. 42.22%, hypertension 32.45% vs. 31.11%, puffy eyes 7.28% vs. 6.67%, respectively. At diagnosis of hypothyroidism, the clinical picture does not correlate with the fT3 concentration in the studied group. Routine thyroid function testing remains the most reliable way to identify patients with thyroid failure.

Keywords: hypothyroidism, symptomatology, free triiodothyronine (fT3), free thyroxine (fT4)

STRESZCZENIE

Niedoczynność tarczycy może przebiegać zupełnie bezobjawowo, zwłaszcza w postaciach subklinicznych, bowiem klasyczne objawy tej endokrynopatii ujawniają się u chorych wraz z obniżonym stężeniem wolnej trójjodotyroniny (fT3), natomiast są rzadkie lub mogą w ogóle nie występować w przypadkach prawidłowego jej stężenia, a jedynie obniżonego stężenia wolnej tyroksyny. Celem badania była retrospektywna analiza symptomatologii niedoczynności tarczycy i poszukiwanie korelacji ze stężeniem fT3 w surowicy krwi. 241 pacjentów ambulatoryjnych (188 kobiet, 53 mężczyzn), średnia wieku 55,4±15,6, z niedoczynnością tarczycy leczonych w 2009 r. podzielono na dwie grupy: grupa I:151 chorych z prawidłowym stężeniem fT3 oraz grupa II: 90 pacjentów, u których odnotowano obniżone stężenie fT3 w surowicy krwi w stosunku do normy w momencie rozpoznania choroby. Na podstawie retrospektywnej oceny dokumentacji medycznej pacjentów poszukiwano zależności pomiędzy występowaniem objawów klinicznych niedoczynności tarczycy a stężeniem fT3. Analizując obraz kliniczny pacjentów z NT stwierdzono częstsze występowanie typowych objawów choroby w grupie II, jednak bez istotności statystycznej. Najczęściej zgłaszanymi objawami w tej grupie chorych były: przyrost masy ciała (26,67%), senność 24,44%, osłabienie 15,56% i suchość skóry 11,11%. Zaś w I grupie dominowały nietypowe

objawy dla NT, związane z układem krążenia, czyli objawy choroby niedokrwiennej serca 15,54% i zaburzenia rytmu serca 11,92%. Porównywalnie w obu grupach występowały: zaburzenia lipidowe (grupa I vs. grupa II) 43,71% vs. 42,22%, nadciśnienie tętnicze 32,45% vs 31,11%, obrzęki powiek 7,28 vs.6,67. W momencie rozpoznania NT obraz kliniczny nie koreluje ze stężeniem fT3 w badanej grupie pacjentów. Najlepszym sposobem rozpoznawania niedoczynności tarczycy pozostają nadal rutynowe testy funkcji tarczycy.

Słowa kluczowe: niedoczynność tarczycy, symptomatologia, wolna trójjodotyronina (fT3), wolna tyroksyna