

*Full Length Research Paper*

# Syndrome of isolated FT3 toxicosis: A pilot study

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When free thyroxine (FT4) concentration is elevated and thyrotropin (TSH) concentration is suppressed, hyperthyroidism is diagnosed. Some patients have normal FT4 concentration and elevated free triiodothyronine (FT3) concentration. This condition is named T3 toxicosis. The aim of the study was to describe the new syndrome of isolated FT3 toxicosis presenting normal TSH and FT4 levels and high FT3 with cardiological and mental complaints. 3026 out-patient individuals for the first time were examined because of thyroid pathology. There were analysed complaints; serum concentration of TSH, FT4, FT3 were measured in blood and ultrasound examination of thyroid was performed for all patients. Isolated FT3 toxicosis was diagnosed to 31 (1.02%) of them: 30 (96.8%) women and 1 (3.2%) man. Patients with arrhythmias or panic and anxiety attacks without clear causes must be examined for isolated FT3 toxicosis.

**Key words:** hyperthyroidism, toxicosis, arrhythmias, anxiety.

## INTRODUCTION

Thyrotoxicosis is a hypermetabolic condition associated with elevated levels of free thyroxine (FT4) and/or free triiodothyronine (FT3) (Lee and Ananthakrishnan, 2009) and low to undetectable thyroid-stimulating hormone (TSH) levels (Schrage, 2009).

Thyrotoxicosis is the clinical syndrome that occurs as a result of exposure of tissues to high levels of circulating thyroid hormones (Gardner and Shoback, 2007). The combination of elevated FT4 and suppressed TSH concentrations enable the diagnosis of hyperthyroidism. This form of thyrotoxicosis is detected for more than 95% of patients (Starkova and Kotova, 2002). Approximately 5% of patients have normal FT4 levels, but elevated serum T3 levels, such a situation is named "T3 thyrotoxicosis" (Gardner and Shoback, 2007; Miers, 1995; Drucker, 2003). The first patient with T3 thyrotoxicosis was identified in 1957 (De Groot, 2007).

There are two subgroups of T3 thyrotoxicosis:

1. T3 toxicosis, when clinical features of hyperthyroidism appear with normal concentration of total thyroxine (T4), FT4, thyroxin binding globulin (TBG), but total triiodothyronine T3 (T3) or FT3 concentrations are increased and TSH concentration is suppressed (Al-Abadi, 2001; Ginsberg, 2003; Ferrari et al., 1983; Drucker, 2003; Bielecka-Dabrowa and Mikhailidis, 2009).
2. Free T3 toxicosis, when TSH concentration is suppressed and concentrations of T4, FT4, TBG, T3 are normal, but FT3 concentration is increased (Al-Abadi, 2001; Figge et al., 1994).

It is believed that up to 10% of elderly hyperthyroid patients may have T3 toxicosis (Starkova and Kotova, 2002; Rehman et al., 2005).

T3 toxicosis is caused by iodine deficiency or compensatory increased hormone production or faster peripheral T4 to T3 conversion or relapse after subtotal thyroidectomy or increased hormone production in the

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early stages of thyrotoxicosis or elevated T3 concentration in Grave's disease, multinodular goiter or the autonomously functioning solitary thyroid nodule (Davis, 2009; Rehman et al., 2005). T3 toxicosis occurs in 5 to 46% patients with toxic nodules (Davis, 2009).

Exogenous T3 toxicosis may develop in patients who use T3 preparations prescribed by physician or without prescription for weight loss purposes or suffering with mental illnesses (Miers, 1995).

Treatment of exogenous T3 toxicosis is discontinuation of T3 preparation. Treatment of endogenous T3 toxicosis is the same as in hyperthyroidism. In clinical practice, it was found that patients with T3 toxicosis usually have long-term remission after antithyroid drug, in contrast to patients with normal thyrotoxicosis (Miers, 1995). If T3 toxicosis is not treated, typical hormones concentration in blood abnormalities, characterizing hyperthyroidism, usually develops. It is believed that T3 toxicosis is an early expression of hyperthyroidism (Hershman, 2008).

Slightly elevated T3 concentration may occur in pregnancy or during estrogen therapy (Drucker, 2003). Isolated FT3 toxicoses, when both T4 and FT4, and also TSH serum concentrations are normal, only FT3 concentration is elevated, is difficult to diagnose, because FT3 concentration is not measured, when thyrotoxicosis is suspected, even if suppressed serum TSH and normal FT4 concentrations are found.

The data on isolated FT3 toxicosis is still very few and quit controversial. So the study seems to be very important and apropos. The aim of our study was to describe peculiarities of cardiological and psychiatric symptoms of new FT3 toxicosis syndrome.

## METHODS

3026 out-patient individuals for the first time were examined because of thyroid pathology in Kaunas, Lithuania. Concentrations of TSH (normal values 0.4 to 4.0  $\mu$ U/ml), FT3 (normal values 0.8 to 2.1 ng/dl), FT4 (normal values - 0.85 to 1.85 ng/dl) were measured in blood, an ultrasound examination of thyroid, rated by size, structure, homogeneity was performed for all these patients. Hormonal measurements were performed by enzyme linked immuno sorbent assay (ELISA) STAT FAX-PLUS device. Thyroid ultrasound examination was performed by "Aloka" company echoscope (SSD – 210 DX Aloka, Japan) 5 MHz sensor using a water-cushion.

31 patients were found to have elevated FT3, but normal TSH and FT4 concentrations. The main complains were cardiological (heart rhythm disturbances, rapid heartbeat, pain in chest) and mental (hypersensitivity, anxiety, tension, fear without reason, insomnia). According to the complains, patients were divided into 3 groups: (1) With cardiological symptoms; (2) With mental symptoms, and (3) With mixed symptoms. According to ultrasound examination data, patients were divided into 2 groups: (1) With diffuse thyroid, and (2) with nodule thyroid.

Statistical calculations were made using the program SPSS 12.0. Significant differences between groups were analyzed by Mann-Whitney test, correlations were analysed by Pearson Correlation test. Descriptive values are given as mean  $\pm$  standart deviation (M  $\pm$ SD). We considered  $p < 0.05$  as statistically significant.

## RESULTS

From patients that had thyroid pathology, 31 (1.02%) patients were with isolated FT3 toxicosis (30 (96.8%) females and 1 (3.2%) male). Since only one male with isolated FT3 toxicosis was identified, we decided for our study to use only data of females. Average age of females was  $45.3 \pm 11.0$  (22 to 68) years. There were 14 (46.7%) patients with cardiological symptoms, 5 (16.6%) with mental symptoms and 11 (36.7%) with mixed (cardiological and mental) symptoms (Figure 1). According to ultrasound study of thyroid tissue, 9 (30%) patients had diffuse thyroid and 21 (70%) had node changes (Figure 2).

Average TSH concentration of all patients was  $1.6 \pm 1.1$   $\mu$ U/ml; average FT4 concentration was  $1.4 \pm 0.3$  ng/dl, and average FT3 concentration was  $2.5 \pm 0.3$  ng/dl. No significant differences were detected in thyroid hormones concentrations between patients with cardiological, mental and mixed symptoms (Table 1). TSH concentration, but not FT4 and FT3 concentration, was significantly higher in patients with diffuse thyroid tissue than in patients with node thyroid tissue (Table 2).

As in the isolated FT3 toxicosis syndrome, only FT3 concentration is evaluated, we considered to be important to present distribution of FT3 concentration of the patients.

Distribution of FT3 concentration in all researched patients is presented in Figure 3. The biggest part of our patients had FT3 concentration between 2.20 and 2.30 ng/dL. One significant correlation was detected: TSH concentration correlated negatively with structure of thyroid tissue (diffuse or node),  $r = -0.43$ ,  $p = 0.018$ .

## DISCUSSION

Some data off scientific literature suggests that the isolated FT3 toxicoses may be another early form of T3 toxicosis. Asymptomatic hypertriiodothyronemia is an occasional finding several months before the development of thyrotoxicosis with elevated T4 levels (De Groot, 2007). But our patients had signs of disease 1 to 2 years, so early T3 toxicosis or early phase of T4 toxicosis was denied. Isolated T3 toxicosis, which is characterized by normal TSH and FT4 levels and increased concentrations of FT3, is a relatively rare thyroid pathology, which occurs in approximately 1 in 80 patients, applying for thyroid pathology. This is especially for women (rather than suffering from other forms of thyrotoxicosis) is characterized by pathology.

46.7% of our patients complained of cardiovascular symptoms such like heart rhythm disturbances, rapid heartbeat, and pain in chest. Atrial fibrillation (AF) occurs in up to 15% of patients with hyperthyroidism and is more common in men and in patient with triiodothyronine (T3) toxicosis (Bielecka-Dabrowa and Mikhailidis, 2009).

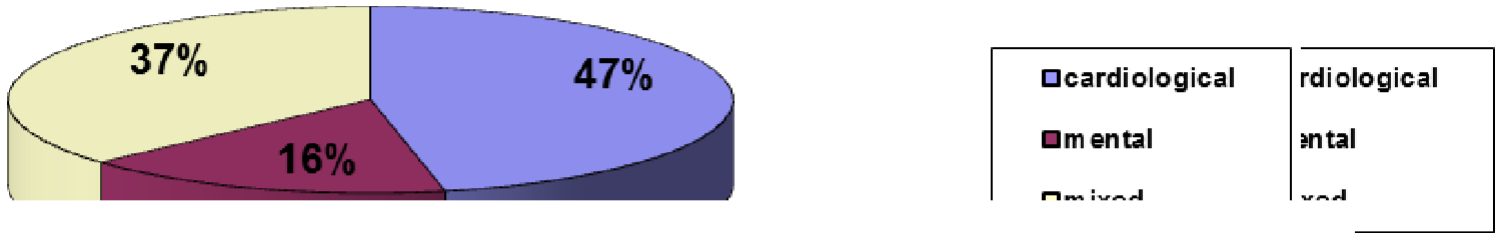


Figure 1. Distribution of patients with cardiological, mental and mixed symptoms.

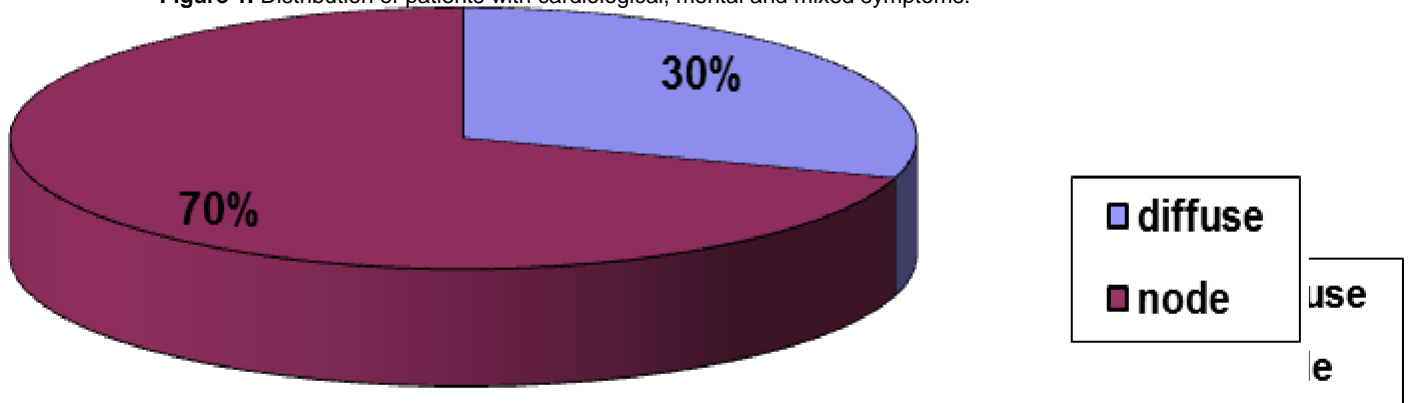


Figure 2. Distribution of patients with diffuse and node thyroid tissue.

Table 1. Differences of thyroid hormones concentrations in patients with cardiological, mental and mixed symptoms.

	Patients with cardiological symptoms (n = 14)	Patients with mental symptoms (n = 5)	Patients with mixed symptom (n = 11)	P (Mann-Whitney test)
Patients with cardiological symptoms (n = 14)	1.6 ± 0.9	1.2 ± 1.0	1.6 ± 1.4	NS
FT4 (ng/dl) (normal values 0.85 - 1.85 ng/dl)	1.4 ± 0.3	1.3 ± 0.4	1.5 ± 0.2	NS
FT3 (ng/dl) (normal values 0.8 - 2.1 ng/dl)	2.5 ± 0.3	2.5 ± 0.3	2.6 ± 0.3	NS

16.6% of patients with this pathology had mental representations - panic, anxiety attacks, insomnia, and increased sensitivity. The remaining patients (36.7 %) had mixed - and the cardiovascular and psychiatric complaints.

When thyrotoxicosis is suspected, diagnostic algorithms recommends analyzing TSH and FT4 concentrations. When these concentrations are normal, FT3 concentration is usually not investigated; because of that isolated FT3 toxicosis usually is not diagnosed. This is especially important in cardiology, because the usual treatment of rhythm disorders with beta-blockers blocks

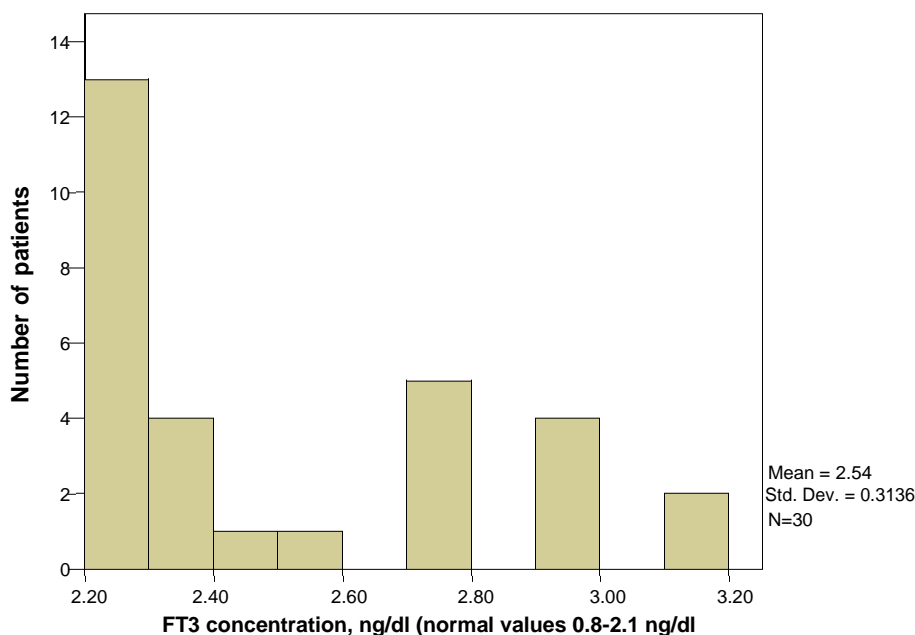
the conversion of T4 to T3. Results are usually good, but unstable (after discontinuation of treatment - arrhythmias recurs).

These findings suggest that the frequency of T3 toxicosis is significantly higher in areas of iodine deficiency (Hollander et al., 1972). Studies have shown the persistence of moderate or even severely affected areas of iodine deficite in several countries of Eastern Europe and in Baltic States (Vitti et al., 2001). Lithuania is one of the three Baltic States.

Limitations of our study are: (1) Not big enough number of researched patients (we considered it as a pilot study),

**Table 2.** Differences of thyroid hormones concentrations in patients with diffuse and node thyroid tissue.

	Patients with diffuse thyroid tissue ( n-9 )	Patients with node thyroid tissue ( n -21)	P (Mann-Whitney test)
TSH( $\mu$ U/ml)	2.3 $\pm$ 1.1	1.3 $\pm$ 0.9	0.017



**Figure 3.** Distribution of FT3 concentration in all researched patients.

and (2) No data on social, demographic and somatic state of patients was investigated. The limitations will serve us as guidance for further research. Despite the aforementioned limitations, our study was important, because it revealed that it is necessary to draw attention to and exploration of FT3 in heart rhythm disorders, panic and anxiety attacks.

Thyroid hormones are of primary importance for the perinatal development of the central nervous system, and for normal function of the adult brain (Aszalós, 2007).

Psychiatric symptoms suggesting panic, affective, and even schizophrenic disorders have been described in thyrotoxic patients (Kolawole and Ikem, 2003). However, none of psychiatric symptoms were found to correlate with serum T3 levels in cross-sectional study with small number of participants (Kolawole and Ikem, 2003). So, the data about connections of thyrotoxicosis, T3 levels and psychological state, are still controversial and needs further investigation. FT 3 toxicosis causes remain unclear. We plan to further investigate patients suffering from panic attacks, control their emotional state, their relation to hormone levels. It is important to draw

attention to the impact of deiodinases conversion of FT4 to FT3, and possible genetic predisposition FT3 toxicosis, incidence of the disease among family members.

## Conclusions

Patients with arrhythmias or panic and anxiety attacks, in the absence of clear reasons for their occurrence, should be tested on the isolated FT3 toxicosis.

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