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Research report

Mood and thyroid immunity assessed by ultrasonographic imaging in a primary health care

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Abstract

Background: Psychiatric morbidity is highly prevalent in the primary health care settings and it may be related to autoimmune thyroid disease (AITD). The aim of this study was to evaluate the impact of thyroid immunity, evident by hypo-echoic thyroid ultrasound pattern, on prevalence of depression and anxiety in a primary care setting.
Methods: In a cross-sectional design, 504 consecutive primary care patients were invited to the study and 474 patients completed the study. They were screened for depression and anxiety using the Hospital Anxiety and Depression Scale (HADS), were interviewed for affective disorders using the Mini International Neuropsychiatric Interview, and were evaluated by ultrasonographic imagining of the thyroid gland.
Results: Among patients with hypo-echoic thyroid ($n=122$) prevailed women and those patients were older than patients with normo-echoic thyroid ($n=352$). Women, but not men, with hypo-echoic thyroid compared to those with normo-echoic thyroid had higher scores on the anxiety subscale of the HADS ($p=0.03$). Among women with hypo-echoic thyroid, only those pre-menopause, but not those post-menopause, had greater prevalence of high scores on the depression subscale of the HADS ($p=0.02$) and a greater likelihood of using psychiatric medications ($p=0.001$).
Limitations: Lack of cytological evaluation of the thyroid gland; lack of serum thyroid antibodies concentrations; and lack of thyroid hormone concentrations.
Conclusions: Thyroid immunity is related to mood symptoms in primary care patients. These effects are gender specific and in women, they are most evident before menopause.

Keywords: Depression; Anxiety; Thyroid; Autoimmunity; Ultrasound; Primary care

1. Introduction

Depression and anxiety disorders are highly prevalent in the general population (Kessler et al., 1994) as well as in the primary health care settings (Sartorius et

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al., 1993; Ansseau et al., 2004). An association between mood disorders and thyroid immunity has been demonstrated in community samples (Pop et al., 1998; Carta et al., 2004), in an endocrine patient population (Bunevicius et al., 2005) and in psychiatric patients (Haggerty et al., 1997; Fountoulakis et al., 2004; Kupka et al., 2002). These studies suggest that an autoimmune thyroid disease (AITD), even without clinical or subclinical thyroid dysfunction, is related to mood and anxiety disorders. However, this has never been studied in an unselected medical population, such as in primary health care patients.

There are two major forms of AITD, autoimmune thyroiditis and Graves' disease. AITD is an autoimmune process characterized by the lymphocytic infiltration of the thyroid gland and by the presence of auto-antibodies against the thyroid antigens (Utiger, 1991). Results of fine needle aspiration biopsy as well as results of autopsy show that up to 40% of women have AITD evident by lymphocytic infiltration of the thyroid gland (Weetman, 2004). Assessment of thyroid antibodies in peripheral circulation show that the prevalence of AITD is close to 17% in the female population (Knudsen et al., 1999). In clinical practice, a diagnosis of AITD is usually based on the presence of thyroid antibodies in serum; however, that approach could miss some patients with AITD, because not all AITD patients are positive for thyroid antibodies in peripheral circulation, including those with thyroid dysfunction (Dayan and Daniels, 1996). In this regard, hypo-echoic ultrasound pattern of the thyroid gland that is related to lymphocytic infiltration of thyroid gland, assessed by ultrasound evaluation, may serve as a sensitive indicator of AITD (Hayashi et al., 1986; Marcocci et al., 1991; Rago et al., 2001). It was demonstrated in recent studies that an abnormal hypo-echoic thyroid ultrasound pattern is highly indicative for AITD (Raber et al., 2002; Pedersen et al., 2003; Smutek et al., 2003).

The aim of this study was to evaluate the association of thyroid immunity, evident by hypo-echoic thyroid ultrasound pattern, with depression and with anxiety symptoms, in primary care patients.

2. Subjects and method

2.1. Subjects

Five hundred and four primary care patients consecutively admitted during a 4-week period to the primary health care medical center in Kaunas, Lithuania were invited to participate in the study. Patients with uncompensated hypothyroidism or uncompensated hyperthyroidism evident by abnormal thyroid hormone or/and thyroid stimulating hormone concentration; and patients without thyroid tissue were excluded from the study. Four hundred seventy-four patients completed the study. All patients gave written informed consent. The study and its consent procedures were approved by the Regional Committee of Ethics in Biomedical Research at the Kaunas University of Medicine, Kaunas, Lithuania.

The mean age of the study population was 52 years, ranging from 18 to 89 years, and 348 (73%) were women. One hundred ninety-five study women (56%) were post-menopausal, based on self-report absence of menses for at least 12 months. Sixty-seven patients (14%) had a history of endocrine disease; sixty-eight patients (14%) had a history of mental disorder. Eighty-four patients (18%) used psychotropic medication, mostly benzodiazepines, 69 patients (15%); no patient used lithium. Six women had diagnoses of hypothyroidism and were treated with L-thyroxine.

2.2. Methods

After visiting their general practitioner all study patients were interviewed for demographic data and general health status, relevant data from medical documentation were collected. Patients were asked to fill out a standard psychiatric questionnaire and were interviewed for psychiatric diagnoses by the same trained general practitioner (JP), and ultrasound evaluation of the thyroid gland was performed by the same endocrinologist (NM). The ultrasound reader was blind to the psychiatric diagnoses and the person performing the psychiatric evaluation was blind to the echoic thyroid pattern.

All patients were assessed for depression and anxiety symptoms using the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983). The HADS is comprised of 14 items scored from 0 to 3 to which patients respond based on their experience over the past week. Seven items relevant to anxiety comprise a subscale for anxiety with a score range from 0 to 21; seven other items comprise a subscale for depression with the same score range. A score of 8–10 suggests, and a score of 11 or more indicates, the presence of depressive disorder or anxiety disorder. The HADS was constructed for self-administration by inpatients and outpatients in non-psychiatric clinical settings.

All study patients were interviewed for mental disorders using mood and anxiety modules of the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). These modules assess current diagnoses of major depression and anxiety disorders,

such as panic disorder, social anxiety and generalized anxiety. The MINI is a structured clinical interview to assess diagnoses using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (APA, 2000) and the International Statistical Classification of Diseases, 10th Revision (ICD-10) Classification of Mental and Behavioural Disorders (WHO, 1992).

Thyroid gland ultrasonographic evaluation was performed with a real-time scanner equipped with 5 MHz liner transducer with water pillow (SSD-210 Dx, Aloka, Japan). Normal echoic thyroid pattern was considered when the density of the thyroid gland was similar to submandibular gland and hypo-echoic to neck muscles; hypo-echoic thyroid pattern was considered when the density of the thyroid gland was hypo-echoic to submandibular gland and hypo-echoic or isohypo-echoic to neck muscles (Raber et al., 2002).

3. Statistical analysis

All continuous data are presented as means ± standard deviations, all categorical data as number and percent. First we examined whether demographic data and measurements of health status are associated with gender. Comparisons between men and women on categorical variables were performed using a two-tailed χ^2 analysis, comparisons on continuous data were performed using non-paired two-tailed *t*-tests. Next we investigated whether scores of depression and anxiety were associated with an echoic thyroid pattern in the total sample of men, and in the total sample of women. General linear multivariate models were employed for these comparisons where scores on subscales of anxiety and depression of the HADS were used as dependent variables, echoic thyroid pattern was used as the independent factor, and age was used as covariate. Eventually the prevalence of mental disorders and the use of psychiatric medication were compared in two subgroups of women with respect to their menopausal status. Comparisons between women with a normo-echoic thyroid pattern and those with a hypo-echoic thyroid pattern were performed using a two-tailed χ^2 analysis separately in pre-menopausal women and in post-menopausal women. A probability level of $p<0.05$ was taken as significant. The SPSS 12.0 for windows program was used for data analyses.

4. Results

Among 474 primary care patients 56 (12%) had scores on the subscale of depression of the HADS higher then 10, indicating a depressive disorder; 121 (26%) had scores on the subscale of anxiety higher then 10, indicating an anxiety disorder; 169 (36%) had specific MINI diagnoses of depression or anxiety disorder. Ultrasonographic evaluation of the thyroid gland revealed that 122 patients (26%) had a hypo-echoic thyroid pattern, indicating AITD. Women compared to men had higher scores on the subscale of

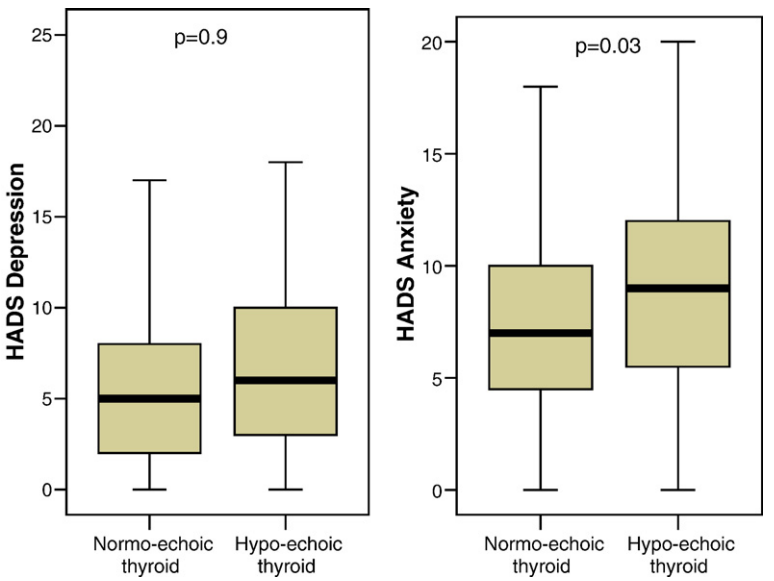

Fig. 1. Differences of scores on subscales of depression and anxiety of the Hospital Anxiety and Depression Scale (HADS) in relation to echoic thyroid pattern in 348 female primary care patients (adjusted for age).

depression (5.9±4.2 vs. 4.9±3.3; $p=0.01$) and on the subscale of anxiety (8.1±4.4 vs.6.7±4.0; $p=0.001$) of the HADS. According to the MINI women had higher prevalence of generalized anxiety disorder (28% vs. 19%; $p=0.04$) and higher total prevalence of depression or anxiety disorder (38% vs. 29%; $p=0.05$). On ultrasonographic evaluation women compared to men had a higher prevalence of a hypo-echoic thyroid pattern (30% vs.14%; $p=0.001$).

Because there were significant gender differences in endocrine and mental status, data pertaining to thyroid immunity were analyzed separately for men and for women. Men and women with hypo-echoic thyroid compared to those with normo-echoic thyroid were significantly older (61±14 vs. 51±20; $p=0.05$; and 64±14 vs. 47±20; $p<0.001$; respectively), so other comparisons were adjusted for age. Fig. 1 shows that women with a hypo-echoic thyroid compared to women with normo-echoic thyroid had higher scores on the anxiety subscale of the HADS (9.0±4.6 vs. 7.8±4.4; $p=0.03$). Scores on the depression subscale of the HADS also were higher among women with a hypo-echoic thyroid; however, this difference lost statistical significance after adjusting for age. Echoic thyroid pattern was not associated with the HADS scores in men nor with the prevalence of MINI diagnoses in men or in women.

When women were divided into two groups in relation to their menopausal status, only pre-menopausal women with hypo-echoic thyroid compared to those with normo-echoic thyroid had higher prevalence of use of psychiatric medication (31% vs. 6%; $p=0.001$), and higher prevalence of depression according to the HADS (19% vs. 3%; $p=0.02$) but there were no difference in the prevalence of specific mental disorders diagnosed by MINI (Table 1). However, prevalence of total MINI depression or anxiety disorders tended to be higher (50% vs. 29%; $p=0.09$) in pre-menopausal women with hypo-echoic thyroid compared to those with normo-echoic thyroid. There were no significant differences in regards to echoic thyroid pattern in the prevalence of mood disorders or the use of psychiatric medication in post-menopausal women.

5. Discussion

The results of this study indicate that thyroid autoimmunity, evaluated by a relatively simple, cost effective but reliable technique, ultrosonographic imaging of the thyroid gland, is associated with mood symptoms in primary health care patients, especially in pre-menopausal women. This observation corresponds to findings from other studies on the relationship between thyroid autoimmunity and mood disorders where thyroid immunity was measured by the assessment of thyroid antibodies in peripheral circulation (Carta et al., 2004; Haggerty et al., 1997; Kupka et al., 2002). Indeed, recent findings (Pedersen et al., 2003; Rago et al., 2001; Smutek et al., 2003) suggest that thyroid hypo-echogenicity found by ultrasonographic evaluation of the thyroid gland is a strong predictor of AITD and there is a close correlation between this marker of the AITD and the presence of thyroid antibodies (Raber et al., 2002).

Table 1
Thyroid echoic pattern and prevalence of mental disorders in primary care female patients before and after menopause (*n* (%))

	Pre-menopausal women, $n=153$			Post-menopausal women, $n=195$		
	Normo-echoic thyroid $n=137$	Hypo-echoic thyroid $n=16$	*p*	Normo-echoic thyroid $n=107$	Hypo-echoic thyroid $n=88$	*p*
Hospital anxiety and depression scale						
Depression>10	4 (3)	3 (19)	0.02	24 (22)	19 (22)	0.9
Anxiety>10	27 (20)	6 (38)	0.2	33 (31)	35 (40)	0.09
MINI diagnoses						
Major Depression	21 (15)	3 (19)	0.7	32 (30)	28 (32)	0.8
Anxiety disorders						
Panic disorder	6 (4)	2 (13)	0.2	2 (2)	2 (2)	0.8
Social phobia	8 (6)	2 (13)	0.3	2 (2)	1 (1)	0.7
Generalized anxiety	30 (22)	5 (31)	0.4	35 (32)	28 (32)	0.9
Depression or Anxiety disorder	40 (29)	8 (50)	0.09	46 (43)	39 (44)	0.9
Use of psychiatric medication	8 (6)	5 (31)	0.001	27 (26)	20 (23)	0.7
Use of benzodiazepines	6 (4)	4 (25)	0.002	22 (21)	17 (20)	0.8

The most important findings of our study pertain to the association between thyroid immunity and mood or anxiety symptoms in primary care female patients, especially in pre-menopausal women. These data are consistent with the report of Pop et al. (1998) who together with colleagues in their community studied 583 randomly selected pre-menopausal women and found that those with elevated thyroid antibody concentrations were especially vulnerable for depression, whereas post-menopausal status and thyroid hormone status did not increase risk of depression. In a similar way it was demonstrated in the post-partum period that women who had a higher serum thyroid antibody concentration post-partum (Harris et al., 1992) or during gestation (Kuijpens et al., 2001) had a higher prevalence of post-partum depression. In combination with our results, these findings, taken together, suggest a role of the female sex hormones in the association of thyroid autoimmune process and mood or anxiety disorders. While this remains an area of further inquiry, evidence that thyroid hormone concentrations (Girdler et al., 1995, 2004) as well as thyroid gland size (Hegedus et al., 1986) vary with phase of the menstrual cycle in pre-menopausal women provide partial support for this supposition.

In our study, it is curious to note that the self-rating instrument to measure symptoms of depression and anxiety, the HADS, revealed associations between mood symptoms and thyroid immunity in pre-menopausal women. However, we found no statistically significant differences in the prevalence of specific mood and anxiety disorders assessed by structured diagnostic interview in relation to thyroid echogenicity. The possible explanation for this inconsistency may be related to the treatment of mental symptoms. Indeed, pre-menopausal women with hypo-echoic thyroid pattern were treated more frequently with psychotropic medication, including benzodiazepines, in comparison to women with normo-echoic thyroid. This may have decreased the incidence of patients that fulfill criteria for specific mental disorders in the hypo-echoic thyroid group.

AITD is frequently related to thyroid dysfunction and it is suggested that even marginal thyroid dysfunction may be associated with mood and anxiety disorders (Prange, 1998). However, a large epidemiological study found no statistical association between clinical or subclinical thyroid dysfunction, and the presence of depression or anxiety disorders in a large unselected population (Engum et al., 2002). Moreover, several studies that reported an association between depression and increased levels of thyroid antibodies found that depression was not related to thyroid dysfunction (Harris et al., 1992; Pop et al., 1998; Kuijpens et al., 2001). A recent study of Grabe et al. (2005) found that a general population of women with AITD, diagnosed by hypo-echoic thyroid pattern and by the presence of thyroid antibodies in serum, showed higher scores of anxiety independently from their thyroid function. It may be that it is not marginal thyroid dysfunction, but rather thyroid autoimmune processes, frequently responsible for this dysfunction (Bunevicius et al., 1994, 1996), that are responsible for co-morbidity with mood disorders. In our study we did not assess thyroid axis hormone concentrations and did not address this important question directly. However, our findings, together with findings of others suggest that thyroid immunity *per se* may be an important predictor of mood disorders.

Involvement of thyroid immunity in brain functioning was reported by several neuro-imagining studies, demonstrating a higher prevalence of brain perfusion abnormalities in euthyroid patients with autoimmune thyroiditis (Zettinig et al., 2003; Piga et al., 2004) and higher levels of anxiety and depression in these patients (Zettinig et al., 2003). These brain perfusion abnormalities are similar to those observed in Hashimoto's encephalopathy (Chong et al., 2003) and may suggest a higher than expected involvement of the brain in AITD.

Findings from this study obtained from an unselected primary care population, along with other studies, provide evidence that an autoimmune thyroid process *per se* may be related to mood and anxiety disorders. A full understanding of the relationship between thyroid autoimmunity and mental functioning awaits a full description. Further studies on the involvement of thyroid immunity in mental disorders as well as on the involvement of mental disorders in euthyroid patients with autoimmune thyroid disease are needed. This possibility can be investigated by the use of different techniques for the evaluation of thyroid autoimmunity: by the measurement of serum thyroid antibodies; by the cytological assessment of thyroid tissue, or by the ultrasonographic evaluation of the thyroid gland.

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