ELSEVIER

Journal of Affective Disorders 69 (2002) 209–217

JOURNAL OF AFFECTIVE DISORDERS

www.elsevier.com/locate/jad

Research report

Hypothyroidism and hyperthyroidism in anxiety disorders revisited: new data and literature review

Naomi M. Simon*, Deborah Blacker, Nicole B. Korbly, Saumya G. Sharma, John J. Worthington, Michael W. Otto, Mark H. Pollack

Anxiety Disorders Program, Massachusetts General Hospital and Harvard Medical School, 15 Parkman Street, WAC 815, Boston, MA 02114, USA

Received 8 November 2000; accepted 2 April 2001

Abstract

Background: The need for thyroid screening of patients presenting with panic disorder (PD), social phobia (SP) or generalized anxiety disorder (GAD) remains uncertain. *Methods*: We examined thyroid histories and serum testing in 169 patients, 92 with PD, 48 with SP, and 29 with GAD. Combined prevalence rates of hyperthyroidism and hypothyroidism were compared with expected rates (2.7%) derived from the population based Whickham Survey. Data from previously published studies were also compared with these expected rates. *Results*: In our sample, only 2/169 patients had thyroid dysfunction detected by serum testing, but 5/169 [1/92 (1%) with PD, 1/48 (2%) with SP, and 3/29 (10%) with GAD], all currently euthyroid, reported a history of thyroid disease. The rates were statistically significant only for GAD (10.4%; $z = 2.56$, $p = 0.01$). However, combining prior PD studies that examined both thyroid history and test results with our data also suggests significantly elevated rates of thyroid dysfunction (6.5%; $z = 4.69$, $p < 0.0001$). *Limitations*: As with previous data, the 95% confidence interval for our findings is broad, reflecting the instability of low rates of illness in relatively small samples. Further, methods for obtaining thyroid histories and tests were not uniform. *Conclusions*: Despite relatively low yields on serum testing, lifetime prevalence of thyroid dysfunction does appear elevated for GAD and PD, with minimal data addressing this issue for SP. The data support the need to query GAD and PD patients regarding thyroid history and perform serum testing in those without prior testing.

Keywords: Anxiety disorder; Hyperthyroid; Hypothyroid; Thyroid; Panic disorder; Generalized anxiety disorder; Social phobia

1. Introduction

The need for thyroid screening of patients presenting with symptoms of panic disorder (PD), generalized anxiety disorder (GAD), or social phobia (SP) remains uncertain. For patients with thyroid dysfunction, particularly hyperthyroidism, the presence of generalized anxiety as well as panic attacks has been well-described for many years (Denicoff et al., 1990; Greer et al., 1973; Katerndahl and Vande Creek, 1983; Kathol et al., 1986; Placidi et al.,

*Corresponding author.
E-mail address: nsimon@partners.org (N.M. Simon).

0165-0327/02/$ – see front matter
PII: S0165-0327(01)00378-0

1998). Symptoms such as palpitations, tremor, sweating and nervousness may be present in the anxiety disorders and in hyperthyroidism or hypothyroidism (Denicoff et al., 1990; Kathol and Delahunt, 1986), and there is a widely held perception of an association between thyroid and anxiety disorders. Thyroid abnormalities are one of a number of medical conditions potentially associated with anxiety disorders. However, data supporting this association remain inconclusive, and thyroid screening is inconsistently applied in both clinical and research settings. In this article, we address this issue by providing additional data from our own database of thyroid screening in psychopharmacology trials of PD, GAD, and SP, and by critically reviewing the available literature.

2. Report of a new study

To address the question of whether there is an elevated prevalence of thyroid dysfunction in patients with anxiety disorders, we examined thyroid histories and serum testing in patients with PD, SP, and GAD. Prevalence rates of thyroid dysfunction in the anxiety disordered samples were then compared with population norms derived from the Whickham Survey, a large epidemiologic study conducted in Britain (Tunbridge et al., 1977). In this study, thyroid history, confirmed by physician records, and serum testing (TSH, T4, T3, T3 uptake), was examined in 2779 randomly selected adults; the prevalence of overt (clinical) hyperthyroidism was 1.1% and hypothyroidism was 0.8%, with mean ages of onset of 48 and 57 years, respectively. Thus, the combined prevalence of hyperthyroidism plus hypothyroidism in the general population may be estimated from the Whickham Survey as 2.7% (95% CI 2.13–3.37), with rates significantly higher for women (4.2%: 95% CI 3.26–5.36).

3. Method

Participants were 169 outpatients who had participated in one of 10 clinical trials in the Anxiety Disorders Program of the Massachusetts General Hospital in which a history of thyroid disease was queried and serum thyroid testing was performed at baseline. Based on DSM-IV criteria as assessed by a physician-administered, structured diagnostic interview with either the Structured Clinical Interview for DSM-IV (SCID; First et al., 1995) or the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), 92 patients met criteria for primary PD [32 (35%) with comorbid agoraphobia], 48 met criteria for primary generalized SP, and 29 met criteria for primary GAD. All study participants provided written informed consent prior to trial entry. Exclusion criteria for the clinical trials included: pregnancy or lactation, unstable medical illness, age <18 or >65 years, alcohol or substance abuse within the last 6–12 months, severe personality disorders, current psychotropic use, history of hypersensitivity to the study drug, ongoing psychotherapy directed towards the anxiety disorder, or past or current history of psychosis, bipolar disorder, obsessive compulsive disorder, or post-traumatic stress disorder.

The specific thyroid tests obtained varied by protocol (see Table 1), reflecting the lack of a clear standard for assessing patients with anxiety disorders. However, all serum thryotropin levels (TSH) were performed by sensitive assays. Medical histories of thyroid disease were also obtained as part of routine history gathering, but were not confirmed through medical records or other outside sources. The normal comparison group was from the aforementioned Whickham Survey.

A laboratory diagnosis of hyperthyroidism or hypothyroidism was defined as an undetectable TSH

Table 1
Thyroid tests obtained per diagnosis in current study

Diagnosis	Total number of patients	Tests performed	Number of patients per test(s)
GAD	29	T4 only	19
		TSH, T4, T3	10
SP	48	TSH, T4 only	34
		TSH, T4, T3	14
PD	92	T4 only	12
		TSH only	22
		TSH, T4 only	14
		TSH, T4, T3	44

GAD, Generalized anxiety disorder; SP, social phobia; PD, panic disorder.

or TSH > 10 mU/l with associated abnormal T4 and/or T3 (Helfand and Redfern, 1998). All patients in this sample with abnormalities on serum testing had both TSH and peripheral (T3 and/or T4) testing.

4. Data analysis

We examined rates of hyperthyroidism or hypothyroidism determined by both reported past history as well as current abnormalities on serum testing for comparison with population rates as reported in the Whickham Survey. Rates of hypothyroidism and hyperthyroidism were combined for the purpose of this analysis, and 95% confidence intervals were calculated. The term *thyroid dysfunction* is used throughout this paper to describe patients who had clinically significant laboratory abnormalities and/or a history of hypothyroidism or hyperthyroidism. Rates observed in our sample, overall and separately for women, were compared with the respective population mean from Tunbridge et al. (1977) and single-sample tests of binomial proportions were calculated.

5. Results

Fifty-five percent of the 169 anxiety disordered patients were women; 86% were Caucasian, 9% African American, 3% Hispanic and 2% Asian. The mean age of the sample was 37±10 years, with an average age of onset for social phobia of 17.2±9.3 years, for GAD of 27.1±12.9 years, and for panic of 27.7±10.7 years. A history of diagnosed thyroid disease was reported by five patients (3%), three with hypothyroidism and two with hyperthyroidism. The mean age of these five patients was 45.2 years; data regarding age of onset of thyroid disease were not available. All five patients were euthyroid on serum testing, largely accounted for by current treatment of their thyroid disorder (i.e., four patients were receiving thyroid replacement hormone, and one was status-post thyroidectomy). The primary anxiety diagnosis for these five patients with thyroid disease by history was GAD for three (10% prevalence; 95% CI 2.2–27), PD for one (1% prevalence; 95% CI 0.03–5.9) and SP for one (2% prevalence; 95% CI 0.05–11).

On serum testing, one patient with PD had overt hyperthyroidism, with a TSH of 0.04, a T3 of 416 (NL range 80–200), and T4 of 20.80 (NL range 4.5–12.5), despite an unremarkable physical exam and medical history, and a family history of PD. Another patient had a mildly low TSH of 0.29 MIU/l (NL range 0.32–5.0), but normal T3 of 128 UG/DL (NL range 80–200) and T4 of 7.10 UG/DL (NL range 4.5–12.5), consistent with Woeber's (1999) definition of subclinical hyperthyroidism; the patient was conservatively considered unaffected for the purpose of these analyses. A third patient had a TSH of 12.4 MIU/l (NL range 0.03–5.0) and a T4 of 0.70 NG/DL (NL range 0.8–1.8), reflecting mild clinical hypothyroidism. This patient had an unremarkable physical exam and a 27-year history of SP as well as major depression.

Thus, one of the 92 patients with PD (1.1%; 95% CI 0.03–5.9) had a significant thyroid test abnormality. None of the 29 (0%; 95% CI 0–12) patients with GAD had thyroid test abnormalities, and only one of the 48 patients with SP (2.1%; 95% CI 0.05–11) had a thyroid abnormality: thus, of 169 patients only 3/169 (1.8%; 95% CI 0.37–5.1) had any test abnormality that might indicate the need for further monitoring or assessment, and 2/169 (1.2%; 95% CI 0.14–4.2) had abnormalities meeting laboratory criteria for overt hyperthyroidism (one) or hypothyroidism (one) (Helfand and Redfern, 1998).

The combination of patients with previously diagnosed thyroid disease and those with current serum abnormalities (none of whom overlapped) yielded a total prevalence of 4.1% (95% CI 1.7–8.3) for all diagnoses, 2.2% (95% CI 0.26–7.6) for PD, 4.2% (95% CI 0.5–14.2) for SP, and 10.4% (95% CI 2.2–27) for GAD. The rate in women was higher at 6.5% (95% CI 2.4–13.7), probably reflecting the higher prevalence of thyroid dysfunction in women in general (Tunbridge et al., 1977). The prevalence of thyroid dysfunction in GAD was significantly greater than that of the general population according to a single-sample test of binomial proportions ($z = 2.56$, $p = 0.01$), but not for PD ($z = 0.355$, $p = 0.72$), SP ($z = 0.64$, $p = 0.52$), or the entire anxious sample ($z = 1.60$, $p = 0.11$). None of the GAD patients with thyroid dysfunction had comorbid major depression, ruling out comorbidity as an

explanation of the GAD finding. In addition, sex did not modify the effect for GAD.

6. Critical review of previous studies

There are a number of methodologic issues that impact the interpretation of the available data, and prevent a formal meta-analysis. First, recommendations for screening have changed over time, resulting in variation in the thyroid tests administered. Many studies examined only TSH, while others reported more extensive peripheral serum testing, including total thyroxine (T4), free T4, triiodothyronine levels (T3) or T3 resin uptake (T3RU). In the 1980s, more sensitive TSH assays capable of screening overt and subclinical hyperthyroidism were developed (Evans et al., 1985; Klee and Hay, 1987, 1988; Masters and Simons, 1996; Ross et al., 1989). This variability in testing and assay sensitivity potentially confounds the comparability of studies, although this issue is more relevant for the detection of subclinical hyperthyroidism. Further, there is a wide variability across studies in their inclusion or exclusion of patients with previously diagnosed thyroid disease, and most available studies lack a comparison group. Thus, we examined available data regarding rates of thyroid abnormalities in individuals with anxiety disorders in the context of the general population norms for hyperthyroidism and hypothyroidism derived from the Whickham Survey (Tunbridge et al., 1977).

7. Panic disorder

A total of 12 previous studies published between 1979 and 1998 addressed the question of thyroid dysfunction in PD (see Table 2). The majority of studies were performed in the 1980s, and in some cases it is not clear which TSH assay was used; this could potentially result in missed cases of subclinical disease. Nonetheless, nine of 11 studies found zero patients with any serum thyroid abnormality. Two studies from the 1980s reported undetectable TSH levels, but the patients were otherwise euthyroid which, with an insensitive assay, could be normal or consistent with suppressed pituitary TSH production due to subclinical hyperthyroidism (Fishman et al., 1985; Munjack and Palmer, 1988).

The potential for more subtle thyroid abnormalities was addressed in four studies examining patients with PD and controls. These studies failed to find abnormalities in mean thyroid levels (Stein and Uhde, 1988; Yeragani et al., 1987), found blunted TSH responses to TRH stimulation in panic patients despite normal peripheral hormone levels (T3, T4, TSH, free T4) (Roy-Byrne et al., 1986), and failed to find any abnormality in tissue-level responsivity to thyroid hormone (Stein et al., 1991). These data further refute the notion that subtle thyroid abnormalities are generally present in all PD patients despite normal peripheral hormone levels. In contrast to the low rates of serum thyroid abnormalities in previous reports, four studies presented data regarding the prevalence of a history of thyroid disease in patients with panic disorder with rates ranging from 4.9% (95% CI 0.6–16.5) to 23% (95% CI 13–36.4) (see Table 2 and Fig. 1). In the report by Orenstein et al. (1988), all of the 23% of patients reporting a history of thyroid abnormalities were women and were significantly older than the rest of the sample.

When reported in the studies, we combine the number of patients with serum thyroid abnormalities and those with a prior history who are currently euthymic (due to treatment) to estimate the lifetime prevalence of hyperthyroidism and hypothyroidism within the anxiety disordered sample. For studies that examined mean peripheral thyroid test levels rather than the presence of frank hyperthyroidism or hypothyroidism (Stein and Uhde, 1988; Stein et al., 1991; Tancer et al., 1990; Yeragani et al., 1987; see Table 2), the prevalence of actual thyroid abnormalities was gleaned from the reported data where possible.

The relatively low sample size in these studies (range: 12 to 165) leaves significant room for error. Examination of the 95% CI suggests that they are generally consistent with the reported population rates of 2.7% (95% CI 2.46–3.08) (see Fig. 1); however, these are small studies and most findings are consistent with higher or lower rates as well.

After excluding studies which did not examine both history and thyroid testing, included subsyndromal PD, or excluded patients based on

Table 2
Studies of thyroid history and serum abnormalities in PD, GAD, and SP

Diagnosis	Author(s)	No. subjects	History thyroid disease (%)	Serum tests used[a]	Serum thyroid abnormality	Controls?	TRH stim. test	Should we screen?
PD	Pariser et al. (1979)	12[b]		T3, T4, FTI	0	No		
	Fishman et al. (1985)	82		TSH, T4, T3RU	0 (22% TSH undetect.)	No		
	Roy-Byrne et al. (1986)	12		TSH, T3, T4, free T4	0	Yes	Blunted	
	Lesser et al. (1987)	165	6.7%	TSH, T4, T3RU	0.6%	No		Yes
	Matuzas et al. (1987)	55[b]	5.5%	TSH, T3, T4, FT4I	7.3%	No		
	Yeragani et al. (1987)	26	Excluded	T3 and T4 RIA	Equal to controls[c]	Yes		
	Stein and Uhde (1988)	26	Excluded	TSH, T3, T4, free T4, TBG	0%; equal to controls[c]	Yes		Yes
	Stein et al. (1991)	15		TSH, T4, Free T4; T3, QKd	Equal to controls[c]	Yes	Normal	
	Chiovato et al. (1998)	87	0%	TSH, free T3, free T4	0	No		
	Orenstein et al. (1988)	56[b] women	23%	TSH, T4, T3RU	0	No		
GAD versus PD	Munjack and Palmer (1988)	52 GAD 41 PD		Free T4, T4, T3RU	0% (TSH undetect. 9% PD 10% GAD)	Yes		No
	Noyes et al. (1992)	32 GAD 41 PD women	28% GAD 5% PD	N/A	N/A	No		
SP	Tancer et al. (1990)	26	Excluded	TSH, T3, T4, free T4	0%; equal to controls[c]	Yes	Equivocal	

PD, Panic disorder; GAD, generalized anxiety disorder; SP, social phobia; TSH, thyroid stimulating hormone (thyrotropin); T4, thyroxine; T3, triiodothyronine; FTI, free thyroxine index; RIA, radioimmunoassay (older assay); T3RU, T3 resin uptake; TBG, thyroxine binding globulin; QKd, a cardiovascular measure used to detect thyroid dysfunction.

[a] Serum thyroid tests varied by study, and TSH sensitivity has dramatically improved in the 1980s; thyroid antibodies are not reviewed here.

[b] Combines patients with panic attacks and panic disorder.

[c] These studies compared means on thyroid tests between patients and controls and not presence of test abnormalities within groups.

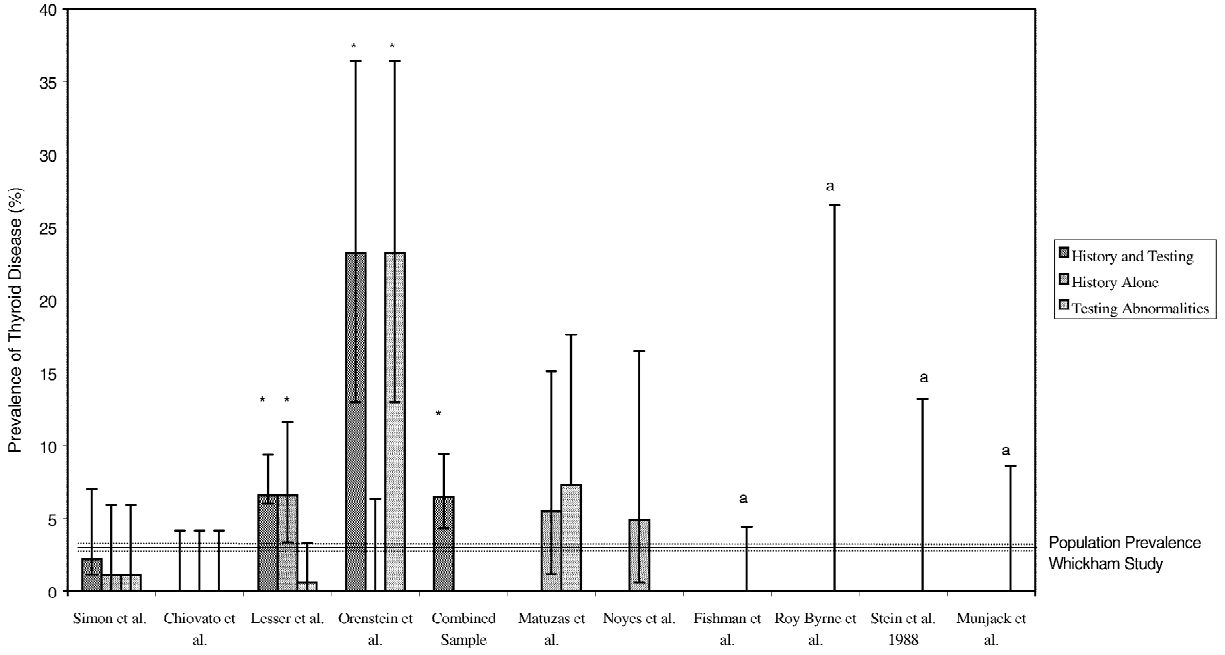

Fig. 1. Panic disorder studies allowing assessment of thyroid testing and combined study data.

prior thyroid history, we were left with three studies that utilized a more optimal methodology for assessing the prevalence of thyroid dysfunction (Chiovato et al., 1998; Lesser et al., 1987; Orenstein et al., 1988) (see Fig. 1). Data from these three studies were combined with our panic data and a weighted average was calculated. Based on this approach, our estimate of the prevalence of thyroid dysfunction based on testing and history in PD is 6.5% (95%CI 4.3–9.4), which is significantly greater than the population norm of 2.7% ($z = 4.69$, $p < 0.0001$, one-sample test for binomial proportions).

8. Generalized anxiety disorder

Two previous studies examined thyroid function in patients with GAD (Table 2). One examined thyroid tests alone for GAD patients compared with PD and controls; there was no significant difference between groups (GAD prevalence 0%, 95% CI 0–6.9) (Munjack and Palmer, 1988). The second study examined a past history of thyroid disease by patient report alone and found higher rates in their GAD group (28%; 95% CI 13.7–46.7) than a PD comparison group (4.9%; 95% CI 0.6–16.5) (Noyes et al., 1992). There is no study prior to our own that examined both thyroid tests and history in GAD patients. Thus the best estimate we have is our finding of a 10.4% prevalence of thyroid dysfunction.

9. Social phobia

The only previous study of thyroid function in social phobia (SP) (Table 2) found no serum thyroid abnormalities (0%, 95% CI 0–22) and no significant differences between mean thyroid tests (TSH, T3, T4 and free T4) for patients compared with controls (Tancer et al., 1990). No studies prior to our own have examined thyroid history in social phobia. Thus, our estimate of a 4.2% prevalence of thyroid dysfunction is the best to date.

10. Discussion

For PD, the totality of evidence from studies that examined both thyroid history and test results suggest significantly elevated rates of thyroid dysfunction (6.5%) compared with population based estimates. This is in contrast to the very low rates of abnormalities in PD studies which assessed serum thyroid testing alone (see Fig. 1). For GAD, the best estimate of lifetime prevalence of thyroid dysfunction is our own sample, which was significantly elevated compared to the population estimate (10.4%). For social phobia, the minimal data available to date do not suggest an elevated prevalence of thyroid dysfunction. This data should be understood as limited by the lack of uniformity of thyroid tests and methods of obtaining thyroid histories in the study samples and comparison group, with the comparison group a population based sample obtained in a separate study. Nonetheless, examination of all currently available data, including our own, addresses several relevant questions to varying degrees.

(1) Are thyroid abnormalities necessary or etiologically inherent to GAD, SP or PD?

The answer to this question appears to be 'no' based on the lack of a uniform presence of even subtle thyroid abnormalities in the vast majority of patients suffering from these disorders.

(2) Does the presence of GAD, SP or PD significantly increase risk of thyroid dysfunction?

Current data and previous reports suggest at minimum that there is not a large increase in risk, particularly for previously undiagnosed hypothyroidism or hyperthyroidism detected by serum screening. Our findings do suggest a small increased risk for lifetime prevalence of hyperthyroidism or hypothyroidism for PD and for GAD. These findings remain significant even when the more conservative Bonferroni adjustment for multiple tests was applied ($\alpha = 0.01$), and represent small to medium effect sizes ($h = 0.17$ for panic, $h = 0.3$ for GAD) (Cohen, 1988). However, as with previous data, the 95% confidence interval for our findings is broad, reflecting the instability of estimates of low rates of illness in relatively small samples. The current data, though quite limited, does not suggest elevated rates of thyroid dysfunction in SP.

(3) Should patients with GAD, SP or PD be routinely tested for thyroid dysfunction?

Despite the fact that yields for thyroid testing of patients with anxiety disorders have generally been low in many previous studies, as well as the current one, many authors have continued to recommend thyroid screening in this population. Although there is no empirical data examining the impact of untreated thyroid dysfunction on anxiolytic treatment response, the adverse health consequences of hyperthyroidism and hypothyroidism in general are well recognized (Danese et al., 1996). Lesser et al. (1987) recommended testing, despite their finding of low yield, as ''the necessity of treating a concurrent hyperthyroid condition is obvious.'' Stein and Uhde (1988) also suggested that screening is still necessary for patients presenting with panic attacks, despite their negative findings. Given that many patients in tertiary care settings, including ours, present years after the onset of their anxiety disorder and tend to be high utilizers of medical services (Roy-Byrne et al., 1999), most patients with thyroid dysfunction are likely uncovered prior to entry into specialty psychiatric services and removed from study samples prior to presentation. Thus, studies at tertiary care centers may suffer from an ascertainment bias by examining a population with a lower likelihood of thyroid dysfunction. On the other hand, Berkson's bias also applies: patients with multiple disorders (i.e., thyroid and anxiety) may be overrepresented in clinical samples compared with epidemiologic samples. Studies examining patients at the point of initial presentation in primary care setting are more likely to be informative on this issue than additional studies in tertiary care venues. Given the findings suggestive of an increased lifetime risk of thyroid dysfunction in individuals with PD or GAD, the relatively low cost of thyroid testing, the high prevalence of thyroid disease in women in general, the morbidity associated with untreated thyroid disease, and the possibility that ascertainment bias may artificially depress the reported prevalence of thyroid dysfunction, it seems prudent to acknowledge the potential, although rarely realized, benefits of thyroid testing in these individuals. However, available data do not support the need for screening in SP in the absence of other risk factors, although a firm conclusion is limited by the small and poten-

tially rarefied samples studied. Thus, currently available data support the need to query GAD and PD patients regarding thyroid history and perform serum testing in those without prior testing. Although the value of repeat testing for patients with a prior history of thyroid assessment is uncertain, rescreening is reasonable in cases where prior test results are uncertain or temporally distant. Screening in this population at increased risk for thyroid dysfunction is warranted to prevent misattribution of thyroid related symptomatology to anxiety, and thus facilitate treatment of affected individuals in order to prevent psychiatric and medical morbidity associated with untreated thyroid dysfunction.

Acknowledgements

We wish to acknowledge the contribution of Douglas Ross, M.D., for his expert assistance with the interpretation of the thyroid data.

References

Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, 2nd Edition. Lawrence Erlbaum Associates, Hillsdale, NJ.

Chiovato, L., Marino, M., Perugi, G., Fiore, E., Montanelli, L., Lapi, P., Cavaliere, R., Ciampi, M., Patronelli, A., Placidi, G., Placidi, G.F., Cassano, G.B., Pinchera, A., 1998. Chronic recurrent stress due to panic disorder does not precipitate Graves' disease. J. Endocrinol. Invest. 21, 758–764.

Danese, M.D., Powe, N.R., Sawin, C.T., Ladenson, P.W., 1996. Screening for mild thyroid failure at the periodic health examination: a decision and cost-effectiveness analysis. J. Am. Med. Assoc. 276, 285–292.

Denicoff, K.D., Joffe, R.T., Lakshmanan, M.C., Robbins, J., Rubinow, D.R., 1990. Neuropsychiatric manifestations of altered thyroid state. Am. J. Psychiatry 147, 94–99.

Evans, M., Croxson, M.S., Wilson, T.M., Ibbertson, H.K., 1985. The screening of patients with suspected thyrotoxicosis using a sensitive TSH radioimmunoassay. Clin. Endocrinol. 22, 445–451.

First, M., Spitzer, R., Gibbom, M., Williams, J., 1995. Structured Clinical Interview For DSM-IV Axis I Disorders – Patient Edition (SCID-I/P Version 2.0). Biometrics Research Department, New York State Psychiatric Institute.

Fishman, S.M., Sheehan, D.V., Carr, D.B., 1985. Thyroid indices in panic disorder. J. Clin. Psychiatry 46, 432–433.

Greer, S., Ramsay, I., Bagley, C., 1973. Neurotic and thyrotoxic anxiety: clinical, psychological and physiological measurements. Br. J. Psychiatry 122, 549–554.

Helfand, M., Redfern, C.C., 1998. Screening for thyroid disease (clinical guideline parts 1 and 2). Ann. Intern. Med. and Am. Coll. Physicians 129, 141–158.

Katerndahl, D.A., Vande Creek, L., 1983. Hyperthyroidism and panic attacks. Psychosomatics 24, 491–496.

Kathol, R.G., Delahunt, J.W., 1986. The relationship of anxiety and depression to symptoms of hyperthyroidism using operational criteria. Gen. Hos. Psychiatry 8, 23–28.

Kathol, R.G., Turner, R., Delahunt, J., 1986. Depression and anxiety associated with hyperthyroidism: response to antithyroid therapy. Psychosomatics 27, 501–505.

Klee, G.G., Hay, I.D., 1987. Assessment of sensitive thyrotropin assays for an expanded role in thyroid function testing: proposed criteria for analytic performance and clinical utility. J. Clin. Endocrinol. Metab. 64, 461–471.

Klee, G.G., Hay, I.D., 1988. Sensitive thyrotropin assays: analytic and clinical performance criteria. Mayo Clin. Proc. 63, 1123–1132.

Lesser, I.M., Rubin, R.T., Lydiard, R.B., Swinson, R., Pecknold, J., 1987. Past and current thyroid function in subjects with panic disorder. J. Clin. Psychiatry 48, 473–476.

Masters, P.A., Simons, R.J., 1996. Clinical use of sensitive assays for thyroid-stimulating hormone. J. Gen. Intern. Med. 11, 115–127.

Matuzas, W., Al-Sadir, J., Uhlenhuth, E.H., Glass, R.M., 1987. Mitral valve prolapse and thyroid abnormalities in patients with panic attacks. Am. J. Psychiatry 144, 493–496.

Munjack, D.J., Palmer, R., 1988. Thyroid hormones in panic disorder, panic disorder with agoraphobia, and generalized anxiety disorder. J. Clin. Psychiatry 49, 229–231.

Noyes, R., Woodman, C., Garvey, M.J., Cook, B.L., Suelzer, M., Clancy, J., Anderson, D.J., 1992. Generalized anxiety disorder vs. panic disorder. J. Nerv. Ment. Dis. 180, 369–379.

Orenstein, H., Peskind, A., Raskind, M.A., 1988. Thyroid disorders in female psychiatric patients with panic disorder or agoraphobia. Am. J. Psychiatry 145, 1428–1430.

Pariser, S.F., Jones, B.A., Pinta, E.R., Young, E.A., Fontana, M.E., 1979. Panic attacks: diagnostic evaluations of 17 patients. Am. J. Psychiatry 136, 105–108.

Placidi, G.P., Boldrini, M., Patronelli, A., Fiore, E., Chiovato, L., Perugi, G., Marazziti, D., 1998. Prevalence of psychiatric disorders in thyroid diseased patients. Neuropsychobiology 38, 222–225.

Ross, D.S., Ardisson, L.J., Meskell, M.J., 1989. Measurement of thyrotropin in clinical and subclinical hyperthyroidism using a new chemluminescent assay. J. Clin. Endocrinol. Metab. 69, 684–688.

Roy-Byrne, P.P., Stein, M.B., Russo, J., Mercier, E., Thomas, R., McQuaid, J., Katon, W.J., Craske, M.G., Bystritsky, A., Sherbourne, C.D., 1999. Panic disorder in the primary care setting: comorbidity, disability, service utilization, and treatment. J. Clin. Psychiatry 60, 492–499.

Roy-Byrne, P.P., Uhde, T.W., Rubinow, D.R., Post, R.M., 1986. Reduced TSH and prolactin responses to TRH in patients with panic disorder. Am. J. Psychiatry 143, 503–507.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (Suppl. 20), 22–33.

Stein, M.B., Muir-Nash, J., Uhde, T.W., 1991. The QKd interval in panic disorder: an assessment of end-organ thyroid hormone responsivity. Biol. Psychiatry 29, 1209–1214.

Stein, M.B., Uhde, T.W., 1988. Thyroid indices in panic disorder. Am. J. Psychiatry 145, 745–747.

Tancer, M.E., Stein, M.B., Gelernter, C.S., Uhde, T.W., 1990. The hypothalamic–pituitary–thyroid axis in social phobia. Am. J. Psychiatry 147, 929–933.

Tunbridge, W.M.G., Evered, D.C., Hall, R., Appleton, D., Brewis, M., Clark, F., Evans, J., Young, E., Bird, T., Smith, P., 1977. The spectrum of thyroid disease in a community: the Whickham survey. Clin. Endocrinol. 7, 481–493.

Woeber, K.A., 1999. The year in review: the thyroid. Ann. Intern. Med. 131, 959–962.

Yeragani, V.K., Rainey, J.M., Pohl, R., Ortiz, A., Weinberg, P., Gershon, S., 1987. Thyroid hormone levels in panic disorder. Can. J. Psychiatry 32, 467–469.