Testing the association between thyroid dysfunction and psychiatric diagnostic group in an iodine-deficient area

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Objective: To test the association between thyroid dysfunction and psychiatric diagnostic group in a large sample of consecutive patients, while controlling for the effects of age, sex, medication and concomitant medical conditions. **Methods:** We compared the distribution of psychiatric diagnostic groups according to the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10), and of selected psychopathological symptoms in 100 newly admitted psychiatric patients who had genuine thyroid disease and 92 psychiatric patients who had nonspecific alterations of thyroid function with the corresponding items for the whole group of admitted patients (n = 1134) during the observation period. This analysis was then repeated using an age-matched and sex-matched comparison group selected from all admitted patients in a random order. **Results:** When all admitted patients were considered, the presence of a genuine thyroid disorder was associated with the diagnosis of a mood disorder (ICD-10 category F3). This effect was no longer detectable when the age-matched and sex-matched comparison group was used, indicating a simple effect of these 2 variables. Nonspecific alterations of thyroid-stimulating hormone (TSH) were associated with the ICD-10 diagnostic group F4 (neurotic, stress-related and somatoform disorders), with demographic variables being similar in this subgroup to those of all admitted patients. These patients also tended to display more symptoms of a mild depressive syndrome. When only patients with nonspecifically decreased TSH concentrations were tested, these findings could not be reproduced. Nonspecifically decreased concentrations of thyroxine and free thyroxine index were found significantly more often in the diagnosis group F1 (mental disorder due to substance use), reflecting results for alcohol-dependent patients. This result could not be replicated using an age-matched and sex-matched control group. **Conclusion:** In newly admitted psychiatric patients with genuine thyroid disease, there was no notable association of thyroid disease and major psychiatric diagnostic groups according to ICD-10, especially depression. This argues against the hypothesis of thyroid disorders being a major risk factor for psychiatric illnesses. Nonspecific alterations of TSH were more frequently seen in patients of diagnostic group F4 and with mild depressive syndromes, possibly representing an altered influence of stress-regulating systems on thyroid function.

Objectif : Analyser le lien entre le dérèglement de la thyroïde et le groupe de diagnostics psychiatriques dans un échantillon important de patients consécutifs tout en contrôlant les effets de l'âge, du sexe, de la médication et de problèmes médicaux simultanés. **Méthodes :** Nous avons comparé la répartition des

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groupes de diagnostics psychiatriques selon la *Classification statistique internationale des maladies et des problèmes de santé connexes*, 10e révision (CIM-10) et de certains symptômes psychopathologiques chez 100 patients nouvellement admis en psychiatrie qui avaient une maladie thyroïdienne véritable et 92 patients en psychiatrie qui présentaient des altérations non spécifiques de la fonction thyroïdienne aux éléments correspondants pour le groupe complet de patients admis (n = 1134) au cours de la période d'observation. On a ensuite répété l'analyse en utilisant un groupe témoin jumelé selon l'âge et le sexe, et dont les membres ont été choisis au hasard parmi tous les patients admis. **Résultats :** Compte tenu de tous les patients admis, on a établi un lien entre la présence d'un trouble véritable de la thyroïde et le diagnostic de trouble de l'humeur (catégorie F3 de la CIM-10). Cet effet n'était plus détectable lorsqu'on a utilisé le groupe témoin jumelé selon l'âge et le sexe, ce qui indique que ces deux variables ont un effet simple. On a établi un lien entre des altérations non spécifiques de la thyréostimuline et le groupe de diagnostics F4 (troubles névrotiques, troubles liés à des facteurs de stress et troubles somatoformes) de la CIM-10, les variables démographiques étant semblables dans ce sous-groupe comparativement à tous les patients admis. Ces patients avaient aussi tendance à montrer davantage de symptômes d'un trouble dépressif bénin. Lorsqu'on a examiné seulement les patients dont les concentrations de thyréostimuline présentaient une diminution non spécifique, on n'a pu reproduire ces constatations. On a constaté plus souvent une baisse statistiquement significative des concentrations non spécifiques de thyroxine et de l'indice de thyroxine libre dans le groupe de diagnostic F1 (troubles mentaux résultant de la toxicomanie), ce qui traduit les résultats des patients asservis à l'alcool. On n'a pu reproduire ce résultat chez les groupes témoins jumelés selon l'âge et le sexe. **Conclusion :** Chez les patients nouvellement admis en psychiatrie qui ont une maladie thyroïdienne véritable ou présentent une altération non spécifique de la fonction thyroïdienne, il n'y a pas de lien notable entre la maladie thyroïdienne et les principaux groupes de diagnostics psychiatriques selon la CIM-10, et en particulier la dépression. Cette absence de lien va à l'encontre de l'hypothèse selon laquelle les troubles de la thyroïde constituent un important facteur de risque de maladie psychiatrique. On constate des altérations non spécifiques de la thyréostimuline plus souvent chez les patients du groupe de diagnostics F4 et chez les patients qui présentent des syndromes dépressifs bénins, ce qui peut représenter une altération de l'influence que les systèmes de régulation du stress exercent sur la fonction thyroïdienne.

Introduction

Severe thyroid dysfunction may mimic almost any psychiatric symptom profile.[1,2] From the era before the determination of serum thyroid hormone concentrations and before suppressive and substitutive thyroid therapies became widely available, there are impressive reports about psychopathological syndromes associated with severe thyroid diseases such as "myxoedematous madness."[1] However, mild or latent thyroid dysfunction may also be associated with more or less subtle psychiatric abnormalities,[3] above all irritability, restlessness or depressed mood. Thus, it has been assumed repeatedly that specific psychiatric disorders may be associated with alterations in thyroid functioning, and subclinical hypothyroidism has been suspected of being a risk factor for depression.[3,4] This hypothesis is supported by the fact that, in selected cases, thyroid hormone therapy has proved useful in the management of refractory depression.[5]

When studying the association between thyroid dysfunction and psychiatric disorders, several methodological caveats (e.g., the presence of genuine diseases of the thyroid gland, a severe illness or the influence of drugs such as lithium) have to be considered. To control for these confounding factors, we developed an algorithm to evaluate altered thyroid function test results and applied the algorithm to data from 880 newly admitted psychiatric patients. The usefulness and results of this algorithm have been described elsewhere.[6] In a subanalysis, we were now able to perform a further analysis of the same study population to examine whether changes in thyroid values were associated with different psychiatric diagnoses or particular psychopathological symptoms.

Methods

Thyroid function was analyzed in 880 of 1134 admitted psychiatric patients whose mean age was 46 (range 16–92, standard deviation [SD] 19) years, and 54% of whom were female. We compared patients who had thyroid disease (n = 100) as well as those who had nonspecific findings (n = 92) with the entire sample of patients admitted during the observation period with respect to the frequency of diagnostic groups F0–F69 as defined in the *International Statistical Classification of Diseases and Related Health Problems*, 10th revision (ICD-10).[7] Because in the ICD system the main diagnoses alone sometimes fail to reflect a patient's actual

psychopathological status (e.g., subjects with dementia or schizophrenia with an additional depressive syndrome), we repeated the analysis focusing on a cluster of symptoms (Box 1)[8] representing a depressive syndrome and on single depressive symptoms that were rated by the treating physician on admission (symptom rating: 0 = not at all, 2 = mild, 3 = moderate, 4 = severe). The usefulness of these symptoms has been documented by the National Committee for the Documentation of Psychiatric Symptoms (AMDP) in Germany[9] and has been validated thoroughly.[8] The diagnostic spectrum in the psychiatric clinic also included sleep disorders, which had been diagnosed and treated in our sleep laboratory.

In a next step, a paired age-matched and sex-matched comparison group was selected from the sample of all admitted patients with unaltered thyroid function and, again, the distribution of the above-mentioned parameters (ICD-10 diagnosis, the cluster of symptoms listed in Box 1 and single depressive symptoms) was analyzed using the χ^2 test or, in the case of fewer than 5 patients per cell, Fisher's exact test. Significance was defined as $p < 0.05$ after Bonferroni correction to eliminate false-positive results from multiple testing of 8 diagnostic groups (Table 1) and 16 psychopathological symptoms (Box 1).

A fluorescence immunoassay (Dade, Miami, Fla.) was used for the analysis of thyroxine (T_4), free thyroxine index (FTI) and thyroid-stimulating hormone (TSH). The kit used for the measurement of TSH was second generation, with a minimum limit of accuracy of 0.05 mU/L. At a TSH concentration of 0.6 mU/L, the test exhibited an intra-assay coefficient of variation of 4%–8% and an interassay coefficient of variation of 10%. Details of the population and a classification of diseases of the thyroid gland discovered in our population may be found elsewhere.[6]

Box 1: Symptoms that characterize a depressive syndrome[8]

- Being inhibited
- Feeling slowed down
- Feeling restricted in thoughts and behaviour
- Brooding
- Numbness
- Lack of vitality
- Dysphoria
- Feeling hopeless
- Feeling inadequate
- Feeling guilty
- Apathy
- Inhibition of drive
- Diurnal variation in mood
- Reduction of social activities
- Problems in staying asleep
- Lack of appetite

Results

Psychopathology in patients with thyroid disease

We compared the group of patients in whom thyroid disease had been detected with the entire group of admitted patients, which revealed a significant association of the endocrinopathy with the diagnostic group F3 (mood disorders) ($p = 0.001$, significant after Bonferroni correction [Table 1]). However, patients with thyroid disease were more likely to be older (55 [SD 17] v. 46 [SD 18] yr) and female (82% v. 54%). When this analysis was repeated using an age-matched and sex-matched comparison group (age 55 [SD 18] yr, 82% female), the difference in distribution of diagnostic groups was no longer demonstrable ($p = 0.88$). Repeating the analysis using single depressive symptoms or a sum score instead of ICD-10 classification did not change this result.

Psychopathology in patients with nonspecific alterations of TSH concentrations

Our group of patients with alterations in thyroid hormone concentrations was not homogeneous. First, we analyzed the subgroup with nonspecific alterations of TSH ($n = 31$). In 27 patients, TSH concentrations were decreased. In 25 patients, TSH alterations were transient and returned to normal at a second measurement 3 weeks later. In 6 patients, TSH alterations persisted, and a complete workup gave no evidence of underlying thyroid disease. The mean age and sex of the subgroup did not differ markedly from that of all admitted patients (43 v. 46 yr, 52% v. 54% female). This subgroup was significantly associated with the diagnostic group F4 (neurotic, stress-related and somatoform disorders) (36% v. 15% in all admitted patients, $p = 0.004$, significant after Bonferroni correction [Table 1]). When our further analysis was restricted to patients with a

decreased concentration of TSH, this association failed to reach significance level ($p = 0.11$ after Bonferroni correction). In addition, our group of patients with nonspecifically decreased TSH concentrations showed no association with the diagnostic group F4 when compared with an age-matched and sex-matched comparison group ($p = 0.21$).

However, with regard to a depressive syndrome, patients with nonspecific decreased TSH tended to score higher than the control group (18.7 [SD 9.4] v. 14.1 [SD 11.6] points, $p = 0.18$). When the presence of a depressive syndrome was divided into mild and moderate, a decreased concentration of TSH was associated with a mild depressive syndrome (cutoff point of 10) compared with controls ($p = 0.042$), but not with a moderate depressive syndrome with a cutoff point of 20 ($p = 0.70$). Patients of this subgroup were, however, significantly more often characterized by "apathy" (70% of patients v. 23% of comparison patients, $p = 0.001$, significant after Bonferroni correction).

Psychopathology in patients with nonspecifically decreased T_4 or FTI, or both

We found nonspecifically decreased concentrations of T_4 or FTI, or both ($n = 31$) to be significantly associated with the diagnostic group F1. Twenty-six percent of these patients were admitted to hospital because of alcohol dependence, in contrast to only 8% of all admitted patients ($p = 0.002$, after Bonferroni correction [Table 1]). When this analysis was repeated using an age-matched and sex-matched control group, the result failed to reach significance level ($p = 0.48$ after Bonferroni correction). Regarding symptoms of a depressive syndrome, no marked difference between groups was revealed. In patients with nonspecifically increased T_4 or FTI, or both, ($n = 30$) no association with any ICD-10 diagnostic group was observed (data not shown in Table 1).

Discussion

We found in our sample of consecutively admitted psychiatric patients that the presence of a genuine thyroid disorder showed no association with any ICD-10 diagnostic group (F0–F6). Diagnosis of a thyroid disorder was confirmed in each case by an internist, and potential confounding variables such as age, sex, ingestion of drugs or coexisting medical conditions were considered.[6]

When the data for our group of patients with nonspecific abnormalities in thyroid hormone concentrations were analyzed, 2 significant associations were observed. First, patients with alterations in TSH concentrations were more frequently given a diagnosis of the ICD-10 group F4 (neurotic, stress-related and somatoform disorders) and, second, a nonspecific decrease in T_4 or FTI, or both, was associated with the diagnostic group F1 (mental disorders due to substance abuse). In our study, every abnormal thyroid hormone

Table 1: ICD-10* diagnostic groups for all admitted patients and for subgroups of patients with various thyroid disorders

		Patients, no. (and %)			
ICD-10 code	Diagnosis	Admitted, $n = 1134$	With thyroid disease, $n = 100$	With nonspecifically altered TSH, $n = 31$	With nonspecifically decreased T_4 and/or FTI, $n = 31$
F00–09	Organic mental disorders	89 (8)	13 (13)	3 (10)	0
F10–19	Mental disorders due to substance use	90 (8)	2 (2)	3 (10)	8 (26)§
F20–29	Schizophrenia, delusional disorders	292 (26)	18 (18)	5 (16)	4 (13)
F30–39	Mood disorders	334 (30)	49 (49)†	8 (26)	7 (23)
F40–49	Neurotic, stress-related and somatoform disorders	173 (15)	14 (14)	11 (36)‡	4 (13)
F50–59	Behavioural syndromes with physiologic disturbances	59 (5)	2 (2)	0	2 (6)
F60–69	Disorders of adult personality and behaviour	58 (5)	2 (2)	1 (3)	2 (6)
G47	Sleep disorders	39 (3)	0	0	4 (13)

Note: FTI = free thyroxine index; T_4 = thyroxine; TSH = thyroid-stimulating hormone.
**International statistical classification of diseases and health-related problems*, 10th rev.[7]
†$p = 0.001$ for comparison with all admitted patients but no significance for comparison with the age-matched and sex-matched group of patients after Bonferroni correction.
‡$p = 0.004$ for comparison with all admitted patients after Bonferroni correction (age and sex in both groups were similar, therefore there was no matched control group of patients).
§$p = 0.002$ for comparison with all admitted patients but no significance for comparison with the age-matched and sex-matched group of patients after Bonferroni correction.

concentration underwent a formal evaluation according to a previously established algorithm.[6] A thorough physical examination of the patients by the internist and an ultrasonographic study of the thyroid gland were carried out each time that TSH was persistently above or below the normal range. Ultrasonographic determination of the thyroid organ's size and the presence of nodules was shown to be superior to clinical examination alone.[10,11] It was on the basis of this design that we generated a subgroup of patients with altered thyroid function, but no genuine thyroid disorder, for our subanalysis.

Possibly because of this rigorous design, the results of our study differ from those of other investigators,[12–15] who observed altered thyroid function in mood disorders. Some of these studies, however, had not differentiated whether the abnormal thyroid hormone levels represented genuine thyroid dysfunction, the influence of drugs such as lithium or other nonspecific findings. Our observations that thyroid disorders are not directly associated with specific psychiatric diagnoses argues against the hypothesis of such a disorder being a major risk factor.

However, when comparing the results of this study with those of other investigators, one must bear in mind the influence of iodine deficiency. Patterns of thyroid hormone levels may show considerable variation depending on the iodine supply of the population studied. Increased concentrations of both T_4[16,17] and TSH[4,16,17] may be observed more often in iodine-rich areas, whereas reduced levels of TSH, as in in our study, are typical of iodine deficiency. In areas with a decreased supply of iodine, individuals may have a higher chance of developing autonomous thyroid hyperfunction, leaving them at risk of hyperthyroidism, manifested by low TSH concentrations. Especially after the age of 40 years, the risk of hyperthyroid decompensation increases continuously.[18] Further risk factors include thyroid volume and the presence of nodules.[18]

Two studies[4,16] that assessed large populations of psychiatric patients in iodine-rich areas (n = 3188 and n = 3756, respectively) detected similar rates of nonspecifically altered TSH (7.1% and 2.3% v. 3.5% in this study). TSH was elevated in 5.6% and 1.2% of the patients and associated with the diagnosis of a mood disorder,[4,16] whereas in the iodine-deficient area of our study, only 0.45% of patients showed an elevated TSH. In contrast to these studies,[4,16] we did not find an association with mood disorders.

As reported earlier in this section, when nonspecific alterations of TSH were analyzed as one subgroup, an association with the diagnostic group F4 (neurotic, stress-related and somatoform disorders) emerged. Most patients in this group (36%) were diagnosed as having adjustment disorders, namely, maladaptation to acute stressors. In a group of 84 patients, which was similar to our subgroup, Bauer et al[19] also observed decreased serum concentrations of TSH as well as T_4. The patients in that study, who had been persecuted in the former German Democratic Republic (East Germany) and had fled to West Germany around the time of the fall of the Berlin Wall, had for the most part been assigned the diagnosis of an adjustment disorder. Our analysis of our subgroup of patients with decreased TSH serum concentrations, however, failed to reveal this association. Animal models as well as studies in selected human populations support the notion that acute stress is capable of altering TSH serum concentration,[20–22] especially in young individuals.[23] Although the detailed mechanism by which TSH is reduced upon exposure to stress is not known, stress has been shown to activate the hypothalamic–pituitary–adrenal system, resulting in increased levels of serum cortisol. As it has been suggested that corticosteroids may inhibit TSH release, this may be one possible mechanism leading to reduced TSH after exposure to stress.[21]

As ICD-10 diagnostic groups are only a rough indicator of specific psychiatric disorders, we refined our analysis by testing a composite of 16 symptoms that characterize a depressive syndrome.[8] A nonspecific decreased TSH level was only associated with a mild, but not a moderate or severe, depressive syndrome. This mild depressive syndrome again may be stress induced and did not represent a major depressive episode.

Although a nonspecific decrease in serum concentrations of T_4 or FTI, or both, was associated with the diagnosis of alcohol dependence in a comparison of all admitted patients, this result could not be reproduced when testing was repeated using an age-matched and sex-matched comparison group. A decrease in T_4 or free T_4 serum concentrations has been observed both during or some time after detoxification in alcoholism.[24] A direct toxic effect of alcohol upon thyroid function has been suggested,[25] with men with alcoholism exhibiting a reduction in thyroid gland volume as well as more fibrosis. Other possible mechanisms of altered thyroid function in chronic alcoholism have been reviewed by Baumgartner et al.[26]

In summary, our results showed no association of nonspecific altered thyroid function and the diagnosis of a mood disorder in an iodine-deficient area. Thus, findings of altered TSH may be related to stress accompanying a mild depressive syndrome, rather than to major depression. These results support the assumption that thyroid dysfunction does not play a major role in the origin of mood disorders.

Competing interests: None declared.

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