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Antithyroid Antibody–Linked Symptoms in Borderline Personality Disorder

Thomas D. Geracioti Jr.,[1,3] Mitchel A. Kling,[1] Robert M. Post,[2] and Philip W. Gold[1]

[1]Clinical Neuroendocrinology and [2]Biological Psychiatry Branches, National Institute of Mental Health, Bethesda, MD; and [3]The University of Cincinnati and Veterans Affairs Medical Centers, Cincinnati, OH

Circulating thyroid autoantibodies are more prevalent in patients with mood disorders than in the general population, but longitudinal clinical data that establish a relationship between thyroid antibody status and the course of any psychiatric syndrome have been lacking. In addition, scant attention has been paid to thyroid hormones and autoimmunity in borderline personality disorder (BPD). We report a case of a patient with classic BPD whose fluctuating mood and, especially, psychotic symptoms—rated using a double-blind method—were directly linked to antithyroglobulin antibody titers serially determined over an inpatient period of 275 d. Significantly lower psychosis and depression ratings were seen during a 4-wk period of relatively low antithyroid antibody titers, during blinded treatment with carbamazepine, than were observed during two high autoantibody epochs. The significant positive correlations between nurse- and patient-rated depression and thyroid autoantibodies over the entire period of inpatient study were similar to those also observed between urinary free cortisol levels and depression; the positive correlation between antithyroglubulin antibody titers and psychotic symptoms was stronger (r = +0.544; $p < 0.002$). Although this patient had biochemical indices of primary hypothyroidism, she showed only marginal improvement to triiodothyronine (T_3) and no apparent clinical response to sustained levorotatory thyroxine (T_4) administration; neither were antithyroid antibody titers significantly associated with changes in T_3, free T_4, or thyroid-stimulating hormone concentrations. She clinically deteriorated during a 50-d fluoxetine trial. The present data demonstrate a clinically significant, longitudinal correlation between fluctuating antithyroid antibody titers and symptoms of borderline psychopathology in our patient. It will be of interest to determine the prevalence, pathophysiologic mechanisms, and treatment implications of this putative autoimmune-BPD link.

Key Words: Borderline personality disorder; carbamazepine; antithyroid antibodies; cortisol; Hashimoto thyroiditis.

Introduction

Although the prevalence of antithyroid autoantibodies in patients with mood disorders—especially in women (including those with postpartum depression) and in patients with bipolar-spectrum disorders—is higher than in the general population *(1–6)*, the pathophysiologic significance of this finding, apart from any impact on thyroid function, is unclear. While most patients with mood disorder with circulating antithyroid antibodies have marginally normal indices of thyroid hormone levels (including normal levels of thyrotropin [thyroid-stimulating hormone, TSH], levorotatory thyroxine [T_4], and triiodothyronine [T_3]), the presence of antithyroid antibodies usually reflects low-grade (so-called subclinical) thyroid dysfunction in patients with mood disorder or, at a minimum, an increased risk of developing clinically significant thyroid dysfunction *(7)*. While both hypo- and hyperthyroidism are well known to be associated with psychiatric symptomatology, a longitudinal relationship between circulating antithyroid antibodies, mood, or psychosis has not been demonstrated. Case reports of postpartum psychosis *(8)* and menstrual-related mood disorder *(9)* have been associated with autoimmune thyroiditis at presentation (or, more properly, with thyroiditis-associated thyrotoxicosis or hypothyroidism, respectively), but follow-up information, much less a detailed time series, on any potential relationship between antithyroid antibody status and the course of psychiatric illness has been lacking.

Borderline personality disorder (BPD) is a common psychiatric syndrome that is associated with reactive mood instability, repeated suicidal behavior or threats, hostile outbursts, impulsivity, intrapsychic splitting of all-good and all-bad imagoes (primitively loved and hated images of significant others are prominent and cannot be represented in mind simultaneously), and chronic feelings of emptiness *(10)*. Transient stress-related periods of paranoid ideation and dissociation (such as depersonalization) might also occur. The sharp,

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Author to whom all correspondence and reprint requests should be addressed: Dr. T. D. Geracioti Jr., Psychiatry Service, Box 116A, Veterans Affairs Medical Center, 3200 Vine Street, Cincinnati, OH 45220. E-mail: Thomas.Geracioti@med.va.gov

often brief, mood swings and frequent overlay of major depressive episodes have much in common with affective-spectrum mood syndromes, such as rapid-cycling bipolar disorder.

About 25% of borderline patients have blunted TSH responses to thyrotropin-releasing hormone infusion *(11)*, about the same percentage of blunting that is seen in patients with depression *(12)*. The prevalence of antithyroid antibodies in patients with BPD is not known.

We report here a novel case of a patient with classic BPD and autoimmune thyroiditis whose fluctuating antithyroid antibody titers were serially measured over a 275-d inpatient period in conjunction with daily, blinded ratings of psychopathology. A direct relationship between thyroid autoimmune activity and borderline psychopathology, particularly psychotic symptoms, was observed.

Case Report and Methods

Prior to her evaluation at the National Institute of Mental Health, Ms. D., a 39-yr-old, never married, nonsmoking, white female with borderline personality disorder gave written, informed consent to participate in institutional research, subpanel-approved experimental protocols. Ms. D. gave a history of intermittent major depressive overlays on a baseline dysthymia that she traced back to her ninth year, and on admission complained of having had, for the past several months, an increasingly depressed—but reactive—mood, intermittent hostile suicidality, increased basal anxiety (but no panic attacks), low energy, poor concentration, social withdrawal, fatigue, hypersomnia with sleep-phase delay, hyperphagia, and weight gain of more than 40 lb. Ms. D., who had a postgraduate degree, reported that she had been unable to work for several months, at a position for which she was overqualified, because of this condition. She had no history of drug or alcohol abuse.

Ms. D. had been evaluated 10 yr earlier at the NIH Clinical Center, had improved without medications, and had done well for approx 5 yr thereafter. During that period she held a professional position. In the past 2 yr, she had been admitted twice to other hospitals, each time for a few days, for suicidal crises.

Her family history was positive for maternal hypothyroidism, but also notable for the relatively successful adjustment of numerous siblings. No unusual trauma or abuse was uncovered in Ms. D's background. She gave evidence that her mother was neither particularly maternal nor empathic, a situation complicated by the presence of numerous siblings, including a brother born only 11 mo after her. She also stated that the chronic bickering of her parents had frequently upset her.

At admission to the NIH Clinical Center, Ms. D. showed normal vital signs, a body mass index of 30.7, and a normal neurologic examination (including normal ankle reflexes). She did not have a goiter. She had a full-scale IQ by Wechsler Adult Intelligence Scale (WAIS) of 128.

The patient and the research nursing staff were blinded to all medications and laboratory results. The nurses rated the patient's level of depression, mania, and psychosis as a team, by consensus, twice per day (morning and evening) using a modified Bunney-Hamburg scale *(13)* that scored symptoms on a scale of 1–15, with higher scores reflecting more severe symptoms. The patient uniformly received the lowest possible rating on the mania scale (indicating absence of manic symptoms). The mean daily nurse psychosis and depression ratings over 275 d are shown in Fig. 1, second and third panels. The patient herself rated her mood twice per day along a digital scale (from 0 to 6).

During the 275-d observation period (the first 73 d of which she remained on [blind] placebo), Ms. D. showed substantial variability in her mood and reality testing (see Fig. 1). Stigmata of BPD were prominent, including feelings of chronic emptiness, mood instability, impulsivity, poorly modulated aggression, "revenge"-motivated suicidal thinking, seemingly insatiable desire for contact with the medical staff, and tendency to paranoia (such as ideas of reference and feelings of being persecuted) under stress. Intrapsychic splitting, denial, and projective identification were prominent; at times she assumed a depersonalized, fugue-like state. At other times she displayed a well-developed sense of humor and was a gracious leader among the research ward inpatients.

The patient had high antithyroglobulin antibody titers (Fig. 1, top panel) in combination with circulating antimicrosomal antibody titers, consistent with autoimmune thyroiditis (Hashimoto thyroiditis or, given the lack of goiter and painless thyroid, atrophic thyroiditis) *(14)*. Antimicrosomal autoantibodies were present in Ms. D's circulation throughout the study period and varied little in concentration (22 of 30 titers were 1:1600). She showed primary hypothyroidism (compensated hypothyroidism or subclinical hypothyroidism), with elevated TSH concentrations (ranging from 4.3 to 14.9 μIU/mL, with a mean of 7.3 ± 2.8 over 13 assessments [mean ± SD]), low-normal free T_4 (mean: 1.0 ± 0.12 ng/dL [reference range: 1.0–1.9]), and normal to low-normal total T_3 (mean: 109 ± 13 ng/dL [reference range: 88–162 ng/dL]). On 4 of 13 occasions she had low FT_4 or T_3 levels in combination with elevated TSH concentrations (indicative of overt hypothyroidism). Consistent with hypothyroidism were findings of hypercholesterolemia (total cholesterol: 243–251 mg/dL) and mild iron deficiency (with low mean corpuscular hemoglobin concentrations of <34 g/dL [reference range: 34–36] and a low-normal hemoglobin of 12.3 g/dL on admission). During the medication-free state, her depression self-ratings tended to correlate negatively with her free T_4 concentrations (i.e., the higher the FT_4 the lower the depression rating or better her mood [$r = -0.521$, df = 12, $p < 0.07$]).

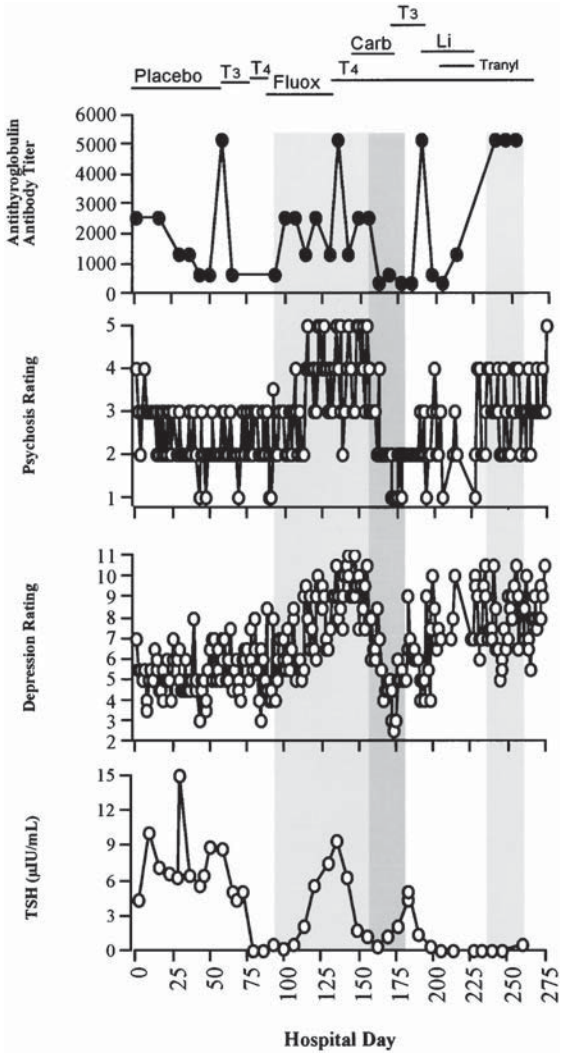

Fig. 1. Antithyroglobulin autoantibody titers (top panel), mean blind daily nurse psychosis ratings (second panel), mean daily blind nurse depression ratings (third panel), thyrotropin (TSH) concentrations (bottom panel), and blind pharmacologic interventions (lines above panels) over 275-d inpatient stay in patient with borderline personality disorder. The blue-shaded area constitutes a 4-wk period of low antithyroid antibody titers, whereas the epochs with the highest titers are shaded in yellow. T_3, triiodothyronine (liothyronine); T_4, levorotatory thyroxine; Fluox, fluoxetine; Carb, carbamazepine; Li, lithium carbonate; Tranyl, tranylcypromine. All medications were blinded to nurses and the patient.

Twenty-nine 24-h urine specimens for free cortisol excretion (24-h UFCs) were obtained during the 71-d medication-free (placebo) period; the mean 24-h UFC excretion was 37 ± 13 μg (normal range: 20–90). Dexamethasone suppression testing (using 1 mg of dexamethasone) showed full suppression of endogenous cortisol release. Thus, Ms. D. was not hypercortisolemic and showed normal feedback inhibition of the HPA axis. Neither did she show adrenal insufficiency. Her cortisol levels rose promptly during a corticotropin (adrenocorticotropic hormone [ACTH])-stimulation test (using 250 μg of ACTH), from 10.5 to a peak of 29.4 μg/dL at 30 min. Her cerebrospinal fluid corticotropin-releasing hormone concentration was 23.8 pg/mL (low normal for this laboratory).

Ms. D. responded neither to a T_3 replacement trial of 50 μg/d for almost 3 wk, nor to a thyroxine trial of 100–125 μg/d (with or without augmentation with T_3 [5 μg/d]). Thyroid hormone doses were sufficient to bring the free T_4 and total T_3 concentrations into the top half of the reference range and to suppress TSH secretion (Fig. 1, bottom). She responded poorly to fluoxetine treatment. However, she improved markedly after 2 wk of a carbamazepine trial. Unfortunately, she developed carbamazepine-related liver toxicity, characterized by significant elevations in alkaline phosphatase, SGOT, SGPT, and γ-glutamyl transferase concentrations. The carbamazepine trial was therefore stopped, and the abnormal biochemical indices rapidly normalized. Lithium or the monoamine oxidase inhibitor tranlcypromine were added to thyroxine without success (Fig. 1, top). The patient and research nurses were blind to medications.

Data Analysis

The relationship between psychiatric symptoms and antithyroid antibodies was examined in two ways: (1) by statistical comparison of the single month-long period of low antibodies (d 160–186, extending from 3 d before through 3 d after, respectively, the first and last antibody titer of the epoch) with the two sustained periods of high antibody titers (d 97–156 and 236–257; see Fig. 1, top panel), and (2) by correlation analysis (linear regression analysis) between antibodies and symptom ratings over all 29 wk when antibody titers were obtained (whereby all weekly thyroid antibody titers and behavioral observations [and self-ratings] were valued equally). Two times, single spikes of high thyroid antibody titers (1:5120) occurred in the midst of at least 1 mo of relative thyroid antibody quiescence; these antibody spikes were of course included in the correlation analysis but were not regarded to constitute, in themselves, sustained periods of high antithyroid antibodies. Symptom ratings of psychosis and depression from the low autoantibody epoch were compared with those obtained during the two high-antibody epochs using two-tailed student's *t*-tests. For use in linear regression analysis, antithyroid antibody titers were monotonically transformed into their natural logs (ln). The log transformation was performed because every successive autoantibody titer constituted a doubling of the prior concentration, but each concentration-doubling interval was regarded as constituting an equivalent effect concerning behavioral parameters. That is, an effect of a change in antithyroglobulin titer from 1:640 to 1:1280 was taken to be equivalent to that seen in a change from 1:2560 to 1:5120.

Results

Psychosis and Antithyroid Antibodies

The mean nurse psychosis rating was significantly higher in both high antithyroid antibody epochs than in the low autoantibody epoch (Fig. 1). The mean psychosis rating was 3.60 ± 0.13 (mean ± SEM) during the first high autoantibody period, d 97–159, but declined to 1.96 ± 0.12 immediately thereafter, during the low autoantibody (d 160–186; $t = 5.04$, df = 24, $p < 0.0001$). A significant increase in mean nurse psychosis rating, to 3.04 ± 13, was associated with the second high autoantibody epoch, d 236–257 ($t = 5.90$, df = 21, $p < 0.001$ vs the low autoantibody epoch).

Over the entire study period, the weekly antithyroglobulin antibody titers significantly correlated with mean psychosis ratings ($r = +0.543$, df = 29, $p < 0.002$, Fig. 2).

Depression and Antithyroid Antibodies

Both the mean nurse's depression ratings and the patient's self-ratings of depression were significantly higher during the high antithyroglobulin antibody epochs than during the low autoantibody epoch. The mean nurse's depression rating was 8.1 ± 2.1 during the first high autoantibody period but declined to 5.4 ± 0.29 immediately thereafter, during the low autoantibody epoch ($t = 3.96$, df = 24, $p = 0.006$). A significant increase in mean nurse depression rating, to 7.8 ± 3.2, was associated with the second high autoantibody epoch ($t = 6.433$, df = 21, $p < 0.0001$ vs the low autoantibody epoch; Fig. 1).

The patient's average self-rated depression scores were significantly higher during the first high autoantibody epoch than during the low autoantibody period (3.86 ± 0.6 vs 3.02 ± 0.10, $p < 0.0001$, $t = 5.09$, df = 25) and also during the second high autoantibody epoch in comparison with the low autoantibody period (4.30 ± 0.15 vs 3.02, $p < 0.0001$, $t = 7.05$, df = 21).

Statistically significant, positive correlations, although weaker than those seen with psychosis, were present between the weekly antithyroid autoantibody titers and mean nurse-rated ($r = +0.372$, df = 29, $p < 0.05$) and self-rated ($r = +0.362$, df = 29, $p < 0.05$) depression scores. Nurse-rated and self-rated depression scores significantly correlated ($r = +0.602$, df = 272, $p < 0.0001$).

Hypothalamic-Pituitary-Adrenal and Pituitary-Thyroid Hormones, Psychopathology, and Antithyroid Antibodies

Twenty-four-hour urinary free cortisol (UFC) excretion positively correlated with both nurse-rated severity of depression ($r = +0.312$, df = 58, $p < 0.02$) and patient self-rated depression ($r = +0.352$, df = 60, $p < 0.006$). However, virtually no relationship between 24-h UFC excretion and psychosis ratings was observed ($r = +0.068$, df = 58, not significant [NS]).

No statistically significant relationships were observed between concentrations of any of the other longitudinally determined hormones (T_3, free FT_4 [FT_4], TSH, serum cortisol) and either mood or psychosis ratings (serial TSH concentrations shown in Fig. 1, bottom panel). The strongest correlations were seen between (1) circulating T_3 and psychosis ($r = –0.212$, df = 29) and (2) T_3 and nurse's depression ratings ($r = –0.236$, df = 29).

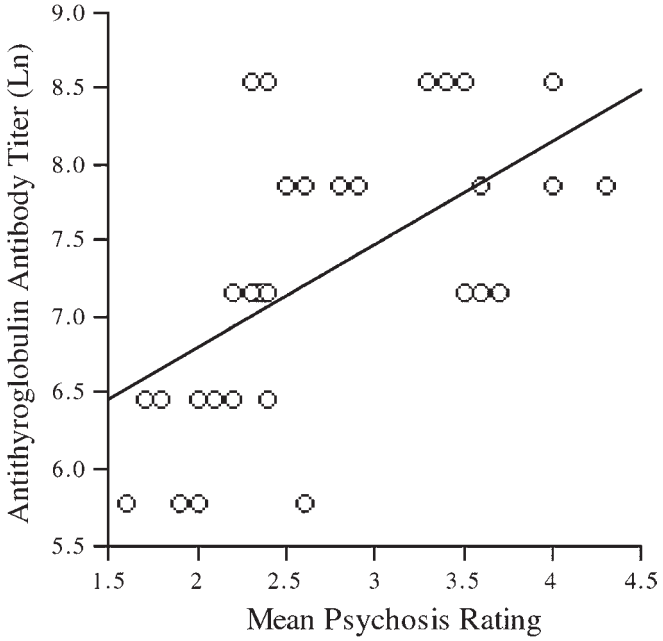

Fig. 2. Relationship between weekly mean nurse psychosis rating and antithyroglobulin autoantibody titer ($r = +0.543$; $p < 0.002$).

Plasma cortisol concentrations did not show any significant relationship to antithyroglobulin antibody titers in blood withdrawn during the same venipunctures ($r = –0.061$, df = 27, NS)—neither did 24-h UFC excretion, although there were few observations ($r = –0.481$, df = 7, $p = 0.228$, NS). Correlation coefficients among T_3, FT_4, or TSH and antithyroglobulin antibodies were all nonsignificant and <0.100.

Discussion

The results of this intensive, 275-d inpatient case evaluation reveal a significant relationship between fluctuations in antithyroid autoantibodies and psychotic and mood symptoms in a woman with borderline personality disorder as determined both by comparison of behavioral and self-ratings from the two periods of highest antibody titers with the single month-long period of low antibody titers and by correlation analysis using all weekly thyroid antibody titers and psychiatric symptom ratings. The strongest correlation was seen between antithyroglobulin antibodies and nurse psychosis ratings, with a correlation coefficient (r) of +0.543 and a coefficient of determination (r^2) of 0.295, indicating that about 30% of the variance in psychosis ratings could

be accounted for by the antithyroglobulin antibody titer. Antimicrosomal antibodies were uniformly positive in this patient, but their titers were practically invariable and thus did not correlate with the highly variable severity of psychiatric symptoms; however, these data do not rule out a relationship between antimicrosomal antibody production and the patient's borderline psychopathology in general. While the rare association between autoimmune thyroiditis and frank encephalopathy (so-called Hashimoto encephalopathy *[15–17]*) is well known, the present finding of a longitudinal association between circulating antithyroid autoantibodies and severity of borderline psychopathology has not been described. Consistent with the present report of autoimmune-linked symptoms of BPD are pilot data that point to a substantially increased prevalence of BPD (40%) in another autoimmune syndrome, rheumatoid arthritis *(18)*.

While the causal mechanisms cannot be inferred from our present data, we postulate that the autoantibody-linked borderline psychopathology in our patient represents, at least in part, subencephalopathic autoimmune-mediated changes in brain function. Hashimoto encephalopathy often responds clinically to glucocorticoids but not necessarily to exogenous thyroid hormones. In our patient, there were no correlations between autoantibody titers and either serum cortisol levels or 24-h UFC excretion, although few 24-h UFC excretion specimens were obtained coincident with antithyroid antibody titers.

The confounding presence of concomitant medications makes it difficult to evaluate the effects that thyroid hormones may have had on our patient's antithyroid antibody titers, yet sustained benefits of thyroxine administration were apparently lacking. Marked improvement was observed in both clinical and autoimmune indices during the 4-wk carbamazepine clinical trial. A potential antiinflammatory effect of carbamazepine in autoimmune thyroiditis might be worthy of investigation (even though carbamazepine is well known to occasionally cause drug-induced lupus erythematosus). In this regard, carbamazepine can suppress immunoglobulin concentrations substantially *(19)* and has long been known to have antithyroid effects *(20)*.

A mechanism whereby antithyroglobulin antibodies might directly effect mood and reality testing is unclear, although the lack of relationship among T_3, T_4, TSH, and antithyroid antibody levels suggests that in our patient, hypothyroidism cannot explain the whole picture. Thyroid gland–linked anti–central nervous system (CNS) or anticerebromicrovascular antigenicity may have been involved. In this regard, it is possible that antithyroglobulin autoantibodies were not themselves CNS antigens but, rather, were an index of a more widespread autoimmune process involving antibrain and/or antipituitary autoimmune activity. Accordingly, Nishino et al. *(21)* found antipituitary antibodies in 18.5% of patients with Hashimoto thyroiditis and a significant, positive correlation between the respective antibody titers.

The positive correlation between severity of depression (both nurse and patient rated) and 24-h UFC seen in our patient is of interest for several reasons. First, in contrast to circulating antithyroglobulin antibody titers, free cortisol excretion was not associated with psychotic symptoms. Second, the correlations between antithyroid antibodies and mood were as strong as those seen between cortisol and mood. Third, although the link between hypercortisolemia and depression is well known, the association between higher cortisol and higher depression ratings in our patient occurred in the absence of hypercortisolemia. Fourth, our patient showed predominantly atypical depressive symptoms—symptoms that are perhaps more commonly seen during hypoactivity of the hypothalamic-pituitary-adrenocortical (HPA) axis *(22,23)*. Finally, the significant relationship between urinary free, but not total serum, cortisol underscores the limited information provided by measures of protein-bound cortisol.

The present data show that depressive and, especially, psychotic symptoms in a patient with BPD are longitudinally correlated with fluctuating antithyroid autoimmune antibody titers. It will be of interest to determine the prevalence, pathophysiologic significance, and treatment implications of the proposed autoimmunity-BPD link.

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