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Thyroglobulin antibodies and risk of readmission at one year in subjects with bipolar disorder

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ABSTRACT

Thyroid autoimmunity has been proposed as an endophenotype for Bipolar Disorder (BD), although its relationship with clinical outcomes remains unclear. We aimed to determine whether thyroid autoimmune status (thyroperoxidase antibodies [TPO-Abs] and thyroglobulin antibodies [TG-Abs]) in BD is associated with a greater risk for readmission at one year. We studied 77 inpatients with BD admitted for an index manic or mixed episode. Serum thyroid antibodies (TPO-Abs and TG-Abs) were determined at admission. We compared the readmission risk at 1 year, based on patients' thyroid autoimmunity profile using survival analyses. Cox regression was used to control covariates. TG-Abs+ but not TPO-Abs+ was associated with a lower risk of relapse. The Kaplan–Meier mean estimated survival times were 341.6 days (CI95% 316.4–366.8) for the TG-Abs+ group and 261.9 days (CI95%: 221.8 to 302.0) for the TG-Abs− group. Cox proportional hazards regression indicated that subjects with TG-Abs+ were 3.7 (1/OR=1/0.27) times less likely to get admitted during the follow-up period than those with TG-Abs−. Our study suggests that an autoimmune biomarker in patients with BD (i.e., the presence of TG-Abs) is associated with a lower risk of psychiatric readmission after an index hospitalization for a manic or mixed episode.

1. Introduction

Thyroid abnormalities have been suggested to play a role in the pathogenesis of Bipolar Disorder (BD) (Bauer et al., 1990). Such thyroid abnormalities may modulate BD expression with implications on the severity, prognosis, and outcome of the illness (Hendrick et al., 1998). For instance, thyroid dysfunction has been associated with rapid-cycling BD in several studies (Bauer et al., 1990; Azorin et al., 2008), although others have failed to show this association (Post et al., 1997; Kupka et al., 2002b; Gyulai et al., 2003).

Psychopharmacological treatments frequently used for BD, e.g., lithium, but also carbamazepine and valproate, have been shown to increase the risk for hypothyroidism (Park et al., 2011). Several mechanisms for lithium-induced thyroid failure have been described, including decreased iodide uptake, low thyroid hormone release and suppression of thyroxine transformation to triodothyronine (Gau et al., 2010). For this reason, most guidelines have suggested regular thyroid function monitoring (Goodwin and Young, 2003); (Azorin and Findling, 2007; Oswald et al., 2007).

The presence of antithyroid antibodies is a common cause for thyroid failure, primarily among women and elderly, and in the general population the prevalence of TG and TPO antibodies are 10% and 12%, respectively (Kupka et al., 2002b; Vanderpump, 2011). Bipolar patients and their healthy relatives show an increased risk of developing autoimmune thyroiditis (with positive thyroperoxidase antibodies [TPO-Abs] and thyroglobulin antibodies [TG-Abs]) compared to the general population. We know that the presence of TPO-Abs is heritable, that it cosegregates with BD in families and is state-independent, which is why TPO-Abs levels have been proposed as a possible endophenotype for BD itself (Lenox et al., 2002; Hasler et al., 2006; Azorin and Findling, 2007; Vonk et al., 2007). To our knowledge, no previous study has addressed whether TG-Abs could also serve as an endophenotype for BD.

Earlier studies that investigated whether TPO-Abs are associated with lithium exposure have produced contradictory findings. Some of them suggest that lithium could induce autoimmune thyroiditis (Wilson et al., 1991), although other studies have refuted this association (Kupka et al., 2002b; Baethge et al., 2005), indicating

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that the presence of TPO-Abs is independent of exposure to lithium treatment (Kupka et al., 2002b). Some studies suggest that in patients with BD and autoimmune thyroid disorder monocyte and T cell activation is reduced in comparison to bipolar patients without autoimmune thyroid disorder (Drexhage et al., 2011).

Although autoimmune thyroiditis has been related to a history of rapid cycling and poorer treatment response (Oomen et al., 1996), there is a lack of information regarding outcome and prognosis issues in prospective studies. Most previous studies have focused on TPO antibodies, thus there is a lack of information regarding TG-Abs and BD.

Patients with BD usually require intensive treatment and hospitalizations during the acute phases of the illness. Readmission is frequent among bipolar patients, with 1-year readmission rates ranging from 25% to 60% (Goldberg et al., 1995; Kessing et al., 1998; Perlick et al., 1999). Rehospitalization has been systematically used as a method for measuring the relapse and recurrence of psychiatric illness (Conley et al., 1999) and has often been used as a safe marker of outcomes in psychiatric disorders (Lin et al., 2010).

We aimed to study whether patients with BD that express a specific endocrinological profile (TPO-Abs+ or TG-Abs+) showed a different clinical profile or a greater risk for readmission over a one year period. The main hypothesis of our study was that those bipolar patients with positive thyroid antibodies would be at greater risk for readmission than those without autoimmune thyroiditis.

2. Methods

2.1. Subjects

Our study sample consisted of 77 subjects (41.6% men) with a mean age of 45.1 years suffering from type 1 BD based on the DSM-IV criteria who fulfilled the following inclusion criteria: (1) admission to the acute inpatient unit of the Department of Psychiatry at Corporació Sanitària i Universitària Parc Taulí between 2009 and 2010, (2) follow-up after discharge at the outpatient unit from the same institution, (3) presence of a blood sample that allowed for the determination of thyroid antibodies, and (4) willingness to participate in the study. Our hospital is a tertiary referral center in Valles Occidental (Catalonia, Spain), serving a population of 480,000 people.

Catalonia is not considered as an iodine-deficient region, and previous epidemiological studies suggest that iodine intake does not influence the development of thyroid dysfunction or thyroid autoimmunity in this population (Lucas et al., 2010).

All public psychiatric care (both inpatient and outpatient) in the Valles Occidental is provided by this institution. The study was approved by the local Ethical Committee. All participants gave written informed consent after receiving a full explanation of the study.

2.2. Clinical assessments

Sociodemographic and clinical data, including age at onset of the disorder and substance use, were assessed via a semi-structured interview on admission. Psychopharmacological treatment or thyroid treatment during admission and follow-up at the outpatient unit was obtained via chart review. All 77 patients were followed-up at the Corporació Sanitària i Universitària Parc Taulí outpatient unit. Psychopathological status was assessed twice during admission (at baseline and at discharge). The Young Mania Rating Scale (Young et al., 1978) was used to explore symptoms of mania. The Global Assessment of Functioning (Hall, 1995) was used to assess functionality. Readmission dates during the follow-up period (1 year after discharge) were obtained by chart review and the electronic records of our institution.

Psychopharmacological treatment during the follow-up period was registered. All 77 patients in the study were taking medication, as follows: 43 (55.8%) were receiving lithium; 25, valproate (32.5%); and 19, other mood stabilizers (24.7%). All but one patient received antipsychotic drugs during the follow-up period: 53 patients (68.8%) were on monotherapy and 23 patients (29.9%) were taking two or more antipsychotics. Patients took the following antipsychotic treatments: risperidone ($n=34$), olanzapine ($n=29$), quetiapine ($n=18$), haloperidol ($n=5$), paliperidone ($n=4$), aripiprazole ($n=3$), ziprasidone ($n=2$), perphenazine ($n=1$), clozapine ($n=1$) and amisulpride ($n=1$). None of the patients were on antidepressants. We controlled for medication adherence during the follow-up period. Poor treatment adherence was defined as low levels of valproate or lithium for those patients taking these drugs and/or by the report of treatment discontinuation by the patient or relatives. This information was obtained by chart review and verification of blood analysis over the follow-up period.

2.3. Thyroid measurements

All blood samples were obtained to determine serum levels of thyroid antibodies between 8 and 9 am to avoid any diurnal variability of antithyroid antibodies levels. Thyroid measurements were obtained at the index admission. TPO-Abs and TG-Abs were determined using a fluoro-enzymatic-immunoassay EliA™ system, Phadia AB, Uppsala, Sweden. The presence of TPO-Abs and TG-Abs was determined by the highest tertile in our sample, being 10 units/mL for TPO-Abs and 15 units/mL for TG-Abs. These levels are similar to cut-off scores used in previous studies that have explored autoimmune thyroiditis in BD patients (Kupka et al., 2002b). TSH and free thyroxine (FT4) were also determined.

2.4. Statistical analysis

SPSS v 17.0 (Chicago, Illinois, USA) was used to perform statistical analyses.

Chi-square tests and *T*-tests were used to compare categorical and continuous data between groups. Significance was set at $p<0.05$ (bilateral).

A survival analysis was conducted to explore the risk of readmission by thyroid autoimmunity. In a first analysis, a Kaplan–Meier method was used to compare groups with the presence of TPO-Abs vs those without TPO-Abs, as well as groups with the presence of TG-Abs vs those without TG-Abs. In addition, we conducted a multivariate survival analysis using a Cox Regression model to control for covariables including age, gender, TSH, substance use, YMRS and GAF at index episode, treatment with mood stabilizers and medication adherence during the follow-up period. *R* and survival package (http://www.r-project.org/) were used to plot Kaplan–Meier curves.

3. Results

In our sample, 38.96% of the sample were TPO-Abs+, and 36.36% were TG-Abs +. The clinical features of the sample based on thyroid autoimmunity groups are described in Table 1. Although the TG-Abs+ subgroup included more female patients, there were no significant differences in the clinical characteristics by thyroid autoimmune groups. The readmission rate after one year of follow-up was significantly lower in those subjects with positive TG antibodies. No differences were found in the risk of readmission between TPO autoimmune groups. Treatment adherence was inversely associated with risk of admission: subjects with poor treatment compliance were admitted at a higher rate than subjects with good medication compliance (45.7% vs 19.5%, $p=0.014$). There were no statistically significant differences in treatment adherence between thyroid status subgroups.

Four of the 77 patients were receiving L-thyroxine, and one patient had subclinical hypothyroidism (i.e., TSH above five with normal free T4). Thus, subclinical or clinical hypothyroidism was present in 6.5% of the sample. The median (standard deviation) levels for TSH and free T4 were 2.04 (1.26) and 1.23 (0.25), respectively, but there were no statistically significant differences in TSH or T4 levels between thyroid autoimmunity groups.

The Kaplan–Meier mean estimated survival times (Fig. 1) were 261.9 days (CI95%: 221.8–302.0) for those subjects with TG-Abs- and 341.6 days (CI95% 316.4 to 366.8) for the TG-Abs+ group. The log-rank test revealed a statistically significant difference between the survival rates over time ($p<0.05$). Thus, TG-Abs+ showed a lower risk of readmission over time when compared to TG-Abs− subjects. There were no significant differences in survival rates between TPO-Abs+ and TPO-Abs− groups (Fig. 1 from Electronic Supplementary Material).

Further analysis using Cox proportional hazards regression (Table 2), which controlled for covariates, indicated that subjects with TG-Abs+ were 3.7 (1/OR=1/0.27) times less likely to be admitted during the follow-up period than those with TG-Abs−.