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Association between thyroid autoimmunity and antidepressant treatment-emergent mania in pediatric mood disorders

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ABSTRACT

Risk factors associated with antidepressant treatment-emergent mania(ATEM) are poorly characterized in child and adolescent populations. To identify better biomarkers, we aimed to explore whether thyroid autoimmunity is associated with ATEM in pediatric mood disorders. We enrolled two groups of pediatric mood disorders, those with ATEM+ ($n = 29$) and those with ATEM- controls ($n = 31$). All diagnoses were made according to structured interviews by the clinicians. Autoimmune thyroiditis (anti-thyroid peroxidase antibodies [TPO-abs] and thyroid function (thyroid-stimulating hormone [TSH] and free thyroxin [FT4]) were assessed. Logistic regression was used to explore the relationship between TPO-abs seroprevalence and ATEM+ while controlling for covariates. Group comparisons showed that the patient with ATEM+ had significantly higher seroprevalence and titer of TPO-abs compared to ATEM- controls. In logistic regression analysis adjusting for age, gender, Tanner stage, body mass index, antipsychotic treatments, smoking status and family history of thyroid disorder, the seroprevalence of TPO-abs (>60 U/mL) was significantly associated with ATEM+ (OR = 3.67, 95% confidence interval [CI] = 1.2-11.1, $p = 0.022$). Our findings demonstrated that seroprevalence and titer of TPO-abs in pediatric mood disorders are associated with ATEM+ status. TPO-abs could potentially serve as a biomarker when assessing the risk of ATEM in the child and adolescent population.

1. Introduction

Bipolar disorder (BD) is one of the leading sources of disability among all diseases worldwide and affecting more than 1% of the population typically around the age of 20 (Carvalho et al., 2020). Previous longitudinal high-risk population studies showed that the majority of cases experience major depressive disorder (MDD) as an index mood episode before the first (hypo)manic episode (Duffy et al., 2007; Mesman et al., 2013). Moreover, these studies reported that the average time between the first mood episode and a BD diagnosis was approximately 5 years (Duffy et al., 2007; Mesman et al., 2013; Van Meter et al., 2016). The interval between the initial symptoms and complete development of BD offers the perfect time to identify and intervene (Post et al., 2020).

Antidepressants are the most commonly prescribed psychotropics in mood disorders and up to 50% of BD cases receive antidepressant treatment at any time point during the disease progression (Baldessarini et al., 2008; Ghaemi et al., 2008). Since the depressive episode is the most common type of index episode seen in BD patients, antidepressants remain standard pharmacotherapy in the child and adolescent population (Cheung et al., 2013; Hetrick et al., 2007; Hughes et al., 2007). Despite their widespread use, antidepressants may shorten the prodromal duration and lead to deterioration of the illness prognosis (Tamada et al., 2006). Another source of concern is whether antidepressants can trigger (hypo)mania in youth (Baldessarini et al., 2013; Gill et al., 2020;

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Joseph et al., 2009). Antidepressant treatment-emergent mania (ATEM) is a phenomenon accepted as a manifestation of BD in the latest edition of the Diagnostic and Statistical Manual (DSM-5) (Association, 2013). Previous consensus reports on antidepressant use in BD have argued for criteria based on uniform definitions of the time interval between the start of antidepressant therapy and the onset of ATEM (Pacchiarotti et al., 2013). The risk period for ATEM has ranged from three weeks to six months; the threshold criteria for symptom severity have ranged from the existence of any manic symptoms to full syndromal mania, and the minimum length for the mood transition after antidepressants medication has ranged from four days to several months (Pacchiarotti et al., 2013; Scott et al., 2017). Given the range of definitions, it is not unexpected that there is a lack of consensus on which clinical variables are related to an increased chance of ATEM. Although this phenomenon has been widely observed in adults, the literature on ATEM is less consistent in the child and adolescent population (Joseph et al., 2009). A seminal epidemiological contribution was made by Martin et al. (2004) proposed peripubertal children were more susceptible to ATEM, compared to the older age groups (Martin et al., 2004). This study has been useful in terms of demonstrating the risks associated with the use of antidepressants in the pubertal age group. Although there exists a considerable body of literature on clinical predictors for ATEM, only a few works in literature investigated possible biomarkers associated with ATEM in the child and adolescent population. A series of recent studies have indicated that age at onset of BD, female gender, the polarity of onset episode, recurrent depressive episodes, bipolar I subtype, presence of concomitant manic symptoms, and previous history of ATEM could be classified as potential clinical risk factors (Frye et al., 2015; Inal et al., 2022; Melhuish Beaupre et al., 2020). A recent meta-analysis of the serotonin transporter gene (5HTTLPR) and ATEM found no significant link between genetic markers at 5HTTLPR polymorphism and ATEM (Biernacka et al., 2012). This has also been explored in prior studies by investigating the association between BDNF gene polymorphism and ATEM, but similarly, they did not demonstrate a significant association (de Aguiar Ferreira et al., 2010; Zai et al., 2007).

For decades, one of the most popular ideas in mood disorder literature is the idea that immune-inflammatory pathways could play an important role in underlying disease pathology (Hansen et al., 2020; Rosenblat et al., 2014). In line with this, the association between autoimmune thyroid disorder and BD has long been known. While previous research on the seroprevalence of anti-thyroid peroxidase antibodies (TPO-abs) in BD has been inconclusive, a recent meta-analysis conducted by Snijders et al. (2020) concluded that the seroprevalence of TPO-abs did not vary significantly between adult patients with BD and healthy controls (Snijders et al., 2020). A previous study by Scott et al. (2017) concluded that thyroid disorder is one of the strongest risk factor for female ATEM patients (Scott et al., 2017). Although they derived data from a large population of BD individuals and used strict patient selection, they did not specify the subtype of thyroid disorder and whether the diagnosis was made based on circulating thyroid autoantibodies or not. Additionally, the potential role of TPO-abs in pediatric mood disorder has rarely been studied directly.

Taken together, studies that can provide better biomarker prediction for which subtype of patients may experience ATEM phenomena have high clinical utility as they provide useful insights into the optimal management of BD at an early age. Our research aims to study the association between autoimmune thyroid disorder and ATEM in the child and adolescent population. We hypothesized that autoimmune thyroid disorder might contribute to the pathogenesis of ATEM and support the idea that TPO-abs could be used as a biomarker for the clinical decision-making process. To test this hypothesis, we determined seroprevalence and titer of TPO-abs in patients with pediatric ATEM cases and compared these with subjects without ATEM phenomena.

2. Materials and methods

2.1. Population and procedure

We performed a cross-sectional study approved by the Dokuz Eylul University Hospital Ethics Committee. Following a thorough explanation of the study, both participants and their parents provided written and informed consent. Recruitment was conducted by consecutive sampling at the pediatric mood disorder outpatient clinic. We studied a population of 60 outpatients, aged between 12 and 18 years. Diagnostic assessments were administered by trained child psychiatrists. Patients with active medical conditions, a history of seizures, schizophrenia spectrum and other psychotic disorders, autism spectrum disorder and substance abuse were excluded. Inclusion criteria for this study were that patients were: (i) 12-18 years old; (ii) meets the DSM-5 criteria for BD-I, BD-II and is currently in the euthymic phase; (iii) it can be classified as ATEM+ cases and ATEM- within the last six month.

For ATEM+ cases:

(i) The occurrence of (hypo) mania within 90 days of the initiation of antidepressant treatment without a known mood stabilizer during the major depressive episode and compliance with DSM-5 (hypo) mania criteria during the ATEM process; and (ii) when the antidepressant is prescribed as monotherapy or given in combination with and/or antipsychotic medication.

For ATEM- controls:

(i) experiencing at least one major depressive episode treated by an antidepressant without a known mood stabilizer; and (ii) no evidence of symptoms of (hypo) mania within 90 days of antidepressant therapy.

Antidepressant treatment (sertraline, fluoxetine, escitalopram, venlafaxine) history was obtained by the youth and parent reports and confirmed by reviewing electronic medical records. The type of antidepressant treatments for the last depressive episode that is defining ATEM+ status was determined. Both youth and their parents were evaluated with Schedule for Affective Disorders and Schizophrenia for School-Aged Children-lifetime Version (K-SADS-PL) (Kaufman et al., 1997; ÜNAL et al., 2019). The euthymic state was confirmed through Children's Depression Rating Scale-revised (CDRS-R; Cut-off used <54) (Guney et al., 2018) and the Young Mania Rating Scale (YMRS; Cut-off used <8) (Young et al., 1978). The Children's Global Assessment Scale (CGAS) is a measurement rating (scores from 0 to 100) of functioning for youth aged 6−17 years old, with higher scores reflecting better functioning (Shaffer et al., 1983). All patients underwent a physical examination and auxological evaluation by a pediatric endocrinologist. Height, weight, body mass index (BMI) and stage of puberty are recorded. BMI was calculated by dividing the patient's weight in kilograms by the square of height in meters. Puberty stages were evaluated with the parental agreement according to Tanner stage pictorial assessments of breast and pubic hair development and physical examination (Dorn and Biro, 2011; Howard et al., 2019).

2.2. Thyroid function and autoimmunity

Fasting blood samples were taken from participants between 9:00 and10:00 am into the tubes which do not include anticoagulants. After waiting for one hour at room temperature, tubes were centrifuged at 2000 g for 10 min. Serum samples were taken from the tubes and they were aliquoted and stored at -800C until analysis. Levels of FT4, TSH and Anti-TPO were determined from serum samples of the participants. FT4 was analyzed by the chemiluminescence method on the Beckman Coulter DXİ-800(Beckman Coulter, Inc, USA). Normal reference range was 0,5−1,51 ng/ml. TSH was analyzed by chemiluminescence method on the Access TSH 3rd IS (Beckman Coulter, Inc. USA). Normal reference range was between 0,38 and 5,33 m(IU)/L. Anti-TPO was analyzed using the chemiluminescence method on Siemens ADVIA Centaur XP (Siemens Healthcare Diagnostics Inc, USA). Measuring range between 28 and 1300 U/L and $>$ 60 U/ml accepted as positive.

2.3. Statistical analysis

All analyses were conducted using STATA statistical software, version 16 (Stata, College Station, TX, USA). Differences between group characteristics were tested using the chi-squared test. The Student's t-test and the Mann–Whitney U test were used to compare continuous demographic and clinical variables between the groups. After log transformation, TSH, fT4 and TPO-abs levels were normally distributed. Differences in TSH, fT4 and TPO-abs levels between the groups of pediatric mood disorder patients were tested with ANCOVA while controlling for covariates including age, gender, Tanner stage, body mass index, antipsychotic treatments, smoking status and family history of thyroid disorder. Additionally, we performed logistic regression analysis to explore the association between the ATEM+ group and TPO-abs positivity while adjusting for same covariates. In these analyses, positive thyroid autoimmunity was used as the dependent dichotomic variable considering the cutoff points (> 60 U/mL). A two-tailed value of $p < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and clinical features

We measured serum TPO-abs levels in a total of 60 euthymic BD patients aged between 12 and 18. Our study included twenty-nine participants who were classified as ATEM+ cases and thirty-one were ATEM- controls. The clinical and demographic characteristics of the subjects studied are detailed in Table 1 and Table 2. There was no significant difference in the mean age and gender ratio between ATEM+ and ATEM- patients group. In Table 1, we also present comparative descriptive analyses of the characteristics of the ATEM+ and ATEM- groups derived from the pediatric endocrine examination. In terms of body mass index and Tanner stage characteristics, there was no significant difference between the groups. The percentage of subjects positive for family history of thyroid disorder was significantly higher in ATEM+ than in ATEM- (41.4% vs 16.1%; $p = 0.030$).

When the treatment type of the most recent depressive episode was examined, it was observed that the ATEM+ group was mostly treated with a combination of antidepressants and antipsychotics ($p = 0.005$). No substantial difference ($p = 0.304$) was detected when the antidepressant type used in depressive episode treatment was compared between groups. Group comparisons demonstrated that the ATEM+ cases had a significantly higher prevalence of comorbid ADHD (55.2% vs. 25.8%; $p = 0.020$) and any anxiety disorders (34.5% vs. 6.5%; $p = 0.007$), compared to the ATEM- controls. ATEM+ patients had higher scores on the YMRS ($p = 0.008$) compared to ATEM- group but did not differ on CDRS-R scores ($p = 0.528$). This finding is consistent with a greater possibility of subsyndromal symptoms in ATEM+ patients (Table 2). Additionally, ATEM+ patients had poorer function (mean CGAS ± SD: 61.7 ± 3.2 vs 71.3 ± 5, $p = .001$) than those ATEM- patients group.

Table 1
Demographic variables in patients with antidepressant treatment-emergent mania (ATEM+) compared to controls (ATEM-).

Variable	ATEM+ ($n = 29$) Mean ± SD or %(n)	ATEM- ($n = 31$) Mean ± SD or %(n)	p values
Age (years)	14.5 ± 3.3	15.8 ± 1.9	0.073[a]
Gender (Female)	79.3 (23)	74.2 (23)	0.640[b]
Education (year)	9.3 ± 1.9	9.9 ± 1.6	0.205[a]
BMI (kg/m^2)	22.7 ± 6.2	24.1 ± 6.5	0.435[a]
Tanner stage			
III	3.4 (1)	3.2 (1)	0.528[b]
IV	20.7 (6)	16.1 (5)	
V	75.9 (22)	80.6 (25)	
Smoking status			
Never	69 (20)	67.7 (21)	0.919[b]
Current	31 (9)	32.3 (10)	
Family history of mood disorder	82.8 (24)	64.5 (20)	0.110[b]
Family history of thyroid disorder	41.4 (12)	16.1 (5)	**0.030**[b]

Note BMI, body mass index
[a] t test.
[b] χ^2 test

Table 2
Clinical characteristics of patients with antidepressant treatment-emergent mania (ATEM+) compared to controls (ATEM-).

Variable	ATEM+ ($n = 29$) Mean ± SD or %(n)	ATEM- ($n = 31$) Mean ± SD or % (n)	p values
Age at onset (years)	12.3 ± 2.4	13.1 ± 3.2	0.275[a]
Diagnosis			
BD-I	58.6 (17)	45.1 (14)	0.297
BD-II	41.4 (12)	54.9 (17)	
Treatment for the last depressive episode[c]			
AD	34.5 (10)	71 (22)	**0.005**[b]
AD + AP	65.5 (19)	29 (9)	
AD prescription for last depressive episode[c]			
Sertraline	34.5 (10)	32.3 (10)	0.304[b]
Fluoxetine	58.6 (17)	51.6 (16)	
Escitalopram	3.4 (1)	16.1 (5)	
Venlafaxine	3.4 (1)	-	
Comorbid diagnosis			
ADHD	55.2 (16)	25.8 (8)	**0.020**[b]
Conduct disorder	27.6 (8)	9.7 (3)	0.073[b]
Anxiety disorders	34.5 (10)	6.5 (2)	**0.007**[b]
OCD	10.3 (3)	16.1 (5)	0.510[b]
CDRS-R score	46.5 ± 6.6	49.3 ± 7.2	0.528[a]
YMRS score	2.8 ±1.7	1.1 ± 0.7	**0.008**[a]
CGAS score	61.7 ± 3.2	71.3 ± 5	**0.001**[a]

Note BD, bipolar disorder; MDD, major depressive disorder; AD, antidepressant treatment; AP, antipsychotic treatment; CGAS, Children's Global Assessment Scale; YMRS, Young Mania Rating Scale; CDRS-R, Children's Depression Rating Scale–Revised; ADHD, attention-deficit hyperactivity disorder; OCD, Obsessive-compulsive Disorder.
[a] t test.
[b] χ^2 test
[c] Antidepressant treatments for last depressive episode that is defining ATEM+ status

3.2. Thyroid function, autoimmunity and use of TPO-abs to distinguish between groups

TSH and FT4 concentrations in the blood were comparable in both groups. Seroprevalence (51.7% vs 22.6%; $p = 0.019$) and titer of TPO-abs (Median TPO-abs (U/mL) [IQR] 63.0 [50.1−76] vs 53.3 [44.3−58]; $F(1, 52) = 4.788$, $p = 0.033$) in ATEM+ patients was significantly higher compared to ATEM- controls. The logistic regression analysis that adjusted for covariates (age, gender, Tanner stage, body mass index, antipsychotic treatments and smoking status) showed that ATEM+ phenotype was significantly associated with TPO-abs positivity (OR = 3.67, 95% confidence interval [CI] = 1.2-11.1, $p = 0.022$) (Table 3).

4. Discussion

In this study, we measured seroprevalence and titer of TPO-abs in patients with pediatric ATEM+ and ATEM- controls. Our results demonstrate that seroprevalence and titer of TPO-abs are significantly higher in ATEM+ than in ATEM-. Furthermore, TPO-abs positivity was significantly associated with ATEM+ while controlling for age, gender, Tanner stage, body mass index, antipsychotic treatments and smoking status. To our knowledge, this is the first study that highlights the role of thyroid autoimmunity in the ATEM process in the pediatric population.

Table 3
Thyroid function tests, seroprevalence and titer of TPO-abs in patients with antidepressant treatment-emergent mania (ATEM+) compared to controls (ATEM-).

Variable	ATEM+ (n = 29) Median [IQR] or %(n)	ATEM- (n = 31) Median [IQR] or %(n)	p values
fT4, ng/dL	0.71 [0.67-0.78]	0.72 [0.68-0.78]	0.744[a]
TSH, m[IU]/L	2.11 [1.58-4.74]	2.23 [1.6-2.93]	0.515[a]
TPO-abs, U/mL	63 [50.1-76]	53.3 [44.3-58]	**0.009**[a]
TPO-abs positivity	51.7 (15)	22.6 (7)	**0.019**[b]

Note TPO-abs, anti-thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone; fT4, free thyroxin
[a] ANCOVA
[b] χ^2 test

A new accepted feature of BD in DSM-5 is the switch to mania during antidepressant treatment. The mechanisms behind such transitions are still elusive and constitute an unmet psychopharmacological demand (Salvadore et al., 2010). Considerable efforts have been made to search into potential clinical risk factors that may play a role in ATEM. A recent meta-analysis investigated clinical (age of onset, sex, BD subtype, rapid cycling feature, comorbid diagnoses, antidepressant type and the number of depressive/manic episodes) and genetic (serotonin transporter and brain-derived neurotrophic factor gene polymorphisms) risk factors associated with ATEM. Based on this meta-analysis, the only clinical risk factors that seem to consistently be associated with a greater risk of ATEM are previous ATEM history and the increased number of depressive episodes. The present study confirmed the findings of lack of association age of onset, sex, antidepressant type and family history of mood disorders with ATEM. Although previous studies suggest that tricyclic antidepressants (TCA) and serotonin and norepinephrine reuptake inhibitors (SNRI) are more often associated with ATEM than selective serotonin reuptake inhibitors (SSRI), we did not find group differences regarding antidepressant type due to the fact that the majority of our participant used SSRI rather than TCA/SNRI (Isabella Pacchiarotti et al., 2013; Post et al., 2006; Tondo et al., 2010). Besides, our study showed that ADHD and anxiety comorbidity were more prevalent in ATEM+ individuals. In a previous prospective antidepressant treatment study on youth at high risk for BD, Strawn et al. showed that ADHD comorbidity linked to antidepressant-related adverse events (Strawn et al., 2014). Furthermore, Scott et al also indicated that alcohol use disorder was one of the risk factors in male BD patients with ATEM+ (Scott et al., 2017). Our results go beyond previous reports, showing that ADHD and anxiety disorders could be associated with ATEM in the child and adolescent population. We also found evidence for the first time that the ATEM+ group presented a poorer clinical functioning score. Conflicting results regarding comorbid diagnoses might be due to a lack of consensus on the definition of ATEM. Mixed findings are partly explained by phenotypic heterogeneity. For this reason, it remains unclear to which established clinical factors are attributed to ATEM. However, in this study, we used strict criteria for defining ATEM status against the potential cofounders and compared them with antidepressant exposed ATEM- controls rather than healthy controls.

Although there are many biomarker efforts to dissect BD phenotypes generally, the research in blood-based biomarker studies for ATEM remains very scarce and only limited to research on genetic polymorphisms. A recent study by Scott et al proposed that individuals with female ATEM patients are more likely to experience thyroid disorder compared to the control group (Scott et al., 2017). One limitation of this study however is that they did not support their findings with seroprevalence and titer of TPO-abs. In the present study, we extended previous findings by differentiating pediatric ATEM patients from psychiatric control subjects, with results indicating a significantly higher seroprevalence of TPO-abs. Importantly, these basic findings constituted the first blood-based biomarker evidence for ATEM rather than genetic polymorphism studies.

The association between BD and thyroid autoimmunity has been studied very extensively. One of the earliest studies conducted by Kupka et al demonstrated that TPO-abs positivity was found in 28% of BD compared with 18% for psychiatric controls (Kupka et al., 2002). In another previous study by Dagner et al exploring the relationship between thyroid autoimmunity and mood disorders, TPO-abs positivity was found in 32.7% of unipolar or bipolar depression (Degner et al., 2015). On the other hand, a recent meta-analysis revealed that thyroid autoimmunity is not associated with BD risk. Interestingly, our study suggested that approximately 50% of ATEM patients were more seropositive for TPO-abs than 22% of psychiatric controls. When comparing our results to those of older studies, it must be pointed out that we used stringent definitions of ATEM phenotype to reduce the heterogeneity in pediatric mood disorders. Although TPO-abs' exact role remains unclear, several *in vitro* and brain imaging studies showed that thyroid autoimmunity may contribute to brain circuit disruption by impairing myelinogenesis (Leyhe and Müssig, 2014). Indeed, a previous postmortem study demonstrated that reduced thyroid-stimulating hormone receptor, which is potential target for thyroid autoantibodies, expression in the limbic region could be associated with the pathophysiology of BD mood switch and BD pathophysiology (Naicker et al., 2019).

The first limitation of the present study is that because of the cross-sectional study design, we could not confirm causality between thyroid autoantibodies and ATEM. Second, the sample size of this study was relatively small and lacked healthy controls. Third, given the fact that thyroid autoantibodies tests are commonly used to detect the presence of autoimmune thyroiditis, thyroid autoimmunity was not confirmed by thyroidal ultrasound. Finally, we only measured TPO-abs. Other comorbid autoimmune conditions that might be associated with underlying BD pathophysiology were not assed in this study.

To conclude, our data suggest that TPO-abs can be used for a blood-based biomarker that might represent a risk factor for a subsequent mood switch from a depressive state, in a subgroup of pediatric BD. For that reason, it could be important for the physician to monitor titer or seroprevalence of TPO-abs in youth at clinical high risk for BD when evaluating the risk versus benefit of antidepressant prescription. Replication studies with larger sample sizes using reliable and valid definitions of ATEM status are certainly warranted.

CRediT authorship contribution statement

Dogukan Koc: Conceptualization, Methodology, Resources, Data curation, Writing – original draft, Writing – review & editing. **Ecem Ince:** Investigation, Data curation, Resources. **Tugba San:** Investigation, Data curation. **Pınar Akan:** Conceptualization, Methodology, Resources. **Ahu Paketci:** Investigation, Data curation, Resources. **Ece Bober:** Conceptualization, Methodology, Resources. **Nese Direk Tecirli:** Conceptualization, Supervision. **Neslihan Inal:** Conceptualization, Supervision, Validation, Funding acquisition, Writing – original draft, Writing – review & editing. **Aynur Pekcanlar Akay:** Conceptualization, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors report no conflict of interest.

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