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Comparison of thyroid-stimulating hormone levels in adolescents with schizophrenia, bipolar disorder, unipolar depression, conduct disorders, and hyperkinetic disorders

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Abstract

The aim of this study was to retrospectively compare values of thyroid-stimulating hormone (TSH) in adolescent patients diagnosed with schizophrenia, bipolar disorder, unipolar depression (UNI-DEP), conduct disorders (CD), and hyperkinetic disorders.

The research involved 1122 patients (718 women, 64%); aged 12 to 18 hospitalized in the Department of Adolescent Psychiatry, Medical University of Lodz. We analyzed TSH levels in the whole study population and compared it between the above-mentioned subgroups of diagnoses.

Mean serum TSH concentration in the studied population (n = 1122) was 2.06 μIU/mL. The values of percentiles were as follows: 2.5th – 0.53 μIU/mL, 10th – 0.89 μIU/mL, 25th – 1.31 μIU/mL, 50th – 1.9 μIU/mL, 75th – 2.6 μIU/mL, 90th – 3.43 μIU/mL, 97.5th – 4.72 μIU/mL. TSH values were negatively correlated with patients' age ($P = .00001$). Patients with bipolar depression had higher TSH levels than patients with CD ($P = .002$). Also, when male and female groups were examined separately we found that female patients with UNI-DEP and bipolar disorder had higher TSH levels than female patients with CD ($P = .001$; $P = .001$).

Our results confirm that there may be a higher prevalence of thyroid dysfunctions in bipolar and UNI-DEP subgroups among adolescents and that it is worthy to consider some kind of interventions regarding thyroid function in depressed individuals.

Abbreviations: AD = antidepressants, BIP = bipolar disorder, BIP-Dep = bipolar depression, BIP-M = bipolar mania, CBCL-DP = child behavior checklist dysregulation profile, CD = conduct disorders, HD = hyperkinetic disorders, Li = lithium, SHZ = schizophrenia, T3 = triiodothyronine, T4 = thyroxine, TSH = thyroid-stimulating hormone, UNI-DEP = unipolar depression.

Keywords: adolescents, bipolar disorder, conduct disorders, depression, hyperkinetic disorders, schizophrenia, thyroid-stimulating hormone

1. Introduction

It is estimated that one third of young individuals meets lifetime criteria of a Diagnostic and Statistical Manual of Mental Disorders mental disorder. The most frequently diagnosed conditions in this group are anxiety disorders, conduct and hyperkinetic disorders (HD), mood disorders, and substance misuse disorders.[1] The number of youths suffering from psychiatric disorders has increased over the past few decades. It is probably partly due to social changes such as disruption of family structure or increasing educational and vocational pressures.[2] The median prevalence rates for different mental disorders among adolescents are 4% to 6% for anxiety disorders, 4% to 6% for conduct disorders (CD), 3% to 5% for depression, 2% to 4% for attention deficit hyperactivity disorder, 2% to 3% for substance misuse disorders, and 0.5% for schizophrenia (SHZ).[2–4] Studies have shown that approximately half of all lifetime psychiatric disorders start by the mid-teens and 3 quarters by the mid-twenties. Unfortunately, treatment of these conditions usually begins a number of years later.[5] The above information shows how crucial it is to gain a better understanding of the causes and risk factors of mental disorders among adolescents.

One of the factors that could influence mental condition of adolescents is the function of the thyroid gland. Thyroid gland is

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stimulated by the thyroid-stimulation hormone (also known as thyrotropic hormone, thyrotropin, TSH) to produce thyroxine (T4) and then indirectly triiodothyronine (T3), diiodothyronine, and monoiodothyronine. TSH is produced and secreted by thyrotrope cells located in the anterior pituitary gland. Its synthesis is stimulated by thyrotropin-releasing hormone which derives from the hypothalamus. It is inhibited both by somatostatin, which is also produced by the hypothalamus, and by T3 and T4 (through a negative feedback loop).[6] Thyroid hormones play an essential role in normal child and adolescent development as regulators of myelination of the nervous system, growth, dental and skeletal development, metabolism and organ functions.[7] Disorders affecting the thyroid gland are common endocrinopathies in adolescents. They can present as a goiter, a nodule (in the majority benign) or a range of different clinical symptoms.[8] As far as acquired hypothyroidism is concerned, the most common cause of this condition among children and adolescents is autoimmune hypothyroidism (mainly Hashimoto thyroiditis) with estimated prevalence rate 1% to 2% and a 4:1 female predominance.[9,10] Similarly, most cases of hyperthyroidism have autoimmune etiology (known as Graves disease). The incidence of this condition among pediatric patients is 0.1 to 3 cases per 100,000 with female predominance and peak incidence between 10 and 15 years of age.[10–12] The etiology and clinical manifestation of thyroid disorders in children and adolescents is clearly different from that occurring in adults.[7] Also, the levels of TSH, T3, and T4 change significantly during childhood and adolescence, which is why adult reference intervals cannot be directly applied to these age groups. Thus, it is necessary to use pediatric reference values and always interpret laboratory results with respect to an individual clinical picture in order to correctly diagnose young patients.[13]

The link between altered thyroid function and mental health problems has long been recognized, especially among adults. Patients with untreated hyperthyroidism can present symptoms of depression, anxiety,[14] and psychosis.[15] They may also be at a greater risk of developing bipolar disorder (BIP).[16] Other studies seem to confirm that there may be higher prevalence of thyroid dysfunctions in patients with mood disorders (both unipolar and bipolar)[17] and that thyroid hormone supplementation may improve clinical response to antidepressant drugs in depressed individuals.[18] However, the issue still needs further investigation. Apart from that, there is evidence that autoimmunity of the thyroid gland is an independent risk factor for developing BIP.[19] Among the elderly, depression was observed more frequently in patients with subclinical hypothyroidism than in those with overt hypothyroidism. Subclinical hypothyroidism also increased the risk of depression more than 4 times in this population.[20] Subclinical hypothyroidism is a condition when serum TSH level is elevated while free thyroid hormone levels are within the normal reference range. The risk of progression to overt hypothyroidism depends on different factors such as initial serum TSH level, family history or presence of goiter. The clinical picture of this condition may vary from being asymptomatic to having mild nonspecific symptoms. It still remains controversial what serum TSH concentration should be considered as the normal upper limit.[21] According to the 2012 guidelines cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association, the normal range of serum TSH level is 0.45 to 4.12 μIU/mL.[22] However, the National Academy of Clinical Biochemistry recommends lowering the upper normal limit to 2.5 μIU/mL.[23] Apart from that, in patients suffering from different thyroid disorders there are higher rates of panic disorder, specific phobia, obsessive–compulsive disorder, major depressive disorder, BIP, and cyclothymia than in general population.[24] There are still only few analyses investigating a connection between thyroid function and different mental disorders in adolescents. In one of the retrospective studies a significant relationship between subclinical hypothyroidism and severe affective and behavioral dysregulation in adolescents was found.[25] However, it was not supported in the analysis performed on a larger study group and published 1 year later.[26] All of the above findings may suggest that the co-occurrence of psychiatric and thyroid disorders may be the result of common biochemical abnormalities.

2. Aim of the study

The main aim of the study was to assess TSH values in patient hospitalized in the Adolescent Psychiatry Department, Central Teaching Hospital in Lodz in the years 2010 to 2016. The secondary aim was to compare TSH values between several groups of patients with different sets of diagnoses, that is, SHZ, bipolar mania (BIP-M), bipolar depression (BIP-Dep), unipolar depression (UNI-DEP), CD, and HD.

We hypothesized that adolescent psychiatric inpatients would have higher TSH level than general population. Additionally, our hypothesis was that there would be significant differences between unipolar and BIP-Dep groups and the rest of groups in terms of TSH.

3. Methods

3.1. Subjects

We retrospectively compared the data from 1122 youth Caucasian patients (718 women, 64%), aged 12 to 18 years who were hospitalized in the Department of Adolescent Psychiatry, Medical University of Lodz. Our psychiatry clinical hospital database was screened for serum TSH levels. Electrochemiluminescence immunoassay (Cobas e601, Roche, Zurich, Switzerland) was used for the quantitative determination of thyrotropin in undiluted serum samples. In case of patients hospitalized many times, only data from their first hospitalization were analyzed. Usually, serum TSH level was measured within 2 days from admission to the hospital, which means that most of the patients were in the acute phase of their mental disorder at that time. Discharge diagnoses were established in accordance with the International Classification of Diseases-10 criteria. Patients who received a thyroid replacement therapy and those who were diagnosed with any kind of thyroid disorder at admission or/and discharge from the hospital were excluded from our study. As far as psychiatric disorders are concerned, patients included in the study were treated with different types of medications. Taking into account the fact that we included patients' first hospitalization, the duration of the treatment was rather short-term (lasting rather days or months than years or more). Number of patients receiving specific classes of drugs is presented below in the Results section of the manuscript. Most of the patients received also nonpharmacological treatment such as psychological support, psychoeducation, psychotherapy, family therapy, and occupational therapy. Generally, we decided not to exlude from the study patients treated with lithium (Li) – despite the fact that this medication is proven to cause a higher rate of

Table 1

Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Caucasian patients aged 12–18 yr	Thyroid replacement therapy
First hospitalization	Thyroid disorder at admission or/and discharge
TSH level measured during the first 2 d of hospitalization	
Discharge diagnosis established according to the ICD-10 criteria (F20, F30, F31.0, F31.1, F31.2, F31.3, F31.4, F31.5, F31.6, F32, F33, F91, F92, F90)	

ICD = International Classification of Diseases.

TSH abnormality in patients suffering from BIP (more frequently in women than in men).[27] This decision was based on the observation that Li is rarely used in population aged under 18 years in our hospital. However, we decided to perform additional analyses on the sample in which we excluded the patients treated with Li to see if the results differed significantly from those performed on the whole study population. We did not exclude patients treated with any other than Li medication either.

Inclusion and exclusion criteria are summarized in Table 1.

At first, TSH levels were analyzed in the whole group of 1122 patients. Then, TSH values were compared between the foregoing subgroups of diagnoses according to International Classification of Diseases-10: SHZ (F20), manic, hypomanic or mixed episodes in BIP (F30, F31.0–F31.2, and F31.6), depressive episodes in BIP (F31.3–F31.5), UNI-DEP (F32 and F33), CD, mixed disorders of conduct and emotions (F91 and F92), and HD (F90). All the inpatients diagnosed with disorders other than those selected above were combined into 1 subgroup (n = 583) which included different mental disorders with the predominance of adjustment disorders. This subgroup was the most heterogeneous one among all the others, consisting of many small diagnostic groups and, thus, very difficult to interpret in terms of TSH values. Therefore, we decided not to include it in our comparative analysis.

3.2. Statistical analysis

Statistical procedures were performed using Statistica Software 13.1 (StatSoft, Polska). Simple descriptive statistics were generated for continuous variables. For discrete variables, number of the patients and percentages are given. Normality of distribution was tested with the Shapiro–Wilk test. TSH level did not follow normal distribution, even after transformation of this variable. Inter-group comparisons were tested with the nonparametric Mann–Whitney *U* test (TSH values between men and women) and the Kruskal–Wallis test (TSH values among multiple diagnostic subgroups). It was followed by the posthoc analysis. The significance level was set at $P < .05$.

4. Results

Figure 1 shows the description of the sample.

4.1. TSH values in the study population

Simple descriptive statistics for TSH levels in the study population are presented in Table 2 below.

In both age categories we analyzed how many patients had TSH levels above the upper normal limit defined as the 97.5th percentile and below the lower normal limit defined as the 2.5th

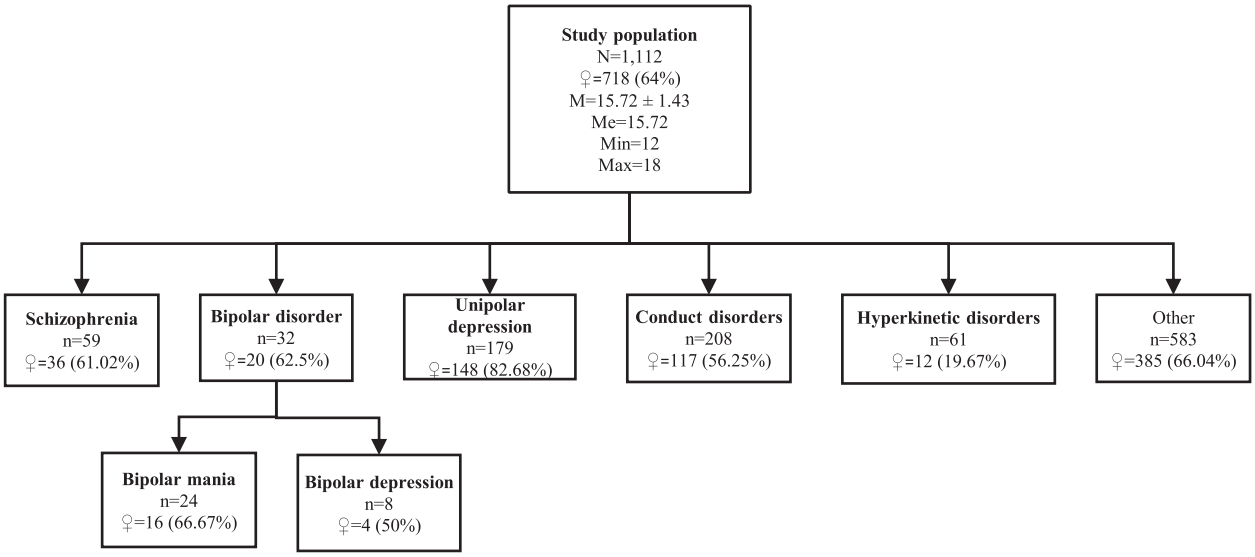

Figure 1. The description of the sample. Figure 1 presents total number of adolescents involved in the study as well as the sex ratio, the mean, median, maximum and minimum age of the patients. It also shows stratification of patients into diagnostic subgroups and the proportion of women in each of them. ♀ = number of female patients, M =mean age, Max = maximum age, Me = median age, Min = minimum age, N = study population, n = number of patients in each diagnostic subgroup.

Table 2

Percentiles for TSH levels [μIU/mL] in different age categories.

							Percentiles							
	Age category	n	M	Me	Min	Max	2.5th	10th	25th	50th	75th	90th	97.5th	SD
Pediatric reference intervals[13]	11–14	355					0.7	1.1	1.6	2.1	2.8	3.6	4.61	
	15–18	233					0.5	0.94	1.3	1.7	2.35	3.3	4.33	
Our study	All	1,122	2.06	1.9	0	9.05	0.53	0.89	1.31	1.9	2.6	3.43	4.72	1.09
	11–14	378	2.25	2.02	0.48	8	0.73	1.08	1.51	2.02	2.77	3.58	5.01	1.1
	15–18	744	1.97	1.78	0	9.05	0.44	0.82	1.22	1.78	2.52	3.32	4.5	1.08

Table 2 presents the values of percentiles for TSH levels in the whole study sample as well as in 2 different age categories, that is, 11–14 years of age and 15–18 years of age. Above them the table displays the values of percentiles for TSH levels from the study performed by Kapelari et al[13] which could be considered as pediatric reference intervals.

M = mean TSH level, Max = maximum TSH level, Me = median TSH level, Min = minimum TSH level, n = number of patients in each age category, SD = standard deviation in TSH level, TSH = thyroid-stimulating hormone.

percentile from the research performed by Kapelari et al.[13] To the best of our knowledge, there are no reference values of Polish population based on the locally used TSH assay. Pediatric reference values of TSH should be personalized, among others, according to ethnicity.[28] Therefore, we decided to use percentiles for TSH levels from the study performed in the European population which is as near to Polish as possible in the context of social level, environmental factors and ethnicity. The study by Kapelari et al is the most detailed and the newest one we have managed to find. Table 3 shows these results.

We observed the right-tailed skewed distribution of TSH levels in the whole investigated population (the value for skewness was 1.47). Also, we found that there was a statistically significant linear negative correlation between TSH concentration and the patients' age ($r = -0.1298$, $R2 = 0.0169$, $P = .00001$). Apart from that, we discovered a linear negative correlation between TSH levels and the patients' age, both in the female and male group. However, it occurred to be stronger for women ($r = -0.1571$, $R2 = 0.0247$, $P = .00002$) than for men ($r = -0.0859$, $R2 = 0.0074$, $P = .0846$). For the whole study group, there was no difference between men ($M = 2.11 \pm 1.1$ μIU/mL) and women ($M = 2.03 \pm 1.09$ μIU/mL) in the case of mean TSH values ($Z = 1.22$, $P = .22$).

4.2. Types of pharmacological treatment

Table 4 presents number of patients treated with different types of drugs. Only 281 patients in the whole study population did not receive any kind of pharmacological therapy. The rest of the patients were treated with at least 1 medications from the following groups: antipsychotics, antidepressants (AD), mood stabilizers, and other. Most of the patients treated with AD received selective serotonin reuptake inhibitors. Other AD that were used in the study population were tricyclic AD, monoamine oxidase inhibitors, mianserin, mirtazapine, tianeptine, trazodone, and reboxetine. There were 4 medications included in the mood stabilizers group: lithium (Li), lamotrigine, carbamazepine, and valproic acid. The group of other medications consisted of different types of drugs such as benzodiazepines, nonbenzodiazepine hypnotics (Z-drugs), other sedatives (eg, hydroxyzine), drugs used in hyperkinetic disorder (eg, methylphenidate and atomoxetine), anticonvulsants, and melatonin. There was 1 person in the whole study population that was treated with electrotherapy and 1 person treated with phototherapy. However, it is worth pointing out that these 2 adolescents also received other types of treatment (pharmacological and nonpharmacological).

4.3. Lithium treated subgroup

Ten of 1122 patients included in this study were treated with Li during hospitalization. Among them there were 7 women (70%). TSH levels of those patients were not significantly different than the values of those not treated with Li ($Z = 1.27$, $P = .2$). It is worth mentioning that a great majority of patients who were treated with Li were part of the BIP-M subgroup. We found out that the TSH values of patients diagnosed with BIP-M and treated with Li were not significantly different than the levels of those who were also diagnosed with this condition but did not receive the medication ($Z = 0.97$, $P = .33$). Apart from that, it is also worth mentioning that all the patients who received Li treatment were in the older age category (between 15 and 18 years of age). In the whole study population, the age of participants treated with Li was not significantly different than the age of those who were not given the treatment ($Z = 1.85$, $P = .06$). However, in the case of BIP-M subgroup, the patients who received Li treatment were significantly older than those who did not undergo the therapy ($Z = 2.1$, $P = .04$). Their mean age was $M = 17.18 \pm 1.3$ years of age, the minimum age was Min = 15.17 years of age and

Table 3

Number of patients with TSH levels above or below the normal limit.

	TSH > 97.5th percentile			TSH < 2.5th percentile		
11–14 yr old	n	%	%N	n	%	%N
	15	3.97%	1.34%	43	5.78%	3.83%
15–18 yr old	n	%	%N	n	%	%N
	17	2.28%	1.52%	7	1.85%	0.62%

% = percentage of patients with TSH levels above or below the normal limit in the younger or older age category, %N = percentage of patients with TSH levels above or below the normal limit in the whole study population, n = number of patients, TSH = thyroid-stimulating hormone.

Table 4

Number of patients receiving different types of psychotropic medications.

						Antipsychotics			
						AP/AP+			
	AP	AP+	AP + AD	AP + MS	AP + 0	AP + AD + MS	AP + AD + 0	AP + MS + 0	AP + AD + MS + 0
	86	302	54	68	50	42	23	41	24
						Antidepressants			
Number of patients						Type of antidepressants			
				SSRI				Other	
				387				66	
						AD/AD+			
	AD	AD+	AD + AP	AD + MS	AD + 0	AD + AP + MS	AD + AP + 0	AD + MS + 0	AD + AP + MS + 0
	210	243	54	41	46	42	23	13	24
						Mood stabilizers			
						Type of mood stabilizers			
	Li	Li + MS		LAM	LAM + MS	CBZ	CBZ + MS	VAL	VAL + MS
	3	7		44	19	88	29	112	28
						MS/MS+			
	MS	MS+	MS + AP	MS + AD	MS + 0	MS + AP + AD	MS + AP + 0	MS + AD + 0	MS + AP + AD + 0
	45	242	68	41	13	42	41	13	24
						No medication			
						281			
						Other			
						85			

+ = plus other types of drugs (eg, AP + AD = antipsychotics plus antidepressants), +MS = plus other mood stabilizers (eg, Li + MS = lithium plus other mood stabilizers), AD = antidepressants, AP = antipsychotics, CBZ = carbamazepine, LAM = lamotrigine, Li = lithium, MS = mood stabilizers, 0 = other medications, SSRIs = selective serotonin reuptake inhibitors, VAL = valproic acid.

the maximum age was Max = 18 years of age. The rest of the BIP-M subgroup consisted of 18 adolescents who did not receive Li treatment. Their mean age was M = 15.7 ± 1.19, the minimum age was Min = 13.1 years of age and the maximum age was Max = 17.3. As a result of these findings, we decided to additionally analyze the patients from the older age category (15–18 years of age) and discovered that the TSH values of the older patients treated with Li were not significantly different than of the TSH levels of those who did not receive the medication ($Z = 1.57$, $P = .12$). After exclusion of the patients treated with Li from the study population, the values of percentiles for TSH levels did not change either in the younger age category (11–14 years of age) or in the older age category (15–18 years of age).

4.4. TSH values in diagnostic subgroups

Mean serum TSH concentrations in each diagnostic subgroup are presented in Table 5 below.

Figure 2 shows the graphical representation of the TSH values in each diagnostic subgroup in the whole study population as well as separately in the female and male group of the patients.

Table 5

Mean TSH levels [μIU/mL] in each diagnostic subgroup.

	Total	Men	Women
Schizophrenia	2.12 ± 1.01	2.11 ± 1.06	2.12 ± 1.01
Bipolar disorder	2.23 ± 1.06	1.65 ± 0.96	2.56 ± 0.98
Bipolar mania	1.96 ± 0.98	1.17 ± 0.73	2.36 ± 0.86
Bipolar depression	3.02 ± 0.9	2.63 ± 0.53	3.4 ± 1.1
Unipolar depression	2.08 ± 1.02	2 ± 1.08	2.1 ± 1.02
Conduct disorders	1.94 ± 1.12	2.14 ± 1.18	1.78 ± 1.05
Hyperkinetic disorders	2.17 ± 0.95	2.19 ± 0.98	2.1 ± 0.85

We discovered that the adolescent patients diagnosed with BIP-Dep had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions ($Z = 3.17$, $P = .002$). Apart from that, we also discovered that the female patients diagnosed with UNI-DEP had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions ($H = 21.98$, $P = .001$). In the case of male patients, we did not find any significant differences between the subgroups of diagnoses and TSH levels ($H = 10.72$, $P = .09$).

Next, we searched for possible differences in TSH level among our subgroups, however, considering BIP as 1 diagnostic entity, we did not divide it into BIP-Dep and BIP-M. Figure 3 presents median TSH levels in the subgroups in the whole study population as well as separately in the female and male group of the participants. At that stage of the study, we did not find any statistically significant differences between the diagnostic subgroups and mean serum TSH levels in the whole investigated population ($H = 9.06$, $P = .11$) or in the male patients ($H = 10.73$, $P = .09$). However, we discovered that the female patients diagnosed with UNI-DEP had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions ($Z = 3.36$, $P = .001$). We also found out that the female patients diagnosed with BIP had significantly higher mean serum TSH levels that those diagnosed with CD and mixed disorders of conduct and emotions ($Z = 3.67$, $P = .001$).

5. Discussion

The aim of this study was to compare TSH values in youth psychiatric inpatients diagnosed with different mental disorders. We have performed a 3-step analysis comparing TSH levels in the whole investigated population, as well as among selected diagnostic subgroups.

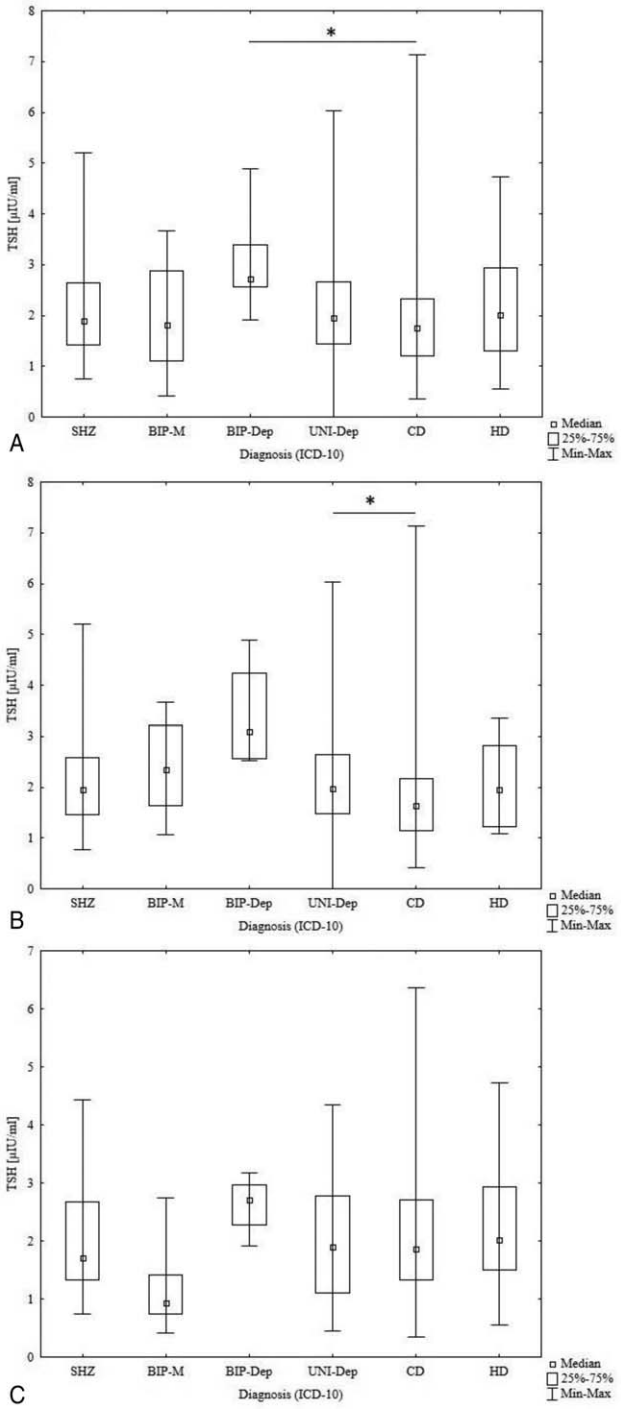

Figure 2. Median TSH levels [µIU/mL] in subjects with schizophrenia (SHZ), bipolar mania (BIP-M), bipolar depression (BIP-Dep), unipolar depression (UNI-Dep), conduct disorders (CD) and hyperkinetic disorders (HD) in the whole study population (A), in the female group (B) and in the male group (C). $^{*}P < .05$.

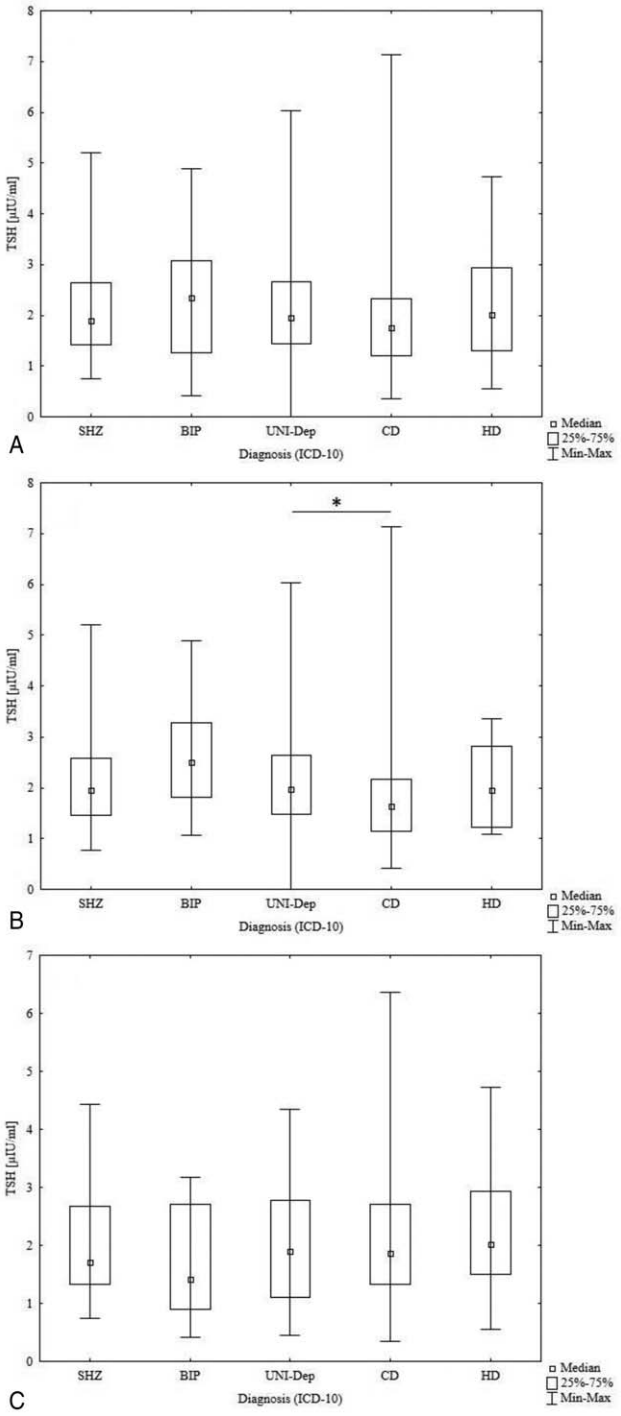

Figure 3. Median TSH levels [µIU/mL] in subjects with schizophrenia (SHZ), bipolar disorder (BIP), unipolar depression (UNI-Dep), conduct disorders (CD) and hyperkinetic disorders (HD) in the whole study population (A), in the female group (B) and in the male group (C). $^{*}P < .05$.

We observed that percentiles of TSH values in the examined population were similar to pediatric reference values.[13] However, the fact that 3.97% of the adolescents aged 11 to 14 had TSH levels above the upper normal limit (97th percentile) may mean that there exists a relation between thyroid dysfunctions and mental disorders in early adolescence. In order to verify the hypothesis and establish whether there is a causal link or rather a common underlying comorbidity, a study with a control group should be conducted.

We also discovered the linear negative correlation between TSH concentration and the patients' age. This result is consistent with 2 different studies. The first one compared TSH values

between adult patients with acute phase of SHZ, UNI-DEP, BIP-Dep and BIP-M.[17] It involved 1685 Caucasian patients (1064 women, 63.1%). The mean age of the patients in the research was 46.4 years. The second one is a study which shows that age is the only independent factor influencing TSH level and it is significantly inversely associated with TSH.[23] The research included 870 adults (18–68 years, 425 women, 48.9%), aged between 18 and 68 years. On the other hand, our findings are contradictory to the results of the population-based National Health and Nutrition Examination Survey.[29] In the study, the positive correlation between age and TSH levels was found in a large sample (N = 17,353) including U.S. civilians aged 12 years and older. In the National Health and Nutrition Examination Survey study, mean serum TSH concentration for the disease-free population was 1.50 μIU/mL. It was higher in females than in males and higher in white nonHispanics than in black non-Hispanics or Mexican Americans.[29] As compared to these findings, in our study sample mean serum TSH level was higher (2.06 μIU/mL). These differences may be explained by the fact that our study was not population-based and included only psychiatric adolescent inpatients.[30] It is also worth pointing out that in our study population the patients' age only partially explains TSH levels, better in case of women than men.

Moreover, we found that the adolescent patients diagnosed with BIP-Dep had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions. Additionally, we discovered that female patients diagnosed with UNI-DEP had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions. It is partly consistent with results of a different study performed on the population of adults in which patients with BIP-Dep had the highest TSH levels among all the other subgroups of psychiatric diagnoses.[17] However, in this study, the highest TSH values were also found among the BIP-Dep subgroup in case of male patients, whereas in our research we did not find any significant differences of TSH between diagnostic subgroups in men. Importantly, our results partially confirm the results of the study in which 53 children and adolescents with severe affective and behavioral dysregulation (identified as Child Behavior Checklist Dysregulation Profile – CBCL-DP) had significantly higher mean serum TSH levels than 61 controls.[25] The CBCL-DP is a pattern of co-occurring deviant scores on the attention problems, aggression behavior and anxiety/depression subscales of the child behavior checklist.[31] This specific profile has been associated with BIP,[32–34] as well as suicidality,[35] anxiety and disruptive behavior disorders.[35,36] On the other hand, in another study there was no significant connection between CBCL-DP scores and serum TSH, fT3 and fT4 concentrations (262 subjects; 63 women, 24%; mean age 10.5 years).[26] The difference between this study and the study performed by Holtmann et al[25] can be explained by the lack of control group and that there were fewer female than male patients. What is more, in the research performed by Zepf et al,[26] posthoc power analyses showed that adequate power existed to detect between-group differences in fT3 and fT4 but not TSH serum concentrations.

When the patients with BIP-Dep and BIP-M were analyzed as 1 subgroup (BIP), we did not find any statistically significant differences between the diagnostic subgroups in mean serum TSH values contradictory to the results in adult population.[17] It could be explained by nontypical clinical picture, higher rates of mixed episodes or co-occurrence of suicidal behavior in adolescent population. Therefore, sometimes diagnoses made during adolescence may change during adulthood. It may be also caused by different thyroid hormones profiles between specific phases of BIP.[37] However, in this analysis we still observed that the female patients diagnosed with UNI-DEP and BIP had significantly higher mean serum TSH values than those diagnosed with CD and mixed disorders of conduct and emotions.

Furthermore, it should not be forgotten that there is a state called "brain hypothyroidism" which can affect patients with depression. It occurs in systemic euthyroidism when the level of the thyroid hormone transport protein, transthyretin, is low[38] or when the thyroid hormone receptor is damaged.[39] The state of "brain hypothyroidism" could also influence our interpretations.

Nevertheless, our study confirms that there may be a higher prevalence of thyroid dysfunctions in bipolar and UNI-DEP subgroups among adolescents. It could be explained by the potential causal link between primary or secondary thyroid dysfunctions and mental health abnormalities, in both directions.[14–20,40–42] Our main finding may also be explained by the fact that psychiatric disorders and pituitary–thyroid abnormalities may have a common underlying comorbidity.

There have been several hypotheses on the issue proposed in the literature such as chronic low-grade inflammation, increased oxidative stress, microbiota changes, psychotropic medications intake, and others. These hypotheses are supported by scientific evidence. Patients diagnosed with different mental disorders present significant elevation in peripheral inflammatory biomarkers, central nervous system markers of immune activation, and reduced effectiveness of immune elements crucial for protection against pathogens. There are preliminary conclusions that immune activity may promote psychiatric disorders at different stages of one's life course.[43] As far as BIP is concerned, there is evidence suggesting that this condition is associated with dysregulation of glial-neuronal interactions and that abnormalities are more apparent in glial elements than in neurons. Especially microglia is associated with the brain's primary immune elements and seems to be overactive in BIP. Apart from that, the inflammation in BIP is also increased in the peripheral parts of the body both in depressive and manic episodes.[44] It all increases the risk for developing multiple medical conditions such as neuroprogression of the disease, accelerated atherosclerosis, dyslipidemia, insulin resistance, and premature mortality.[45] In the case of the thyroid gland, the link between thyroid dysfunction and inflammation has long been recognized. Inflammatory diseases of the thyroid gland are the most common thyroid disorders. They may be caused by infection, radiation, trauma, autoimmune conditions, medications or an idiopathic fibrotic process. The most common inflammatory diseases of the thyroid gland are Hashimoto disease, subacute granulomatous thyroiditis, postpartum thyroiditis, subacute lymphocytic thyroiditis, and drug-induced thyroiditis (caused by amiodarone, interferon-alfa, interleukin-2 or Li). Patients suffering from thyroiditis may present euthyroidism, hyperthyroidism or hypothyroidism. One condition often evolves into another over time.[46,47] All the above evidence could suggest that the cause of co-occurrence of mental disorders and thyroid dysfunctions among adolescents may be a systemic inflammation. This hypothesis needs to be proven by further studies which should include measurements of serum fT3 and fT4 concentrations, antithyroid autoantibodies, and ultrasound examinations of the thyroid gland. Furthermore, they should include the age of the patient when mental disorder and thyroid dysfunction occurred

for the first time as well as his/her past medical history, family history of these conditions and any medications that were taken by the patient, as well as information on any acute or chronic inflammatory conditions in the patient life.

All of these would be helpful in discovering the causes of psychiatric disorders and thyroid dysfunctions among adolescents, select cases when these conditions co-occur and find possible explanations. Identifying the common cause of these conditions among adolescents would help us to treat them successfully and achieve long-term remission of the symptoms. We could also predict occurrence of specific psychiatric disorders and try to prevent them, not only in adolescence but also in adulthood.

5.1. Study limitations

There is no doubt that our study has some limitations. Firstly, we lack data on detailed thyroid assessment such as serum fT3 and fT4 concentrations, antithyroid autoantibodies, ultrasound examinations or the values of transthyretin in the cerebrospinal fluid which makes it difficult to properly interpret TSH levels. Therefore we decided not to classify serum TSH concentration as hyperthyroidism, hypothyroidism or subclinical hypothyroidism.

Moreover, we do not have precise data on past thyroid or psychiatric disorders, their treatment or used psychotropic or other medications (apart from Li) as potential confounding factors. In our study we decided not to exclude patients who received Li. However, we performed additional analyses and discovered that the TSH values of the participants treated with Li were not significantly different from those observed in the individuals who did not take the medication. Moreover, after excluding the subjects treated with Li from the study population, the values of percentiles for TSH levels did not change in any of the age categories. We did not collect data on duration of Li treatment but it is worth pointing out that our study involves adolescents. Therefore, it seems likely that this treatment was rather low-dose and short-term (lasting rather months than years or dozens of years as in the case of adults suffering from BIP). Unfortunately, we cannot exclude the effect of treatment with medications such as AD, antipsychotics or valproic acid, carbamazepine on serum TSH concentrations. There is evidence that different psychiatric medications can alter thyroid function.[48,49] Moreover, we do not have data on prolactin level, and it can influence TSH level. Furthermore, intoxication status secondary to some of the addictive or suicidal behaviour may possibly cause some thyroid abnormalities and we do not have precise data on this. Similarly, we had no data on the general medical condition of the included individuals which could also be a potential confounding factor.

Furthermore, specific subtypes of BIP (type I, type II and rapid cycling) were not assessed. Also, the diagnostic subgroups selected in our study were small. For instance, the BIP subgroup was remarkably smaller than all the other subgroups (n = 32); this is especially true for the BIP-Dep subgroup (n = 8). It could have had an impact on the comparison between different diagnostic subgroups. The reason for all these limitations is that our study is a retrospective study and we do not have the access to all of the additional data.

6. Conclusion

In conclusion, our study confirms that there may be a higher prevalence of thyroid dysfunctions in adolescent patients diagnosed with bipolar and UNI-DEP. However, these results are only in comparison to other investigated psychiatric diagnoses. It may mean that it is worth considering screening for thyroid abnormalities in psychiatric, especially depressed, adolescent population to promptly administer potential proper diagnosis and treatment. The strength of our study is that we investigated the large study sample consisting of adolescent inpatients and compared 5 different clinical subgroups (SHZ, BIP, UNI-DEP, CD, and HD). Further research is needed to elucidate the influence of thyroid function on psychiatric disorders. An idea for future research may be a longitudinal analysis of the data.

7. Ethics

As the study is retrospective and based on medical records and the subjects' personal data are anonymous, an approval of the Bioethics Committee for this research was not required.

Author contributions

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