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ORIGINAL ARTICLE

Presentation and clinical outcome of adolescents with Graves' disease

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ABSTRACT

Background: Only a limited number of studies have investigated the characteristics of pediatric Graves' disease (GD). These studies include limited number of participants with varying treatment protocols, definition of remission, and follow-up duration.

Objective: This study aimed to determine the clinical characteristics, remission and relapse rates of adolescents with GD, focusing on potential predictors of remission at diagnosis in adolescents receiving antithyroid drugs (ATD).

Methods: Clinical, laboratory, and radiologic features of 19 patients (F/M:13/6) under 18 years of age, who were followed for GD from 2013 to 2025 at our hospital were retrospectively assessed. Remission was defined as sustained euthyroid state without relapse for at least 12 months after discontinuing ATD.

Results: Patients were diagnosed with GD at a median age of 15 years (IQR: 11.6-15.9). 7 (36.8%) presented with palpitation while 3 (15.8%) presented with weight loss. Tachycardia was observed in 9 (47.4%) and hypertension in 1 (5.3%). Goiter was detected in 13 (68.4%) and ophthalmopathy in 8 (42.1%). Thyroid ultrasonography revealed goiter (6.6 SDS, IQR: 3.6-10.3). 18 (94.7%) of patients had findings consistent with thyroiditis and 4 (21.1%) had thyroid nodules.

Five patients were solely treated with methimazole (MMI) while 14 received both MMI and a β-blocker. Median initial MMI dose was 0.3 mg/kg/day (0.2–0.4). Median follow-up time was 13.0 months (4.5–96.0). MMI was discontinued after a median of 38 months (20–96) at a median dose of 0.02 mg/kg/day (range, 0.02–0.03) in 8 (42.1%) of patients. GD (or thyrotoxicosis) was relapsed in 5 (62.5%) of pateints after a median of 4 months (3–22). Remission was achieved in 3 (15.7%). It was observed that patients with higher thyroid volume SDS at diagnosis tended to have a higher relapse rate. Definitive treatment methods, including radioiodine ablation (n=2) and total thyroidectomy (n=3), were performed in 26.3%, and papillary thyroid carcinoma was detected in one.

Conclusion: ATD is an effective treatment option in adolescents with GD. Thyroid volume at diagnosis may serve as a potential predictor of remission hence further studies are needed to confirm this observation. It should also be noted that thyroid nodules in children with GD may be associated with papillary thyroid carcinoma and therefore thyroid nodules warrant careful evaluation.

Keywords: Graves' disease, adolescence, thyroid nodule, hyperthyroidism, methimazole

INTRODUCTION

Graves' disease (GD) is an autoimmune disorder in which thyroid-stimulating hormone (TSH) receptor antibodies (TRAb) stimulate thyroid gland, leading to excessive secretion of thyroid hormones. It is the most common cause of hyperthyroidism in childhood [1]. Typical clinical manifestations include findings of hyperthyroidism such as tachycardia, hypertension, tremor, weight loss despite increased appetite, nervousness, hyperactivity, menstrual irregularities, heat intolerance, and diarrhea, in addition to findings of goiter and ophthalmopathy on physical examination [2]. GD is rarer in children than adults and tends to present with more severe symptoms at onset. Its incidence is approximately 0.1 per 100,000 person-years in children and 3 per 100,000 person-years in adolescents [3].

Main treatment strategies for GD include long-term pharmacological treatment with antithyroid drugs (ATD), radioactive iodine ablation (RAI), and total thyroidectomy. European Thyroid Association (ETA) guidelines recommend long-term pharmacologic approach as the first-line treatment for children with GD. Although RAI and total thyroidectomy are accepted as definitive second-line treatment options, the choice among these approaches should be determined based on patient-specific factors (such as thyroid volume and disease severity), as well as local practices and available resources by clinicians [4]. Efficacy and adverse effect profiles of these treatment options vary between pediatric and adult populations.

Propylthiouracil (PTU), methimazole (MMI), and carbimazole (CBZ) are ATDs used in GD. MMI which inhibits iodothyronine organification and reduces thyroid hormone synthesis is the first choice in children [5,6]. PTU, is no longer used because of its frequent and serious adverse effects, particularly severe hepatotoxicity [7]. In patients with moderate to severe symptoms of hyperthyroidism, a cardioselective beta-blocker (i.e. atenolol or propranolol) may be administered along with ATDs to alleviate symptoms until euthyroid state is achieved [6]. Adverse reactions are more frequent in pediatric population. Minor and usually transient side effects (i.e. rash, arthralgia, myalgia, and mild elevation of liver enzymes) have been reported in 20-35% of subjects treated with MMI [8,9]. Severe adverse effects such as agranulocytosis, Stevens-Johnson syndrome, and hepatic dysfunction have been observed in about 0.5% [9].

Remission with ATD can be achieved in 30-70% of adults [5]. It is much lower in pediatric population [4]. Relapse risk of children with GD is also lower than that of adults; approximately 20–30% of pediatric cases experience relapse after two years of continuous ATD [2,10]. A limited number of studies including small number of participants have investigated characteristics of children with GD. Treatment protocols, definitions of remission, and follow-up duration vary among centers, and many patients are lost to follow-up on the long term. Therefore, this study aimed to determine clinical characteristics, remission and relapse rates of adolescents with GD, focusing on identifying potential predictors of remission at diagnosis in those receiving ATD.

METHOD

46 patients (F/M: 37/8) under the age of 18 who were followed at our center for hyperthyroidism from 2013 to 2025 were retrospectively evaluated. Of these, 19 were tested positive for TRAb and were diagnosed with GD (Figure 1). Twenty-seven were tested negative for TRAb and were tested positive only for thyroid autoantibodies (anti-thyroid peroxidase (anti-TPO) and/or anti-thyroglobulin (anti-Tg)) and were diagnosed with hyperthyroidism due to Hashimoto thyroiditis and were excluded from the study group.

Demographic characteristics (age, sex), medical and family history, anthropometric measurements (bodyweight, height, and body mass index [BMI]), and findings of physical examination of patients diagnosed with GD were recorded retrospectively from medical records. BMI was calculated using bodyweight (kg)/height (m^2) formula. Height, bodyweight, and BMI standard deviation scores (SDS) were calculated according to age and sex-specific reference data from the Centers for Disease Control and Prevention (CDC) charts.

Laboratory parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), TSH, free T4 (fT4), free T3 (fT3), TRAb, anti-TPO, and anti-Tg, were retrospectively extracted

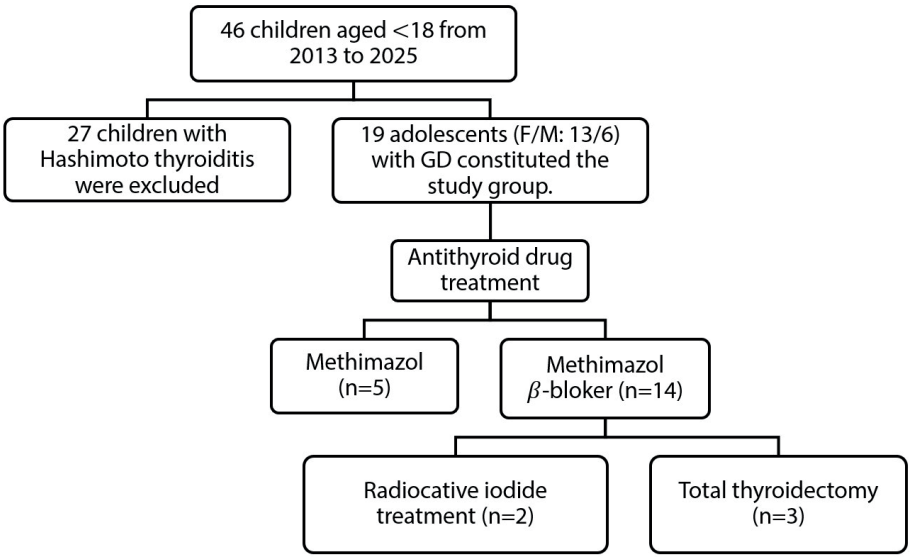

Figure 1. Clinical and treatment characteristics of the study group

from medical records. Serum levels of TSH, fT4, fT3, and thyroid autoantibodies were measured by chemiluminescence assay (Abbott Architect 12000). Reference ranges were 3.3–4.8 ng/dL for fT3, 0.7–1.5 ng/dL for fT4, and 0.4–4.5 IU/mL for TSH. Tachycardia was defined as heart rate exceeding age and sex specific references. On physical examination. Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile of age, gender and height specific norms. Thyroid ultrasonography (USG) was performed at diagnosis and when clinically indicated by an experienced radiologist. Findings, including thyroid gland volume and parenchymal characteristics, were recorded. Thyroid gland volume was compared with age and sex specific references, and SDS were recorded. Ophtalmologic examination was conducted by an ophtalmologist in all of the patients with GD.

Anthropometric measurements and laboratory parameters were repeated every three months and when clinically indicated. Remission was defined as maintenance of euthyroid state and absence of relapse for at least 12 months after discontinuation of ATD [1,11]. Patients with GD were categorized into two groups: those who achieved remission (n=3) and those who relapsed (n=5) and clinical, laboratory, and radiological characteristics at diagnosis were evaluated.

Ethical approval

This study was conducted according to Decleration of Helsinki and local ethical approval for this study was obtained (Date: 08/05/2024; number: 2024-BÇEK/75).

Statistical analysis

Analysis was conducted in SPSS version 22.0 for Windows software package (IBM Corp. Armonk, NY). The Shapiro–Wilk test was used to assess the normality of data distribution. Descriptive statistics and categoric variables were presented as frequency (n) and percentage (%), numeric variables were presented as mean, standard deviation, median, interquartile range.

RESULTS

19 patients (F/M: 13/6) with GD were included. 7 (36.8%) patients presented with palpitations while 3 (15.8%) patients had weight loss, 3 (15.8%) patients had ocular symptoms, and 3 (15.8%) patients had a family history of thyroid disease. Neck swelling suggestive of goiter was noticed in one, and in another, decreased school performance was the presenting complaint (Table 1). Family history of thyroid disease was present in 14 (73.7%) patients. On physical examination, 9 (47.4%) patients were tachycardic and 3 (5.3%) patients were hypertensive. Median weight was -0.4 SDS (IQR: -1.7/1.5), median height was 0.1 SDS (IQR: -0.4/0.5), and median BMI was -1.4 SDS (IQR: -1.8/0.3). Goiter was observed in 13 (68.4%) patients and ophthalmopathy in 8 (42.1%) patients and all of them were pubertal (Table 1).

Table 1. Descriptive findings, presenting complaints and findings oo phsical examination in children with GD

	Results
Sex (F/M)	13/6
Median age (years)	15 (IQR: 11.6-15.9)
Family history of thyroid disease, n (%)	14 (73.7%)
Presenting complaints	
Palpitations, n (%)	7 (36.8%)
Weight loss, n (%)	3 (15.8%)
Ocular symptoms, n (%)	3 (15.8%)
Family history of thyroid disease, n (%)	3 (15.8%)
Neck swelling, n (%)	1 (5.2%)
Decreased school performance, n (%)	1 (5.2%)
Physical examination	
Median weight, SDS (IQR)	-0.4 (-1.7/1.5)
Median height, SDS (IQR)	0.1 (-0.4/0.5)
Median BMI, SDS (IQR)	-1.4 (-1.8/0.3)
Tachycardia, n (%)	9 (47.4%)
Hypertension, n (%)	3 (5.3%)
Goiter, n (%)	13 (68.4%)
Ophthalmopathy, n (%)	8 (42.1%)

At a median age of 15 years (IQR: 11.6-15.9), they were diagnosed with GD as median TSH was 0.008 mIU/mL (IQR: 0.08–0.008), fT4 was 2.6 ng/L (IQR: 1.5-3.4), and fT3 was 12.4 ng/L (IQR: 6.5-20.0). Liver transaminases at diagnosis were elevated in 15.3%. All of the patients were TRAb positive, and 89.5% were positive for anti-TPO and/or anti-Tg. Thyroid USG of the study group revealed goiter (thyroid gland volume: 6.6 SDS, IQR: 3.6-10.3). Findings consistent with thyroiditis were observed in 18 (94.7%) patients, and thyroid nodule were detected in 4 (21.1%) patients .

Five patients were treated with MMI alone while 14 patients received both MMI and a β-blocker. Median initial MMI dose was 0.3 mg/kg/day (0.2-0.4). Median follow-up time was 13.0 months (4.5-96.0). MMI was discontinued and remission was evaluated in 8 (42.1%) patients after a median of 38 months (20-96) at a median MMI dose of 0.02 mg/kg/day (0.02-0.03). However, relapse occurred in 5 (62.5%) patients after a median of 4 months (3-22). Remission was achieved in three (15.7%) patients. Due to the limited number of patients achieving remission, potential predictors of remission could not be statistically analyzed; however, patients with higher thyroid volume SDS at diagnosis tended to have a higher relapse rate. Adverse effects related to medication were not observed during follow-up.

Definitive treatment strategies including RAI (n=2) and total thyroidectomy (n=3) were applied in 26.3%.. All of these patients had initially received ATD. RAI was indicated in one patient who presented with marked goiter (grade III) and exophthalmos and did not achieve remission after three years of ATD. In another, RAI was chosen as she relapsed four months after discontinuation of ATD following four years of treatment. Among those who underwent total thyroidectomy, one had been using MMI for nine years, with three unsuccessful discontinuation attempts. In another one, a 14×10×10mm heterogeneous nodule with focal calcification was detected on thyroid USG four months after initiating MMI. Fine-needle aspiration biopsy revealed papillary thyroid carcinoma. She underwent total thyroidectomy with lymph node dissection and has since been followed with suppressed TSH levels under Na-levothyroxine. The remaining patient had experienced relapse after discontinuation of ATD following three years of treatment, and total thyroidectomy was performed as thyroid nodule was detected.

DISCUSSION

This study presents 19 adolescents diagnosed with GD from a single center. Consistent with the literature, the majority were female, and most of them had a family history of GD [12]. They presented with symptoms of hyperthyroidism, were diagnosed based on laboratory findings, and received ATD as first-line treatment. Median follow-up time was 13 months, and at a median of 38 months, ATD was discontinued for evaluation of remission. Remission was achieved in 15.7%. Although being at the lower end of the reported range (11–49%), this rate was comparable to those reported in other pediatric GD studies [1,2,13]. These findings supported the view that remission rates in pediatric GD are considerably lower than those reported in adults (39.5%-85%) [1].

Studies evaluating optimal timing for treatment discontinuation of ATDs report variable results. Current guidelines recommend tapering or discontinuing ATD after at least two years of maintained euthyroid state. However, these recommendations are largely based on adult studies. More recent studies in children and adolescents have shown that those using ATD

who remain euthyroid for prolonged periods may sustain remission for up to four years [1]. In 2012, Léger et al. reported that among 154 French children with GD, remission was achieved in 20%, 37%, 45%, and 49% of patients after 4, 6, 8, and 10 years of ATD, respectively [3]. Wong et al. compared patients who achieved remission with those who did not and reported that the duration of ATD treatment was significantly longer in the remission group (28 vs. 21 months; p=0.024) [1]. In another study, patients who received long-term MMI (96-120 months) were compared with those treated for a shorter period (median=22 months), and those who received long-term treatment had threefold higher remission rate [14]. These findings suggest that relatively lower remission rates observed in this study when compared with previous studies may be attributed to the relatively shorter follow-up duration [1,2,13].

Thionamides inhibit TPO enzyme blocking the oxidation and organification of iodine. The precise mechanism by which thionamides reduce TRAb and induce remission in patients with GD remains to be elucidated. Several mechanisms have been proposed. Studies have shown that hyperthyroidism itself increase TRAb production, leading to persistence and even exacerbation of autoimmunity. It was shown that by controlling thyroid autoimmunity, this vicious cycle was interrupted in patients with GD who remain euthyroid for extended periods. As a result, the likelihood of remission increased while recurrence was prevented [1]. Changes in antigen presentation or a direct immunomodulatory action of ATDs were put forward as possible mechanisms [1]. These proposed mechanisms and observations suggest that longer utilization of ATD prior to proceeding with definitive treatment options may be more appropriate for childhood GD. In line with this, the latest ETA guideline recommends maintaining ATDs for at least three years, or up to five years in patients with a lower likelihood of remission [10].

One of the objectives of this study was to determine prognostic factors for remission at diagnosis and to define clinical characteristics that may justify earlier consideration of definitive treatment in pediatric GD. However, due to limited number of patients who achieved remission, statistical analysis of these potential predictors could not be performed. It was observed that relapse rate was higher in patients with higher thyroid volume SDS at diagnosis. Our observation was consistent with previous studies. Previous studies evaluating predictive clinical features for remission or relapse concluded that younger age at diagnosis, male sex, non-Caucasian ethnicity, higher TRAb and fT4 at diagnosis, larger thyroid gland volume, and absence of other autoimmune disorders were associated with lower remission and higher relapse rates [2,3,13-16]. In another study, time required for TRAb normalization was proposed to be the strongest predictor of remission. It was reported that patients whose TRAb levels normalize within the first year have a 70% likelihood of remission, whereas if TRAb levels normalized during the second year they had 50% likelihood [2].

Remission rates with ATDs are lower in childhood. As life expectancy is longer and there are potential adverse effects of definitive treatment options, ATDs are usually the preferred first-line treatment. In this study, 26.3% of adolescents with GD who have received long-term ATD (3–9 years) but could not discontinue treatment or those with suspected malignancy had to proceed with definitive treatments of either RAI or total thyroidectomy. RAI exerts its effect by inducing thyroiditis through β-emission radiation, leading to follicular cell destruction and subsequent hypothyroidism. RAI is recommended in those who fail to achieve remission, demonstrate relapse, adverse drug reaction or poor adherence to ATD [12]. Total thyroidectomy may be considered in patients with larger thyroid gland who fail to achieve remission with ATD with severe orbitopathy. Other reasons may be the need for rapid control of hyperthyroidism, or patient preferences [12].

Thyroid USG revealed nodules in 21.1% of the patients included in the study, and fine-needle aspiration biopsy identified papillary thyroid carcinoma in one, for which total thyroidectomy was performed. Papillary thyroid carcinoma has previously been reported in children with GD. In a study by McFarland et al., 1.8% of 151 children with GD had papillary thyroid carcinoma [17]. In a meta-analysis evaluating the prevalence of papillary thyroid carcinoma among adults with GD, papillary thyroid carcinoma was detected in 22.2% with solitary thyroid nodule [18]. Tuli et al. reported a 16-year-old patient with hereditary spherocytosis and GD who underwent total thyroidectomy after

euthyroid state could not be achieved following one year of ATD. Incidentally, a 2.8-mm papillary thyroid carcinoma foci was identified in the thyroidectomy specimen [19]. Shimura et al. reported an 8-year-old with GD in whom thyroid nodule was not detected at diagnosis. Four years later, the patient developed rapidly progressive metastatic papillary thyroid carcinoma. The authors suggested that this aggressive course might be associated with low expression of *SLC5A5* in the tumor tissue, preservation of TRAb expression, and the presence of a *TFG/NTRK1* rearrangement [20]. Despite this observation of Shimura et al. of a more aggressive course, Macfarland et al. noted that when children with GD and papillary thyroid carcinoma and those with papillary thyroid carcinoma were compared, significant difference in tumor burden, extrathyroidal extension, lymph node metastasis, or prognosis were not found. They reported that incidental papillary thyroid microcarcinomas were more frequent among patients with GD [17].

Limitations

This study has several limitations. Firstly, this study was carried out in a limited number of patients with relatively short follow-up duration. Due to limited number of patients who achieved remission, statistical analysis of these potential predictors could not be performed. Secondly, due to the retrospective design, some of the important data were lost.

CONCLUSION

This single-center study highlights the clinical characteristics of adolescents with GD. ATD is proven to be an effective treatment in adolescents with GD. Although not statistically significant, larger thyroid volume at diagnosis may serve as a potential marker for predicting lower likelihood of remission hence further studies are needed to confirm this observation. Thyroid nodules in children with GD should also be carefully evaluated, as they may be associated with papillary thyroid carcinoma. Given the rarity of pediatric GD, multicenter studies with larger cohorts are warranted to identify predictive factors of remission and to better guide treatment strategies in this population.

Author contribution

Study conception and design: YU and ADB; data collection: NY; analysis and interpretation of results: YU, NY and ADB; draft manuscript preparation: YU, NY. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Atatürk Sanatoryum Training and Research Hospital ethics committee (Protocol no. 2024-BÇEK/75/08.05.2024).

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Conflict of interest

The authors declare that there is no conflict of interest.

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