

Evaluation of Clinical Characteristics and Treatment Outcomes of Graves' Disease in Children and Adolescents

Alev Aldemir Sönmez¹✉, İbrahim Mert Erbaş²✉, Sezer Acar²✉, Korcan Demir²✉, Ece Bober²✉, Ayhan Abacı²✉

¹ Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Izmir, Turkey

² Dokuz Eylül University Faculty of Medicine, Division of Pediatric Endocrinology, Izmir, Turkey

Cite as: Aldemir Sönmez A, Erbaş İM, Acar S, Demir K, Bober E, Abacı A. Evaluation of clinical characteristics and treatment outcomes of Graves' disease in children and adolescents. Trends in Pediatrics 2021;2(1):18-27.

Received: 18 January 2020

Accepted: 13 February 2021

Publication date: 30 March 2021

Keywords: Hyperthyroidism, methimazole, pediatrics, remission, relapse

Alev Aldemir Sönmez

Dokuz Eylül University Faculty of Medicine, Department of Pediatrics, Balçova Izmir - Turkey

ORCID: 0000-0002-3023-1550

✉ aldemiralev@hotmail.com

İ. M. Erbaş 0000-0001-9368-8868

S. Acar 0000-0002-0768-835X

K. Demir 0000-0002-8334-2422

E. Bober 0000-0001-8828-0892

A. Abacı 0000-0002-1812-0321

ABSTRACT

Objective: The most common cause of hyperthyroidism in childhood and adolescence is Graves' disease. In this study, we aimed to evaluate the demographic characteristics, clinical and laboratory findings, treatment processes, and remission outcomes in patients followed up with the diagnosis of Graves' disease.

Methods: Medical records of 44 patients who were diagnosed with Graves' disease in the period between 1999-2018 in our clinic, were retrospectively reviewed. Patients were included in the analysis according to risk groups (low, medium, and high) for relapses.

Results: The median age of the patients was 13.2 years (9.2-15 years) and 35 (79.5%) of them were females. The most common complaints at the first admission were palpitations (52.3%) and sweating (52.3%), and the most common physical examination finding was tachycardia (43.1%) followed by goiter (40.9%). Propylthiouracil was started in 23 (52.3%) and methimazole in 21 (47.7%) patients. In the clinical follow-up, five patients (11.4%) achieved remission while relapses occurred in none of the patients. Among the patients who did not achieve remission, total thyroidectomy or radioactive iodine treatment were applied to 10 (25.6%) and four (10.2%) patients, respectively. As for the risk groups, 10 patients (35.7%) were in the low-risk, 17 (60.7%) in the moderate-risk, and one patient (3.6%) in the high-risk group. Remission occurred in two patients (20%) in the low-risk and in three patients (17.6%) in the moderate-risk group with a median time to remission being 25 and 18 months, respectively.

Conclusion: In this study, remission rates were found to be low in pediatric Graves' disease in accordance with the literature. We showed that long-term anti-thyroid therapy can be used to increase remission rates and alternative treatment options can be preferred in patients who are non-adherent to treatment and who do not achieve remission.

INTRODUCTION

Hyperthyroidism is a metabolic disorder characterized by increased synthesis and release of thyroid hormones.¹ The most common cause of hyperthyroidism in childhood and adolescence is Graves' disease, accounting for 10-15% of cases with thyroid diseases in this age group. The incidence of pediatric Graves' disease is approximately 1/10.000. Graves' disease is rare under the age of five and the peak incidence of the disease occurs in the age range between 11-15 years. The incidence of Graves' disease is 6-8 times higher in girls.² Thyrotropin-

stimulating hormone (TSH) receptor antibody (TRAb) is generally found positive at the time of diagnosis and this finding is helpful for the diagnosis.¹

Anti-thyroid drugs (ATD), surgery, and radioactive iodine (RAI) are current treatment options in Graves' disease.³ The effectiveness of these three modes of treatment differs depending on the development of relapse and in association with emergent side effects in the short and long term. Although the ideal mode of treatment for pediatric hyperthyroidism is debatable, medical treatment is recommended as the first-line option.⁴ The indications for RAI or



surgical treatment in Graves' disease include development of relapse after adequate ATD, non-adherence to medications, and ATD-related toxicity.⁵

The aim of this study was to evaluate the demographic and clinical characteristics, laboratory findings, treatment processes, and remission outcomes in children and adolescents; who were followed up with Graves' disease in our clinic.

MATERIALS and METHODS

The medical records of 66 patients who were followed up with the diagnosis of hyperthyroidism in our pediatric endocrinology clinic in the period between 1999 and 2018, were retrospectively reviewed. Patients' gender, age, complaints at the first admission, family histories of thyroid diseases, physical examination findings, laboratory findings, results of imaging studies, treatment methods, and treatment responses were recorded. After excluding patients with incomplete medical records, the study was conducted on 44 patients.

Anthropometric measurements

Height was measured with the Harpenden stadiometer with an accuracy of 0.1 cm, and body weight was measured using a scale (SECA, Hamburg, Germany) with a sensitivity of 0.1 kg while wearing light clothing. Standard deviation (SD) scores for weight, height, and body mass index (BMI) were calculated using the online calculator designed for pediatric endocrinologists (Child Metrics)⁶, based on the reference values created for the Turkish population by Neyzi et al.⁷ The pubertal stage was determined according to Tanner.⁸

Diagnosis and descriptions

As for hormonal evaluations, the levels of serum free T3 (fT3), free T4 (fT4), and TSH at the time of diagnosis were studied via the chemiluminescent microparticle immunological assay method using a Beckman Coulter Dxl800 brand device. The reference values for thyroid hormones as fT3, fT4, and TSH were 2.5-3.9 pmol/l, 0.5-1.51 pmol/l, and 0.38-5.33 μ IU/ml, respectively. TRAb, as one of the thyroid autoantibodies, was measured via immunological assay method using an Immunotech Beckman Coulter A15728 brand device. The

reference ranges for TRAb levels for the years between 1999 and 2009 were as follows: 0-9 U/l: negative, 9-14 U/l: borderline, and >14 U/l: positive. The reference ranges for TRAb levels for the years between 2009 and 2018 were as follows: 0-0.1 U/l: negative, 0.1-1.5 U/l: borderline, and > 1.5 U/l: positive.

The diagnosis of hyperthyroidism was made in the presence of increased serum fT3 and/or fT4 levels accompanied by TSH suppression (<0.38 μ IU/ml) and clinical signs of hyperthyroidism. Patients; who had clinical and laboratory findings of hyperthyroidism (TRAb positive or negative) and who received ATD for at least six months, were considered to have Graves' disease.

Remission was defined as being in a state of clinical and biochemical euthyroidism for at least one year after the discontinuation of ATD and as the maintenance of the euthyroid state without relapses during the clinical follow-up period. Relapse was defined as the occurrence of TSH suppression accompanied by increased fT4 and/or fT3 levels and positive TRAb levels in the follow-up of previously remitted patients. Failure to achieve remission was defined as the continuation of ATD therapy, resumption of treatment due to maintenance of the euthyroid status for less than one year after discontinuation of ATD, discontinuation of ATD but the maintenance of the euthyroid status for less than a year in the study period/inadequate follow-up records, and in whom received RAI or undergone surgery.

The final clinical conditions of the patients were examined by classifying them into three groups based on the duration of ATD therapy as less than 1 year, for 1-2 years, and more than 2 years, and on the outcomes as achieving remission, the occurrence of relapses, and failure to achieve remission. In addition; according to the study by Kaguelidou et al.⁹, the patients were divided into risk groups based on the clinical and laboratory findings, demographic characteristics at diagnosis, and the estimated duration of ATD treatment. The patients were scored according to five criteria including ethnicity, age at diagnosis, the fT4 level at diagnosis, the TRAb level at diagnosis, and the duration of treatment. Based on the scores; the patients were classified as Group

A (low-risk group, 0-3 points), Group B (moderate-risk group, 4-7 points), and Group C (high-risk group, 8-11 points). Then, remission and relapse states were examined by the groups.

Ethics

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee (Ethics approval number: 2017/18-13), and an informed written consent form was not obtained due to the retrospective nature of the study.

Statistical Analysis

Statistical analyses were performed using the SPSS 24.0 software (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp.). The homogeneous distribution of the data was evaluated by the Kolmogorov-Smirnov test. For descriptive statistics, numbers and percentages were used for categorical variables; mean±standard deviation for numerical data conforming to the normal distribution parameters, and the median values (25p-75p) were used for numerical data not conforming to the normal distribution parameters.

RESULTS

The median age of the patients was 13.2 years (9.2-15 years) and 35 (79.5%) of them were

females. Twenty-three of the patients (52.3%) were pubertal and the frequency of thyroid disease in the family history was 75%. Weight, height, and BMI SD scores were -0.17 [(-1.2)-(+1.2)], 0.17 [(-1.2)-(+1.2)], and -0.24 [(-1.3)-(+0.5)], respectively. The most common complaints were palpitations and sweating, and the most common physical examination findings were tachycardia and goiter. The complaints and clinical findings of the patients are summarized in Table 1. Laboratory and imaging findings of the patients at the time of diagnosis are presented in Table 2.

Propylthiouracil (PTU) and methimazole (MTZ) treatments were initiated in 23 (52.3%) and 21 (47.7%) patients, respectively. Propranolol was given additionally in 33 patients (75%) due to concurrent tachycardia. L-thyroxine was added (block and replace treatment model) to the treatment in 30 (68.1%) patients due to high TSH levels detected during the clinical follow-up. Side effects associated with ATD were 4-5 times elevated transaminase levels in two (4.5%) and leukopenia in one patient (2.3%).

The median duration of the follow-up of the patients was 32 months (22-55 months). Five patients (11.4%) achieved remission during the clinical follow-up period and the median time to remission was 22 months (11.0-26.5 months). No relapses occurred in any of the remitted patients during the follow-up.

Table 1. The complaints and clinical findings of the patients at the time of diagnosis (n=44)

Complaints [n (%)]		Clinical findings [n (%)]	
Palpitations	23 (52.3)	Tachycardia	19 (43.1)
Sweating	23 (52.3)	Goiter	18 (40.9)
Weight loss	17 (38.6)	Hypertension	9 (20.5)
Tremor	15 (34.1)	Exophthalmus	7 (15.9)
Irritability	13 (29.5)	Pre-hypertension	1 (2.3)

Table 2. Laboratory and imaging results of the patients at the time of diagnosis (n=44)

Laboratory results		Thyroid ultrasonography [n (%)]	
TRAb positive [n (%)]	37 (84)	Heterogeneity	20 (45.4)
TSH (μIU/mL)	0.01 (0.0045-0.017)	Hypoechoogenicity	15 (34.1)
ft3 (ng/dL)	13.0 (7.9-21.3)	Pseudonodular pattern	8 (18.2)
ft4 (ng/dL)	3.8 (2.9-5.6)	Diffuse hyperplasia	5 (11.4)
		Normal	4 (9.1)
		Nodule	3 (6.8)

Data are given as median values (25p-75p).

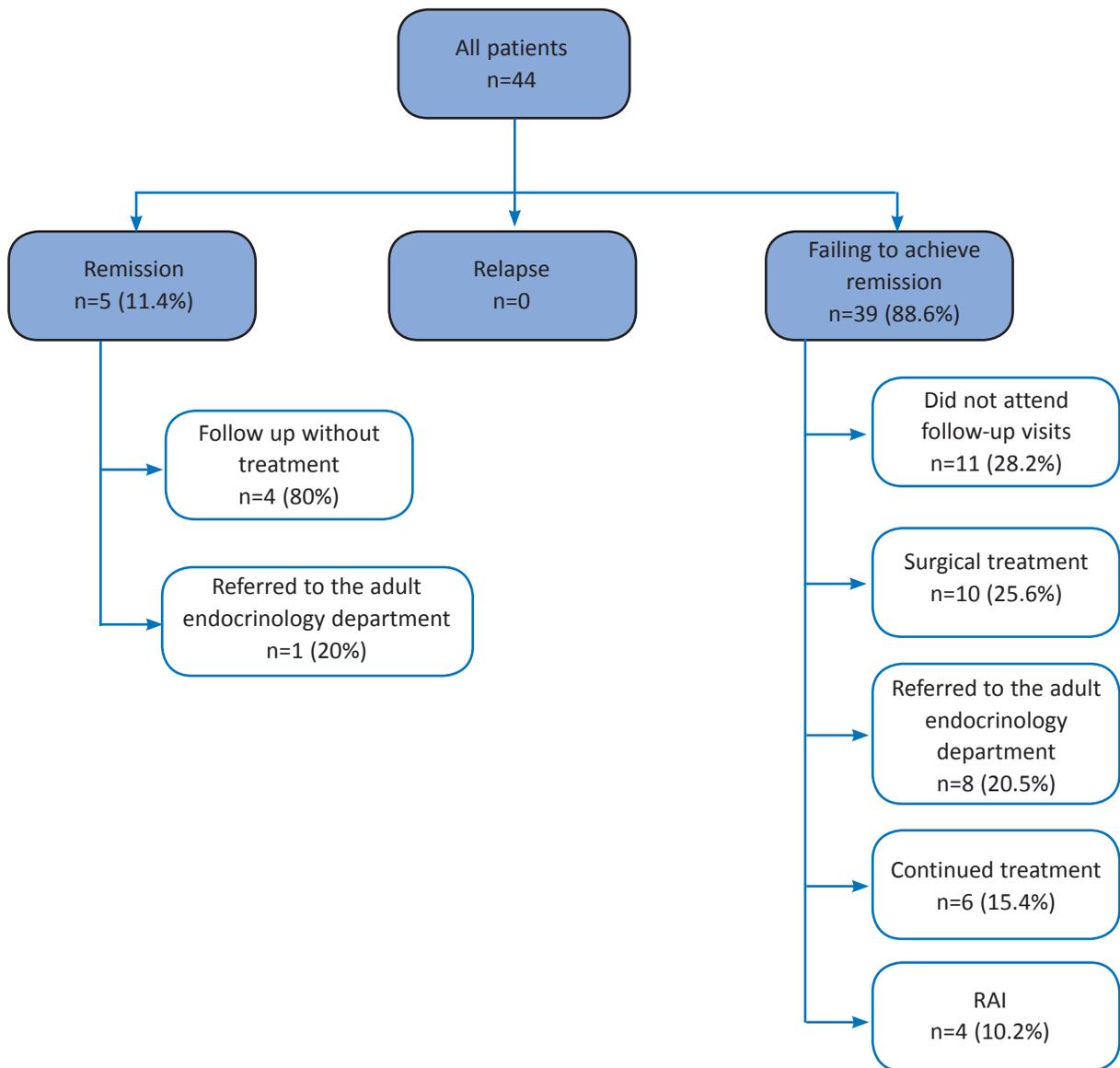


Figure 1. Final status of the patients when classified according to the remission and relapse rates (n=44)

The final status of the patients who failed to achieve remission are shown in Figure 1.

When the final status of the patients was classified according to the duration of medical treatment, two out of three patients who received treatment for less than one year and two out of 25 patients who received treatment for more than two years were found to be in remission (Figure 2).

When 28 patients with no missing data were evaluated by the risk groups; it was found that 10 patients (35.7%) were in the low-risk group, 17

patients (60.7%) in the moderate-risk group, and one patient (3.6%) in the high-risk group. In the low-risk group, two patients (20%) achieved remission; the median time to remission was 25 months, and none of the patients relapsed. In the moderate-risk group, three patients achieved remission (17.6%); the median time to remission was 18 months, and none of the patients relapsed. There was only one patient in the high-risk group; however, the final status of the patient could not be assessed because this patient did not attend follow-up visits (Table 3).

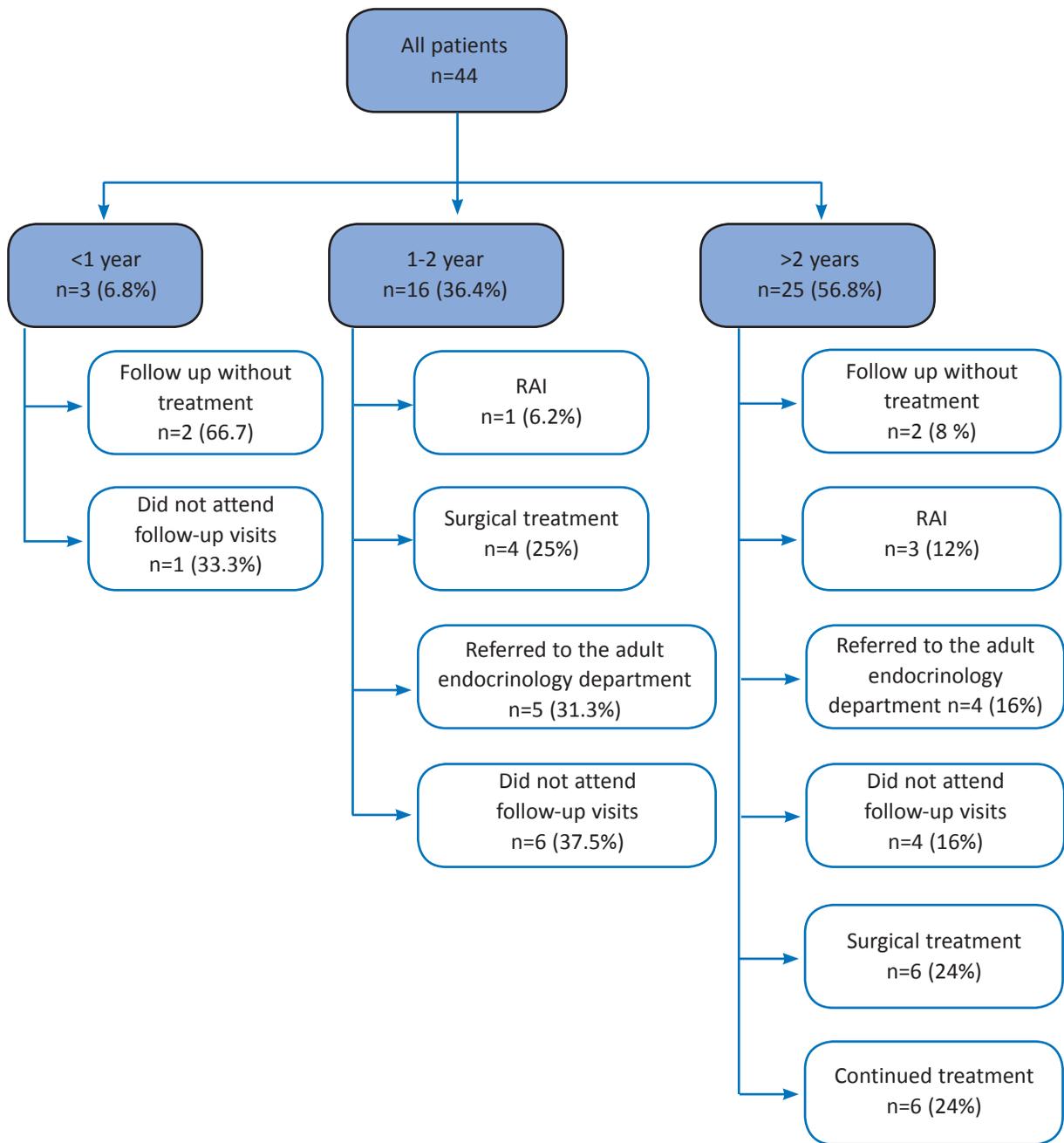


Figure 2. Final status of the patients when classified according to the duration of medical treatment (n=44)

DISCUSSION

In this study, we presented children and adolescents with Graves' disease with a female/male ratio of 4/1. The majority (52.3%) of our patients were pubertal at admission and the median age at diagnosis was 13.2 years (9.2-15.0). More than half of the patients presented with palpitations. These results were all in

accordance with the previous studies.^{12,10-18} It has been reported that Graves' ophthalmopathy is an inflammatory disease of the orbital tissues with prevalence rates ranging from 17% to 86% in children and adolescents with Graves' disease.¹⁹⁻²² In recent studies from our country, the incidence of ophthalmopathy has been reported in the range of 10-24%.^{12,13} We found that ophthalmopathy was

Table 3. Risk groups of the patients and clinical follow-up results (n=28)

Risk group	n (%)	Clinical follow-up results	n (%)
Low	10 (35.7)	Remission (%) Relapse (%) Median time to remission (month)	2 (20) - 25
Moderate	17 (60.7)	Remission (%) Relapse (%) Median time to remission (month)	3 (17.6) 0 18
High	1 (3.6)	Remission (%) Relapse (%) Median time to remission (m)	- - -

present in approximately one-sixth (15.9%) of the patients, as reported in the literature. Since the diagnosis of ophthalmopathy is usually based on the physical examination, the varying frequencies in the literature may be associated with individual descriptions of clinicians.

TRAb is specific for Graves' disease. TRAb positivity is detected in more than 95% of untreated newly diagnosed patients with Graves' disease.²³ Some studies demonstrated the frequency of TRAb positivity in a range of 68-92%.^{12,13} The prognostic value of pretreatment TRAb levels has been shown in recent studies.^{24,25} In the study conducted by Kaguelidou et al.²⁶, it was found that TRAb levels in children with a diagnosis of Graves' disease were significantly higher in five-year-old or younger patients at the time of diagnosis compared to those older than five years of age, and in patients with severe baseline symptoms compared to those without. In our study, TRAb was positive in 84% of the patients. Although the cause of hyperthyroidism in Graves' disease is antibodies that stimulate the thyroid gland, the TRAb levels were reportedly very low or undetectable in a small number of patients.²⁷ Theoretically, TRAb should not be negative in Graves' disease but the low sensitivity of laboratory methods may be responsible for false-negative results.

Treatment options for Graves' disease in children include ATD, RAI, and surgery. Each of these treatment approaches is associated with specific risks.^{13,17,28} ATD is the first-line treatment option preferred in children in most countries.²⁹ However, ATD is associated with a variety of minor and major adverse

effects. Fumarola et al.³⁰ associated the side effects of MTZ therapy with the dose of the medication but they reported that the adverse effects of PTU treatment were independent of dosage. Rivkees et al.³¹ showed liver failure due to PTU in 14 children. Hepatic failure due to PTU is rapidly progressive and usually irreversible. In 2009, the United States Food and Drug Administration (FDA) recommended that PTU should not be used in children.^{32,33} In another study, MTZ-associated adverse effects were found in 19% of the patients. The most common side effects were reported as skin rash and urticaria, while neutropenia and lymphopenia were found in low frequencies as 1-2%.³⁴ Rabon et al.¹¹ demonstrated that 21% of patients using MTZ developed adverse effects, including skin rash, arthralgia, increased transaminase levels, and neutropenia in order of decreasing frequency. Bayramoğlu et al.¹⁴ reported that 22.9% of the patients using MTZ had side effects. They reported that 4.1% of the patients had a severe skin reaction that caused the discontinuation of MTZ therapy, 10.4% had increased levels of transaminases, and 8.2% had neutropenia.¹⁴ Tunç et al.¹³ reported that ATD-associated side effects occurred in two patients (4.4%) receiving PTU. Of these patients, one had increased levels of transaminases and the other developed skin rash.¹³ In this study, we found that ATD was administered to all Graves' disease patients as the first-line treatment. As for the physicians' preferences for selecting an ATD, it was observed that treatment with PTU was started in more than half of the patients. We interpreted that this finding has resulted from reviewing patient data of previous years for the study but such adverse effect studies have become

more common recently. Adverse effects observed in our study were slight increases in transaminase levels in two and mild leukopenia in one patient. One patient with leukopenia and one patient with increased transaminase levels were both using PTU; which was replaced by MTZ. The other patient with increased transaminase levels was using MTZ. Although antithyroid therapy with MTZ was considered safe in pediatric patients, these patients should be carefully monitored for the potential adverse effects.

When remission cannot be achieved via medical treatment or when medication-associated serious side effects develop, other alternative treatment methods, which are RAI and surgery, should be considered. The American Thyroid Association recommends that radical treatment options should be considered in cases where remission cannot be achieved after two years of ATD treatment in children.³⁵ Gastaldi et al.³⁶ reported that 55% of the patients failed to achieve remission continued ATD treatment for more than two years, 25% underwent surgery, and 19% underwent RAI. Esen et al.¹² showed that 14.9% and 12.8% of the patients; who developed relapses after the discontinuation of ATD, underwent RAI and surgery, respectively. Another study reported that 47% of the patients receiving ATD developed relapses after drug discontinuation and 19% and 9.5% of these patients underwent surgery and RAI, respectively.¹³ In this study; when the patients were examined in three groups according to the duration of ATD therapy, it was found that surgery (22.7%) was preferred over RAI (9.1%) as a second-line therapy option in non-remitters consisting of patients who received ATD for 1-2 years (n=16:36.4%) and more than two years (n=25:56.8%).

There is no consensus on the optimal duration of ATD treatment to ensure long-term remission in children. Tunç et al.¹³ emphasized that radical treatment can be delayed even if remission is not achieved after two years of ATD therapy. They reported remission and relapse rates as 53.4% and 46%, respectively. They also noted that the total duration of ATD treatment is longer in remitted patients (42.14±14.35 months) which was an important predictor for the likelihood of long-term

remission.¹³ Esen et al.¹² found the cumulative remission rate as 17.6% and the median duration of treatment as 22.8 months (0.3-127) in patients who received ATD as the first-line therapy. In our study, the remission rate was 11.5% and none of the patients developed a relapse. The median length of ATD therapy before remission was 22 months (11.0-26.5). In a multicenter prospective study by Kaguelidou et al.²⁶; 154 children diagnosed with Graves' disease were followed up for the development of relapses during the 1st and 2nd year after 24±3 months of MTZ treatment and it was reported that the relapse rates were 59% and 68% in the first and second years after discontinuation of ATD, respectively. The point to be noted here is the different definitions of remission and relapse among studies which can explain the different remission and relapse rates in our study and in other studies in the literature.

There are several studies investigating the predictive factors for remission or relapses and examining the necessity of early-stage radical treatment. Kaguelidou et al.⁹, classified children with Graves' disease into prognostic risk groups based on the clinical and laboratory findings, demographic characteristics, and the estimated duration of ATD therapy. Patients were categorized into three groups as Group A (low risk), Group B (moderate risk), and Group C (high risk). The relapse rates in the two years after discontinuation of medical therapy were 46%, 77%, and 98% in Groups A, B, and C, respectively.⁹ Leger et al.³⁷ reported that a total of two years of ATD therapy in children was associated with increased remission rates. Ohye et al.³⁸ reported a relationship between cumulative remission rates and the duration of treatment. Bayramoğlu et al.¹⁴ reported remission in 24% of the patients who received treatment for more than two years; they reported that lower ft4 values and longer durations of MTZ therapy were associated with remission, but male gender was a factor for increased risk of relapses. Mussa et al.³⁹ showed that low TRAb levels at the diagnosis and throughout ATD therapy were associated with remission. Gestaldi et al.³⁶ suggested that a high TRAb value was a predictive factor for the development of relapses. In this study, we divided patients into risk groups according to the criteria used in the study

by Kaguelidou et al.⁹ and found remission in two patients (20%) in the low-risk group and three patients (17.6%) in the moderate-risk group. Since the patient in the high-risk group did not attend follow-up visits, no conclusions could be drawn about the final status of the patient. Also, none of our patients developed relapses. We found that remission rates were lower in pediatric Graves' patients but the relapse rate was lower in remitted patients. The low relapse rate in our patients was thought to be associated with the heterogeneous follow-up periods of our patients receiving ATD treatment. Also, a two-year follow-up period of remitted patients might be considered as a cause of insufficient data collection. However, the median lengths of ATD use before remission were 25 and 18 months in patients in the low and high-risk groups, respectively. Consistent with the literature data, this finding can be interpreted as indicating a low risk for relapse in patients who received long-term treatment with ATD.

CONCLUSION

In conclusion, we found that children and adolescents with Graves' disease had low remission rates similar to the previous reports and that medical treatment-associated complications were low and transient. Besides, long-term ATD therapy can be used to increase remission rates and that alternative treatment options can be preferred in patients, who are non-adherent to treatment and who do not achieve remission.

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Local Ethics Committee (Ethics approval number: 2017/18-13).

Conflict of Interest: The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding: The authors received no financial support for the research, authorship, and/or publication of this article.

Informed Consent: An informed written consent form was not obtained due to the retrospective nature of the study.

REFERENCES

1. Abacı A, Acar S. Diagnosis and treatment of hyperthyroidism in children. In: Haspolat YK (eds). *Tiroid Diseases in Children and Adolescents*. 1st. ed: Orient Publish 2019. p. 227-48.
2. Rivkees SA. Pediatric Graves' disease: Controversies in management. *Horm Res Paediatr*. 2010; 74(5):305-11. <https://doi.org/10.1159/000320028>
3. Rivkees SA. The treatment of Graves' disease in children. *J Pediatr Endocrinol Metab*. 2006;19(9):1095-111. <https://doi.org/10.1515/JPEM.2006.19.9.1095>
4. Committee on Pharmaceutical Affairs, Japanese Society for Pediatric Endocrinology, and the Pediatric Thyroid Disease Committee, Japan Thyroid Association (Taskforce for the Revision of the Guidelines for the Treatment of Childhood-Onset Graves' Disease), Minamitani K, Sato H, Ohye H, Harada S, Arisaka O. Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016. *Clin Pediatr Endocrinol*. 2017;26(2):29-62. <https://doi.org/10.1297/cpe.26.29>
5. Levy WJ, Schumacher OP, Gupta M. Treatment of childhood Graves' disease. *Cleve Clin J Med*. 1988;55:373-82. <https://doi.org/10.3949/ccjm.55.4.373>
6. Demir K, Konakçı E, Özkaya G, et al. New features for Child Metrics: Further growth references and blood pressure calculations. *J Clin Res Pediatr Endocrinol*. 2020;12(2):125-9. <https://doi.org/10.4274/jcrpe.galenos.2019.2019.0127>
7. Neyzi O, Bundak R, Gökçay G, et al. Reference values for weight, height, head circumference, and body mass index in Turkish children. *J Clin Res Pediatr Endocrinol* 2015; 7(4):280-93. <https://doi.org/10.4274/jcrpe.2183>
8. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Arch Dis Child*. 1976;51:170-9. <https://doi.org/10.1136/adc.51.3.170>
9. Kaguelidou F, Carel JC, Léger J. Graves' disease in childhood: Advances in management with antithyroid drug therapy. *Horm Res Paediatr*. 2009;71(6):310-7. <https://doi.org/10.1159/000223414>
10. Williamson S, Greene SA. Incidence of thyrotoxicosis in childhood: a national population based study in the UK and Ireland. *Clin Endocrinol (Oxf)*. 2010;72(3):358-63. <https://doi.org/10.1111/j.1365-2265.2009.03717.x>
11. Rabon S, Burton AM, White PC. Graves' disease in children: Long-term outcomes of medical therapy. *Clin Endocrinol (Oxf)*. 2016;85(4):632-5. <https://doi.org/10.1111/cen.13099>
12. Esen İ, Bayramoğlu E, Yıldız M, et al. Management of thyrotoxicosis in children and adolescents: A Turkish Multi-center Experience. *J Clin Res Pediatr Endocrinol*. 2019;11(2):164-72.

- <https://doi.org/10.4274/jcrpe.galenos.2018.2018.0210>
13. Tunç S, Köprülü Ö, Ortaç H, et al. Long-term monitoring of Graves' disease in children and adolescents: a single-center experience. *Turk J Med Sci.* 2019;49(2):464-71.
<https://doi.org/10.3906/sag-1804-177>
 14. Bayramoğlu E, Elmaogulları S, Sagsak E, et al. Evaluation of long-term follow-up and methimazole therapy outcomes of pediatric Graves' disease: A single-center experience. *J Pediatr Endocrinol Metab.* 2019;32(4):341-6.
<https://doi.org/10.1515/jpem-2018-0495>
 15. Franchi SL. Hyperthyroidism. In: B. S. Drs. Robert Kliegman, Richard Behrman, Drs. Joseph St. Geme and Nina Schor editors. *Nelson textbook of pediatrics.* 19 ed. 2011. pp. 1909-13.
 16. Weetman AP. Graves' disease. *N Engl J Med.* 2000; 343(17):1236-48.
<https://doi.org/10.1056/NEJM200010263431707>
 17. Bauer AJ. Approach to the pediatric patient with Graves' disease: when is definitive therapy warranted? *J Clin Endocrinol Metab.* 2011;96(3):580-8.
<https://doi.org/10.1210/jc.2010-0898>
 18. Lazar L, Kalter-Leibovici O, Pertzalan A, et al. Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. *J Clin Endocrinol Metab.* 2000;85(10):3678-82.
<https://doi.org/10.1210/jcem.85.10.6922>
 19. Gjirkopulli A, Tomori S, Kollçaku L, et al. Graves' disease in Albanian children. *Curr Health Sci J.* 2014;40(3): 190-4.
 20. Szczapa-Jagustyn J, Gotz-Więckowska A, Kociecki J. An update on thyroid-associated ophthalmopathy in children and adolescents. *J Pediatr Endocrinol Metab.* 2016;29(10):1115-22.
<https://doi.org/10.1515/jpem-2016-0122>
 21. Azizi F, Amouzegar A. Management of thyrotoxicosis in children and adolescents: 35 years' experience in 304 patients. *J Pediatr Endocrinol Metab.* 2018;31(2):159-65.
<https://doi.org/10.1515/jpem-2017-0394>
 22. Lee JH, Park SH, Koh DG, et al. Thyroid peroxidase antibody positivity and triiodothyronine levels are associated with pediatric Graves' ophthalmopathy. *World J Pediatr.* 2014;10(2):155-9.
<https://doi.org/10.1007/s12519-014-0476-y>
 23. Zöphel K, Roggenbuck D, Schott M. Clinical review about TRAb assay's history. *Autoimmun Rev.* 2010;9(10):695-700.
<https://doi.org/10.1016/j.autrev.2010.05.021>
 24. Quadbeck B, Hoermann R, Roggenbuck U, et al. Basedow Study Group. Sensitive thyrotropin and thyrotropin-receptor antibody determinations one month after discontinuation of antithyroid drug treatment as predictors of relapse in Graves' disease. *Thyroid.* 2005;15(9):1047-54.
<https://doi.org/10.1089/thy.2005.15.1047>
 25. Okamoto Y, Tanigawa S, Ishikawa K, et al. TSH receptor antibody measurements and prediction of remission in Graves' disease patients treated with minimum maintenance doses of antithyroid drugs. *Endocr J.* 2006;53(4):467-72.
<https://doi.org/10.1507/endocrj.K05-121>
 26. Kaguelidou F, Alberti C, Castanet M, et al. French Childhood Graves' Disease Study Group. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. *J Clin Endocrinol Metab.* 2008;93(10):3817-26.
<https://doi.org/10.1210/jc.2008-0842>
 27. Prummel MF, Laurberg P. Interferon- α and autoimmune thyroid disease. *Thyroid.* 2003;13(6):547-51.
<https://doi.org/10.1089/105072503322238809>
 28. Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association Guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. *Thyroid.* 2016;26(10):1343-421.
<https://doi.org/10.1089/thy.2016.0229>
 29. Glaser NS, Styne DM. Predicting the likelihood of remission in children with Graves' disease: A prospective, multicenter study. *Pediatrics.* 2008;121(3):e481-e8.
<https://doi.org/10.1542/peds.2007-1535>
 30. Fumarola A, Di Fiore A, Dainelli M, et al. Medical treatment of hyperthyroidism: state of the art. *Exp Clin Endocrinol Diabetes.* 2010;118(10):678-84.
<https://doi.org/10.1055/s-0030-1253420>
 31. Rivkees SA, Mattison DR. Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of Use. *Int J Pediatr Endocrinol.* 2009; 2009:132041.
<https://doi.org/10.1186/1687-9856-2009-132041>
 32. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. *J Clin Endocrinol Metab.* 2010;95(7):3260-7.
<https://doi.org/10.1210/jc.2009-2546>
 33. Rivkees SA. 63 years and 715 days to the "boxed warning": unmasking of the propylthiouracil problem. *Int J Pediatr Endocrinol.* 2010;2010:658267.
<https://doi.org/10.1186/1687-9856-2010-658267>
 34. Rivkees SA, Stephenson K, Dinauer C. Adverse events associated with methimazole therapy of Graves' disease in children. *Int J Pediatr Endocrinol.* 2010;2010(1):176970.
<https://doi.org/10.1186/1687-9856-2010-176970>
 35. Rebecca SB, Henry BB, David SC, et al. Hyperthyroidism and other causes of thyrotoxicosis: Management guidelines of the american thyroid association and american association of clinical endocrinologists. *Thyroid.* 2011;21(6):593-646.
<https://doi.org/10.1089/thy.2010.0417>
 36. Gastaldi R, Poggi E, Mussa A, et al. Graves' disease in children: thyroid-stimulating hormone receptor antibodies as remission markers. *J Pediatr.* 2014;164(5):1189-94.
<https://doi.org/10.1016/j.jpeds.2013.12.047>
 37. Léger J, Gelwane G, Kaguelidou F, et al. French

- Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. *J Clin Endocrinol Metab.* 2012;97(1):110-9.
<https://doi.org/10.1210/jc.2011-1944>
38. Ohye H, Minagawa A, Noh JY, et al. Antithyroid drug treatment for Graves' disease in children: A long-term retrospective study at a single institution. *Thyroid.* 2014;24(2):200-7.
<https://doi.org/10.1089/thy.2012.0612>
39. Mussa GC, Corrias A, Silvestro L, et al. Factors at onset predictive of lasting remission in pediatric patients with Graves' disease followed for at least three years. *J Pediatr Endocrinol Metab.* 1999;12(4):537-41.
<https://doi.org/10.1515/JPEM.1999.12.4.537>