Revista Portuguesa
de Endocrinologia, Diabetes e Metabolismo

www.spedmjournal.com

Artigo Original

Graves Disease: 18 Years in a Pediatric Endocrinology Unit

Fábia Carvalho [a,*], Sílvia Paredes [b], Maria Miguel de Sá Gomes [c], Ana Sofia Martins [c], Olinda Marques [b], Ana Antunes [c]

[a] Departement of Pediatrics / Hospital de Braga, Braga, Portugal
[b] Departement of Endocrinology / Hospital de Braga, Braga, Portugal
[c] Pediatric Endrocrinology Unit of Pediatric Departement / Hospital de Braga, Braga, Portugal

INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ Recebido: 2019-07-06
Accepted/Aceite: 2024-08-12
Publicado / Published: 2024-09-13

Keywords:
Child;
Graves Disease/diagnosis;
Graves Disease/drug therapy.

A B S T R A C T

Introduction: Graves' disease (GD) is the first cause of hyperthyroidism in children. Choosing best treatment is challenging.
Our objective was to report the experience of a Pediatric Endocrinology Unit from the past 18 years in a Tertiary Hospital.
Methods: Retrospective study of GD patients diagnosed from January/2000 to April 2018. Results are expressed as mean and standard-deviation, *p*-values <0.05 considered significant.
Results: We found 21 patients, 19 girls, 38.0% diagnosed in the last two years. At diagnosis, mean age was 11.94±3.50 years, 6 patients with ophthalmopathy and 6 were pre-pubertal. Five patients presented family history of thyroid disease. All patients received anty-thyroid drugs (ATD) as first treatment.
Mean time since diagnosis until thyroid stimulating hormone (TSH) normalization was higher for propylthiouracil (6.50±0.71 months [6.00-7.00]) versus methimazole (4.39±2.94 months [0.81-10.00]) - *p*=0.049. No adverse effects were reported with methimazole, one patient treated with propylthiouracil developed hepatitis.
Mean treatment duration was: PTU 40.60±35.54 and MMI 28.90±13.20 months; *p*=0.282; remission rate was 23.80%, similar for both ATD (*p*=0.643) and relapse rate was 25.,00%. After TSH normalization, ATD maintenance mean time was: PTU 20.50±2.10 and MMI 24.51±14.00 months - *p*=0.323. Definitive treatment was used in 8 patients, RAI in 6; one patient needed a second dose and there were no adverse reactions. After surgery, one patient developed persistent hypoparathyroidism.
Conclusion: Despite a rapid achievement of euthyroidism, treatment duration was longer than reviewed in literature and only 23.80% of patients entered remission. Surgery and RAI were used as second line treatment options, with high rate of success and with only one reported case of adverse effects.

Palavras-chave:
Criança;
Doença de Graves/diagnóstico;
Doença de Graves/tratamento farmacológico.

Doença de Graves na Pediatria: Casuística dos Últimos 18 Anos numa Unidade de Endocrinologia Pediátrica

R E S U M O

Introdução: A doença de Graves (DG) é a principal causa de hipertiroidismo em idade pediátrica. A escolha do tratamento mais adequado é ainda um desafio.
O presente estudo pretende avaliar a experiência dos últimos 18 anos de uma Unidade de Endocrinologia Pediátrica no tratamento e seguimento dos doentes pediátricos com DG.
Métodos: Estudo retrospetivo dos doentes diagnosticados com DG entre janeiro de 2000 e abril de 2018. As variáveis em estudo foram analisadas estatisticamente e os resultados expressos em média, percentagens e desvio-padrão. O nível de significância estatística definido foi <0,05.
Resultados: Dos 21 doentes estudados, 19 eram do sexo feminino e 38,00% foram diagnosticados

* Autor Correspondente / Corresponding Author.
E-Mail: fsgc_carvalho@hotmail.com (Fábia Susana Ginja de Carvalho)
Departement of Pediatrics, Hospital de Braga,
R. das Sete Fontes, 4710-243 Braga, Portugal

https://doi.org/10.26497/ao190025

nos últimos dois anos. A idade média ao diagnóstico foi 11,94±3,50 anos, 6 pacientes apresentavam oftalmopatia e 6 eram pré-púberes. Cinco pacientes tinham história familiar de patologia tiroideia. Todos foram medicados com anti-tiroideus (ATD) como tratamento de primeira linha.

O tempo médio desde o diagnóstico até à normalização da TSH foi superior para o propiltiouracilo (6,50±0,71 meses (6-7) versus metimazole 4,39±2,94 meses (0,81-10,0) - *p*=0,049). Não se registaram efeitos adversos com o metimazole, um paciente tratado com propiltiouracilo desenvolveu um quadro de hepatite.

A duração média do tratamento foi: propiltiouracilo 40,60±35,54 meses e metimazole 28,90±13,20 meses, *p*=0,282; a taxa de remissão foi 23,80%, semelhantes para ambos os fármacos (*p*=0,643) e a taxa recaída foi de 25,00%.

Após normalização da TSH, o tempo médio de manutenção dos ATD foi: propiltiouracilo 20,50±2,10 e metimazole 24,51±14,00 meses - *p*=0,323. Oito pacientes foram submetidos a tratamento definitivo, 6 deles a iodo; um paciente submetido a iodo necessitou de segunda dose, sem efeitos adversos. Após cirurgia, um paciente desenvolveu hipoparatiroidismo persistente.

Conclusão: Apesar de rapidamente se atingir o eutiroidismo, a duração de tratamento é superior ao encontrado na literatura e apenas 23,80% dos pacientes entraram em remissão. A terapêutica definitiva, utilizada como tratamento de segunda linha, apresentou uma elevada taxa de sucesso sem efeitos adversos com apenas um efeito adverso reportado.

Introduction

Graves' disease (GD) is the major cause of hyperthyroidism in children and adolescents with a reported incidence of 0.1 per 100 000 person/year in young children and 3 per 100 000 person/year during puberty (peak age of diagnosis between 11-15 years), with a female-to-male predominance (5-10:1).[1–4] In pediatric age the main clinical features associated with untreated or partially treated thyrotoxicosis are goiter, tachycardia, nervousness, hypertension, tremor, weight loss despite increased appetite, hyperactivity, irregular menses, ophthalmopathy, heat intolerance and diarrhea.[2,5–7]

Thyrotropin receptor stimulating antibodies (TRAbs) play an important role in GD's physiopathology by stimulation of the TSH receptor with consequent increase in thyroid hormone production and release and thyroid tissue growth.[2,7]

The treatment of pediatric patients with GD is still a matter of controversy and a particular challenge in children under 5 years. In fact, the risks after radioactive iodine (RAI) and post-surgical complications are thought to be higher in those children but progressively declining when used in advanced ages.[2,4] From all therapeutic options available such as anti-thyroid drugs (ATD), RAI and thyroidectomy, it is somehow consensual that all children should start treatment with ATD, unless there is some contraindication.[2,3,8–10] Since 2010, methimazole (MMI) is the only ATD approved as first line choice in childhood, since FDA has contraindicated propylthiouracil (PTU) for the high risk of PTU-induced severe hepatitis.[2,3,11] If remission is not achieved after a course of therapy with ATDs, then RAI or surgery should be considered. Alternatively, MMI therapy may be continued for long term or until the child is considered old enough for surgery or RAI.[2,3,10] Considering RAI therapy, it is recommended that it should be administered in a single dose to render the patient hypothyroid. Poor remission rates have been described with lower doses which are also associated with higher risk of thyroid neoplasia. Recommended doses are usually >5.55 MBq/g and in large glands (50–80 g) 7.40–11.10 MBq/g. Before RAI administration thyroid volume should be evaluated by scintigraphy or ultrasonography.[2,12,13]

Another controversial issue of GD's treatment in pediatric age is duration of ATD. Remission rates are lower (15%-30% vs 40%-60% in adults) despite more prolonged treatments (over 2 years) and relapse rates can be as high as 70%.[1,3,10,14] Recent studies have been focusing on finding predictive factors that can correlate with a greater likelihood of remission. An older age, a greater body mass index (BMI) at diagnosis, a smaller goiter size, a greater initial dosage, lower levels of TRAbs and prolonged drug treatment have been identified as positive predictive factors of remission.[1,9,15]

The purpose of the present descriptive study was to evaluate the long-term treatment outcome of GD patients followed in a Tertiary Hospital Pediatric Endocrinology Unit in the past 18 years.

Material and Methods

Between January 2000 and April 2018, 25 children and adolescents with GD were diagnosed in the Pediatric Endocrinology Unit of Hospital de Braga. All patients were younger than 18 years, with at least 6 months follow-up, independent of time of diagnosis. Two patients were excluded because they have lost follow-up and another 2 patients because they have not accomplished minimum follow-up time.

For the remaining 21 patients, a detailed personal history was documented including: gender, age, past medical history, age at diagnosis, pubertal stage at diagnosis, age at discharge and total follow-up time, as well as family medical history.

Anthropometric data (weight, height and BMI) before and after each treatment course was also recorded.

Measurements

Thyroid stimulating hormone (TSH), serum free T4 (FT4) and total T3 (T3) and TRAbs were registered at diagnosis and after each treatment adjustment. Serum FT4 and T3 were measured by chemiluminescence technique, TSH by immunochemiluminometric assay and TRAbs with immunoenzimatic assay.

Our lab reference ranges of serum parameters for euthyroid subjects used were (16): TSH in prepubertal children 0.60-5.50 µU/mL, in pubertal children 0.50-4.80 µU/mL; T3 2.00-6.00 pg/mL; FT4 in prepubertal children 5.50-12.80 µg/dL, in pubertal children 4.90-13.00 µg/dL; TRAbs negative <1 U/L, equivocal 1.10-1.50 U/L and positive >1.50 U/L.

Thyroid volume assessment was performed by ultrasonography and compared to reference values obtained in normal children. The formula used to obtain volume was: volume of each lobe (mL) = anteroposterior diameter (cm) x mediolateral diameter (cm) x craniocaudal diameter (cm) x 0.479, and both lobe volumes were summed.[17]

Anti-Thyroid Drug Treatment

About ATD treatment the authors included: first drug used, initial dosage, drug adverse effects, time since the initiation of treatment until normalization of T3, FT4 and TSH; total duration of ATD treatment, remission rate, disease-free time and disease`s relapse.

Remission and Relapse

Those terms were defined according to most published series.[2,14] Thus, "Remission" refers to disease-free time, without therapy, for 12 or more months and "Relapse" states to recurrence of disease after 12 months of ATD withdrawal.

Definitive Treatment

The authors reported the number of patients that were selected for definitive treatment, type of treatment (RAI or surgery), associated acute and chronic complications, including hypothyroidism with RAI. Individual RAI dose and thyroid volume were estimated from scintigraphy according to Allen's formula.[12]

Statistical Analysis

Results are expressed as numerical values (%) and mean±standard deviation (SD). Baseline and outcome variables were compared using Student's t-test for continuous variables with normal distribution, Mann-Whitney test for qualitative variables without normal distribution and x^2-test for categorical variables, with *p*-values <0.05 being considered significant.

The data collection was conducted according to the Hospital's Ethical Committee proceedings and the Declaration of Helsinki.

Results

Patient Characteristics

Twenty one patients were included, 19 female and 2 male (9.5:1 ratio), with a mean age at diagnosis of 11.90±3.50 years (4.00-16.00). The youngest patient was diagnosed at 4 years of age. The first diagnosis occurred in 2001 and the latest one was included in October 2017. The authors reported an increase in the number of diagnosis since 2010, with 38.00% of patients included in the last two years (Fig. 1). Six patients were prepubertal (28.06%) and 15 (71.40%) were pubertal at diagnosis.

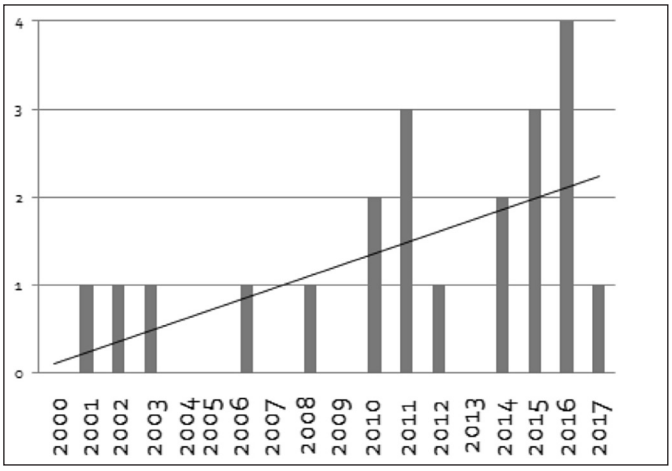

Figure 1. Number of diagnosis of GD in each year since January 2000 until April 2018.

The line represents the increasing tendency in the number of diagnosis through the years.

Mean BMI at diagnosis was 19.50±2.90 kg/m^2 and at the moment of discharge or last consultation was 22.00±2.50 kg/m^2.

Family history of thyroid disease was present in 23.80% (n=5) patients, all of them female; two patients presented a relative with hypothyroidism, one had a mother with medullary thyroid carcinoma, another patient had three maternal relatives with toxic multinodular goiter (TMNG) and the last one presented history of GD in her mother and TMNG in her grandfather; 23.80% (n=5) had personal history of allergic disease and 19.00% (n=4) had another auto-immune disease (type 1 diabetes mellitus in two patients, idiopathic juvenile arthritis and Kawasaki disease).

Six patients (28.60%) presented Graves` ophthalmopathy at the moment of diagnosis.

Twelve patients still maintain follow-up in Pediatric Endocrinology Unit, the remain were discharged to adult's Unit, mean age 14.60±2.60 (10.40-17.20). Mean follow-up time after discharge was 6.00±4.50 years. Those that maintain follow-up have a mean follow-up time of 2.73±1.87 years.

Analytic and Ultrasonography Evaluation

All patients presented with overt hyperthyroidism at diagnosis (increased serum FT4 and/or T3 and suppressed TSH levels). Mean increase of serum FT4 levels was 7.7 times (range 0-35) from the basal levels and 2.1 times (range 0-5.7) for FT3. TRAbs titer was obtained at diagnosis in 67.00% of patients (n=14) and was positive in 85.70% of patients (n=12), mean 27.5 times (range 0-188) above maximum reference ranges. Anti-thyroglobulin and anti-thyroid peroxidase (TPO) antibodies were measured in 85.70% of patients (n=18) and were positive in 88.90% (n=16) and 90.50% (n=19) of them, respectively.

Thyroid volumes were above 97th percentile for age and gender in all patients (median volume of 24.1±9.1 mL – range 9.2-41.5).

Treatment with Anti-Thyroid Drugs

All patients received ATD as first option treatment. PTU was first choice in 23.80% (n=5) of patients before 2010, after that all patients started treatment with MMI (71.40% - n=15). One patient, diagnosed in France, was initially treated with carbimazole, which is not available in Portugal. Only one patient was on "block and replace" therapy. Propranolol was administered in 42.80% (n=9) during the first few months.

Mean initial dose for PTU was 3.80±4.77 mg/kg (range 0,12-10.9) and for MMI was 0.32±0.11 mg/kg (range 0.18-0.50), according to most recent recommendations.[2]

There were no adverse effects reported with MMI. One patient treated with PTU developed severe hepatitis without liver failure and no need for transplantation.

Comparing PTU and MMI results, both presented similar outcomes except concerning time until TSH normalization which was significantly superior for PTU - *p*=0.049 (Table 1).

Reported remission rate was 23.80% (n=5) with a relapse rate of 25.00% (n=1) without significant differences between PTU and MMI (*p*=0.217). Three patients changed ATD and 38.00% (n=8) were proposed for definitive treatment. Five patients achieved remission: 2 remitted 12 months after discharge from Pediatric clinic (and they have been in remission for 43 and 15 months); 2

Table 1. Summary of comparison between PTU and MMI.

Variable	MMI	PTU	*P*
Time until TSH normalization (months)	**4.4**±2.9 (0.8-10.0)	**6.5**±0.7 (6.0-7.0)	***p=0.049***
Time until T3 and FT4 normalization (months)	**3.3**±2.9 (0.4-10.0)	**3.0**±1.4 (2.0-4.0)	*p=0.844*
Mean treatment duration (months)	**28.9**±13.2 (14.0-56.0)	**40.6**±35.5 (4.0-98.0)	*p=0.280*
Maintenance time of ATD after TSH normalization (months)	**24.5**±14.0 (6.0-54.0)	**20.5**±2.1 (19.0-22.0)	*p=0.323*
TRAbs titer after normalization of thyroid function	**5.2**±9.3 (0.0-24.7)	**18.7**	*p=0.199*

ATD - anti-thyroid drugs; TRAbs - thyrotropin receptor stimulating antibodies; MMI – methimazole; PTU - propylthiouracil.

remitted in pediatric age after first treatment, one after 98 months of therapeutic with PTU and is still on remission for 58 months and the other one remitted after 21 months of MMI treatment, maintaining remission for 20 months; the last one was initially treated with PTU for 29 months, changed to MMI, went on remission and one month later relapsed. Median time in remission was 20.00 months (1.00-58.00). The patient who initiated treatment with carbimazole after 25 months changed to PTU.

About 33.30% (n=7) of patients maintain treatment with ATD with a mean duration time of 22.90±9.00 months (14.00-36.00).

Definitive Treatment

In our cohort, 38.00% (n=8) patients were proposed for definitive treatment: 75.00% (n=6) were submitted to RAI and 25.00% (n=2) to surgery. Patients submitted to RAI presented no adverse reactions. One of them needed a second dose of RAI to achieve total suppression of thyroid function. Mean patient age at the moment of RAI therapy was 15.80±2.30 years (11.90-18.30), median thyroid volume estimated by scintigraphy was 36.00 g (20.00-80.00), median administered RAI dosage was 556.5 mBq (374.00-572.00), with median dose per thyroid volume of 12.90 mBq/g (5.60-27.90). The lowest dose was administered to the patient that needed a second course of RAI therapy which was also the one who had the larger thyroid volume. One patient submitted to RAI presented ophtalmophaty and was on corticotherapy before RAI; we found no exacerbation.

Mean time until achievement of hypothyroidism was 4.00±1.90 months (2.00-6.00).

One patient did a total thyroidectomy without complications and another one developed a persistent hypoparathyroidism after being submitted to a subtotal thyroidectomy.

All patients submitted to RAI therapy developed hypothyroidism and are under hormonal replacement therapy.

Discussion

In this 18-year retrospective study of management of pediatric GD, the patients' characteristics (gender and age at diagnosis) were similar to those found in the literature with a predominance of female pubertal patients. The follow-up included patients who transitioned to adult department.

One of the main conclusions the authors would like to emphasize is the increasing number of cases verified in the last decade. This was an important observation since we believe it has impaired some of the conclusions of this study. In fact, 47.60% (n=10) of the cohort had less than 4 years of follow-up so it would be less likely that they have reached remission by the time the study was performed. However, we have reported similar remission rates as in previous studies with larger cohorts (23.80% vs 33-64% in other series).[3,4,14,18,19] Also it is well known that in pediatric population, remission rates increase with duration of ATDs treatment. Hamburger demonstrated it in his study in 1985 involving 120 pediatric patients that were treated with ATD in one center.[18] His results demonstrated that after 1 year of therapy with ATDs, 25% of patients were in remission; after 2 years, 26%; after 4 years, 37%; and after 4–10 years, 15%.[10,14,18,20]

Despite increasing duration of therapy, we also verified in our cohort (mean treatment durations of 30 months, that can be as high as 98 months), very high relapse rates, sometimes reaching 50% demonstrating that a substantial proportion of patients will never achieve remission. We reported a relapse rate of 25% and we believe that it is lower than other reported studies probably because we have many patients requiring definitive treatment and our mean follow-up time is very short owing to the previously referred increasing number of recent diagnosis; 33.30% of our patients maintain ATDs for about 22.90 months.[8,14,20,21] For the same reasons, we also have not reported long term remissions (more than 4 years) in this cohort (maximum of 58 months).[19]

The best treatment option for pediatric patients is still controverse and largely depends on the experience of the centers, accessibility to therapeutic options and parents and patient's informed opinion. Defenders of prolonged medical treatment with ATD advocate that it can restore the normal homeostasis of the hypothalamus – pituitary – thyroid and that patients can have periods free of medication.[14] However, with prolonged therapy, poor adherence is enhanced, there is the need for frequent monitoring of thyroid function and the risk of adverse effects is highly increased, the last one especially worrisome in vulnerable patients like children. Although in our study ATDs were very well tolerated, with no adverse effects related to MMI, we reported one case of severe hepatitis with PTU before 2010. According to 2016 and 20188 guidelines and all the reported results, in our center MMI was the first-line treatment in all patients since 2010.

In this cohort 38.00% of patients were proposed for definitive treatment, the majority of them performed RAI therapy and we had a high rate of success. In fact, until now, we have not reported any side effects and the only patient that needed a second RAI dose had a large thyroid volume (80 g) and was submitted to a first dose of 131-I near the lowest recommended of more than 5.55 mBq/g.[2] We have been using RAI therapy for 14 years and there are no reported cases of thyroid neoplasia or other tumors. There is some concerning that 131-I may aggravate pre-existing ophtalmopathy and some centers avoid its use. In our limited experience, like other studies have stated, we used prophylactic corticosteroid treatment simultaneously with RAI administration to prevent worsening of previous mild ophtalmopathy.[22,23] RAI therapy's goal is to achieve hypothyroidism, which usually occurs within 2-4 months, with 40% of patients being hypothyroid by the second month and more than 80% by the fourth month. In our cohort 60% of patients achieved hypothyroidism by the end of the third month and initiated T4 replacement treatment.[2,24]

Most studies advocate that thyroidectomy must be performed by an high-volume thyroid surgeon so that the surgical risk can be

minimized.[2,20,25] Since 2011, our patients have access to an expert team, fact that we consider the justification for the very low rates of complications associated with the surgery in our center. One of our patients developed a permanent hypoparathyroidism after a subtotal thyroidectomy that was not performed by our team of surgeons.

Our study has several limitations, some of them have already been appointed previously. The main one was the short follow-up time due to the increasing number of cases diagnosed in the last decade. Thus we were unable to determine predictive factors of ATD's response, remission and relapse. We believe that more studies are needed in this area in order to standardize treatment options between centers so that results could be compared and the management of pediatric patients with GD could be optimized.

Contributorship Statement / Declaração de Contribuição:

All authors contributed substantially to the conception or design of the work; acquisition, analysis and interpretation of data, participated in the writing and critical review of the work.

Todos autores contribuíram substancialmente para a conceção ou desenho do trabalho; aquisição, análise e interpretação dos dados, participaram na redação e revisão crítica do trabalho.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.
Fontes de Financiamento: Não existiram fontes externas de financiamento para a realização deste artigo.
Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.
Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.
Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.
Financing Support: This work has not received any contribution, grant or scholarship
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).
Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências

1. Gastaldi R, Poggi E, Mussa A, Weber G, Vigone MC, Salerno M, et al. Graves Disease in Children: Thyroid-Stimulating Hormone Receptor Antibodies as Remission Markers. J Pediatr. 164:1189–1194.e1. doi:10.1016/j.jpeds.2013.12.047
2. Burch HB, Cooper DS, Ross DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid. 2016;26:1343-21. doi: 10.1089/thy.2016.0229. Erratum in: Thyroid. 2017;27:1462. doi: 10.1089/thy.2016.0229.correx
3. Marques O, Antunes A, João M. Endocrinología, Diabetes y Nutrición Treatment of Graves ' disease in children. SEEN; 2018. [accessed May 2022] Available from: http://dx.doi.org/10.1016/j.endinu.2017.11.014
4. Azizi F, Amouzegar A. Management of thyrotoxicosis in children and adolescents: 35 years' experience in 304 patients. J Pediatr Endocrinol Metab. 2018;31:159–65. doi: 10.1515/jpem-2017-0394.
5. Hall P, Lundell G, Holm LE. Mortality in patients treated for hyperthyroidism with iodine-131. Acta Endocrinol. 1993;128:230–4.
6. Burch HB, Wartofsky L. Life-threatening thyrotoxicosis. Thyroid storm. Endocrinol Metab Clin North Am. 1993;22:263–77.
7. Rivkees SA. Controversies in the management of Graves ' disease in children. J Endocrinol Invest. 2016;39:1247-57. doi: 10.1007/s40618-016-0477-x.
8. Kaguelidou F, Claude J, Juliane C. Graves ' Disease in Childhood : Advances in Management with Antithyroid Drug Therapy. Horm Res. 2009;71:310-7. doi: 10.1159/000223414.
9. Liu LIN, Lu H, Liu Y, Liu C, Xun C. Predicting relapse of Graves ' disease following treatment with antithyroid drugs. Exp Ther Med. 2016;11:1453-8. doi: 10.3892/etm.2016.3058.
10. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018;7:167-86. doi: 10.1159/000490384.
11. Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil Era. Int J Pediatr Endocrinol. 2014;2014:10. doi: 10.1186/1687-9856-2014-10.
12. Vieira LDO, Kubo R, Sapienza MT, Willegaignon J, Chammas MC, Courafilho GB, et al. Correlação entre volume tireoidiano determinado pelo método de ultrassonografia. Arq Bras Endocrinol Metab.2011;55:696-700. doi:10.1590/S0004-27302011000900005
13. West JD, Cheetham TD, Dane C, Natarajan A, West JD, Dane C, et al. Should radioiodine be the first-line treatment for paediatric Graves' disease? J Pediatr Endocrinol Metab. 2015;28:797-804. doi: 10.1515/jpem-2014-0176.
14. Léger J, Carel J. Arguments for the prolonged use of antithyroid drugs in children with Graves' disease. 2017;59–67. Eur J Endocrinol. 2017;177:R59-R67. doi: 10.1530/EJE-16-0938.
15. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P LJ. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab. 2008;93:3817–26.
16. Laboratory Corporation of America® Holdings. Expected values & S.I. Unit Conversion Tables. Chicago: LCA; 2017.
17. Zimmermann MB, Hess SY, Molinari L, De Benoist B, Delange F, Braverman LE, et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. Am J Clin Nutr. 2004;79:231-7. doi: 10.1093/ajcn/79.2.231.
18. Hamburger JI. Management of hyperthyroidism in children and adolescents. J Clin Endocrinol Metab. 1985;60:1019–24.
19. Gjikopulli A, Tomori S, Kollçaku L, Hoxha P, Grimci L, Ylli Z. Graves' disease in Albanian children. Curr Health Sci J. 2014;40:190-4. doi: 10.12865/CHSJ.40.03.06.
20. Jevalikar G, Solis J, Zacharin M. Long-term outcomes of pediatric Graves' disease. J Pediatr Endocrinol Metab. 2014;27:1131-6. doi: 10.1515/jpem-2013-0342.
21. Okawa ER, Grant FD, Smith JR. Pediatric Graves' disease: decisions regarding therapy. Curr Opin Pediatr. 2015;27:442-7. doi: 10.1097/MOP.0000000000000241.
22. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998;338:73-8. doi: 10.1056/NEJM199801083380201.
23. Lai A, Sassi L, Compri E, Marino F, Sivelli P, Piantanida E, et al. Lower

dose prednisone prevents radioiodine-associated exacerbation of initially mild or absent graves' orbitopathy: a retrospective cohort study. J Clin Endocrinol Metab. 2010;95:1333–7. doi: 10.1210/jc.2009-2130.
24. Stan MN, Durski JM, Brito JP, Bhagra S, Thapa P, Bahn RS. Cohort study on radioactive iodine-induced hypothyroidism: implications for Graves' ophthalmopathy and optimal timing for thyroid hormone assessment. Thyroid. 2013;23:620-5. doi: 10.1089/thy.2012.0258.
25. Sugino K, Ito K, Mimura T, Fukunari N, Nagahama M, Ito K. Surgical treatment of Graves' disease in children. Thyroid. 2004;14:447-52. doi: 10.1089/105072504323150769.