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Clinical Features And Follow-Up Results Of Children With Hyperthroidism

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Research Article

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ABSTRACT

Objective: Hyperthyroidism is a rare clinical condition in childhood that can cause serious problems. Information on the epidemiological features, follow-up and treatment of pediatric patients with hyperthyroidism is quite limited. In this study, clinical and laboratory findings and follow-up results of children with hyperthyroidism are presented.

Materials and Methods: The data of children with hyperthyroidism between 2005-2022 at Atatürk University and Erzurum Health Sciences University Pediatric Endocrinology clinics were retrospectively analyzed.

Results: 43 (81.1%) female and 10 (18.9%) male patients aged 2-18 years (14.05±3.0) were included in the study. Of the patients, 36 (67.9%) had Graves' disease (GD), 14 (26.4%) had Hashimoto's thyroiditis (HT), 2 (3.8%) had subacute thyroiditis, and 1 (1.9%) had hyperactive thyroid nodules. The most common symptoms were palpitations (75.5%), sweating (60.4%), tremors in the hands (49.1%), heat intolerance (45.3%) and weight loss (32.1%). Mean SD values of height, body weight and body mass index at the time of diagnosis were -0.05±1.16, -0.67±1.20 and -0.77±1.25, respectively. Goitre and exophthalmos were present in 69.8% and 30.2% of the cases, respectively. At the time of diagnosis, mean serum thyroid stimulating hormone (TSH), free tri-iodothyronine, free tetra-iodothyronine, thyroglobulin, anti-thyroid peroxidase, anti-thyroglobulin and TSH receptor antibody levels were 0.03±0.09 mIU/L, 13.0.34±7.07 pg/ml, 3.30±1.70 ng/dl, 101.93±180.35 ng/ml, 600.30±858.58 IU/ml, 322.82±644.08 IU/ml, and 12.41 ±14.37 IU/L, respectively. 42 (79.2%) patients were treated with propranolol and methimazole, 3 (5.7%) patients were treated with propranolol and propylthiouracil, and 4 (7.5%) patients were treated with propranolol, while 4 (7.5%) patients were untreated. The mean duration of treatment was 14.67±17.51 months. The mean time to euthyroid state antithyroid drug (ATD) was 24.80±14.33 days. While no serious drug-related side effects were detected in any patient, urticaria rash developed in 1 (1.9%) patient in the 1st month of treatment. Total thyroidectomy was performed in 3 cases with GD and 1 case with hyperactive thyroid nodules. Radioactive iodine treatment was not given to any of the cases. The remission rate in patients with GD was 46.7% at the early stage of treatment and 16.7% during the entire follow-up. The recurrence rate was 71.4%. At the last visit, 15 (28.3%) patients were euthyroid, 1 (1.9%) hyperthyroid, and 5 (9.4%) hypothyroid. While 21 (39.6%) of the cases were still using antithyroid medication, 11 (20.8%) were excluded from follow-up.

Conclusion: The first and second most common causes of hyperthyroidism in children and adolescents are GH and HT, respectively. TRAb positivity, thyroid scintigraphy findings and clinical follow-up may be useful in distinguishing between GH and HT. ATD therapy is effective and safe in keeping GH in remission.

Keywords: Hyperthyroidism, Graves' disease, Hashimoto thyroiditis, Hashitoxicosis, Thyrotoxicosis

Hipertiroidizm Saptanan Çocukların Klinik Özellikleri ve Takip Sonuçları

ÖZ

Amaç: Hipertiroidizm çocukluk çağında nadir görülen ve ciddi sorunlara yol açabilen bir klinik durumdur. Hipertiroid çocuk hastaların epidemiyolojik özellikleri, takip ve tedavileri hakkındaki bilgiler oldukça sınırlıdır. Bu çalışmada hipertiroidizm saptanan çocukların klinik ve laboratuvar bulguları ve takip sonuçları sunulmaktadır.

Yöntem: Atatürk Üniversitesi ve Erzurum Sağlık Bilimleri Üniversitesi Çocuk Endokrinoloji kliniklerinde 2005-2022 yılları arasında hipertiroidizm saptanan çocukların verileri geriye dönük olarak incelendi.

Bulgular: Yaşları 2-18 yıl (14.05±3.0) arasında olan 43 (%81.1) kız ve 10 (%18.9) erkek hasta çalışmaya dâhil edildi. Hastaların 36 (%67.9)'sında Graves hastalığı, 14 (%26.4)'ünde Hashimoto tiroiditi, 2 (%3.8)'sinde subakut tiroidit ve 1 (%1.9)'inde hiperaktif tiroid nodülü tespit edildi. En sık saptanan belirtiler çarpıntı (%75.5), terleme (%60.4), ellerde titreme (%49.1), sıcağa tahammülsüzlük (%45.3) ve kilo kaybı (%32.1) idi. Tanı anında ortalama boy, vücut ağırlığı ve vücut kitle indeksi SD değerleri sırasıyla -0.05±1.16, -0.67±1.20 ve -0.77±1.25 bulundu. Olguların %69.8'inde guatr ve %30.2'sinde ekzoftalmus saptandı. Tanı anında ortalama serum tiroid sitümülan hormon (TSH), serbest tri-iyodotironin, serbest tetra-iyodotironin, tiroglobülin, anti-tiroid peroksidaz, anti-tiroglobülin ve TSH reseptör antikor düzeyleri sırasıyla, 0.03±0.09 mIU/L, 13.34±7.07 pg/ml, 3.30±1.70 ng/dl, 101.93±180.35 ng/ml, 600.30±858.58 IU/ml, 322.82±644.08 IU/ml ve 12.41±14.37 IU/L idi. Olguların 42 (%79.2)'sine propranolol ve metimazol, 3 (%5.7)'üne propranolol ve propiltiourasil, 4 (%7.5)'üne propranolol verilirken, 4 (%7.5)'üne tedavi verilmedi. Tedavi süresi ortalama 14.67±17.51 ay idi. Antitiroid ilaç (ATİ) tedavisi başlandıktan sonra ötiroid olana kadar geçen ortalama süre 24.80±14.33 gün bulundu. Hiçbir olguda ilaca bağlı ciddi bir yan etki saptanmazken, 1 (%1.9) olguda tedavinin 1. ayında ürtikeryal döküntü gelişti. Graves hastalığı olan 3 ve hiperaktif tiroid nodülü olan 1 olguya total tiroidektomi yapıldı. Radyoaktif iyot tedavisi hiçbir olguya verilmedi. Gravesli hastalardaki remisyon oranı tedavinin başında %46.7 iken, tüm takip boyunca %16.7 idi. Rölaps oranı %71.4 bulundu. Son vizitte olguların 15 (%28.3)'i ötiroid, 1 (%1.9)'i hipertiroid ve 5 (%9.4)'i hipotiroid durumda idi. Olguların 21 (% 39.6)'i halen antitiroid ilaç kullanıyorken, 11(%20.8)'i takipten çıkarılmıştı.

Sonuç: Hipertiroid çocuk ve adölesanlarda birinci ve ikinci en sık neden sırasıyla GH ve HT'dir. TRAb pozitifliği, tiroid sintigrafi bulguları ve klinik takip ile GH ve HT birbirinden ayırt edilebilir. GH'nin remisyonda tutulmasında ATİ tedavisi etkili ve güvenilirdir.

Anahtar sözcükler: Hipertiroidi, Graves hastalığı, Hashimoto tiroiditi, Hashitoksikoz, Tirotoksikoz.

Süreç

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Introduction and Aim

Hyperthyroidism is characterized by elevated blood thyroid hormone levels and accelerated metabolism, and is a rare clinical condition in childhood.[1] The most common cause of hyperthyroidism in children is Graves' disease (GD).[1] Other causes include Hashimoto's thyroiditis (HT), toxic nodular goitre, acute or subacute thyroiditis, chronic lymphocytic thyroiditis, and acute or chronic exposure to thyroid drugs or iodides.[2] The incidence of GD is 0.1/100,000 in young children and 3/100,000 in adolescents.[2] GD is more common in children with an autoimmune disease or a positive family history of autoimmune disease.[1] Although GD can be seen at any age in childhood, its incidence increases with age and peaks at puberty. It is more common in girls than boys.[1]

HT is an autoimmune disease characterized by tissue destruction caused by autoantibodies against the thyroid gland.[3] The clinical manifestations of the disease are variable. According to thyroid function tests, patients may be in a hyperthyroid, euthyroid, or hypothyroid state.[3] Diagnosis is based on typical ultrasound findings and the presence of antithyroid antibodies.[4]

Irrespective of the cause, the main goal in the treatment of HT is to keep the patient in a euthyroid state.[1] The therapeutic options in children and adolescents with GD are medical therapy, surgery, and radioactive iodine therapy. The age of the child, the ineffectiveness or side effects of antithyroid drugs (ATDs), the size of the thyroid gland, the presence of thyroid nodules and concomitant diseases are all considered when deciding on treatment.[5] Therefore, treatment should always be individualized.

There are only two studies investigating clinical and medical treatment features in pediatric patients with hyperthyroidism in Turkey. The first study was carried out by Işık et al. in 2013 at Hacettepe University, and the other in 2019 by Esen et al. in a multi-center study.[6,7] There is no study investigating clinical findings and follow-up features in children with hyperthyroidism in the Eastern Anatolia region of Turkey. This study aimed to examine the clinical and laboratory findings and follow-up results of children with hyperthyroidism in the Eastern Anatolia region of Turkey.

Material and Method

The data of patients diagnosed with hyperthyroidism in Atatürk University and Erzurum Health Sciences University Pediatric Endocrinology Clinics between 2005 and 2022 were retrospectively analyzed. Gender, family history, concomitant autoimmune diseases, drugs used, iodine exposure, chronological age at diagnosis, height and body weight measurements, pubertal stage, complaints at time of admission, vital signs, clinical and laboratory findings, therapy chracteristics and follow-up results were obtained from file records.

Symptoms such as palpitation, sweating, weight loss, and heat intolerance, and clinical findings such as tachycardia, tremor in the hands, goitre, and exophthalmos were determined as clinical manifestations of hyperthyroidism.

Height, weight, and body mass index (BMI) standard deviation (SD) values were obtained with the help of an online application (Child Metrics)[8] using data from Neyzi et al.

Reference ranges for serum free tri-iodothyronine (fT3), free tetra-iodothyronine (fT4), thyroid-stimulating hormone (TSH), TSH receptor antibody (TRAb), antithyroid peroxidase antibody (anti-TPO), and anti-thyroglobulin antibody (anti-TG) were 3-4.7 pg/ml, 0.6-1.2 ng/dl, 0.6-4.9 µIU/ml, 0-4.2 IU/L, 0-75 IU/ml, and 0-150 IU/ml, respectively. Patients with serum TRAb, anti-TPO, and anti-TG levels above the upper reference limit were defined as antibody-positive, and those with levels within reference ranges as antibody-negative. Patients with serum sT3 and sT4 levels above the upper reference limit and TSH levels below the lower reference limit and who had symptoms and findings of hyperthyroidism were considered hyperthyroid. Among these cases, TRAb-positive patients were accepted as GD while patients with TRAb-negative, positive anti-TPO and/or anti-TG antibodies, using short-term ATD, and no recurrence in follow-up were accepted as HT. Transient remission was defined as the absence of clinical signs of HT and the presence of thyroid hormones within normal limits for at least three months after discontinuation of ATD therapy. If this period was at least one year, it was defined as permanent remission.

Recurrence of clinical findings related to hyperthyroidism in patients in remission, serum fT3 and fT4 levels above the upper limit and TSH levels below the lower limit were defined as relapse.

Radiological examination of the thyroid gland was performed using thyroid ultrasonography and thyroid Doppler ultrasonography. In this way, the thyroid gland parenchyma was evaluated and the dimensions of the thyroid lobes were measured. According to the dimensions obtained, the thyroid gland was defined as normal, mildly enlarged, or markedly enlarged.[9]

The study was approved by the local ethics committee of Health Sciences University Erzurum Medical Faculty Erzurum Regional Training and Research Hospital (decision no. 2022/04-13 dated 11.04.2022).

Statistical analysis was performed on SPSS-22 software. The Shapiro-Wilk test was used to analyze whether the data were normally distributed in patients with GD and HT. Normally distributed data were compared with Student's t test, and non-normally distributed data were compared with Mann Whitney U test. Descriptive statistical data were presented as mean ± standard deviation and median value (lower rank-upper rank) for normally and non-normally distributed data, respectively. *p* values <0.05 were regarded as significant.

Results

Fifty-three children with hyperthyroidism between ages 2 and 18 years (14.05±3.0) were included in the study. 43 (81.1%) were girl and 10 (18.9%) were boy. Of the patients, 5 (9.4%) were younger than 10 years old, 28 (52.8%) were between 10-15 years old, and 20 (37.7%) were older than 15 years. While puberty had not started in 9 (17%) patients, 44 (83%) patients were at different stages of puberty. 49.1% of patients lived in Erzurum, 17% in Ağrı, 13.2% in Kars, 9.4% in Muş, 5.6% in Iğdır, 3.8% in Erzincan, and 1.9% in Adana.

Thirty-six patients (67.9%) had been diagnosed with GD, 14 (26.4%) with HT, two (3.8%) with subacute thyroiditis, and one (1.9%) with hyperactive thyroid.

The most common symptoms and signs at presentation were palpitation (40/53, 75.5%), sweating (32/53, 60.4%), tremor in hands (26/53, 49.1%), heat intolerance (24/53, 45.3%), and weight loss (17/53, 32.1%). Other signs and symptoms are shown in Table 1.

Table 1. Signs and symptoms during presentation

Signs and symptoms	n	%
Palpitation	40	75.5
Sweating	32	60.4
Hand tremor	26	49.1
Heat intolerance	24	45.3
Weight loss	17	32.1
Swelling in the neck	15	28.3
Irritability	12	22.6
Weakness	12	22.6
Sleep disturbance	11	20.8
Diarrhea	9	17
Ophthalmopathy	7	13.2
Shortness of breath	5	9.4
Hair loss	3	5.7
Pruritus	1	1.9
Ocular drift	1	1.9

The mean duration of symptoms was 74.36±88.36 (2-365) days.

While no accompanying disease was present in 47 patients (88.6%), type 1 diabetes mellitus, celiac disease, vitiligo, chronic urticaria, ovarian cyst, and osteochondroma were present in one patient each. None of the patients had a history of drug use.

While family history was negative for thyroid disease in 9 (17%) patients, it was positive for goitre in 11 (20.8%) patients, for hyperthyroidism in three (5.7%) patients, for HT in three (5.7%) patients, for thyroid cancer in three (5.7%) patients, and for thyroid nodules in two (3.8%) patients.

Mean height, weight, and BMI values at presentation were -0.05±1.16, -0.67±1.20, and -0.77±1.25, respectively.

At the time of admission, 14 patients (26.4%) had grade 1 goitre, 14 patients (26.4%) had grade 2 goitre, 9 patients (17%) had grade 3 goitre, and 16 patients (30.2%) had no goitre. Tachycardia in 45 patients (84.9%), exophthalmia in 16 patients (30.2%), increased pulse pressure in 12 patients (22.6%), hypertension in two patients (3.8%), splenomegaly in one patient (1.9%), and hyperpigmented nevus in one patient. (1.9%) were detected.

Mean serum TSH, fT3, fT4, and thyroglobulin levels at time of presentation were 0.03±0.09 mIU/L (normal: 0.6-4.9), 13.34±7.07 pg/ml

(normal: 3-4.7), 3.30±1.70 ng/dl (normal: 0.6-1.2), and 101.93±180.35 ng/ml (normal: 1.6-60), respectively. Mean serum anti-TPO, anti-TG, and TRAb levels were 600.30±858.58 IU/ml (normal: 0-75), 322.82±644.08 IU/ml (normal: 0-150), and 12.41±14.37 IU/L (normal: 0-4.2), respectively. Mean serum TRAb levels were higher in children with GD than in children with HT (14.89±2.51 and 9.33±2.58, respectively, p<0.001), while there was no significant difference in mean serum TSH, fT4, fT3, thyroglobulin, anti-TPO and anti-thyroglobulin levels between children with GD and HT (p>0.05).

In thyroid ultrasonography, thyroid gland dimensions were significantly large in 23 (43.4%) patients, significantly small in 13 (24.5%) patients, and normal in 17 (32.1%) patients. Thyroid parenchyma was homogeneous in seven patients (26.4%) and heterogeneous in 39 (73.6%). Nodules and pseudo-nodules were detected in 10 (18.9%) and 14 (26.4%) patients, respectively. Doppler ultrasonography showed increased blood flow in 38 (71.7%) patients and decreased blood flow in six (11.3%) patients. Nine patients (17%) had normal doppler ultrasonography findings.

Thyroid scintigraphy was performed in 35 (66%) patients. Radioactive iodine uptake was normal in three (8.6%) patients, increased in 27 (77.1%) patients, and decreased in four (11.4%) patients. One (2.9%) patient had hyperactive nodule. Radioactive iodine uptake was higher in GD diagnosis than other diagnoses (p<0.05).

Forty-two (79.2%) patients were treated with propranolol and methimazole, three (5.7%) patients with propranolol and propylthiouracil, and four (7.5%) patients with propranolol. Four (7.5%) patients were followed-up without treatment. The mean duration of treatment was 14.67±17.51 months. Duration of treatment was less than one year in 31 (58.4%) patients, 1-2 years in 11 (20.8%), patients and longer than two years in 11 (20.8%) patients. The mean methimazole dose was 0.36±0.14 mg/kg/day. The mean time to euthyroid state after ATD therapy was 24.80±14.33 days.

Four (7.5%) patients underwent total thyroidectomy during follow-up. Two of the patients had shortness of breath due to tracheal compression that developed six and 19 months after diagnosis. The third patient with GD relapsed 11 months after cessation of medical therapy. That patient had multinodular goitre in thyroid ultrasonography and had received medical therapy for eight years. The last patient had a hyperactive nodule on thyroid scintigraphy. Therefore, fine needle aspiration biopsy was performed to exclude thyroid gland malignancy. Histopathological examination of the biopsy specimen revealed suspicious findings suggestive of malignancy. However, no malignant histopathological change was detected in the surgically removed thyroid gland.

Eruption evaluated as urticaria developed in the first month of treatment in only one patient (1.9%) receiving ATD treatment. Medication was discontinued in a short time. No recurrence of the cutaneous eruption was observed when drug therapy was restarted.

At the last visit, fifteen (28.3%), one (1.9%) and five (9.4%) patients were euthyroid, hyperthyroid, and hypothyroid, respectively. The hypothyroid patients were receiving Na-L-thyroxin therapy. While 21 (39.6%) patients continued ATD treatment, 11 (20.8%) patients were excluded from follow-up.

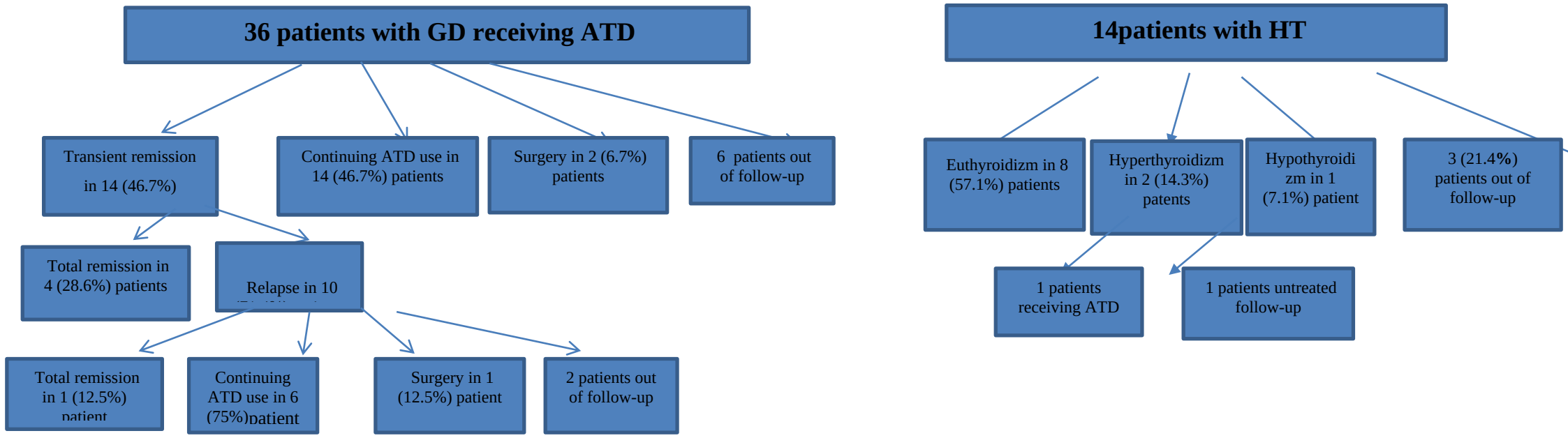
Twenty (55.5%) patients with GD received ATD, while five (13.9%) were in euthyroid state and in complete remission. Three (8.3%) patients were receiving Na-L-thyroxine therapy for hypothyroidism due to total thyroidectomy. Eight (22.2%) patients were excluded from follow-up.

Eight (57.1%) of 14 patients with HT were in euthyroid state. One patient was receiving thyromazole and one patient was receiving Na-L-thyroxine treatment. One patient with hyperthyroidism was followed up without medication. Three patients were excluded from follow-up.

Two patients who were followed up with the diagnosis of subacute thyroiditis became euthyroid without any ATD during the follow-up.

Temporary remission was achieved in 14 (46.7%) patients with GD. Relapse developed in 10 (71.4%) of these patients. The mean time from discontinuation of ATD to relapse was 3-6 months in five (50%) patients, 6-12 months in three (30%) patients, and 1-2 years in two (20%) patients. The duration of ATD use was less than one year in seven (70%) of these patients, and longer than two years in three (30%) patients.

The clinical conditions and treatments received by patients diagnosed with GD and HT are shown in Figure 1.



GD: Graves' disease, HT: Hashimoto's disease, ATD: antithyroid drug

Figure 1. The clinical conditions during follow-up of patients with Graves' disease and Hashimoto's thyroiditis

Discussion

Data on the epidemiology of childhood hyperthyroidism are limited. Reported incidences from northern Europe and China range from 1 to 6.5 per 100,000.[1] A study conducted in France reported an incidence of 4.58/100,000 in children aged six months to 17 years.[10,11] A figure of 0.9/100,000 has been identified among children under the age of 15 in the UK, with children with GD accounting for 95% of cases.[12] In a study conducted in Ankara, Turkey in 2013, the frequency of GD in children with hyperthyroidism was reported as 77.5%.[7] Esen et al.[6] reported a figure 75% in a multicenter study in 2019. In our study, this rate was 67.9%. This finding suggests that the frequency of GD in patients with hyperthyroidism in our region is comparable to different regions of Türkiye. The second most common cause of hyperthyroidism in childhood is HT-related Hashitoxicosis. The prevalence of Hachitoxicosis was reported between 0.5% and 22% in previous studies.[6] In two studies from Turkey, the prevalence of HT in hyperthyroid patients was reported as 14.9% and 16.3%.[6,7] In our study, the frequency of HT was 26.4%, and the disease was the most common cause of hyperthyroidism after GD. Regional differences may be a reason for the higher frequency of HT in our study compared to previous studies. In addition, the fact that patients with HT are taken to the hospital instead of neglect may be another reason. This is because the signs and symptoms of hyperthyroidism are milder in patients with HT than in patients with GD. A significant portion of patients with HT do not even receive treatment for this reason. This study represents the latest research from Turkey. The increase in the socio-cultural level and the increase in access to public health services in parallel with the economic development in Türkiye may have caused the referral of children with mild HT symptoms to our hospital.

In childhood, GD is most common in the 11-15 age group and is 6-8 times more common in girls.[13] In a study conducted in England, Gill et al.14 reported that 54.1% of patients with hyperthyroidism were between the ages of 10-16 and the female/male ratio was 4.1. Another study from France reported that 46.6% of patients with hyperthyroidism were between the ages of 15 and 17, with a female/male ratio of 3.21.[11] Two previous studies from Turkey showed that the female/male ratio was 3.1 and 4.[6,15] We found that 52.8% of the patients were between the ages of 10-15 and the female/male ratio was 4.7. Our findings suggest that, despite wide geographic and racial differences worldwide, hyperthyroidism is more common in adolescents and girls.

In two studies from Turkey, 83% and 71% of patients with GD were at puberty at the time of diagnosis.[15,16] In our study, this rate was 83%. Puberty in girls begins a year earlier than in boys. Considering that the disease is more common in adolescence and in girls than in boys, it is not surprising that the majority of patients are in puberty at the time of diagnosis. The difference in puberty rates between studies may be due to the difference in male/female ratios.

A study from Turkey revealed that symptoms such as palpitations, weight loss and sweating were the most common complaints.[6] The most common symptoms in our study were palpitation, sweating, and tremor in the hands. Weight loss was one of the rarer manifestations. The reason for this may be that the time elapsed between the onset of symptoms and the application to the health institution is shorter in our patients.

Studies from all over the world have shown that the rate of comorbidity in children with autoimmune thyroid disease varies between 3% and 16%.[11,14] Having any autoimmune disease in a child or family member is known to increase the risk of pediatric GD.[2] A study conducted in Turkey showed that 75% of patients with GD had a positive family history of autoimmune diseases.[17] Another study found that 72% of patients had a family history of autoimmune thyroid disease.[15] In our study, 71% of the patients had a family history of thyroid disease. In addition, 7.7% of our patients had another autoimmune disease. The findings of other studies from Turkey and our study suggest that the prevalence of other autoimmune diseases in children with hyperthyroidism is higher than those reported from other countries. This may be due to environmental factors and racial differences arising from geography.

Goitre is one of the most common findings in patients with hyperthyroidism. This finding was found to be 85% by Tunç et al.[15], 40.9% by Sönmez et al.[17], and 75% by Gill et al.[14] In this study, goitre was found in 69.8% of the patients. Accordingly, it can be said that the prevalence of goitre is consistent with previous studies.

Exophthalmos may develop in GD. The cause of exophthalmos is edema that develops in the retroorbital tissue due to inflammation, which can also develop in the muscles in severe cases. Edema then leads to functional deterioration of the eye muscles. Patients' vision may be affected or ptosis may develop. This condition, known as ophthalmopathy, is seen in 50-75% of children with GD and causes complaints such as pain, foreign body sensation, and diplopia. The incidence and severity of ophthalmopathy in children with GD is lower than in adults.[18] In studies reported from Turkey, the rate of exophthalmos varies between 15.9% and 31.2%.[6,15,17] In our study, 30.2% of the patients had exophthalmos, and ophthalmopathy did not develop in any of the patients. These findings suggest that the incidence of exophthalmos and ophthalmoplegia is similar to other studies and that inflammation in the ocular tissues exhibits a benign course.

The first choice in the treatment of GD is still ATD treatment. Surgical treatment is applied in cases with recurrence, drug incompatibility, ATD toxicity, compression findings or suspected malignancy. In this study, ATD treatment was the first-line treatment for all patients. However, surgery was performed in two patients due to compression findings and one due to multinodular goitre and recurrence.

Most side effects associated with ATD treatment occur within the first three to six months of treatment. The frequency of side-effects is generally dose-dependent.[1] The rate of side effects related to ATD varies between 6% and 35%.[18] No serious adverse events were observed in any of the patients in this study. However, urticaria developed in one patient in the first month of treatment. Drug treatment was interrupted for a while and then restarted, and no recurrence of skin rash was observed.

Findings indicating a higher probability of remission in GD include a greater chronological age, mild disease at diagnosis, small thyroid gland size, high BMI, onset of puberty, and decreased TRAb values during follow-up. [18] It has been shown that remission is possible in 30% of children treated with ATD for two years.[19] After 18 months of ATD treatment, the rate of remission was reported as 36% by Azizi et al.[20] and 31% by Gill et al.[14]. Tunç et al.[15] applied ATD treatment for an average of 23.2 ± 13.2 months (10-73 months) and reported a 53% remission rate at the end of this period. Esen et al.[6] reported a remission rate of 58% and a cumulative remission rate of 17.6%. In our study, the initial remission was 46.7% and cumulative remission was 16.7%. All these findings suggest that response rates to ATD treatment are not affected by geographical and racial differences.

Studies from around the world have reported recurrence in approximately 75% of patients within the first six months after discontinuation of ATD therapy. This rate decreases to 10% 18 months after discontinuation of treatment.[2] In a study from Turkey, it was reported that the transient remission rate in these patients was 43.8% and relapse developed in 66.6% of these patients.[16] In our study, the relapse rate was 71.4%, and relapse occurred in 50% of the patients in the first 3-6 months. The duration of ATD use was one year or less in seven (70%) of the relapsed cases, and longer than two years in three (30%) cases. Long-term treatment with the lowest dose of ATD that keeps patients in a euthyroid state is recommended to increase remission rates.[21] The findings of this study suggest that the duration of ATD use is short in our patients and relapse develops in case of long-term ATD use. One reason for the short use of ATDs may be incompatibility of patients and parents. Therefore, when ATD treatment is decided, both patients and parents should be informed that the treatment is long-term and this should be emphasized at each visit.

Conclusion

GD and HT are the most common and second most common causes of hyperthyroidism in children and adolescents, respectively. It is not always easy to distinguish GD from hashitoxicosis caused by HT. However, it may be possible to distinguish these entities with TRAb positivity, thyroid scintigraphy findings and clinical follow-up. Anti-thyroid drug treatment is safe and effective in keeping GD in remission. Further prospective studies are needed to evaluate the duration and long-term side effects of ATDs that should be administered until cure is achieved.

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