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Çocuk ve adölesan tirotoksikosiz vakalarının değerlendirilmesi-tek merkez deneyimi

Outcomes of thyrotoxicosis in childhood and adolescence-single center experience

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Abstract

Purpose: To evaluate the clinical and biochemical features and treatment outcomes of chilhood and adolescence thyrotoxicosis.

Materials and methods: Medical records of the patients who had been diagnosed with thyrotoxicosis between 2015 and 2019 in the pediatric endocrinology clinic were screened retrospectively.

Results: Of the 18 patients, 14 (77.7%) were females, 4 were (22.2%) males. The median age at diagnosis was 14.58±2.1 years. Fifteen (83.3%) patients had been diagnosed with Graves' disease and 3 (16.6%) patients had hashitoxicosis. The most common presenting complaints among patients with GD were malaise, tachycardia/palpitation and swelling in the neck. The other complaints were weight loss, tremor, enlargement of eyes. Twelve (66.6%) patients have family history. Goiter was detected in the physical examination of 9 (50%) patients. Of the 15 patients who diagnosed with GD, 5 (33%) patients had ophthalmopathy. The mean initial dose of methimazole was 0.4±0.3 (range 0.1-1) mg/kg/day and median follow-up duration was 22.3±6.3 months. Two of 3 patients diagnosed with hashitoxicosis were managed only with beta blocker and one patient did not need any treatment. Eleven (73%) of 15 GD patients received beta blocker initially. The mean initial dose of beta blocker was 31.6±10.2 (range 20-80) mg/day. Side effects were not seen in any of 15 patients treated with methimazole.

Conclusion: Graves' disease and hashitoxicosis are the most common form of thyrotoxicosis in both children and adults. These two diseases should be distinguised at diagnosis since the prognosis is better in hashitoxicosis However, there is no evidence-based strategy for the management of childhood thyrotoxicosis, methimazol is the first treatment option in Graves' disease. More experience of treatment responses are essential to understand thyrotoxicosis in children and adolescents.

Key words: Thyrotoxicosis, Graves' disease, hashitoxicosis, childhood, adolescence.

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Özet

Amaç: Çocukluk ve adölesan çağındaki tirotoksikozis vakalarının klinik ve biyokimyasal özelliklerini, tedavi sonuçlarını değerlendirmek.

Gereç ve yöntem: 2015-2019 yılları arasında pediatrik endokrin kliniğinde tirotoksikozis tanısıyla izlenen hastaların dosyaları geriye dönük incelendi.

Bulgular: Çalışmaya dahil edilen 18 hastanın 14'ü (%77,7) kız, 4'ü (%22,2) erkekti. Tanı anındaki ortalama yaş 14,58±2,1 yıldı. On beş (%83,3) hasta Graves hastalığı, 3 (%16,6) hasta ise hashitoksikoz tanısı aldı. Graves hastalığı tanısı alan hastaların en sık başvuru şikayetleri halsizlik, taşikardi/çarpıntı, boyunda şişlikti. Diğer şikayetler, kilo kaybı, tremor ve gözde büyümeydi. On iki (%66,6) hastada hipertiroidi açısından aile öyküsü pozitifti. Dokuz (%50) hastanın fizik muayenesinde guatr saptandı. Graves hastalığı tanısı alan 15 hastanın 5 (%33)'inde oftalmopati vardı. Metimazol başlangıç dozu 0,43±0,3 (0,1-1) mg/kg/gün ve ortalama izlem süresi 22,3±6,3 aydı. Hashitoksikoz tanısı alan 3 hastanın 2'sinin semptomları sadece beta-bloker tedavisiyle kontrol altına alınırken bir hastanın hiçbir medikal tedaviye ihtiyacı olmadı. 15 Graves hastasının 11 (%73)'ine tedavi başında beta bloker başlandı. Ortalama beta bloker dozu 31,6±10,2 (20-80) mg/gün saptandı. Metimazol başlanan hiçbir hastanın izleminde yan etki görülmedi.

Sonuç: Graves hastalığı ve hashitoksikoz çocukluk ve adölesan dönemde görülen tritoksikoz vakaların çoğunu oluşturur. Hashitoksikozun prognozu daha iyi olduğu için bu iki hastalığı başlangıçta ayırt etmek gereklidir. Her ne kadar çocukluk ve adölesan çağı tirotoksikoz tedavisi için kanıta dayalı stratejiler olmasa da metimazol tedavide ilk seçenektir. Çocukluk ve adölesan çağı tirotoksikozu anlayabilmek için daha çok merkezin deneyimlerini paylaşmasına ihtiyaç vardır.

Anahtar kelimeler: Tirotoksikozis, Graves hastalığı, hashitoksikoz, çocukluk dönemi, ergenlik.

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Introduction

Thyrotoxicosis is a clinical condition caused by excessive amounts of circulating thyroid hormones, irrespective of the source. It can be due to increased thyroid hormone synthesis and secretion, or increased secretion of preformed thyroid hormones as in the initial phaseof thyroiditis, or excessive ingestion of exogenous thyroid hormones [1].

The most common form of thyrotoxicosis in both children and adults is Graves' disease (GD), which is characterized by diffuse goiter, ophthalmopathy. GD occurs as a result of thyroid stimulation by thyroid-stimulating hormone (TSH) receptor stimulating antibodies (TSH receptor antibodies [TRABs]) [2]. However, GD is rare in childhood, with the incidence of 0.1-3 per 100.000, increasing incidence rate have been reported by several studies [3, 4]. Toxic adenom, toxic multinoduler goiter, Hashimoto's disease, transient neonatal hyperthyroidisim, McCune Albright syndrome are other rare causes of thyrotoxicosis [1, 5].

There are 3 major treatment options for childhood thyrotoxicosis: antithyroid drugs (ATD), thyroidectomy, and radioactive iodine (RAI) treatment. Medical therapy is usually recommended as the first-line treatment and it is associated with side effects and high relapse risk even after prolonged therapy. Patients with thyrotoxicosis who do not respond to medical therapy or who have adverse reactions to ATD must be managed with a second line treatment, such as RAI or thyroid surgery [6]. Less than 30% of pediatric patients remain in remission after discontinuation of on average 2 years ATD treatment [5]. Relapse rates are higher in children than in adults [7]. The factors affecting remission and relapse remain a matter of debate.

Still there is no evidence-based strategy for the management of childhood thyrotoxicosis and optimal duration of ATD treatment. For this reason, it is important to share the experiences of centers. We aimed in this study to describe clinical characteristics, biochemical features, clinical course and treatment outcomes of thyrotoxicosis in children and adolescents, especially GD.

Materials and methods

Medical records of the patients who had been diagnosed with thyrotoxicosis between 2015 and 2019 in the pediatric endocrinology clinic were screened retrospectively. Thyrotoxicosis was defined as the presence of low TSH (0.34-5.6 µIU/mL), high fT4 (0.8-1.12 ng/dL) and fT3 (2.6-4.35 pg/mL) along with the clinical findings as tachycardia, goiter, weight loss, tremor, irritability, exophthalmos and hot intolerance. TRAB positivity is defined as the level above 14 U/L. Normal level of anti-TPO or anti-Tg antibodies is defined as 0-4 IU/ml and 0-9 IU/ml respectively. GD was diagnosed based on clinical and laboratory evidence, including thyrotoxicosis, diffuse goiter, with or without ophthalmopathy, elevated free T4 and/or T3 and suppressed TSH levels, and presence of TRAB positivity [8]. Thyroid ophthalmopathy was evaluated by ophthalmologists. The thyrotoxic phase of Hashimoto's disease (hashitoxicosis) was defined as thyrotoxicosis with the presence of at least one of the anti-TPO or anti-Tg antibodies in patients.

Medical records were reviewed for clinical details including gender, anthropometric measurements (weight, height and body mass index [BMI]; the weight in kilograms divided by the square of the height in meters) age at diagnosis, family history, presence of goiter, ophthalmopathy, initial thyroid hormone levels, TRAB positivity, treatment details including initial dose of ATD, presense of beta blocker, side effects and second line treatments. Standard deviation scores (SDS) of weight, height and BMI of patients were calculated by using reference values for Turkish children [9].

Patients were initially followed at 2-4-week intervals and then every 3 months after thyroid function test results normalized. Remission was defined as having normal thyroid function tests for at least 3 months and no recurrence of thyrotoxicosis during the follow-up period after cessation of ATD. Relapse was defined as recurrence of thyrotoxicosis at any time off treatment.

Ethical approval for this study was obtained from Gaziosmanpaşa Training and Research Hospital Clinical Research Ethical Committee.

Statistical analysis

Continuous variables were described as median and ranges, and all analyses were performed using IBM SPSS Statistical Software (version 22, SPSS Inc., Chicago, IL, USA).

Results

Atotal of 18 patients were studied. The majority of the patients were female (14 females, 4 males). The median age at diagnosis was 14.58±2.1 years (9.2-17.8). 15 (83.3%) patients had been diagnosed with GD and 3 (16.6%) patients had hashitoxicosis. The mean weight SDS, height SDS, BMI SDS was 0.98±0.5, 0.44±0.2, 0.88±0.3 respectively. The most common presenting complaints among patients with GD were malaise, tachycardia/ palpitation and swelling in the neck. The other complaints were weight loss, tremor, enlargement of eyes. While a patient with a diagnosis of hashitoxicosis was detected incidentally, other two patients' complaints were malaise and palpitations. Of the 18 patients who entered the study, 12 (66.6%) patients have family history (9 patients diagnosed with GD and 3 patients with hashitoxicosis). Goiter was detected in the physical examination of 9 (50%) patients (7 patients diagnosed with GD and 2 patients with hashitoxicosis). Of the 15 patients who diagnosed with GD, 5 (33%) patients had ophthalmopathy.

The mean TSH, fT4 and fT3 levels at diagnosis were 0.011±0.018 (range 0.015-0.07) µIU/mL, 3.4±1.9 (range 1.98-5.47) ng/dL, 12.7±5 (range 6.91-30) pg/mL, respectively. While anti-TPO antibody was positive in all patients, anti Tg antibody was positive only in 12 patients. The mean level of anti-TPO and anti-Tg antibodies were 328±66.8 IU/ml, 21.6±5.4 IU/ml respectively. TRAB was positive in all patients with diagnosed GD.

Methimazole treatment was started after diagnosis in GD, and the dose adjustment was made considering the increase in fT4 and fT3. The mean initial dose of methimazole was 0.43±0.3 (range 0.1-1) mg/kg/day and median follow-up duration was 22.3±6.3 (range 6-47) months. Other three patients, diagnosed with hashitoxicosis did not receive ATD. When thyroid hormone levels were normalized, methimazol doses were reduced to maintain a euthyroid state (dose reduction regimen). Two of 3 patients diagnosed with hashitoxicosis were managed only with beta blocker and one patient did not need any treatment. Eleven (73%) of 15 GD patients received beta blocker initially. The mean initial dose of beta blocker was 31.6±10.2 (range 20-80) mg/day.

Side effects were not seen any of 15 patients treated with methimazole. In two cases liver enzymes were mildly elevated at the begining of the treatment. Metimazol was adjusted lower dose. No additional cause was found in these patients who were investigated in terms of etiology of liver dysfunction. Their liver enzymes were found to be in the normal range during follow-up.

Methimazole was stopped in three of patients for possible remission after mean 28±6 (range 24-30) months follow-up time. One patient remained in remission till the study end (for 7 months). Other two patienst (13%) had relapse. In the relapsing cases, the relaps was observed in the first year (after 3 and 7 months). These patients were restarted on methimazole and were planned to underwent second line treatment. 2 of 15 GD patients underwent thyroidectomy (second line treatment) after 36 months follow-up duration (ATD could not be ceased during following up) and became hypothyroid. The remaining 10 patients have been still taking methimazole therapy. The patients who diagnosed with hashitoxicosis achived remission after mean 7.2±1.3 (range 3-10) months.

Discussion

So far there is no optimal accepted treatment for childhood and adolescence thyrotoxicosis. Therefore, we need more experience of treatment responses. However, the prognostic factors that could effect remission and the predictive markers of relapse are contraversial. Although the number of patients in this study is small, sharing of centers' own experiences is important in the management of juvenile thyrotoxicosis.

However GD is the most common cause of the thyrotoxicosis in children and adolescents, hashitoxicosis is the second most frequent cause with variable prevalence from 0.5% to 22% in different studies [10]. Hashitoxicosis can remit spontaneously with propranolol alone same as our patients in this study. Therefore,

it is important to distinguish between GD and hashitoxicosis. In this study, it was noted that patients with hashitoxicosis applied with more fuzzy complaints. However the differentiation between two diseases requires thyroid receptor antibody measurement. Neverthelessan absolute distinction between the two disorders may be difficult; indeed some authorities consider them to be at different ends of a continuum [11]. In this study 66% of patients have family history. Therefore, individuals with thyrotoxicosis in their family should be monitored more closely.

Goiter was detected in the physical examination of 9 (50%) patients. this emphasizes that thyroid examination is important in physical examination. Graves' ophthalmopathy is an inflammatory disease of the eye and orbital tissues, and its prevalence has been previously reported to range from 17.1-67.6% in children and adolescents with GD [12]. Among patients, 33% ophthalmopathy was seen. Methimazol was the first option treatment option in all GD patients as the other studies. Propylthiouracil is not recommended for use in children because of its potential severe hepatotoxicity [13].

However there are many side effects of methimazole as pruritic rash, jaundice, acolic stools, dark urine, arthralgias, abdominal pain, nausea, fatigue, fever, pharyngitis [14], we did not determine any of them. Nevertheless, all patients and their caregivers should be informed of side effects.

There is no precise duration of ATD therapy required to provide remission. It has been argued that prolonged medical treatment increases the the chance of remission. One study reported remission rates of 20%, 37%, 45%, and 49% after 4, 6, 8, and 10 years follow-up of 154 children treated with ATD and the use of methimazole in this group of children was associated with a very low rate of medication side effects [15]. In another study, conducted by Bayramoğlu et al. [16], has shown that the duration of treatment with ATD was significantly longer in the remission group than the relaps group. These data suggest that treatment for longer periods (1-3 years) is also reasonable, as long as side effects to medication do not occur. Consistent with the literature, medical treatment of patients who did not undergo spontaneous remission and had no drug side effects continued for up to 30 months.

Remission rates after ATD cessation varied in different studies ranging from 33% to 64% [14, 17, 18]. In this study, 1 patient remained in remission for seven months. Important number of patients may never achieve remission with ATD or may relaps after remission. In this study, relaps rate was 13%. Literature has shown that relaps rates are highly variable and it is higher than adults. In a study Leger and Carel [7] determined that 75% of the relapses were seen within the first 6 months, 10% after 18 months after cessation of ATD therapy. We had seen the relaps in two patients in the 7 months. This information underline the importance of regular controls during the first year after cessation of ATD.

Age, gender, size of the thyroid gland, severity of biochemical hyperthyroidism at the time of diagnosis, TRAB levels at the beginning, duration of medical treatment were defined as prognostic factors of remission risk or relapse risk of childhood GD. Since GD is a multifactorial disease the factors associated with remission may vary from person to person. This may be the results of the differences of the studies [6].

The studies suggest that for patients who do not achieve remission after approximately 2 years treatment with ATD therapy, experienced side effects or had difficulties with compliance, RAI orsurgery should be considered [10]. Thyroidectomy is an effective treatment for GD, but it is associated with a higher complication rate in children than in adults [18]. Thyroidectomy should be performed in children who are too young for RAI, an provided by the surgeons who are experienced in conducting thyroidectomies in children [14]. Total thyroidectomy is preferred to subtotal thyroidectomy due to the high risk of remission [19]. After total troidectomy patients should use levothyroxine to the end of the life. However, it is easier to treat hypothyroidism than hyperthyroidism, in practise to maintain normal TSH during life and adhererence is a problem. Total thyroidectomy was preferred for two patients who could not discontinue ATD.

The major limitation of this study was its retrospective nature and due to low number of patient, GD and hashitoxicosis groups could not compared. Additionally, thyroid enlargment was subjective. Since TRAB was working in different centers, the exact values could not be given.

In conclusion, GD and hashitoxicosis are the most common form of thyrotoxicosis in both children and adults. Since it is known that GD is affected by multipl environmental and genetic factors, different experiences of many centers will provide more enlightenment. Long term follow-up is essential and compliance with treatment should be supported.

Conflict of interest: The author has no conflict of interest to declare.

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Informed consent: Written informed consent was obtained from patients who participated in this study.