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Hyperthyroidism in Pediatric Patients in a University Hospital: Ten Years of Experience

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Abstract

Although rare in childhood, hyperthyroidism is diagnosed by suppressed serum thyrotropin (TSH) levels and increased levels of free triiodothyronin (fT3) and free thyroxine (fT4) in addition to history and physical examination findings. In this study, we aimed to investigate the causes of hyperthyroidism and the clinical features of the disease in children and to evaluate the treatment. A total of 39 patients with hyperthyroidism diagnosed between 2010 and 2019 in the pediatric endocrinology department were included in the study. The diagnosis of hyperthyroidism was established on the basis of the suppressed serum TSH level and increased fT3 and/or fT4 levels with clinical findings. Thirty-one (79.5%) patients were female, and the mean age of admission was 14.4 (4.3-17.5) years. Of the cases, 33 (84.6%) were diagnosed with Graves' diseases and 6 (16.7%) with Hashimoto thyroiditis. The most frequent complaints of patients diagnosed with hyperthyroidism were irritability (24, 61.5%), palpitation (22, 56.9%), and sweating (21, 53.8%). The most frequent findings were goiter in 31 (79.5%) patients and tachycardia in 27 (69.2%) patients. Serum TSH levels were suppressed in all patients, fT3 levels were increased in 94.4% of them, and fT4 levels were increased in 80.5% of them. In patients with Graves' disease, TSH receptor antagonist was positive in 31 (93.9%) cases, and at least one of the thyroid autoantibodies was positive in all patients. Antithyroid drug treatment was initiated in all patients; 35 of them received methimazole and 4 of them received propylthiouracil. Radioactive iodine treatment was applied to three patients, and two patients were treated surgically who did not respond to antithyroid drug treatment. Antithyroid drug adverse effects were observed in 7 (21.2%) patients, requiring drug discontinuation in 1 patient. Although hyperthyroidism is rare in childhood, its treatment is difficult and requires close follow-up. Treatment options are different for adult patients. There is a need for multicenter studies to evaluate treatment efficacy and long-term outcomes in children.

Keywords: Hyperthyroidism, child, TSH, Graves' disease

Introduction

In childhood, hyperthyroidism is a rare thyroid gland disease caused by increased thyroid hormone levels. Increased synthesis and secretion of thyroid hormones results in increased metabolism. The most common cause is Graves' diseases in childhood.[1] Other reasons include; thyroiditis, toxic adenoma, hyperthyroidism due

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to iodine excess, thyroid hormone resistance, pituitary adenoma producing thyrotropin (TSH), and occasionally exogenous high-dose thyroid hormone intake.

The incidence of Graves' disease, the main cause of hyperthyroidism in children, is approximately 1/10.000 in this age group. Graves' disease is an immunogenetic disease characterized by diffuse goiter, hyperthyroidism, and infiltrative ophthalmopathy. It is more common in females and peak in the adolescent age group.[2] Anti-thyroid drugs, radioactive iodine (RAI) therapy, and surgery are treatment options for hyperthyroidism. The level of TSH receptor antagonist (TSHRAb) and the size of the thyroid tissue are often helpful in determining the efficacy of drug treatment.[1,3]

Here, we evaluated patients with hyperthyroidism who were followed up in the pediatric endocrine department of a university hospital.

Material and Method

Patient Selection

A total of 39 pediatric patients between 0 and 18 years of age who were followed up with a diagnosis of hyperthyroidism in the department of pediatric endocrinology between 2010 and 2019 were included in the study.

The age of admission, age at diagnosis of patients who were diagnosed in another center, gender, consanguinity, family history of thyroid disease, accompanying disease, medication use, admission complaints, clinical findings, thyroid hormone and thyroid autoantibody levels, treatment regimens, adverse effects, and treatment outcomes were retrospectively recorded from the patient files.

Body weight and height measurements of the patients at diagnosis were recorded. Body mass index (BMI), standard deviation scores (SDS) of height, and BMI were calculated. The physical examination findings (heart rate, systolic and diastolic blood pressure, presence of goiter, ophthalmopathy, tremor, and pubertal status (pre-pubertal and pubertal) at the time of admission were recorded. Systolic and diastolic blood pressures were assessed according to reference values determined by age and gender. Hypertension was defined as blood pressure above 95th per centile of normal for age and gender. Pulse pressure was defined as the difference between systolic and diastolic blood pressure, and >40 mmHg was accepted as an increased pulse pressure.[4]

The study was approved by the Necmettin Erbakan University Non-pharmaceutical and Non-medical Device Research Ethics Committee (date: 15.01.2018; number: 1164).

Clinical, Laboratory, and Radiological Evaluations

Exophthalmos on physical examination, retraction of the upper eyelid, and presence of at least one of the lid lag findings were accepted as ophthalmopathy.[5] Ophthalmopathy was assessed according to the evaluation of a pediatric endocrinologist who subjectively examined the patient. Pubertal status was assessed according to Tanner staging.[6,7]

The free triiodothyronin (fT3), free thyroxine (fT4), and TSH levels of the patients at diagnosis were recorded. The reference values were; fT3: 2.5-5.2 pg/mL, fT4: 0.97-1.67 ng/dL, TSH: 0.27-4.2 µIU/mL.[3] TSHRAb, anti-thyroid peroxidase antibody (antiTPO), and antitiroglobulin antibody (antiTG) levels were recorded as thyroid autoantibodies. Thyroid ultrasonography (thyroid gland size, parenchymal echogenicity, presence of nodule) and thyroid scintigraphy results were recorded. Thyroid volume for each lobe was calculated according to measurements on ultrasonography using the formula: height width depth 0.529. The arithmetic sum of the volume of both lobes was used to determine the total volume of the gland. The volume of the thyroid gland was assessed by comparison with the reference values of World Health Organization according to age and gender.[8]

Definitions

Hyperthyroidism was defined as an increase in fT3 and/or fT4 levels and suppression of TSH levels with clinical findings. Euthyroidism was defined as serum TSH, fT4, and/or fT3 levels within the normal reference range.[3] The diagnosis of Graves' disease was established by the presence of clinical and laboratory findings of hyperthyroidism, positive TSH receptor antibodies, and/or ophthalmopathy. The diagnosis of Hashimoto thyroiditis was established by clinical findings of hyperthyroidism and the absence of TSH receptor antibodies, increased thyroid autoantibody levels, and/or the presence of goiter and the presence of increased thyroid echogenicity on ultrasonography.[1] Clinical and biochemical euthyroid status at least 1 year after the discontinuation of antithyroid drug therapy or clinical and biochemical hypothyroidism without antithyroid drug therapy was defined as remission. Relapse was defined as the reappearance of signs and symptoms of hyperthyroidism after at least 18 months of antithyroid drug therapy.[1]

Statistical Analysis

Statistical analyses were performed using SPSS software version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, version 19.0. Armonk, NY: IBM Corp.) Categorical data were presented with n and %, and numerical data with mean ± standard deviation if normally distributed, and median (IQR) if non-normally distributed.

Results

Thirty-one (79.5%) patients were female. The median age at admission was 14.4 (4.3-17.5) years. The demographic and clinical data of the patients are summarized in **Table 1**. Thirty-one (79.5%) patients were in the pubertal period. In 9 (23.1%) patients, there was a consanguineous marriage between parents. Thirteen (33.3%) patients had a family history of autoimmune thyroid disease. Down syndrome in 1 patient, asthma in 1 patient, and type 1 diabetes mellitus in 1 patient were accompanying diseases.

Thirty-three (84.6%) patients with hyperthyroidism had Graves' disease, and 6 (16.7%) had Hashimoto

thyroiditis. The most frequent complaints of the patients were nervousness (n=24, 61.5%), palpitation (n=22, 56.9%), sweating (n=21, 53.8%), weight loss (n=20, 51.2%), and fatigue (n=19, 48.7%). Other symptoms included heat intolerance, swelling in the neck, tremor, increased appetite, exophthalmos, attention deficit, hyperactivity, and sleep disturbance.

The most frequent physical examination findings in patients with hyperthyroidism was goiter in 31 (79.5%) patients, tachycardia in 27 (69.2%) patients, increased pulse pressure in 23 (59%) patients, and exophthalmos in 15 (38.5%) patients.

Median heart rate was 110 beats/min, mean systolic blood pressure was 107.5±15.2 mmHg and mean diastolic blood pressure was 67.5±14.0 mmHg. In 3 (8.3%) patients, systolic blood pressure was above 95th percentile. The median BMI SDS of patients with hyperthyroidism was 0.02 (-2.13; 1.50) and the median height SDS was 0.15 (-2.38; 2.60).

The median fT3 level of the patients was 9.76 (4.92-27.67) pg/mL, median fT4 level was 4.55 (1.43-9.02) ng/dL, and median TSH level was 0.035 µIU/mL (0.0006-0.85). TSH was suppressed in all patients, fT3 level was increased in 94.4%, and fT4 level was increased in 80.5% of them. In patients with Graves' diseases, TSHRAb levels were found to be positive in 31 (93.9%) patients. Thyroid microsomal antibody level was positive in 20 (60.6%) patients and antithyroglobulin antibody were positive in 23 (69.7%) patients. In 33 patients with Graves' diseases, at least one of the thyroid autoantibodies was positive.

The thyroid ultrasonography was normal in 7 (19.4%) patients, the parenchyma was heterogeneous and the gland was enlarged in 29 (74.4%) patients, and parenchymal fibrosis was present in 3 (7.7%) patients. Hyperactive diffuse involvement was detected in 13 (81.2%) of the 16 patients who underwent thyroid scintigraphy, and mild involvement was detected in 3 (18.8%) patients.

All patients were initially treated with antithyroid drug therapy, and in 21 (53.8%) patients, a tachycardia beta-blocker was also administered. At the time of first diagnosis, 35 patients were administered methimazole (MTZ) and 4 patients were administered propylthiouracil (PTU) therapy (**Table 2**). The median MTZ dose was 20 mcg (15-30 mcg) at baseline and follow-up. Antithyroid drug therapy was discontinued at the median 9th month (2-33 months). Six of the patients who were taking MTZ therapy were transferred to the adult endocrine unit at the age of 18. In 9 patients, antithyroid therapy was ongoing, and the median follow-up duration was 13 months (3-26 months). Total thyroidectomy was performed in two patients who were unresponsive to antithyroid drug treatment and had advanced goiter at the 18th and 30th months of treatment. No significant relationship was found between antithyroid drug doses and thyroid hormone levels, and remission and remission periods. RAI treatment was administered to three patients. A total of 9 patients were started on thyroid hormone replacement. This included 4 patients with Hashimoto's thyroiditis, 3 patients after RAI treatment, and 2 patients after total thyroidectomy. In one of them, the reason was neutropenia due to PTU and unresponsiveness to drug treatment. In one patient, MTZ treatment was switched to PTU due to drug rash. The most recent status of seven patients who did not continue follow-up could not be determined.

In our study, adverse effects of antithyroid drugs were detected in 7 patients (21.2%), including MTZ-induced agranulocytosis and widespread rash, 2 cases of rash, 2 cases of mild transaminase elevation, and 1 case of mild thrombocytopenia. The remaining 5 cases were mild and did not require drug discontinuation.

Highlights

- Hyperthyroidism is a rare thyroid gland disease caused by increased levels of thyroid hormones in childhood.
- Graves' disease is by far the most common cause of hyperthyroidism in children and adolescents, is more common in females, and usually presents during adolescence.
- Clinical manifestations of hyperthyroidism include modest acceleration of linear growth and epiphyseal maturation, weight loss or failure to gain weight, excessive retraction of the eyelids causing lid lag and stare, tachycardia and increased cardiac output, increased gastrointestinal motility, proximal muscle weakness, tremor, hyperreflexia, sleep disturbance, distractibility with unexplained poor school performance, and emotional lability.

Discussion

Hyperthyroidism is a rare condition in children, and the most common cause is Graves' disease. It especially peaks during adolescence. The gender distribution of Graves' disease is 5/1, in favor of females.[1] The most common cause of hyperthyroidism in our study was Graves' diseases while Hashimoto thyroiditis was the second. The median age of the patients was 15.7 years, and 80.5% of them were female. Four-fifths of the cases were diagnosed in the pubertal period. The age and gender distribution of the patients was found to be consistent with the literature.

Symptoms and signs may be minimal in the early stages of the disease because the establishment of the disease could take months. Usually, the first signs are changes in behaviors and failure in school. Insomnia, restless sleep, and nocturia are frequently observed and are usually associated with fatigue and lethargy during the daytime. In addition, palpitations, frequent defecation, and increased sweating are common symptoms.[1,9] In our patients, it was thought that the first complaints were ignored and they were usually admitted when more disturbing findings emerged, such as nervousness and palpitations. When we evaluated retrospectively, we found that behavioral changes and failure in school were frequent.

Graves' diseases is an immunogenetic disease, and 60% of patients have a family history of autoimmune thyroid disease. It has been shown that there is a relationship between Graves' disease and a single nucleotide polymorphism in the *PTPN22* gene on

chromosome 1p13. The concordance rate between monozygotic twins is 20-60%, which indicates the role of environmental factors in the development of disease.[10-12] In our study, family history of autoimmune thyroid disease was 33%, which is less than that reported in the literature. Graves' disease may be accompanied by autoimmune diseases such as Hashimoto thyroiditis, vitiligo, systemic lupus erythematosus, rheumatoid arthritis, Addison's disease, myasthenia gravis, type 1 diabetes mellitus, and pernicious anemia.[13] One of our patients was diagnosed with type 1 diabetes mellitus in addition to Graves' diseases.

Thyromegaly (goiter) is present in many patients.[14] The thyroid gland usually grows symmetrically and is smooth, soft, and painless. A palpable thrill or audible murmur may be present, indicating increased blood flow in the gland. In our study, the most common finding was goiter.

Table 1.
Demographic data and clinical findings of the patients with hyperthyroidism

Age, month (median, range)	4.4 (4.3-17.5)
Gender, female, n (%)	31 (79.5)
BMI, SDS (median, range)	0.02 (-2.13;1.50)
Height, SDS (median, range)	0.15 (-2.38;2.60)
Heart rate, min (median, range)	110 (82-148)
Systolic blood pressure, mmHg (mean ± SD)	107.5±15.2
Diastolic blood pressure, mmHg (mean ± SD)	67.5±14.0
Complaints, n (%)	
Nervousness	24 (61.5)
Palpitation	22 (56.9)
Sweating	21 (53.8)
Weight loss	20 (51.2)
Fatigue	19 (48.7)
Heat intolerance	13 (33.4)
Neck swelling	11 (28.2)
Tremor	9 (23.1)
Eye edema	9 (23.1)
Others	7 (17.9)
Physical examination findings, n (%)	
Goitre	31 (79.5)
Tachycardia	27 (69.2)
Increased pulse pressure	23 (59)
Exophthalmos	15 (38.5)
Laboratory	
Free T3 pg/mL	9.76 (4.92-27.67)
Free T4 ng/dL	4.55 (1.43-9.02)
TSH µIU/mL	0.035 (0.0006-0.85)
TSHRAb positivity n (%)	32 /33 (97)
Anti-thyroid peroxidase antibody positivity, n (%)	20/33 (60.6)
Antitiroglobulin antibody positivity, n (%)	23/33 (69.7)

BMI; Body mass index, SDS; Standard deviation scores, SD; Standard deviation, T3; Triiodothyronin, T4; Thyroxine, TSH; Thyrotropin, TSHRAb; TSH receptor antagonist

Table 2.
Treatment modalities and recent status of patients

Treatment/recent status	n (%)
Antithyroid drug (initial); Methimazole Propytiouracil	 35 (89.7) 4 (11.3)
β-blocker	21 (53.8)
Radioactive iodine	3 (7.7)
Surgery	2 (5.1)
Antithyroid drug users who are in remission	10 (25.6)
Follow-up without treatment	6 (15.4)
Patients who developed hypothyroidism and are receiving L-thyroxine treatment	9 (23.1)
Transferred to adult endocrine unit	7 (17.9)
Not continuing follow-up	7 (17.9)

More than half of children and adolescents with Graves' disease may have ophthalmic abnormalities. In most patients, signs and symptoms are relatively mild. These include; lid lag, retraction in the lid, proptosis, conjunctival injection, chemosis, periorbital edema, and less frequent pain in the eye, restlessness, and diplopia.[15,16] Exophthalmos was present in 36.1% of our patients. Because ophthalmopathy is mild in childhood, it is usually self-limiting and does not require treatment. Eye symptoms usually regress after controlling hyperthyroidism. Rarely, symptomatic treatment is needed, such as oral corticosteroids, orbital radiation, and surgical decompression. In our study, symptomatic treatment was not required for patients with eye findings.

In almost all hyperthyroid patients, serum TSH levels are either too low or unmeasurable.[1,17] In our study, TSH was suppressed in all patients, consistent with the literature, and the median level was 0.035 μIU/mL (0.0006-0.85). The number of patients with increased fT3 levels was greater than the number of patients with increased fT4 levels, similar to the literature. TSHRAb positivity was detected in 93.8% of patients with Graves' diseases. In Graves' diseases, thionamide treatment reduces TSHRAb levels via an immunomodulatory effect. Two patients with negative TSH receptor antibody had been given antithyroid treatment, which may be the reason for this negativity. In addition, Graves' disease with negative TSHRAb levels has also been reported.[18,19]

Hyperthyroidism is resistant and progressive in untreated Graves' disease patients. Spontaneous remission in children with Graves' disease is very rare, approximately 30%. Low levels of TSHRAb and low thyroid gland volume may indicate remission with medical treatment. If the TSHRAb level is high and the thyroid gland is large, the spontaneous remission rate is low. There are three treatment options for children and adolescents with hyperthyroidism; medical treatment, surgical treatment, and RAI.[20] Antithyroid drug therapy is used as the first option in childhood, but its long-term use is not recommended because of the low remission rate and serious adverse effects. The drugs used for antithyroid treatment are PTU and MTZ. In the initial treatment, MTZ was administered to 35 patients and PTU was administered to 4 patients. These drugs are iodinated and degraded in the thyroid gland, thus preventing the formation of T4 and T3. These drugs may have serious adverse effects such as agranulocytosis, hepatotoxicity, and systemic vasculitis, and if these adverse effects develop, they should be discontinued immediately. In addition, urticaria, arthritis, nasal discharge, abnormal taste sensation, and pruritus are other moderate side effects. In the literature, the frequency of adverse effects is reported to be approximately 13%.[20,21] In our study, adverse effects were detected in 21.2% of patients. It was higher than that reported in the literature, and we considered that this situation could have resulted from the admission of more complicated cases to our clinic because our clinic is a reference hospital.

While RAI therapy has been used for many years in adults as a first-line treatment for hyperthyroidism, its use in children and adolescents is limited, and it is preferred as a second option in the treatment. In children and adolescents, there is a concern that free RAI administration may increase the frequency of thyroid cancer and leukemia over a long follow-up period. It has been reported that iodine doses administered for treating hyperthyroidism do not induce mutagenesis. Improvement is usually achieved within 3 to 6 months with RAI treatment, and second or third doses are rarely needed.[22,23] In our study, single-dose RAI treatment was administered to 3 patients because of adverse effects and unresponsiveness to treatment, and permanent hypothyroidism developed during follow-up.

Surgical treatment is the fastest-acting option of the treatment. Before surgery, iodine preparations are recommended for at least 10-14 days and then subtotal or total thyroidectomy is performed. Surgery is rarely recommended because of the increased use of RAI therapy in children. Nevertheless, numerous goiter, medical treatment failure, cases not accepting RAI treatment, patients under the age of 5 years and solid "cold" nodules are indications for surgical treatment.[2,17,24] In our study, total thyroidectomy was performed in two patients due to a large goiter.

Conclusion

In conclusion, although hyperthyroidism is rare in childhood, its treatment is difficult and requires close follow-up. Treatment options differ from those of adult patients, and there is a need for multicenter studies evaluating treatment efficacy and long-term outcomes.

Ethical Approval: The study was approved by the Necmettin Erbakan University Non-pharmaceutical and Non-medical Device Research Ethics Committee (date: 15.01.2018; number: 1164).

Informed Consent: Retrospective study.

Author Contributions: Kocabey Sütçü Z: Surgical and Medical Practices, Concept, Design, Data Collection or Processing, Analysis or Interpretation, Literature Search, Writing.; Eklioğlu BS: Surgical and Medical Practices, Design.; Atabek ME: Surgical and Medical Practices, Design, Analysis or Interpretation.

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