

Graves' Disease in Albanian Children

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ABSTRACT: Background: Graves' disease (GD) accounts for 10–15% of thyroid disorders in patients less than 18 years of age. It is the most common cause of thyrotoxicosis in children and accounts for at least 95% of cases in children. Pediatric Treatment of Graves' disease consists of anti-thyroid drugs, radioactive iodide and thyroidectomy but the optimal treatment of GD in children is still controversial. **Objective:** To review treatment outcome of pediatric Graves' disease in Albania. **Material and Method:** Descriptive review of 15 children with Graves' disease, diagnosed from Jan.2007 to Dec. 2013, at the Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania was performed. **Results:** All patients, mean age 10.56 ± 3.37 years, (range 2.02-16.09 years) were presented with goiter and increased serum FT4, mean 39.80 ± 16.02 ng/mL, (range 21.0-74.70 ng/mL), serum FT3, mean 12.98 ± 3.45 pg/mL, (range 6.90 -17.90 pg/mL) and suppressed TSH levels, mean 0.02 ± 0.01 mUI/L, (range 0.01-0.05 mUI/L). Anti TSH Receptor were positive in 100% of patients mean value 6.51 ± 3.61 UI/mL (range 1.63 – 14.10 UI/mL). Anti-thyroglobulin and Anti-TPO antibodies were positive in 60% and 46.6% respectively. Clinical course of 15 patients after treatment with anti-thyroid drugs mainly MMI for 3.19 ± 1.48 (range 0.60 - 6.20) years is as follows: seven (46.66%) underwent remission, five out of seven (71.41%) who underwent remission, relapsed. Three of them (20%) were treated with I^{131} , and two (13.3%) underwent to total thyroidectomy. **Conclusion:** MMI was the most common first line therapy in the presented patients with Graves' disease. Remission rate was 46.66% after an average 1.48 ± 0.71 years (range 0.60 – 2.70 years) of treatment with anti-thyroid drugs. Remission period was 2.70 ± 0.36 years (2.1 – 3.1 years) Relapse occurred in 71.41% of patient. I^{131} and thyroidectomy were used as second line therapy in the present study.

KEYWORDS: Graves' disease, Antithyroid drugs, Remission, Relapse, Radioactive iodide, Thyroidectomy

Introduction

Graves' disease is the most common cause of thyrotoxicosis in children and accounts for at least 95% of cases in children. It accounts for 10–15% of thyroid disorders in patients less than 18 years. of age [1, 2]. The incidence progressively increases throughout childhood. Graves' disease is more common in girls than in boys. The most of children with Graves' disease present classic symptoms and signs such as goiter, tachycardia, nervousness, exophthalmos, tremor, increase appetite, and hyperactivity. Important initial laboratory tests including elevated serum T4 and T3 with suppressed TSH.

Therapeutic options of Graves' disease are anti-thyroid drugs (ATD), radioactive iodide (RAI) treatment with I^{131} and thyroidectomy. To date, the best treatment is still controversial. Treatment with ATD is well known to be associated with low remission rates and high adverse side effects. Serious side effects including agranulocytosis and hepatitis occur rarely but can be fatal. However, anti-thyroid drugs are frequently used as a first-line therapy in children in many institutions. RAI is a highly effective treatment of Graves' disease. Many physicians avoid RAI as a first-line of treatment

in pediatric Graves' disease because the concerns of potential long-term consequences, especially thyroid neoplasm. Meanwhile, thyroidectomy yields high remission rates but requires highly-experienced thyroid surgeons.

The purpose of the present descriptive study was to evaluate the long-term treatment outcome of Graves' disease in 15 Albanian children.

Material And Method

The authors retrospectively reviewed the charts of 15 children treated for Graves' disease from Jan.2007 to Dec. 2013, at the Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital Centre "Mother Teresa", Albania. The diagnosis was confirmed by classic symptoms and signs, biochemical evidence of hyperthyroidism at diagnosis. TSH, FT4, FT3, At-TPO, At-TSH-receptor, At-TG, were measured by *IRMA AcM*, *RIA AcM*, *ICMA*, *RBA*, *ICMA* respectively. Thyroid volumes were measured by ultrasonography and were compared with reference values for thyroid diagnostics by age and gender [3]. All patients were initially given anti-thyroid drugs mainly methimazole. Propanolol was used in all patients with adrenergic symptoms. When hypothyroidism occurred during treatment of

Graves' disease, the doses of anti-thyroid drugs were decreased. Radioactive iodide (RAI) and thyroidectomy was the second line of treatment in patient with relapse. The age of the patients, duration of treatment and therapeutic outcome were recorded. The data are presented as mean \pm SD (range). Remission means successful cessation of anti-thyroid medication for more than 2 years. Relapse means reappearances of clinical or biochemical hyperthyroidism after discontinuation of anti-thyroid drugs.

Results

Patient characteristics

There were 11 girls and 4 boys (girls: boys = 2.75:1), mean age 10.56 ± 3.37 years, (range 2.02-16.09 years). The age of diagnosis in girls and boys were 10.84 ± 2.58 years (7.91-16.09 years) and 9.78 ± 5.45 years (2.02 -14.50 years) respectively. Seven children (46.66%), five girls

and two boys were pre-pubertal. Mean body mass index (BMI) was 15.45 ± 1.73 kg/m² (13.29 -19.57 kg/m²). Family history of thyroid disease was present in 33.3% of the patients. All patients had increased serum FT4, mean 39.80 ± 16.02 ng/mL, (range 21.0-74.70 ng/mL); serum FT3, mean 12.98 ± 3.45 pg/mL, (range 6.90 - 17.90 pg/mL) and suppressed TSH levels mean 0.02 ± 0.01 mUI/L, (range 0.01-0.05 mUI/L). Anti TSH Receptor were positive in 100% of patients, mean value 6.51 ± 3.61 UI/mL (range 1.63 – 14.10 UI/mL). Anti-thyroglobulin, mean value 696.84 ± 1170.82 UI/mL (range 2.30 – 3500.00 UI/ml) and Anti-TPO antibodies, mean 2195.89 ± 3528.31 UI/mL (range 5.60 – 11815.00 UI/mL) were positive in 60% and 46.6% respectively.

Thyroid volumes were above the 97th percentile for age and gender in 93% of patients (Fig. 1 and 2).

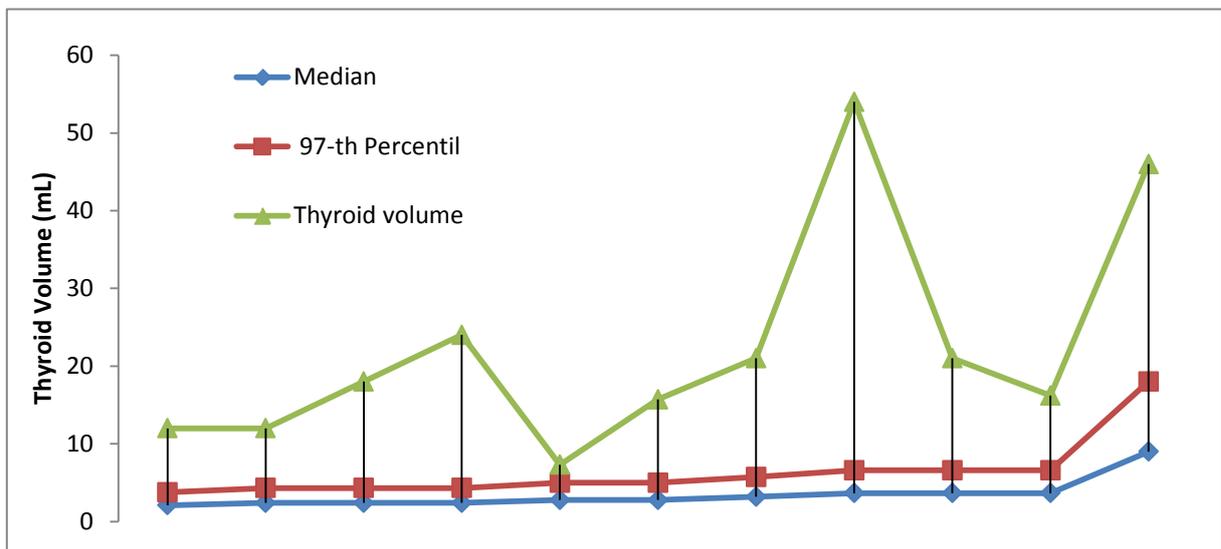


Fig.1. Thyroid volume in female with GD

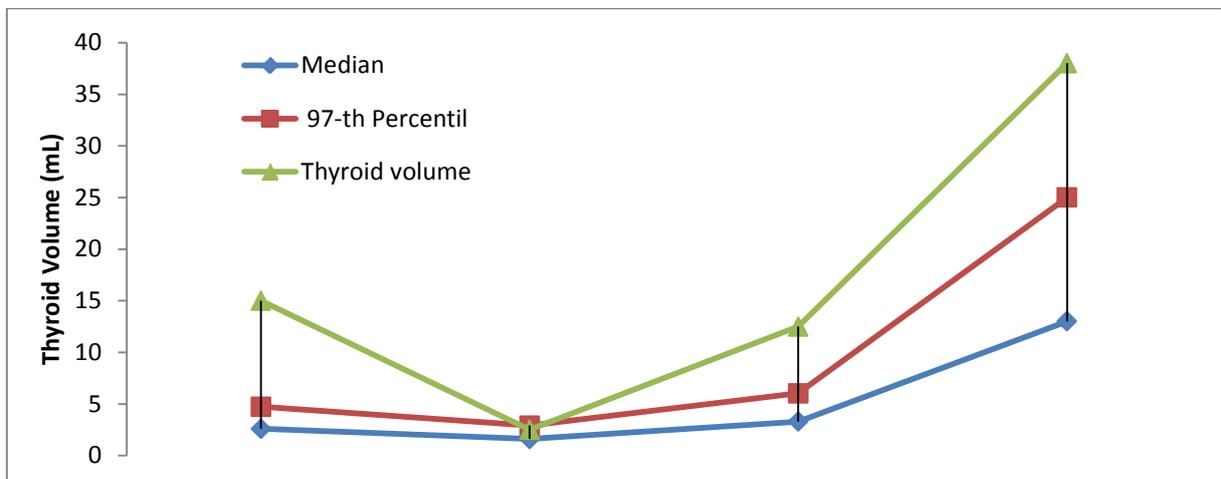


Fig.2. Thyroid volume in male with GD

Clinical presentation

Fourteen patients (93.3%) presented goiter while exophthalmos was present in thirteen (86.6%) of patients. Other signs and symptoms and their frequency are shown in Table 1.

Table 1. Signs and symptoms of GD

Symptoms and signs	Nr.	Percentage
Goiter	14	93.33%
Exophthalmos	13	86.67%
Irritability	12	80.00%
Tachycardia	12	80.00%
Sleep disturbance	10	66.67%
Fine tremor	9	60.00%
Increase appetite	8	53.33%
Weight loss	8	53.33%
Lose appetite	5	33.33%
Heat intolerance	4	26.67%
Dysphagia	4	26.67%
Heat intolerance	4	26.67%
Alopecia	3	20.00%
Vitiligo	1	6.67%
Dyspnoe	1	6.67%

Treatment outcome

Clinical course after initiation of anti-thyroid drugs

All patients ($n = 15$) received anti-thyroid drugs for 3.19 ± 1.48 (range 0.60 - 6.20) years. Seven patients (46.66%) underwent remission after 1.48 ± 0.71 years (range 0.60 - 2.70 years) of treatment with anti-thyroid drugs. Mean remission was period 2.70 ± 0.36 years (2.1 - 3.1 years).

Five out of seven patients (71.4%) who underwent remission had relapse. They received anti-thyroid drugs for 1.23 ± 0.04 years (1.20 - 1.25 years) before treatment discontinuation. Three of them had treatment with I^{131} . Two others underwent a total thyroidectomy.

Further outcome in ten patients (66.66%) is yet to be followed. MMI was just discontinued in two patients who are still in remission. Eight patients (53.33%) had never been off anti-thyroid drugs.

Two patients who were treated with MMI (mean duration 1.20 ± 0.71 years (range 0.71 - 1.70 years) were subsequently switched to PTU

(median dose 5.0 mg/kg/day, range 2.0-8.0 mg/kg/day) due to adverse reactions. One 9.5 years old girl developed hepatitis with mild elevated of transaminases and skin rash after 0.7 year of treatment with MMI. The other girl 9.6 years old had skin rash and arthralgia after 1.7 years of treatment with MMI. Adverse reaction subsided after MMI was discontinued in both patients.

Propranolol was administered in 12 patients (80.00%) to reduce adrenergic symptoms during the first few months

Radioactive iodide treatment with I^{131}

Three patients (20.00%) underwent I^{131} treatment due to relaps and persistent hyperthyroidism while being on anti-thyroid drugs. Initial doses of I^{131} were 150 μ Ci/gram of thyroid tissue. Mean age of patients treated with I^{131} was 14.91 ± 1.44 years (range 13.36 -16.22 years). These patients maintained euthyroidism after the follow up period of 0.6-0.9 year. One girl developed ophthalmopathy 6 months after of I^{131} and underwent to corticotherapy.

Thyroidectomy

Two girls (13.3%) underwent to total thyroidectomy. One was 15.21 years old, after 4.3 years of treatment (MMI for 1.7 years and PTU for 2.6 years). The indications of thyroidectomy were large goiter and poor compliance with PTU. The other girl was 14.94 years old, and she went to thyroidectomy after 3.6 years treatment with ATD (MMI for 8 months and PTU for 2.9 years).

Discussion

In this 7-year retrospective study of the treatment outcome of Graves' disease in 15 Albanian children, the authors demonstrated that remission rate following anti-thyroid medication mainly MMI was only 46.6% after average 1.23 years of treatment. In the present study, Graves' disease was more common in girls than in boys (girls: boys = 2.75:1) as previously reported [4]. Mean age of diagnosis was 10.56 years, which was comparable to other studies [5]. Goiter is the most common presenting symptom in pediatric Graves' disease. It has been reported to be present approximately in 90-100% of cases [5,6]. It was present in 93.3% of patients in our study. In previous studies, eye signs were present up to 70% of children with Graves' disease [6]. Exophthalmos was present in only 86.6% of patients in the present study. Other symptoms and signs of excessive thyroid hormone activity including tachycardia and irritability, were present in 80% of our patients.

Sleep disturbance, fine tremor, increase the appetite and weight loss were present in more than 50% of cases. Heat intolerance, dysphagia and dispnoea were less common. Family history of thyroid disease was present in 33.3% of the patients. All patients had increased serum T4, T3, At-TSH-receptor, and suppressed TSH levels. Anti-thyroglobulin and Anti-TPO antibodies were positive in 60% and 46.6% respectively.

Three therapeutic options are used to treat pediatric Graves' disease including anti thyroid drugs, radioactive iodide, and thyroidectomy. MMI and PTU are the available as anti-thyroid drugs in Albania. MMI was the most common first-line therapy for pediatric Graves' disease in the present study. When patients failed to medication, then radioactive iodide or thyroidectomy became second-line therapy. Remission rate after treatment with antithyroid drugs alone was achieved in only 46.66% of patients following mean duration of treatment of 1.5 years. Previously has been reported that remission rate was widely varied between 11-77%, but usually was less than 30-40% [7,8]. Duration of medical therapy before successful remission has been reported to be ranging from 2 to 6 years [9], 0.6 to 2.7 years in the present study. Side effects were seen in only 13.3% of MMI-treated patients.

The side effects associated with PTU in the present study was less than previously reported, due to small numbers of presented subjects that were treated with PTU. In other studies, side effects occurred in 20-30% of children during therapy with anti-thyroid drugs [7, 8, 10]. Major reactions including hepatitis and vasculitis were reportedly more common in patients who were treated with PTU than with methimazole [11]. Because less chance of developing major side effects, better compliance and possible better therapeutic outcome with methimazole[12, 13], it was more commonly used in children with Graves' disease in the present study.

To date, there is no consensus regarding the optimal length of anti-thyroid medication before considering cessation of medication in these children. I¹³¹ or thyroidectomy should be offered to patients who still had biochemical hyperthyroidism while on antithyroid drugs for an extended period of time. Radioactive iodide (RAI) treatment for children with Grave's disease has become more popular in many countries. The goal of RAI therapy is to destroy sufficient thyroid tissue to cure hyperthyroidism. Remission rate in pediatric Graves' disease has

been reported up to 95% in patient who were treated with I¹³¹[14]. In the present study, patients who underwent I¹³¹ treatment had received anti-thyroid drugs previously. The reasons of switching to I¹³¹ were persistent hyperthyroidism after relapse, poor adherence with medication and side effects of anti-thyroid drugs. Calculated I¹³¹ dose in three patients who were treated with RAI therapy was approximately 150 µCi/g of thyroid tissue. They became hypothyroid within 0.6-0.9 year.

Many physicians are reluctant to use RAI treatment in children with Graves' disease due to concern that these patients might later develop thyroid carcinoma. Previous data have shown that RAI treatment is not associated with moderate or high risks of future thyroid carcinoma in children older than 5 years [14]. In the present study, the authors treated their patients with RAI only in children who were older than 13 years since safety data are limited for very young children. The presented patients who had biochemical hypothyroidism after I¹³¹ treatment were followed for less than 2 years. Long-term follow-up of thyroid function is needed in these patients.

In the past, when thyroidectomy was indicated in children with Graves' disease, subtotal thyroidectomy was commonly performed in order to maintain euthyroid state. However, subtotal thyroidectomy resulted in a high recurrent rate (10-15%) of hyperthyroidism [15]. Hypothyroidism post thyroidectomy has become more acceptable and not been considered as a complication of thyroidectomy[16]. Two patients underwent total thyroidectomy due to a large goiter and persistent hyperthyroidism; one after 4.3 years of treatment and poor compliance with PTU, the other after 3.6 years treatment with ATD and large goiter.

Conclusion

MMI was the most common first line therapy in the presented patients with Graves' disease. Remission rate was only 46.66% after an average 1.5 years of treatment with anti-thyroid drugs. I¹³¹ and thyroidectomy were used as second line therapy in the present study. They were offered to those who developed side effects, had poor compliance or failed medication. For those who received I¹³¹, higher dose (150 µCi/g of thyroid tissue) seemed to be effective.

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