Treatment Outcome of Graves' Disease in Thai Children

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Background: *Graves' disease is the most common cause of thyrotoxicosis in children. 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 Graves' disease in Thai children.*

Material and Method: *Retrospective review of 32 children with Graves' disease, diagnosed between Jan.1994 and Dec. 2004, at the Division of Pediatric Endocrinology, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand was performed.*

Results: *All patients (median age 10.5 yrs, range 2.85-15 yrs) presented with goiter and increased serum T4 (median 18.4 mcg/dL, range 8.8-30 mcg/dL), serum T3 (median 443 ng/dL, range 206-800 ng/dL) and suppressed TSH levels (median 0.009 mU/L, range 0-0.18 mU/L). Anti-thyroglobulin and Anti-microsomal antibodies were positive in 70% and 82% respectively. All patients except two were initially treated with propylthiouracil (PTU). Two patients were initially treated with methimazole. Adverse reaction of PTU occurred in two patients (One girl had arthralgia, positive pANCA, nephritis and another girl had skin rash and arthralgia).Clinical course of 32 patients after treatment with anti-thyroid drugs mainly PTU for 3.4 (range 0.3-11.2) years is as follows: six (18.8%) underwent remission (cessation of PTU > 2 yrs), three (9.4%) relapsed, one (3.1%) underwent subtotal thyroidectomy, and seven (21.9%) had I^{131} treatment. All patients (6 of 7) who received I^{131} dose of 100 μCi/g of thyroid tissue required more than a single dose of I^{131} treatment. Further outcome in fifteen patients (46.9%) is yet to be followed. Among these patients PTU was just discontinued in four and eleven had never been off anti-thyroid drugs (four still had biochemical hyperthyroidism and seven were biochemically euthyroid).*

Conclusion: *PTU was the most common first line therapy in the presented patients with Graves' disease. Remission rate was only 18.8% after an average 3.5 years of treatment with anti-thyroid drugs. I^{131} or thyroidectomy was 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 I^{131}, higher dose (200 μCi/g of thyroid tissue) seemed to be more effective than the lower dose (100 μCi/g).*

Keywords: *Graves' disease, Children, Antithyroid drugs, Radioactive iodide, Thyroidectomy*

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Graves' disease is the most common cause of thyrotoxicosis in children. The incidence progressively increases throughout childhood. Graves' disease is more common in girls than in boys. Most children with Graves' disease present with classic symptoms and signs such as goiter, tachycardia, nervousness, exophthalmos, tremor, increase appetite, and hyperactivity. Important initial laboratory tests include 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

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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 treatment in pediatric Grave' disease because of 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 32 Thai children.

Material and Method

The authors retrospectively reviewed the charts of 32 children treated for Graves' disease from 1994 to 2004, at the Division of Pediatric Endocrinology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand. The diagnosis was confirmed with classic symptoms and signs, biochemical evidence of hyperthyroidism at diagnosis. Thyroid stimulating immunoglobulin was not routinely performed at the institution. All patients were initially given anti-thyroid drugs (either propylthiouracil (PTU) or methimazole). Propanolol was used in some patients to reduce adrenergic symptoms. If hypothyroidism occurred during treatment of Graves' disease, the doses of anti-thyroid drugs were kept the same and thyroxine was added or the doses of anti-thyroid drugs were decreased at each physician's preference. Radioactive iodide (RAI) and thyroidectomy were the second line therapy in some patients. The age of the patients, duration of treatment and therapeutic outcome in each individual were recorded. Since the presented data are not normally distributed, they are presented as median (range).

Remission means successful cessation of anti-thyroid medication $\geq$ 2 years. Relapse means reappearances of clinical or biochemical hyperthyroidism after discontinuation of anti-thyroid drugs.

Results

Patient characteristics

There were 24 girls and 8 boys (girls:boys = 3:1, median age 10.5 years, range 2.85-15 years). The age at diagnosis in girls and boys were 10.1 (2.9-13.7) years and 11.1 (7.7-15) years respectively. Most children (71.9%) were pre-pubertal. Median body mass index (BMI) was 15 (12.3-21.6) kg/m^2.

Table 1. Clinical characteristics of children with Graves' disease at their initial visits (n = 32)

Symptoms and signs	%
Goiter	100
Tachycardia	91
Irritability	78
Exopthalmos	63
Palpitation	69
Heat intolerance	50
Fine tremor	44
Weight loss	31
Diarrhea	27
Sleep disturbance	6

Family history of thyroid disease was present in 43.8% of the patients. All patients had increased serum T4 (median 18.4 mcg/dL, range 8.8-30 mcg/dL), T3 (443.4 ng/dL, range 206-800 ng/dL) and suppressed TSH levels (0.009 mU/L, range 0-0.18 mU/L) at initial diagnosis. Anti-thyroglobulin and Anti-microsomal antibodies were positive in 70% and 82% of patients respectively.

Clinical presentation

All patients presented with goiter while exophthalmos was present in 58% of patients. Other signs and symptoms are shown in Table 1.

Treatment outcome

All patients received anti-thyroid drugs as first line therapy. All patients except two were initially treated with PTU (median dose 6 mg/kg/day, range 2.3-10 mg/kg/day). Two were initially treated with methimazole (median dose 0.6 mg/kg/day, range 0.64-0.65 mg/kg/day). Five patients who were treated with PTU (median duration 2.2 years, range 1.2-3.2 years) were subsequently switched to methimazole due to poor compliance. Propranolol was administered in 27 patients (84.4%) to reduce adrenergic symptoms in the first few months. Thyroxine replacement was added in 13 patients (40.6%) to maintain euthyroidism.

Clinical course after initiation of anti-thyroid drugs

All patients (n = 32) received anti-thyroid drugs for 3.4 (0.3-11.2) years

Six patients (18.8%) underwent remission (median remission period 3.8 years, range 2.1-5.3 years) after 4.2 (2.4-11.2) years of PTU.

Three patients (9.4%) relapsed at 2.2 (1.9-5.5) years after discontinuation of anti-thyroid drugs (one received PTU, two received methimazole). They received anti-thyroid drugs for 3.7 (2.2-5.7) years before treatment discontinuation.

PTU was discontinued for less than 2 years (median 0.9 years, range 0.2-1.8 years) in four patients (12.5%). They had received PTU for 2.5 (2-3.7) years. One girl was diagnosed with systemic lupus erythematosus and subsequently died from mitral valve prolapse and congestive heart failure.

Eleven patients (34.4%) had never been off PTU. Among these, five still had biochemical hyperthyroidism after treatment with PTU for 2.6 (0.3-5.8) years. Six patients were euthyroid after 1.95 (0.3-5.4) years of PTU**.** However, all eleven patients were clinically euthyroid.

One 9 yr-old girl developed myasthenia gravis after 10 months duration of Graves' disease. Adverse reactions of PTU occurred in two patients (6.3%). One girl had arthralgia, positive perinuclear anti-neutrophil cytoplasmic antibodies (pANCA) and nephritis. This girl also developed chronic dacryoadenitis, an inflammatory disorder associated with autoimmune thyroiditis. The other girl had skin rash and arthralgia. Adverse reaction subsided after PTU was discontinued in both patients.

Thyroidectomy

One boy (3.1%) underwent subtotal thyroidectomy at the age of 18.6 years after 6.8 years of treatment with PTU. The indications of thyroidectomy were large goiter and his poor compliance with PTU. He still had biochemical hyperthyroidism 3 months after thyroidectomy and later was treated with PTU.

Radioactive iodide treatment with I^{131} (Table 2)

Seven patients (21.9%) underwent I^{131} treatment due to persistent hyperthyroidism while being on anti-thyroid drugs (median duration of anti-thyroid drugs 3.8 years, range 0.3-8.3 years). Initial doses of I^{131} were 100 μCi/gram of thyroid tissue in six patients (patients no.1-6) and 200 μCi/gram of thyroid tissue in one patient (patient no. 7). After first I^{131} treatment, patients no. 1-6 required more than one dose but patient no. 7 required only single dose of I^{131}. Median age of patients when treated with I^{131} was 15.2 years (range 11.0-18.9 years). Four patients developed hypothyroidism within 1.5-2 months after the last doses of I^{131}. Three patients maintained euthyroidism after the follow up period of 0.8-1.7 years.

Table 2. Clinical characteristics and treatment outcome of 7 children with Graves' disease who received I^{131} treatment

Patient number	Sex	Age at Dx (years)	Age of 1st I^{131} treatment (years)	Calculated first I^{131} dose (μCi/g of thyroid tissue)	Times of I^{131} treatment	Duration between 1st and 2nd dose, 2nd and 3rd dose	Outcome after last I^{131} treatment	Duration after last I^{131} treatment before developing hypothyroid	Follow up periods
1	Female	9.9	11	100	2	10 months	Hypothyroid	1.5 months	2 years
2	Female	10.3	15.4	100	2	2 months	Hypothyroid	2 months	1.75 years
3	Female	11	15.2	100	2	10 months	Euthyroid	-	0.7 years
4	Female	11.3	14.1	100	2	8 months	Hypothyroid	2 months	1.6 years
5	Male	11.3	18.6	100	2	10 months	Euthyroid	-	0.8 years
6	Male	15	18.9	100	3	13 and 10 months	Euthyroid	-	1.7 years
7	Female	13.7	13.8	200	1	-	Hypothyroid	1.5 months	1.3 years

Discussion

In this 10-year retrospective study of the treatment outcome of Graves' disease in 32 Thai children, the authors demonstrated that remission rate following anti-thyroid medication mainly PTU was only 18.8% after average 3.5 years of treatment.

Graves' disease is the most common cause of thyrotoxicosis in children. It is a significant medical problem that can be life-threatening and can adversely alter physical growth and development, including a child's ability to learn. In the present study, Graves' disease was more common in girls than in boys as previously reported[1].

Mean age of diagnosis in the present study was 10.3 years, which was comparable to other studies[2].

Goiter was present in all patients in the present study. Goiter is the most common presenting symptoms and sign in pediatric Graves' disease. It has been reported to be present approximately in 90-100% of cases [3-4]. Exophthalmos was present in only 58% in the present study. In previous studies, eye signs were present up to 70% of children with Graves' disease[3]. Other symptoms and signs of excessive thyroid hormone activity including tachycardia, irritability, and palpitation were present in > 50% of the presented patients. Weight loss, diarrhea, fine tremor, and sleep disturbance were less common. Since history of symptoms was obtained by recall, the prevalence of such symptoms might not be accurate. The diagnosis of Graves' disease was straightforward in the presented patients. All patients had increased serum T4, T3 and suppressed TSH levels.

The three therapeutic options used to treat pediatric Graves' disease include anti-thyroid drugs, radioactive iodide, and thyroidectomy. PTU and methimazole are the available anti-thyroid drugs in Thailand. PTU was the most common first-line therapy for pediatric Graves' disease in the present study. When patients failed medication, then radioactive iodide or thyroidectomy became second-line therapy.

Sustained remission after treatment with anti-thyroid drugs alone was achieved in only 18.8% of the presented patients following mean duration of treatment of 3.5 years. Remission rate after medical treatment has been previously reported to be widely varied between 11-77%, but is usually less than 30-40%[4,5]. Duration of medical therapy before successful remission has been reported to be ranging from 2 to 6 years[6].

In the present study, the authors found minor side effects in only 6% of PTU-treated patients. The side effects associated with PTU in the present study was less than previously reported. This could be due to small numbers of presented subjects. In other studies, side effects occurred in 20-30% of children during therapy with anti-thyroid drugs[4,5,7]. Major reactions including hepatitis and vasculitis were reportedly more common in PTU-treated patients than methimazole[8]. Despite less chance of developing major side effects, better compliance and possible better therapeutic outcome with methimazole[9,10], PTU was more commonly used in children with Graves' disease in the present study.

Regarding the association between Myasthenia gravis and autoimmune thyroid disease, myasthenia gravis has been reported in 0.2% of patients with autoimmune thyroid diseases[11].

In the present study, there were patients who still had biochemical hyperthyroidism while being on PTU. To date, there is no consensus regarding the optimal length of anti-thyroid medication before considering cessation of medication in these children. I^{131} or thyroidectomy should be offered to patients who still had biochemical hyperthyroidism while on anti-thyroid drugs for an extended period of time.

Only one patient underwent subtotal thyroidectomy due to a large goiter, persistent hyperthyroidism after almost 7 years of PTU, and poor compliance with PTU. Nevertheless, his hyperthyroidism relapsed. 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[12]. Currently, total thyroidectomy is recommended. Hypothyroidism post thyroidectomy has become more acceptable and not been considered as a complication of thyroidectomy.

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%[14]. In the present study, patients who underwent I^{131} treatment received anti-thyroid drugs previously. The reasons of switching to I^{131} were persistent hyperthyroidism, poor adherence with medication and side effects of anti-thyroid drugs.

Most of the presented patients required repeated RAI treatment. Calculated I^{131} dose in all patients who needed 2nd and 3rd RAI therapy was approximately 100 μCi/g of thyroid tissue. Only one

patient received only single dose of I^{131} 200 μCi/g of thyroid tissue and became hypothyroid within 1.5 months. Although the number of patients who received I^{131} in the present study was small, higher dose of I^{131} seemed to be more effective than the lower dose. Accumulating data have shown that an I^{131} dose of at least 150 μCi/g of thyroid tissue in pediatric Graves' disease is safer and effective than a lower dose[13]. Moreover, low doses of I^{131} (< 75 μCi/g of thyroid tissue) was associated with an increased risk of benign thyroid neoplasm in children[14].

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 of age[14]. In the present study, the authors treated their patients with RAI only in children who were > 10 years old since safety data are limited for very young children.

In the present study, 57% of patients who received of I^{131} became hypothyroid within 2 months after last doses of I^{131}. High percentage of hypothyroidism within 6 months after I^{131} in the present study could be due to cumulative effect of repeated doses of I^{131}. In general, 60-90% of children treated with a single dose of 150-200 μCi/g thyroid will become hypothyroid[13]. The presented patients who had biochemical euthyroidism after I^{131} treatment were followed for less than 2 years. Long-term follow-up of thyroid function is needed in these patients.

Conclusion

PTU was the most common first-line therapy in the presented patients with Graves' disease. The remission rate was only 18.8% after an average 3.5 years of treatment with antithyroid drugs. I^{131} or thyroidectomy was 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 I^{131}, higher dose (200 μCi/g of thyroid tissue) seemed to be more effective than the lower doses (100 μCi/g).

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ผลการรักษา Graves' disease ในเด็กไทย

ปวินทรา หะริณสุต สมนึก, ภาวนา ภู่สุวรรณ, สุภาวดี ลิขิตมาศกุล, จีรันดา สันติประภพ, ไพรัลยา สวัสดิ์พานิช

ภูมิหลัง: *Graves' disease เป็นสาเหตุที่พบบ่อยที่สุดของภาวะไทรอยด์เป็นพิษในเด็ก การรักษาประกอบด้วยยาต้านไทรอยด์, I^{131} และการผ่าตัดต่อมไทรอยด์ แต่ยังไม่มีข้อสรุปว่าวิธีใดเป็นการรักษาที่ดีที่สุด*

วัตถุประสงค์: *เพื่อศึกษาผลการรักษา Graves' disease ในผู้ป่วยเด็กไทย*

วัสดุและวิธีการ: *เป็นการศึกษาย้อนหลังในผู้ป่วยเด็ก 32 รายที่ได้รับการวินิจฉัยเป็น Graves' disease ในช่วงมกราคม พ.ศ. 2537 – ธันวาคม พ.ศ. 2547 ที่หน่วยต่อมไร้ท่อ ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล*

ผลการศึกษา: *ผู้ป่วยทุกราย (ค่ามัธยฐานของอายุ 10.5 ปี, พิสัย 2.85-15 ปี) มีคอพอกและมีการเพิ่มขึ้นของซีรัม T_4 (ค่ามัธยฐาน 18.4 ไมโครกรัม, พิสัย 8.8-30 ไมโครกรัม), ซีรัม T_3 (ค่ามัธยฐาน 443 นาโนกรัม/ดล., พิสัย 206-800 นาโนกรัม/ดล. และมีการลดต่ำลงของซีรัม TSH (ค่ามัธยฐาน 0.009 ไมโครยูนิต/ลิตร, พิสัย 0-0.18 ไมโครยูนิต/ลิตร 70% และ 82% ของผู้ป่วยมี antithyroglobulin และ antimicrosomal แอนติบอดีสูงในซีรัม ผู้ป่วยทุกราย (ยกเว้น 2 ราย ได้รับการรักษาด้วย methimazole) ได้รับการรักษาเริ่มแรกด้วย PTU ผู้ป่วย 2 รายมีผลข้างเคียงจาก PTU (เด็กหญิง 1 รายมีปวดข้อ, pANCA$^{\oplus}$ และไตอักเสบ ส่วนเด็กหญิงอีก 1 ราย มีผื่นและปวดข้อ) ผู้ป่วย 32 ราย ที่ได้ยาต้านไทรอยด์เป็นเวลาเฉลี่ย 3.4 ปี (พิสัย 0.3-11.2 ปี) 6 ราย (18.8%) หายจาก Graves' disease (สามารถหยุดยาได้ $\geq$ 2 ปี), 3 ราย (9.4%) กลับมาเป็นใหม่, 1 ราย (3.5%) ได้รับการผ่าตัดไทรอยด์แบบ subtotal และ 7 ราย (21.9%) ต้องได้รับการรักษาโดย I^{131} ผู้ป่วยทุกรายที่ได้รับ I^{131} ขนาดเพียง 100 μCi/กรัม ของต่อมไทรอยด์ (6 รายจาก 7 ราย ที่ได้รับการรักษาโดย I^{131}) ต้องได้ I^{131} มากกว่า 1 ครั้ง ขณะนี้ยังไม่สามารถสรุปผลการรักษาในผู้ป่วย 15 ราย (46.9%) จาก 32 ราย เนื่องจากยังติดตามไม่นานพอ 4 ราย เพิ่งหยุดยาน้อยกว่า 2 ปีและ 11 ราย ยังคงกินยาต้านไทรอยด์อยู่ ไม่เคยหยุดยา*

สรุป: *PTU เป็นการรักษาที่ใช้มากที่สุดเป็นอันดับแรกในผู้ป่วยเด็กที่เป็น Graves' disease ที่คลินิกต่อมไร้ท่อ ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล อัตราการหายขาดมีเพียง 18.8 % หลังจาก ได้ยาต้านไทรอยด์เป็นเวลาเฉลี่ย 3.5 ปี การรักษาด้วยการผ่าตัดต่อมไทรอยด์หรือการให้ I^{131} ได้ถูกใช้เป็นการรักษาลำดับที่ 2 ในการศึกษานี้โดยมักจะใช้ในผู้ป่วยที่มีผลข้างเคียงของยา ไม่ให้ความร่วมมือกับการรักษาด้วยยา หรือ รักษาโดยการให้ยาไม่ได้ผล การรักษาด้วย I^{131} ขนาดสูง ($\geq$ 200 μCi/กรัมของต่อมไทรอยด์) ดูจะได้ผลดีกว่า I^{131} ขนาดต่ำ (100 μCi/กรัมของต่อมไทรอยด์) ในการศึกษานี้*