

Case Report

Five cases of childhood-onset Graves' disease treated with either surgery or radio-iodine therapy

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Abstract. There are three major therapeutic options for the treatment of Graves' disease (GD): antithyroid drugs (ATDs), thyroidectomy, and radio-iodine (RAI) therapy. ATDs are the initial treatment option for children. However, some pediatric GD patients who are initially treated with ATDs require other type of treatments later on. We reviewed the medical records of childhood-onset GD cases retrospectively to report the clinical course of patients who received either surgery or RAI therapy subsequent to treatment with ATDs. Childhood-onset GD was successfully managed in five girls with non-ATD treatments at the age of 7–14 yr following an unfavorable outcome of initial ATD treatment. Four cases had surgery and one case was managed with RAI therapy. The reasons for switching to non-ATD treatment included poor compliance, failure to maintain remission, serious adverse events resulting from ATDs, and religious background. In conclusion, surgery and RAI therapy could be good alternative treatment options for children with GD.

Key words: Graves' disease, childhood-onset, antithyroid drug, radio-iodine, thyroidectomy

Introduction

There are three major therapeutic options for the treatment of childhood-onset Graves' disease (GD): antithyroid drugs (ATDs), thyroidectomy, and radio-iodine (RAI) therapy. Of these options, ATDs are used as the initial treatment (1, 2). Surgery and RAI therapy are considered final

options in the treatment of pediatric patients due to the associated risk of complications. Post-surgical complications are often more serious in children than adults (3–5). In Japan, RAI therapy is avoided because of the potential risk of tumorigenesis in the long term. However, some GD cases initially treated with ATDs fail to maintain remission and eventually require non-ATDs options (6). So far, only a few reports have described the clinical details of patients who have received non-ATDs treatments.

Here we report the clinical course of five pediatric GD patients who received either surgery or RAI therapy following ATD treatment. These patients were selected from 88 GD patients who were 0–15 yr at diagnosis, and were observed in Tokyo Metropolitan Children's Medical Center from March 2010 to February 2017 by retrospective chart view.

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Table 1. Clinical and biochemical characteristics of the patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Female	Female	Female	Female
Age at diagnosis (yr)	13	11	7	11	13
Additional therapy	Surgery	Surgery	Surgery	RAI therapy	Surgery
Indication for additional therapy	Poor compliance	Poor compliance, rash from MMI	Failure to achieve sustained remission	Cholangitis by MMI, refusal of blood transfusion because of religious beliefs	Agranulocytosis by MMI
Age at surgery or RAI therapy (yr)	14	18	14	11	13
Duration between diagnosis of hyperthyroidism and either surgery or RAI therapy	21 mo	7 yr	7 yr	8 mo	3 mo

Case Reports (Table 1)

Case 1

A 13-yr-old girl visited the hospital complaining of goiter, tachycardia, weight loss, and fatigue. GD was diagnosed based on the following data: serum fT3 30.5 pmol/L (normal range 3.8–5.8 pmol/L), fT4 77.2 pmol/L (10.4–14.5 pmol/L), TSH 0.02 mIU/L (0.46–3.72 mIU/L), and anti-TSH receptor antibody (TRAb) 5.2 IU/L (< 1.0 IU/L). She was initially treated with methimazole (MMI), and potassium iodide (KI) was added because of poor improvement of fT3 and fT4 levels. However, the patient failed to comply with the therapy and remission could not be achieved. A total thyroidectomy was performed to prevent exacerbation of the disease resulting from non-adherence to the therapy. All four parathyroid glands were left intact. No severe complications other than hypothyroidism occurred after surgery. The patient is currently being treated with 125 mcg/day of levothyroxine (LT4).

Case 2

An 11-yr-old girl presented with complaints

of neck swelling, exophthalmos, tachycardia, weight loss, and fatigue. GD was diagnosed based on serum fT3 46.0 pmol/L (3.8–5.8 pmol/L), fT4 118.6 pmol/L (10.4–14.5 pmol/L), TSH < 0.05 mIU/L (0.46–3.72 mIU/L), and TRAb 54.8% (< 15%). Her paternal grandmother also suffered from GD. Administration of MMI was started, but three weeks later, when skin rashes appeared all over the body, medication was switched to propylthiouracil (PTU). The use of PTU during childhood has recently been withheld due to an associated high risk of hepatotoxicity (3, 7, 8); therefore, medication was switched back to MMI, resulting again in the appearance of severe skin rashes. Subsequently a subtotal thyroidectomy sparing approximately 3 grams of thyroid parenchyma in each lobe was performed without any severe complications. Euthyroidism was achieved with administration of 112.5 mcg/d of LT4. She had notable obesity before surgery and 500 mg of metformin was added to her medication because of recent complication of type 2 diabetes mellitus.

Case 3

A 7-yr-old girl with Down syndrome (DS)

was referred to our clinic due to thyrotoxicosis, which was suspected during a routine follow-up for DS. A family history revealed that her mother had suffered from Hashimoto's disease. GD was confirmed from the following measurements obtained from the blood samples: serum fT3 26.5 pmol/L (3.8–5.8 pmol/L), fT4 77.2 pmol/L (10.4–14.5 pmol/L), TSH < 0.05 mIU/L (0.46–3.72 mIU/L), and TRAb 73.3% (< 15%). The thyroid hormone levels were unstable, showing no improvement even after 7 years of treatment with MMI. This long-term abnormalities in the thyroid hormone levels, for example, the discrepancy between the fT3 and fT4 levels and an acute exacerbation of thyrotoxicosis (although no thyroid crisis according to the criteria) at 14 yr, led to the decision to perform a total thyroidectomy. No complication occurred after the surgery, and the patient is currently being treated with 100 mcg/d of LT4.

Case 4

An 11-yr-old girl presented to our hospital complaining of continuous tachycardia. GD was diagnosed based on the following observations: serum fT3 23.5 pmol/L (3.8–5.8 pmol/L), fT4 45.9 pmol/L (10.4–14.5 pmol/L), TSH < 0.02 mIU/L (0.46–3.72 mIU/L), and TRAb 10.9 IU/L (< 2.0 IU/L). The patient was diagnosed with congenital biliary atresia in the neonatal period and a portoenterostomy was performed at 5 mo of age. Progressive liver cirrhosis was observed even after the surgery. As complications of this condition, she had portal hypertension resulting in esophageal varix and repeated episodes of upper gastrointestinal bleeding. She had no history of cholangitis. Her family history revealed no cases of thyroid disease. The patient and her mother were both Jehovah's Witnesses. Eighteen days after the initiation of MMI, the patient developed a high fever, which continued to be elevated for the three days. Cholangitis was suspected due to elevated serum enzyme levels in the hepatobiliary system (AST 49 U/L, ALT 38 U/L, γ -GTP 118 U/L, T-Bil 6.6 mg/dL, D-Bil 4.1

mg/dL) and an increased level of an inflammation marker (CRP 5.68 mg/dL). MMI therapy was discontinued due to the risk of exacerbating the cholangitis. The cessation of MMI administration exacerbated the thyrotoxicosis in a few days. Administration of PTU, another type of ATD, was not possible in this patient because of the potential risk of liver toxicity resulting from the aggravation of the pre-existing cirrhosis. Surgery was also ruled out as a therapeutic option because of religious beliefs of the family. Therefore, 500 mBq (= 38.8 mBq/g) RAI therapy was initiated 8 mo after the diagnosis of GD. The patient's condition improved after RAI therapy, and she is currently being treated with 87.5 mcg/day of LT4.

Case 5

A 13-yr-old girl presented with complaints of appetite loss, weight loss, amenorrhea, fatigue, and palpitation. A diagnosis of GD was made based on the following values: serum fT3 15.8 pmol/L (3.8–5.8 pmol/L), fT4 40.7 pmol/L (10.4–14.5 pmol/L), TSH < 0.02 mIU/L (0.46–3.72 mIU/L), and TRAb 43.6% (< 15%). Her paternal grandmother had also suffered from GD. Administration of MMI normalized her serum thyroid hormone levels within two months. Unfortunately, agranulocytosis (minimal granulocyte count: 20/mcl) developed three months after the initiation of MMI administration, and a total thyroidectomy was performed. She is currently in good condition following surgery and is being treated with 137.5 mcg/day of LT4.

Discussion

We reported five cases of pediatric GD treated with either surgery or RAI therapy. Serum thyroid hormone levels (especially fT3) were extremely elevated and TRAb levels were more than 2.5 times higher than the normal upper limit at the first examination in all cases, which are indicators of the difficulty of disease

management by ATDs (9–12). The thyroid volume was estimated in three cases, of which two showed obvious enlargement; thyroid enlargement is another predictor of the difficulty of disease management (13). Four cases had surgery, and one case was managed with RAI therapy. The reasons for the switch to non-ATDs treatments included poor compliance, failure to maintain remission, serious adverse events resulting from ATD use, and religious background. All five patients are in good condition after receiving the alternative treatments.

Childhood GD is characterized by difficulties with ATD treatment. Among pediatric patients, a lower remission rate after 2-yr ATD treatment than among adult patients (approximately 30% vs. 40–60%), a consequently longer duration of drug administration, and a higher occurrence of adverse events were reported (8, 14). Therefore, surgery and RAI therapy could be better options for the treatment of GD in pediatric ages (than in adulthood). However, the options of surgery and RAI therapy are not found to be as one of the first-line treatments in the latest Japanese guideline for childhood-onset GD (15).

Four of our five cases were in good condition after their surgery, indicating the safety of the surgery in pediatric GD. In particular, case 2 had subtotal thyroidectomy without any complications in a different location than the other patients. In this hospital, subtotal thyroidectomy was considered the best choice for young patients, because it minimizes the risk of decreased quality of life due to complications. The patients in this hospital had no complications, indicating that subtotal thyroidectomy may be in general a good option for GD patients, even for childhood cases of GD. Surgical complications are more frequently reported in children than in adults (3–5). Peters *et al.* reported that surgery should be restricted to GD patients who respond poorly to RAI therapy or present with huge goiters (7). However, in our opinion, the option of surgery should be considered not only for patients meeting the conditions described above,

but also for patients showing poor compliance, failure to maintain remission with ATDs, and serious adverse events even in pediatric ages.

Although RAI therapy in children has been avoided because of the possible long-term risk of tumorigenesis, its feasibility has been reconsidered in the recent years. Approximately 1,000 GD pediatric patients treated with RAI therapy have been reported in the literature. Read *et al.* followed the long-term outcomes (with the average duration of 26 yr) of 106 childhood-onset cases with GD (aged between 3 yr and 7 mo and 19 yr and 9 mo) treated with RAI therapy (16), and reported few serious complications (5); only four had complications such as thyroid cancer. Altogether, these reports suggest that RAI therapy is no longer a contraindication in childhood cases, and can be especially applicable in patients more than 5 yr of age (3).

In conclusion, we reported five cases of childhood-onset GD initially treated with ATDs but subsequently treated with either surgery or RAI therapy because of an unfavorable outcome of the initial treatment. Surgical treatment and RAI therapy are acceptable options for treatment of childhood-onset GD when the patients have either poor compliance, failure to maintain remission, severe adverse events, or refuse certain treatment options.

Conflict of Interest: All authors report to have no conflict of interest related to this manuscript.

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