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ORIGINAL ARTICLE

Surgical management of pediatric Graves' disease: an effective definitive treatment

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Abstract
Purpose The optimal treatment for pediatric Graves' disease (GD) is controversial. Antithyroid drugs are often used initially, but they are associated with a high failure rate. Therefore alternative therapies have become important. In the present study, we analyze our institution's experience regarding the safety and efficacy of thyroid surgery among pediatric patients with GD.
Methods This is a retrospective chart review of 27 pediatric patients (age $\leq$ 18 years) with GD who underwent thyroid surgery between 1991 and 2009 at a single academic Institution. We recorded preoperative, intraoperative, and short-term postoperative data.
Results All 27 patients were initially treated with thionamides. The high rate of hyperthyroidism relapse after discontinuation of medical treatment, age $<$ 5 years, adverse reaction to medical therapy, severe ophthalmopathy, and patient preference justified the final decision to proceed with surgery as definitive therapy. All patients underwent total thyroidectomy. We had no mortality; surgical complications were rare: 4 (14.8 %) cases of transient hypocalcemia, 1 (3.7 %) of permanent hypocalcemia, 3 (11.1 %) of transient RLN neuropraxia, and 2 (7 %) of keloid scar. No bleeding, permanent RLN palsy or relapse hyperthyroidism were reported.
Conclusions Surgical therapy for pediatric GD performed by experienced thyroid surgeons is a safe, definitive and cost-effective treatment.

Keywords Graves' disease · Thyroidectomy · Radioactive iodine · Children · Adolescents

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Abbreviations

ATD	Antithyroid drug therapy
BMI	Body mass index
GD	Graves' disease
RAI	Radioactive iodine ablation
RLN	Recurrent laryngeal nerve
TPOAb	Thyroid peroxidase autoantibodies
TRAb	Thyroid-stimulating hormone receptor antibodies
TT	Total thyroidectomy

Introduction

The management of pediatric Graves' disease (GD), the most common cause of thyrotoxicosis, remains one of the great controversies in endocrinology. The three currently available treatment options are antithyroid drug therapy

(ATD), radioactive iodine ablation (RAI), and thyroidectomy. None of these is able to consistently restore euthyroidism without any risk. Therefore the best therapeutic approach remains a matter of debate.

In Europe, ATD is usually recommended as an initial treatment, despite the difficulty in control of thyroidal function, known side effects and the low rate of remission (generally 20–30 % of pubertal and 15 % of prepubertal patients) [1–4]. For all these reasons, a definitive therapy, such as surgery or RAI, is commonly used as a second step, ultimately leading to permanent hypothyroidism.

The choice between RAI and surgery as a definitive treatment of GD is centered on the potential adverse consequences of RAI versus the complication of thyroidectomy.

RAI appears to be quite safe; much of the controversy surrounding its use for pediatric GD concerns its potential carcinogenic and teratogenic effects. However, the few studies existing in the literature suggest that there is no evidence of increased risk of cancer with RAI for pediatric GD [5], and of reproductive dysfunction or a higher frequency of genetic abnormalities in the offspring of treated patients [6–10]. Unfortunately, to date, there are only few studies reporting long-term follow-up, making this treatment a less attractive modality than surgery to both pediatric endocrinologists and patients' parents [11].

The decision to perform thyroidectomy in pediatric GD is taken by a pediatric endocrinologist in cooperation with a surgeon specialized in thyroid surgery. Clear indications for thyroidectomy include large glands (>80 g) due to a poor response to RAI [12, 13], obstructive or compressive symptoms, requirement for immediate control of the disease, and age younger than 5 years. Even if the worsening of Graves' ophthalmopathy (that may be prevented by coadministering a short course of corticosteroids [14]) has been reported in a small percentage of adults treated with RAI [15], there is no evidence of such complication in children and adolescents undergoing RAI [16]. However, for this reason, some patients with moderate to severe ophthalmopathy may prefer surgery to RAI.

During thyroidectomy, the anesthesiologic risk is low and mortality is nearly zero. Surgical complications depend on numerous factors and increase with patients' age, size of goiter, degree of hyperthyroidism and, most importantly, they are inversely related to the experience of the surgeon [10].

Complications of thyroid surgery include wound infection, keloid formation at the site of the incision, intraoperative bleeding (0.7 %), transient hypocalcemia (10 %), permanent hypoparathyroidism (2 %), and paresis or permanent recurrent laryngeal nerve (RLN) injury (1 %). Hypothyroidism generally is considered a consequence of surgery, rather than a complication.

Considering the rarity of the disease, published studies about GD and its surgical treatment are limited until now, and they are conducted on small numbers. The strength of the present study is a large series of pediatric patients with GD treated surgically at the same center. This retrospective study was performed to evaluate the presentation, management and the outcome of children and adolescents treated surgically for GD at a single institution.

Materials and methods

Demographics and data set

A total of 80 pediatric patients were diagnosed with GD at our institution between 1991 and 2009. Of these, 27 children and adolescents (34 %) underwent surgery as definitive treatment, 15 (19 %) received RAI, and 15 (19 %) achieved remission after discontinuation of thionamide administration. The remaining 23 patients (28 %) are still receiving medical treatment, either due to difficulties in the control of thyroid function or due to refusal of definitive therapy.

Focusing on the surgery subgroup ($n = 27$), 5 patients (18 %) were male, while 22 (82 %) were female. Complete medical records of these patients were retrospectively assessed from the database of our Department of Surgery and from the medical records of our Pediatrics Department.

Diagnosis and indications for surgery

All patients were diagnosed at the Pediatric Endocrinology Department of our institution and all of them were initially treated with medical therapy.

Indications for thyroidectomy, all given by a pediatric endocrinologist, were as follows: failure of medical therapy, adverse effects of ATD or noncompliance with thionamides, requirement for immediate control of disease, large goiter, age younger than 5 years, and patient preference. All the surgical procedures were performed by only two general surgeons trained in endocrine surgery.

All patients participating in this study gave informed consent prior to surgery.

Perioperative details

All 27 surgical patients received Lugol's iodine solution for 10 days preoperatively, in order to achieve either euthyroidism or hypothyroidism (assessed by TSH measurement). The complete preoperative evaluation also included general blood tests, electrocardiogram and chest X-ray.

All patients underwent TT. This procedure was carried out following the standard technique: low and short

transverse skin incision, creation of flaps and gradual removal of the gland starting from the superior pole and proceeding to the inferior one, regardless of the side. The arterial branches pertaining to the gland were ligated. The recurrent laryngeal nerve and the parathyroid glands must be carefully identified. Inadvertent removal of parathyroid glands was followed by their reimplantation into the ipsilateral sternocleidomastoid muscle.

Postoperative course

The mean follow-up was 48 months (range 8–144 months).

In the present study, we considered a short-term clinical course data: mortality, overall morbidity, incidence of single complication as transient hypocalcemia (any patient discharged with oral calcitriol and calcium supplementation—due to serum total calcium levels lower than 1.87 mmol/L, equal to 7.5 mg/dL; it was carried out until serum calcium normalization and it commonly happened between two and three weeks after surgery), permanent hypocalcemia (persistent requirement of calcium and calcitriol supplementation, 6 months after surgery), transient RLN neuropraxia, permanent RLN palsy, perioperative bleeding, and keloid development.

Statistical analysis

Descriptive statistics was calculated for all the variables analyzed: quantitative variables were described through mean and range, while qualitative ones were expressed through frequencies and percentages.

Results

Between 1991 and 2009, more than 3,700 patients diagnosed with benign or malignant thyroid disease underwent thyroid surgery at Endocrine Surgery Department of our institution. The pediatric subgroup consisted of 67 patients. Of these pediatric patients, 27 with diagnosis of GD required thyroidectomy. The mean time of medical therapy before TT was 5.9 years (range 0.7–15.0 years).

Among the patients who underwent surgery ($n = 27$), 5 patients (18 %) were male, while 22 (82 %) were female; the male:female ratio was 1:4.4.

Mean age at diagnosis of GD was 9.2 years (range 3.5–15.5 years); specifically, in the male group it was 11.1 years (range 8.5–14.6 years), while in the female group it was 8.8 years (range 3.0–15.5 years).

The clinical signs and symptoms of hyperthyroidism at diagnosis of GD were as follows: goiter (81 %), tachycardia and palpitations (81 %; heart rate was considered significant if higher than 97° percentile according to the age), irritability (64 %), ophthalmopathy (54 %), weight loss (44 %), tremors (31 %), polyphagia (21 %), profuse sweating (19 %), insomnia or sleep disorders (17 %), hyperdefecation but not diarrhea (12 %), and rash (5 %). A great majority of patients also experienced an increase in the arterial differential pressure. In 3 % of the cases the diagnosis was occasional.

Regarding the autoimmune status, 100 % of the patients had a significant titer of TRAb at diagnosis of GD, whereas 85 % of patients had a significant titer of TPOAb.

Fourteen patients (52 %) had a positive family history for autoimmune disorders in first-degree relatives, whereas a positive family history for autoimmune thyroid disease was observed in 11 subjects (41 %). Five patients (18 %) were also diagnosed with other autoimmune diseases: two patients were diagnosed with celiac disease, two with Type 1 Diabetes Mellitus, and one with autoimmune thrombocytopenia.

All 27 patients were initially treated with thionamides without ever achieving good control of thyroid function. Surgery was considered as a definitive therapy in those patients who had a high rate of relapse of hyperthyroidism after discontinuation of ATD treatment ($n = 18$, 67 %), age < 5 years ($n = 7$, 26 %), compressive sign and symptoms due to a large goiter ($n = 12$, 45 %), adverse reaction or poor compliance to medical therapy ($n = 7$, 26 %), and severe ophthalmopathy ($n = 6$, 22 %). In 8 subjects (30 %), the patient and family preferences were crucial for the final decision. In many patients, the choice of surgery was influenced by the controversial role of RAI in the treatment of pediatric GD (Table 1).

The mean age at surgery was 15.2 years (17.4 years in the male group; 14.6 years in the female group). All our patients ($n = 27$) underwent TT. The average hospital stay was about 3.5 days.

Table 1 Operative complications among 27 patients referred for thyroid surgery for pediatric GD

Complication	*n*	%
Mortality	0	0
Transient hypocalcemia	4	14.8
Permanent hypocalcemia	1	3.7
Reimplantation of parathyroid glands	2	7
Keloid development	2	7
Transient RLN neuropraxia	3	11.1
Permanent unilateral RLN palsy	0	0
Permanent bilateral RLN palsy	0	0
Intraoperative bleeding	0	0
Postoperative bleeding	0	0
Postoperative infections	0	0

Concerning postoperative course, we had no mortality. Regarding postoperative morbidity, we observed transient hypocalcemia in four cases (14.8 %), permanent hypocalcemia in one case (3.7 %), and transient RLN neuropraxia in three cases (11.1 %). Two patients (7 %) presented with keloid scar. We did not observe any case of bleeding, postoperative infections or permanent RLN palsy. 2 patients (7 %) required reimplantation of parathyroid glands into the ipsilateral sternocleidomastoid muscle, due to their inadvertent removal during surgery; these subjects did not suffer from either transient or permanent hypocalcemia.

After surgical treatment, all 27 patients developed permanent iatrogenic hypothyroidism, requiring replacement therapy with L-thyroxine. None of these patients experienced complications related to replacement therapy. No patient developed recurrence of hyperthyroidism.

Discussion

GD is very uncommon among children, with an incidence of 0.1–3 per 100,000 children [17] and a prevalence of 1 in 10,000 children in the United States [18]. Despite its rarity, autoimmune hyperthyroidism remains of great interest to endocrinologists because there is still no consensus on the best therapeutic approach in children, leaving the final decision to physicians' personal experience.

The choice of treatment varies in different parts of the world. RAI is preferred by endocrinologists in the United States, whereas European and Asian clinicians favour ATD (at least 18–24 months of continuous therapy) followed by definitive therapy (surgery or RAI)—hard to suggest to parents by its nature.

The lack of long-term studies regarding RAI safety in children justifies cautiousness in its use as definite therapy. On the other hand, there is strong evidence about safety and efficacy of surgical treatment for pediatric autoimmune hyperthyroidism. In detail, the literature reports no mortality, extremely low rate of postoperative complications, and no relapse when TT is performed.

Thyroidectomy has been the first definitive therapy introduced for pediatric GD. Cumulative experience over time has led to changes in surgical technique, mainly regarding procedure radicality and wound closure. Concerning the radicality of the procedure, there has been a long-time debate on the best approach for patients with GD, whether subtotal (ST) or total thyroidectomy. Complication rates were low with both the procedures. In the past, ST was the preferred approach, in an effort to maintain thyroid function after surgery. Recent studies suggest that TT should be favoured to ST, since this technique is virtually never associated with recurrence of hyperthyroidism, while there is evidence of disease relapse in patients who underwent ST. Even though TT renders patients permanently hypothyroid, this is predictable and can be easily treated with thyroid hormone replacement immediately after surgery, avoiding transient hypothyroidism. Furthermore, the pharmacological management of surgery-derived hypothyroidism is easier than medical treatment of hyperthyroidism associated with GD. For all these reasons, nowadays TT could represent the procedure of choice [19–21].

Regarding wound closure and scarring, the great improvements in surgical techniques (with steel staples instead of intradermal suture) help to reassure the parents about final aesthetic results. This is important considering psychological consequences of surgery in this age group.

GD represents a challenge for the surgeon, being a surgically hardest thyroid disease to deal with: the technical problems especially related with this pathological condition (the specific features of glandular tissue and their relationship with important surrounding anatomical structures) explain the need to refer patients to high-volume thyroid surgery centers, because it has been shown that greater surgeon experience is associated with better postoperative outcomes [22].

The present study, referring to a high-volume experience, confirms the safety of this procedure in children. According to the available literature, we describe a low rate of postoperative complications that are mainly temporary and resolve definitely over time. Only a small fraction of patients developed permanent postoperative complications.

Surgical complications, except for rare cases of nerve palsy, are not generally debilitating; hypocalcemia is easily managed with regular blood test and with supplementation of calcium and calcitriol.

Generally, preparation of patient for surgery is not a complex procedure, because almost all subjects are euthyroid on thionamide therapy before surgery, that should be continued until the day of thyroidectomy. In addition, a 7–10-day preoperative administration of inorganic iodine (Lugol's solution) is frequently used to decrease hormone synthesis and vascularity of the thyroid gland to limit the onset of thyrotoxicosis [23].

Especially in the United States, RAI is considered as a low-cost procedure, due to the need of a single treatment session. However, it should be remembered that this treatment requires regular and frequent blood tests, and the disease relapse can occur even many years after iodine administration. On the contrary, surgery appears as a true hyperthyroidism definitive treatment, allowing for a gradual thinning of blood controls, once the right hormone dose has been found.

Although there is still no consensus, some authors report that hyperthyroidism recurrence rate could be higher

among patients receiving RAI [24–26] compared to surgical patients: among subjects who undergo RAI it is reported an increased risk of persistence of antigenic tissue potentially able to trigger an autoimmune response leading to hyperthyroidism. According to this theory, surgery appears as an effective technique for its radicality.

In conclusion, the management of pediatric autoimmune hyperthyroidism is still debated, not only because randomized studies on this topic analyzing large samples are missing, but also because parents who are offered a definitive therapy frequently have concerns. We often have to face with parents' doubts and fears. Even if RAI has been shown to be effective in the short term, the current lack of data regarding its long-term safety as well as its limited diffusion in Europe has led us to consider surgery as a definitive therapy for pediatric GD more often than RAI. Furthermore, in agreement with the current literature, the present study highlights the ineffectiveness of prolonged medical therapy for long periods among patients experiencing difficulty in control of thyroid function with thionamide or adverse effects related to its administration.

Conclusions

At present, the choice between surgery and RAI as definitive therapy for pediatric GD is the result of close interaction between the physician, the patient and his family. The therapeutic decision is strongly influenced by single physician's experience or "geographic" medical culture, as well as by the individual consideration of the risks and the benefits of different approaches. However, while some issues of RAI still need to be investigated, surgical therapy is nowadays a well established definitive, low-risk, and cost-effective treatment option for pediatric patients with GD.

References

1. Glaser NS, Styne DM (2008) Organization of pediatric endocrinologists of northern California collaborative Graves' disease study group: predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. Pediatrics 121(3):e481–e488
2. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW (1997) Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. Thyroid 7(5):755–760
3. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Léger J (2008) French Childhood Graves' Disease Study Group: predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 93(10):3817–3826
4. Lazar L, Kalter-Leibovici O, Pertzelan A, Weintrob N, Josefsberg Z, Phillip M (2000) Thyrotoxicosis in prepubertal children compared with pubertal and postpubertal patients. J Clin Endocrinol Metab 85(10):3678–3682
5. Read CH Jr, Tansey MJ, Menda Y (2004) A 36-year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' patients. J Clin Endocrinol Metab 89(9):4229–4233
6. Safa AM, Schumacher OP, Rodriguez-Antunez A (1975) Long-term follow-up results in children and adolescents treated with radioactive iodine (131I) for hyperthyroidism. N Engl J Med 292(4):167–171
7. Hayek A, Chapman EM, Crawford JD (1970) Long-term results of treatment of thyrotoxicosis in children and adolescents with radioactive iodine. N Engl J Med 283(18):949–953
8. Crile G Jr, Schumacher OP (1965) Radioactive iodine treatment of Graves' disease: results in 32 children under 16 years of age. Am J Dis Child 110(5):501–504
9. Freitas JE, Swanson DP, Gross MD, Sisson JC (1979) Iodine-131: optimal therapy for hyperthyroidism in children and adolescents? J Nucl Med 20(8):847–850
10. Starr P, Jaffe HL, Oettinger L Jr (1969) Later results of 131-I treatment of hyperthyroidism in 73 children and adolescents: 1967 follow-up. J Nucl Med 10(9):586–590
11. Lee JA, Grumbach MM, Clark OH (2007) The optimal treatment for pediatric Graves' disease is surgery. J Clin Endocrinol Metab 92(3):801–803
12. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H (1997) Treatment of Graves' hyperthyroidism with radioiodine: results of a prospective randomized study. Thyroid 7(2):247–251
13. Peters H, Fischer C, Bogner U, Reiners C, Schleusener H (1996) Reduction in thyroid volume after radioiodine therapy of Graves' hyperthyroidism: results of a prospective, randomized, multicenter study. Eur J Clin Invest 26(1):59–63
14. Tallstedt L, Lundell G (1997) Radioiodine treatment, ablation, and ophthalmopathy: a balanced perspective. Thyroid 7(2):241–245
15. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, Bruno-Bossio G, Nardi M, Bartolomei MP, Lepri A, Rossi G, Martino E, Pinchera A (1998) Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 338(2):73–78
16. Krassas GE (2003) Ophthalmic complications in juvenile Graves' disease—clinic and therapeutic approaches. Pediatr Endocrinol Rev 1(Suppl 2):223–229 (discussion 229)
17. Lavard L, Ranløv I, Perrild H, Andersen O, Jacobsen BB (1994) Incidence of juvenile thyrotoxicosis in Denmark, 1982–1988: a nationwide study. Eur J Endocrinol 130(6):565–568
18. Rivkees SA, Mattison DR (2009) Propylthiouracil (PTU) hepatoxicity in children and recommendations for discontinuation of use. Int J Pediatr Endocrinol 2009:132041
19. Miccoli P, Vitti P, Rago T, Iacconi P, Bartalena L, Bogazzi F, Fiore E, Valeriano R, Chiovato L, Rocchi R, Pinchera A (1996) Surgical treatment of Graves' disease: subtotal or total thyroidectomy? Surgery 120(6):1020–1024
20. Palit TK, Miller CC 3rd, Miltenburg DM (2000) The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res 90(2):161–165
21. Lal G, Ituarte P, Kebebew E, Siperstein A, Duh QY, Clark OH (2005) Should total thyroidectomy become the preferred procedure for surgical management of Graves' disease? Thyroid 15(6):569–574
22. Sosa JA, Bowman HM, Tielsch JM, Powe NR, Gordon TA, Udelsman R (1998) The importance of surgeon experience for clinical and economic outcomes from thyroidectomy. Ann Surg 228(3):320–330

23. Erbil Y, Ozluk Y, Giriş M, Salmaslioglu A, Issever H, Barbaros U, Kapran Y, Ozarmağan S, Tezelman S (2007) Effect of Lugol solution on thyroid gland blood flow and microvessel density in the patients with Graves' disease. J Clin Endocrinol Metab 92(6):2182–2189
24. Grodski S, Stalberg P, Robinson BG, Delbridge LW (2007) Surgery versus radioiodine therapy as definitive management for Graves' disease: the role of patient preference. Thyroid 17(2):157–160
25. Boostrom S, Richards ML (2007) Total thyroidectomy is the preferred treatment for patients with Graves' disease and a thyroid nodule. Otolaryngol Head Neck Surg 136(2):278–281
26. Schüssler-Fiorenza CM, Bruns CM, Chen H (2006) The surgical management of Graves' disease. J Surg Res 133(2):207–214