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Thyroidectomy for Graves' Disease in Children: Indications and Complications

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Structured Abstract

Background—The utilization of thyroidectomy for Graves' disease remains controversial; we aim to evaluate the indications for and complications of thyroidectomy for Graves' in children.

Methods—A retrospective analysis was performed on all Graves' patients who underwent thyroidectomy from 2009–2013 at a high volume academic center. Pediatric patients were < 18 years old, and a comparative analysis of indications for surgery and complications was performed.

Results—167 patients underwent thyroidectomy: 31 pediatric patients and 136 adults. Failure of antithyroid medications was the indication for surgery in 55% of the children vs 36% of adults (p=0.05). Mean duration of medications prior to surgery was similar. No children had failed RAI therapy prior to surgery, but 12.5% of the adult population had (p=0.04). Surgical outcomes were similar.

Conclusion—Clinicians may be more likely to refer children who fail medical treatment to surgery over RAI. Thyroidectomy at a high volume hospital should be discussed as a treatment option for children with Graves'.

Keywords

Thyroidectomy; pediatric Graves' disease; pediatric hyperthyroidism; shared decision making

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Graves' disease is the most common etiology of hyperthyroidism in children and adolescents [1]. Although presenting symptoms are similar to the adult population in many ways, children and adolescents may present with non-specific symptoms that can be overlooked or attributed to normal changes children go through, such as nervousness, fatigue, sleep disturbances, or behavioral and learning disorders. These can have severe negative effects on

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Similar to adults, there are three modalities that can be employed in the treatment of pediatric Graves' disease: anti-thyroid medications, radioactive iodine ablation or thyroidectomy. Anti-thyroid drugs (ATD) include methimazole and propylthiouracil (PTU) which reduce thyroid hormone synthesis. In 2009, because of the unacceptably high rates of PTU-induced liver injury requiring liver transplant in children, the medication is no longer approved in the pediatric population [2,3]. Methimazole may be used, but care should be taken to administer the lowest effective dose as dangerous side effects such as agranulocytosis are generally dose-dependent [4]. Anti-thyroid medications alone are not curative therapy, they simply mitigate the symptoms of hyperthyroidism until the Graves' disease goes into spontaneous remission or a definitive treatment is chosen. Remission rates in children are around 20–30%, and seem to be worse for patients with large glands, high antibody levels or very high free T4 levels at diagnosis [4]. Younger children have lower remission rates and higher relapse rates than older adolescents and adult patients [5].

Radioactive iodine (RAI) ablation is the most frequently used definitive treatment modality for adults with Graves' disease in the United States [6]. When properly dosed, RAI seems to be effective for children [7], but there are concerns about radiation exposure. Children's growing bodies are more sensitive to all types of radiation than adults, but no data have ever proven an increase in any long-term adverse events such as increased risk of cancer or genetic damage [8] in children who were exposed to treatment doses of ^{131}Iodine. Even with this lack of definitive evidence, the American Thyroid Association guidelines [9] exercise caution and recommend avoiding RAI in children under the age of 5 and limiting the dose for children between the ages of 5 and 10.

Surgery is gaining acceptance as a first-line definitive treatment for Graves' disease in adults [10], but several studies looking at pediatric populations have shown higher complication rates in children, with outcomes directly related to the surgeon experience and volume [11,12]. Given that thyroid disease is relatively uncommon compared to other surgical childhood diseases, pediatric surgeons generally do relatively few thyroidectomies, and most adult endocrine surgeons rarely operate on children. Thyroid surgery for Graves' disease can be more challenging than for other indications such as cancer or nodules given the inflammation and vascularity of the gland [11], and collaboration between pediatric surgeons and endocrine surgeons can improve quality of care.

Given the increased risks involved in all three treatment modalities for Graves' disease in a pediatric population compared to adults, we hypothesized that there may be different indications for surgery in pediatric patients at our institution. We specifically looked at length of time that a patient took ATD prior to thyroidectomy to determine if clinicians used medications for longer periods of time in an attempt to avoid the risks of RAI or surgery in children. We further hypothesized that complication rates of surgery by our high volume surgeons is no higher for children than for adults.

Materials and Methods

To determine if there were any differences in indications or duration of medical management before referral for definitive therapy for Graves's disease in children compared to adults, we performed an analysis at our institution of all patients who underwent thyroidectomy between September 2009 and March 2014. Patients were identified by reviewing our IRB-approved, prospectively collected endocrine surgery database of all thyroid operations at our institution, and including only those with a diagnosis of Graves' disease as documented by hyperthyroidism and extra-thyroidal manifestations of Graves', presence of autoantibodies, or documented diffuse uptake on radioactive uptake scan. Surgeries were performed by our fellowship-trained endocrine surgeons who each perform more than 100 thyroidectomies each year or by fellowship-trained pediatric surgeons. Some of the operations were performed as co-surgeons with the involvement of both surgeon specialists.

The initial management for almost every hyperthyroid patient at our institution was ATD, whether that is with the intention of giving the medication for 12–18 months as the only treatment, or just to render the patient euthyroid prior to definitive management with surgery or radiation. The number of months that each patient took ATD prior to surgery was recorded. We did not exclude patients who had undergone previous RAI, as failure of prior treatment is an indication for surgery that was important to capture. Patients with concomitant thyroid nodules were also included, again, because these are often an indication for surgery over other treatment modalities.

A comparative analysis of age, gender, indication for surgery, duration of ATD, operative time, surgical complications and length of stay was completed for pediatric patients compared to adult patients who underwent thyroidectomy during the same time period. Indication for surgery was defined by extracting information from the patients chart either from the referring physician or the operating surgeon. Failure of ATD was defined for the purposes of this study as any documented discussion that there was difficulty maintaining a euthyroid state on medications. There were multiple underlying factors for this which could include patient non-compliance, but also individual physician factors that played a role – some physicians were quite comfortable managing fluctuating thyroid levels for many months or even years, while others made very early referrals for surgery if the levels fluctuated beyond their comfort level. This indication also included some patients who presented with thyrotoxicosis requiring hospitalization and no physician felt comfortable waiting for definitive management. Failure of ATD differs from the indication labeled side effects of ATD, which we defined as agranulocytosis, liver function abnormalities, or other patient reported side effects that drove the decision to undergo thyroidectomy. Failure of RAI means that a patient had at least one round of treatment with radioactive iodine but remained hyperthyroid or had return of symptoms after a period of euthyroidism. Ophthalmopathy and compressive symptoms were extracted from the chart and were patient reported in order to capture these as possible reasons for considering surgery; we did not require a patient to have been evaluated by an eye specialist or to have objective studies showing swallowing dysfunction. Thyroid nodules did not have to be biopsied prior to surgery, though we follow the American Thyroid Association published guidelines for thyroid nodules and biopsy nodules that are larger than 1 cm. There were other indications in adults such as pregnancy and family planning issues that were not felt to be relevant in the pediatric population, so we made note of these but did not use them in our comparisons. Patients may have had more than one indication for surgery.

Specific complications included transient hypocalcemia requiring therapeutic calcium administration (either oral or intravenous) that resolved before six months. Serum parathyroid hormone (PTH) levels for all patients were measured in the recovery room, and low PTH levels guide our decision to send patients home with calcium and/or activated vitamin D. It has been the authors' experience that patients with Graves' disease may sometimes have hypocalcemia symptoms after surgery even in the setting of normal PTH, and also not every patient with low PTH after surgery develops symptoms of hypocalcemia [13]. Therefore, we defined transient hypocalcemia as a patient reported symptom of numbness or tingling of the hands, feet or mouth after surgery that improved with calcium administration; serum calcium was not necessarily measured at the time of symptom reporting. Symptoms that required therapeutic doses of calcium (> 2000 mg calcium carbonate per day) and/or activated vitamin D beyond six months after surgery were categorized as permanent hypoparathyroidism. Transient nerve palsy was defined either by the surgeon reporting visual damage to or loss of signal from a recurrent laryngeal nerve during the operation *and* patient hoarseness documented in the postoperative period, or patient reported hoarseness beyond the usual voice fatigue from intubation in the immediate postoperative period that resolved within six months after surgery. Direct laryngoscopy is not routinely obtained on our patients, so the number of clinically silent nerve palsy is likely underreported in this dataset, but clinically significant nerve palsies were captured. Permanent nerve injuries persisted beyond six months and were usually documented by direct laryngoscopy as these patients generally underwent further interventions or voice therapy.

Bivariate analysis and multivariate models were created using Stata v.11 (Stata Corporation; College Station, TX). This study was reviewed and approved by the institutional review board at the University of Wisconsin, informed consent was waived for patients, and all data were stored on secure, HIPAA-compliant servers within the health system.

Results

Over the four and a half year study period, 167 patients underwent thyroidectomy for Graves' disease. Over 80% of the patients were female, and the study population included 31 pediatric patients < 18 years old (19%) and 136 adults (81%). The mean age of the pediatric group was 14 years compared to 43 years in the adult group, and the youngest child was 4 years old.

Table 1 shows the indications for surgery and the duration of treatment with ATD prior to surgery. Failure of ATD was the primary indication for surgery in 55% of the pediatric patients vs 36% of adults (p=0.05). No children had undergone a failed attempt at RAI therapy prior to surgery, but 12.5% of the adult population had (p=0.04). Eye symptoms were reported more frequently in adults than children (40% vs 23%, p=0.06), but the groups showed no difference in patient reported compressive symptoms, presence of thyroid nodules, or side effects of ATD. In adults, 16% were either pregnant, desired pregnancy in the near future, or had small children at home, so were unable to undergo RAI as their primary treatment; no children had any of these as indications for surgery and this is not shown on the table. The mean duration of ATD administration prior to surgery was similar for children and adults (13 vs. 15 months). In order to test the hypothesis that clinicians may be more willing to try ATD for a longer period of time in children to avoid the side effects of RAI or surgery, we looked specifically at how many patients took ATD for longer than 18 months. This number was 26% for children and 27% for adults (p=0.9).

Table 2 shows perioperative information as well as complications. Mean operative times were similar and length of stay was ≤1 day in almost all patients with no difference between children and adults. Mean PTH levels in the PACU were similar (33 pg/mL for adults vs 29 pg/mL for children, p=0.4), though there seemed to be a trend that more children were prescribed calcitriol after surgery (32% vs. 18%, p=0.07). The percent of children who reported transient hypocalcemia symptoms was 35% compared to 21% of adults, though this number was not significant (p=0.14). Rates of transient nerve palsy were also slightly higher in children based on percentages (10% vs 5% of adults), but this number was too small to demonstrate a significant difference (p=0.3). The rates of permanent complications were low and consistent with previous literature in both groups, and showed no statistical difference (3% and 2% for permanent hypoparathyroidism, 0 and 1% for permanent nerve injury, Table 2).

Discussion

The treatment of Graves' disease in children remains controversial due to the uncertain risks of exposing a growing child to RAI [7,9,14], the potential higher toxicity of ATD in children, and the previously reported higher complication rates of surgery for children [8,15,16]. Several groups, including our own, have reported acceptably low rates of thyroidectomy-specific complications in children when performed at high-volume centers [12,17–20]. Only a few of these studies looked specifically at Graves' disease as the indication for thyroidectomy, and, at least in the adult population, use of thyroidectomy as a first-line treatment for Graves' disease seems to be on the rise [21].

Few studies have looked at surgical outcomes for pediatric Graves' disease patients, and because of small numbers have had to accrue patients over a long period of time. Even fewer studies report on the indications for surgery in children compared to adults, and there is not a good sense from the literature whether use of thyroidectomy for definitive management this is changing over time for children as it is for adults. This study identified 31 children who underwent thyroidectomy for Graves' disease at one high-volume endocrine surgery center over the past 5 years. We were able to accrue this many patients over a relatively short time period because of our institution's high utilization of thyroidectomy as a first line treatment for Graves' disease. Peroni, *et al* found similar low rates of complications for a cohort of 27 children who underwent thyroidectomy for Graves' disease between 1991 and 2009 [19]. Breuer, *et al* reported on a cohort of 30 children between 2002 and 2010, and found rates of temporary hypocalcemia were higher but long-term outcomes were equivalent in children compared to adults [22]. The largest series of pediatric thyroidectomy for Graves' disease was from Mayo, and they reported on a cohort of 78 children between 1986 and 2003 [1]. That cohort included 18 patients who underwent subtotal thyroidectomy prior to 1993, when that particular operation was abandoned at Mayo because of its higher recurrence rates. The authors report acceptably low complication rates, and they also report indications for surgery. In their historic cohort, similar to our findings in a more contemporary group, failure of medical therapy was the indication for surgery in 60%, and side effects of ATD was the indication in another 10% of patients. Three patients in their series (4%) failed RAI treatment prior to surgery, and while this was a fairly frequent indication in our adult population [23], no children in our series had failed RAI as the indication for their surgery.

In our current patient-centered healthcare environment, it is important to consider patient preferences and values when discussing treatment options. For adults with Graves' disease, the decreasing complication rates and increasing access to high-volume surgeons, the rapid and predictable resolution of hyperthyroid symptoms, and the low recurrence risk have made surgery a more attractive first-line option in recent years [21,24,25]. Obviously, this choice is a more difficult one to make for a child, particularly if it is not clear whether complication rates for surgery are higher. Our study found that indications for thyroidectomy are similar, but not identical, for children and adults. The notable exception was that no children underwent surgery after failed RAI treatment. With relatively few children and a short time frame, it is possible that this was a sampling error, or it is possible that RAI was just very successful during the study period. If this is a real trend, however, one possible explanation is that children were referred directly to a surgeon if a trial of ATD failed. Perhaps it is an indication of the growing acceptance of surgical management at our institution as a first line treatment instead of a last resort. It is important to note that none of the three treatment options are perfect or risk-free, but with acceptably low complication rates at a high-volume center, surgery may be considered as a first-line option for children with Graves' disease. During treatment discussions with patients and their parents, surgery should not necessarily be presented as the risky, invasive option to be used only if RAI or ATD treatments fail. The risks and benefits of all options should be discussed as part of the shared decision making process.

A limitation of our study is that we looked only at our surgical series and did not have access to children only treated with RAI or ATD for Graves' disease. We do not have a good sense of the overall population of children with Graves' disease at our institution, only those who ultimately underwent surgery. A further limitation was that, despite our institution performing a very high volume of thyroidectomy for Graves' disease, the sample size was too small to discern statistical significance. This will be a limitation of any single institution study, and a multi-institutional study is needed in order to accumulate enough numbers to show whether there is truly a higher complication rate in children in the modern era of endocrine surgery. Finally, we examined indications for and complications of surgery, but did not follow these patients long term to determine whether surgery had any influence on quality of life or learning and development of these children. It would be very useful to know whether children treated with surgery over RAI or ATD fared better or worse with respect to absenteeism from school or other important indicators specific to the pediatric population, but that was outside the scope of this current study.

Conclusions

In this contemporary series (2009–2014) of pediatric thyroidectomy for Graves' disease, we found that indications for surgery are similar for children and adults, except that no children who underwent surgery had previously failed RAI therapy. We did not find that pediatric patients were treated for a longer period of time with medications than adult patients. We also report that permanent complications rates of surgery are low in both children and adults when performed by our high volume surgeons. Transient complications of hypocalcemia and voice hoarseness seemed higher in our pediatric population, but a single institution study will never be sufficiently powered to detect any significant difference in these rare outcomes. To help parents and guardians make informed, patient-centered decisions about treatment for Graves' disease in children, a multi-institutional study that involves collaboration between pediatric endocrinologists, pediatric surgeons and endocrine surgeons is needed.

Abbreviations

ATD	Anti-thyroid drugs
PTU	Propylthiouracil
RAI	Radioactive iodine
PTH	Parathyroid hormone

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Table 1

Demographics, indications for surgery, duration of medications

Variable	Children n=31	Adults n=136	p-value
Age, years (mean ± SD)	14 ± 4	43 ± 13	<0.001
Female (%)	87	81	0.4
Indication for surgery (%)			
Failure of ATD	55	36	0.05
Failure of RAI	0	13	0.04
Ophthalmopathy	23	40	0.06
Compressive Symptoms	16	21	0.5
Thyroid nodules	10	19	0.2
Side effects of ATD	13	10	0.7
Duration of ATD, months (mean ± SD)	13 ± 12	15 ± 19	0.6
Patient on ATD > 18 months prior to surgery (%)	26	27	0.9

SD = standard deviation

ATD = anti-thyroid drugs

RAI = radioactive iodine ablation

Table 2

Peri-operative findings and complications

Variable	Children n=31	Adults n=136	p-value
Operative time, min (mean ± SD)	103 ± 35	110 ± 35	0.2
Length of stay <23 hours (%)	90	96	0.2
PTH (pg/mL) in recovery room (mean ± SD)	29 ± 29	33 ± 26	0.4
Calcitriol prescribed postoperatively (%)	32 (n=10)	18 (n=24)	0.07
Transient hypocalcemia (%)	35 (n=11)	21 (n=29)	0.14
Transient nerve palsy (%)	10 (n=3)	5 (n=7)	0.3
Permanent hypoparathyroidism (%)	3 (n=1)	2 (n=3)	0.5
Permanent nerve injury (%)	0 (n=0)	1 (n=1)	0.6

SD = standard deviation

PTH = parathyroid hormone