



## Thyroidectomy for Graves' disease in children: Indications and complications<sup>☆</sup>



Dawn M. Elfenbein<sup>\*</sup>, Micah Katz<sup>1</sup>, David F. Schneider, Herbert Chen<sup>2</sup>, Rebecca S. Sippel

University of Wisconsin, Department of Surgery, Section of Endocrine Surgery, 600 Highland Ave, K4/739, Madison, WI 53792

### ARTICLE INFO

#### Article history:

Received 13 January 2016

Received in revised form 10 March 2016

Accepted 18 March 2016

#### Key words:

Thyroidectomy

Pediatric Graves' disease

Pediatric hyperthyroidism

Shared decision making

### 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 to 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'.

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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 learning and development, and prompt recognition and treatment for children is important to minimize these negative consequences.

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].

**Abbreviations:** ATD, Anti-thyroid drugs; PTU, Propylthiouracil; RAI, Radioactive iodine; PTH, Parathyroid hormone.

<sup>☆</sup> Disclosure statement: The authors have nothing to disclose, this research was presented as a poster at the American Association of Endocrine Surgeons annual meeting in Nashville, TN, May 2015.

<sup>\*</sup> Corresponding author at: University of California, Irvine, Department of Surgery, Division of Surgical Oncology, 333 City Blvd West, Suite 1600, Orange, CA 92668. Tel.: +1 714 456 6327; fax: +1 714 456 8870.

E-mail address: [delfenbe@uci.edu](mailto:delfenbe@uci.edu) (D.M. Elfenbein).

<sup>1</sup> Present address: University of Utah School of Medicine, Department of Surgery, 30 N 1900 E, Salt Lake City, UT 84132.

<sup>2</sup> Present address: University of Alabama, Birmingham, Department of Surgery, Boshell Diabetes Building, #502, 1808 7th Ave S, Birmingham, AL 35294.

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 <sup>131</sup>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 are no higher for children than for adults.

## 1. 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.

## 2. 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

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