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Disease impacts more than age on operative morbidity in children with Graves' disease after total thyroidectomy

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ABSTRACT

Background: In pediatric Graves' disease, operative morbidity after total thyroidectomy remains ill defined. The present study aimed to clarify whether total thyroidectomy entails greater operative morbidity in children with Graves' disease, in particular when they are very young, as compared with an age-matched reference group of children with hereditary C-cell disease who underwent total thyroidectomy at the same time.

Methods: Operative morbidity after total thyroidectomy for Graves' disease was determined in relation to the child's age and in comparison with a reference group of age-matched children with hereditary C-cell disease.

Results: Included in the study were 58 children with Graves' disease (51 girls and 7 boys) and 108 children with hereditary C-cell disease (59 girls and 49 boys). When children with Graves' disease and children with hereditary C-cell disease were compared across and within the 4 age increments (≤ 3, 4–6, 7–12, and 13–18 years), operative mortality did not differ significantly among and within age increments. Children with Graves' disease had a 1.7-fold greater overall risk of transient hypoparathyroidism (29% versus 17%; $P = .073$) than children with hereditary C-cell disease. Permanent hypoparathyroidism was nil in either group. Transient recurrent laryngeal nerve palsy, wound hemorrhage, and wound infections were infrequent (≤ 3% each), resolving spontaneously and after reoperation, respectively.

Conclusion: Disease impacts more than age on operative morbidity in children with Graves' disease after total thyroidectomy but is fairly low overall and rarely permanent in experienced hands.

Introduction

Graves' disease, an autoimmune disorder in which autoantibodies are raised against the thyroid TSH receptor, is the most common cause of hyperthyroidism. The incidence of pediatric Graves' disease, favoring girls, is estimated at between 0.1 and 3 per 100,000 children,[1] with a prevalence of 1 in 10,000 children in the United States.[2] Pediatric Graves' disease is rare in children under the age of 5 years and has a peak incidence in youth at 10–15 years of age.[3] Three therapeutic options are available for Graves' disease: antithyroid drugs, radioactive iodine ablation, and thyroidectomy. Relative to adults, children have a lower likelihood of remission with antithyroid medication.[4] In children younger than 10 years of age and children with large goiters in whom conventional drug and radioiodine therapies are less effective, definitive surgical therapy is recommended.[3]

Small children feature smaller and more delicate anatomic structures in a shorter neck, marrying greater tissue vulnerability with considerable space constraints.[5] In infants and young children, the parathyroid glands are small, translucent, and difficult to distinguish from adjoining soft tissues, thymus, and central neck nodes.[6] Besides, the thymus of infants and young children may reach the size of a normal thyroid gland, decreasing surgical exposure further.[7] In Graves' disease, this situation is compounded by severe inflammation and fragility of the thyroid gland, precipitating intraoperative bleedings that imbue adjacent soft tissues and jeopardize preservation of parathyroid glands and the recurrent laryngeal nerve. In recurrent hyperthyroidism, this situation is aggravated by scarring from previous neck surgery, augmenting the risk of complications on reoperation.

Owing to the need for removal of the effector organ to prevent recurrent hyperthyroidism, total thyroidectomy has replaced subtotal thyroidectomy as the definitive treatment of Graves' disease.[8,9]

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In children with Graves' disease, data are limited as to operative morbidity after total thyroidectomy, deriving from 32 children or fewer from single institutions.[10–13] These series were too small to resolve the controversy whether younger children have greater operative morbidity than older children[14] or not.[15]

Because children with normal thyroid glands rarely require total thyroidectomy, children with hereditable C-cell disease confined to normal-sized thyroid glands, who essentially feature normal thyroid tissue, may be better suited as a reference standard than children with nodular thyroid disease and enlarged thyroid glands, in whom severity of disease can vary tremendously.

The present study aimed to clarify whether total thyroidectomy entails greater operative morbidity in children with Graves' disease, as compared with an age-matched reference group of children with hereditary C-cell disease who underwent total thyroidectomy at the same time.[16]

Patients and Methods

Study cohort and reference group

Included in this study were all children and adolescents aged 18 years or younger who were referred to the authors' institution between November 1994 and April 2018 to undergo total thyroidectomy for drug-refractory Graves' disease (study cohort) or pre-emptive thyroidectomy without node dissection for hereditary C-cell disease[16] (reference group).

A diagnosis of Graves' disease was typically based on elevated free thyroxine (T4) or serum triiodothyronine (T3); suppressed serum thyrotropin (TSH); and presence of thyroid stimulating antibodies. For operative therapy, children with Graves' disease were prepared with carbimazole therapy and thyroxine replacement therapy tailored to the child's TSH serum levels.

A total of five staff surgeons performed all total thyroidectomies in a standard fashion. Before embarking on thyroid dissection, the inferior parathyroid glands, and subsequently the recurrent laryngeal nerves were identified using optical magnification, bipolar forceps coagulation, and intraoperative nerve monitoring as an institutional standard of care since December 1997.[17] The thyroid gland was dissected off the thyroid bed, keeping the line of dissection to the thyroid capsule as closely as reasonably feasible.

All children had calcium and intact parathyroid hormone serum levels determined before thyroidectomy, upon discharge, and subsequently at the discretion of the attending physicians elsewhere. Informed consent was obtained before surgery, which represented the standard of care.

For retrospective analysis of existing data sets from routine patient care, no institutional review board approval is required under national law and applicable institutional regulations.

Protection of recurrent laryngeal nerves and parathyroid glands

Every attempt was made to identify and preserve the parathyroid glands and recurrent laryngeal nerves, as detailed elsewhere. In infants and young children, great care was exercised to protect the parathyroid glands from harm during mobilization of the thyroid gland, minimizing parathyroid manipulation. Every effort was made to preserve the thymus in small children to avoid damaging the blood supply of lower parathyroid glands lodging within the thymus. Only in the event of complete devascularization were affected glands removed and autografted onto the right sternocleidomastoid muscle.[18]

Clinical outcome

Each child's vocal fold function was determined on laryngoscopy before and after the operation, routinely on the second postoperative day.[19] If abnormal, laryngoscopic examinations were repeated to confirm recovery of the recurrent laryngeal nerve.

When signs and symptoms of early postoperative hypoparathyroidism were present, patients were started on calcium and vitamin D replacements for 2 weeks and then instructed to taper off as permitted by clinical symptoms and calcium and intact parathyroid hormone serum levels.

Outcome information was collected from other institutions, general practitioners, or the patients or their parents. Special emphasis was laid on postoperative vocal fold status based on laryngoscopic examination, current need for calcium and vitamin D replacements, and the most recent serum levels of the intact parathyroid hormone.

Any calcium and vitamin D replacements or vocal fold palsies persisting for more than 6 months were considered as permanent vocal fold palsy and postoperative hypoparathyroidism, respectively.

Statistical analysis

Categoric and continuous data were tested with the Fisher exact test and the exact Mann-Whitney-Wilcoxon rank sum test, respectively. Children and adolescents were grouped into age increments of $\leq$ 3, 4–6, 7–12, and 13–18 years in an attempt to ensure sufficiently large numbers of patients and events in each group.

Results

Demographics, early operative morbidity, and follow-up by thyroid disease

Included in the study cohort were 58 children with total thyroidectomy for Graves' disease and in the reference group 108 children with total thyroidectomy without central node dissection for hereditary C-cell disease (82 children with C-cell hyperplasia and 26 children with 0.6–5.0 mm large medullary thyroid cancers confined to the thyroid gland) who carried germline mutations in the *RE*arranged during *T*ransfection *(RET)* proto-oncogene. Before the operation, all 58 children with Graves' disease, none of whom ever received radioiodine therapy, had failed antithyroid drug therapy or discontinued it for drug-related adverse events; whereas the 108 asymptomatic gene carriers underwent total thyroidectomy based on evidence of *RET* germline mutations, raised calcitonin levels, or both.[16]

Table 1 reveals that children with Graves' disease were significantly older at the time of thyroidectomy (mean age of 13.1 years versus 6.1 years; $P < .001$) and included significantly more girls (88% versus 55%; $P < .001$) than children with hereditary C-cell disease. In terms of operative morbidity and duration of follow-up, the two groups of children were comparable in essence. Children with Graves' disease tended to have a 1.7-fold greater overall rate of postoperative hypoparathyroidism (29% versus 17%; $P = .073$) than children with hereditary C-cell disease (Table 1).

No permanent hypoparathyroidism or permanent recurrent laryngeal nerve palsy were seen. At mean follow-up periods of 64.9 months and 74.6 months after total thyroidectomy, respectively, no child with Graves' disease had evidence of recurrent hyperthyroidism or recurrent Graves' disease, and no child carrying a *RET* gene mutation had developed recurrent C-cell disease or recurrent medullary thyroid cancer.

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