Editorial

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Optimal Management of Graves' Disease in Childhood and Adolescence

Graves' disease is the most common cause of thyrotoxicosis in children and adolescents. According to Zimmerman et al, Graves' disease has a profound impact on the physical development, learning, school performance, and quality of life in children.[1] Ideally, the treatment should be effective and safe, with minimal immediate and long-term adverse effects. The options for the treatment of Graves' disease in children and adolescents have remained constant over many decades. These treatment options include antithyroid drugs (ATDs), radioactive iodine (RAI) therapy, and thyroidectomy.

Antithyroid drugs continue to be the first-line of therapy for most patients with pediatric Graves' disease. Unfortunately, antithyroid drugs are associated with low remission and high relapse rates in children (80%), drug toxicity, and issues centering around patient compliance. More recent studies documenting fatal hepatic failure with propylthiouracil in children has raised further concerns about the safety and efficacy of antithyroid drugs in kids.[2]

Definitive therapy, therefore, depends on the use of either radioactive iodine or surgery. In many countries, like the United States, radioiodine ablation is the treatment of choice in adults. At the Mayo Clinic, over 95% of adults with Graves' disease are treated with radioactive iodine. Many large studies have demonstrated both the safety and efficacy of radioactive iodine in the adult population.[3] Today, the goal of radioactive iodine therapy is to completely ablate the gland and render the patient hypothyroid, thus requiring thyroid hormone replacement therapy. Indications for thyroidectomy in adults include large gland Graves' disease (glands weighing greater than 60 grams), failure of antithyroid drugs during the second trimester of pregnancy, a suspicious or biopsy-proven associated malignant thyroid nodule, or severe associated Graves' ophthalmopathy.

Unfortunately, we have a paucity of data on children and adolescents; in particular, prepubertal children. Much of what is claimed about the safety of radioactive iodine in children is extrapolated from studies in adults. As pointed out by Reddy, the high susceptibility of young children to the carcinogenic effects of radiation to the thyroid contrasts with the very low susceptibility in adults.[4] This is indeed consistent with experimental studies on animals that suggest greater radiation effects during periods of rapid cell proliferation, such as is observed during the development of the thyroid gland. Previous studies in children and adults have demonstrated an increased risk of both and malignant thyroid nodules in thyroid glands treated with lower doses of radioactive iodine. As pointed out by Gambhir et al in this month's journal, in children treated with more than 200 to 250 Gy (approximately 220 to 275 μCi/gm), hypothyroidism is achieved in nearly 95% of patients.[5] With these complete ablations, an increased rate of thyroid cancer has not been observed and should not be observed in the future. Of concern, however, is the risk of second non-thyroid malignancies developing in children treated with radioactive iodine during a period of time when their cells are particularly susceptible to the carcinogenic effects of radiation. In our recent study, looking at long-term outcomes of children treated with surgery and radiation for papillary thyroid carcinoma, we saw only two papillary thyroid cancer deaths in 215 patients observed over 60 years.[6] However, mortality from all causes was double from what would have been expected for age- and sexmatched controls. The vast majority of these deaths were due to second primary malignancies, and nearly three-fourths of these individuals had some form of adjuvant radiation in addition to their thyroid surgery. One can ponder as to whether or not this relates to an increased predisposition for second malignancies among children who develop thyroid cancer or overzealous treatment of cells more susceptible to the damaging effects of ionizing radiation. The fact that this was more prevalent in the radiation group certainly raises cause for concern. Primary hyperparathyroidism also appears to be more prevalent among patients treated with radioactive iodine. Dosimetry data in children is also woefully lacking.

Gambhir et al also commented on the use of radioiodine in more than 1200 children in a recent study from China, pointing out that patients as young as 1 year of age were treated with I-131 with excellent outcomes. On closer review of this retrospective study, the cure rate for radioactive iodine was 49.8%, and no long-term outcome data were available with regard to malignancy.[7]

The most often quoted study regarding the safety and efficacy of radioactive iodine in children comes from Read et al.[8] This was a retrospective study of less than 100 children. Follow-up was based on a questionnaire sent to their family physicians some 26 to 36 years later. This study was hailed as strong evidence of the safety of radioactive iodine, but the study, as pointed out, had significant limitations in that it was retrospective, observational, and questionnaire based involving only a smaller number of subjects. The dose of radioactive iodine was small compared to what is typically used today, and there was a paucity of subjects in the preadolescent period. This can hardly be used as evidence of the long-term safety of radioactive iodine in children.

What about the surgical management of Graves' disease? We reviewed our experience with 78 patients under the age of 18 who were surgically managed at the Mayo Clinic for Graves' disease.[3] Ninety percent of children with Graves' disease are managed at Mayo Clinic with thyroidectomy. Eighty-seven percent were female, and the median age was 13.8 years. The most common presenting signs and symptoms included heat intolerance (61%), decreased academic performance (50%), tremor (49%), and Graves' ophthalmopathy (43%). All of the patients had clinical and laboratory evidence of autoimmune thyrotoxicosis. Sixty-nine percent chose operative therapy because of failure of medical therapy or adverse drug reaction. Near-total or total thyroidectomy was the most common surgical procedure performed. Unrecognized malignancies were identified in 5% of the patients. Six percent of the patients had transient hypoparathyroidism, and there was one patient with a transient recurrent laryngeal nerve palsy. In a small subset of patients who underwent subtotal thyroidectomy during the early part of that study, relapse developed in three patients. Eighty-five percent of the patients with Graves' ophthalmopathy noted improvement, while only one patient experienced worsening of their eye symptoms following surgery. There were no permanent complications and no major concerns regarding the neck incision. Several other major referral centers around the world have also demonstrated the safety and efficacy of thyroidectomy when performed in high volume centers with experienced thyroid surgeons.[3]

The biggest concern in operative management of Graves' disease in children centers around the avoidance of hypoparathyroidism. Although total thyroidectomy is the preferred operation, near-total thyroidectomy, leaving a tiny remnant of thyroid tissue associated with one superior parathyroid gland, ensuring its viability, has diminished significantly the risk of permanent hypoparathyroidism in children undergoing surgery for malignancy and Graves' disease without altering long-term outcomes.

In conclusion, more recent concerns regarding the safety of antithyroid drugs and the paucity of data on the long-term outcomes of radioactive iodine with regard to a second malignancy, in my opinion, favor a surgical approach, when the patient can be treated at a high volume center by an experienced thyroid surgeon. Although thyroidectomies in children are relatively uncommon, surgeons who perform large numbers of adult thyroidectomies are in the best position to perform the safest pediatric thyroid operations.

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