Challenges in Graves Disease

Written by Lori Alexander

Graves disease is the leading cause of hyperthyroidism in the United States (US), and its diagnosis and management can be difficult. Treatment decision-making is especially challenging in two specific populations of individuals with Graves disease: individuals with Graves ophthalmopathy and children/adolescents with the disease.

Managing Graves Ophthalmopathy

More than half of individuals with Graves disease will have some degree of ophthalmopathy, and the clinical heterogeneity in ophthalmopathy calls for disease assessment as a crucial first step in management, said Rebecca S. Bahn, MD, Mayo Clinic, Rochester, Minnesota, USA. It is important to distinguish disease activity from severity, as immunosuppressive treatment is more effective when disease is active rather than severe. Active Graves eye disease is defined as a score of at least 3/7 or 4/10 on the Clinical Activity Score (CAS), whereas severity of disease is determined by clinical assessment of the degree of lid retraction, soft tissues, exophthalmos, diplopia, and corneal exposure.

Mild Disease

Symptomatic treatment is appropriate for most patients with mild Graves ophthalmopathy. Interventions include lubricant eye drops, eye ointment and taping of eyelids at night, sunglasses to decrease photophobia, prismatic correction for diplopia, and elevation of the head of the bed. Dr. Bahn added that diuretics are not useful and that glucocorticoids are rarely justified, as the risks in this group of patients outweigh the benefits. A smoking cessation program is an essential element of treatment.

The antioxidant selenium has recently been studied as treatment for mild Graves ophthalmopathy. Although selenium at a dose of 100 µg twice daily led to a significant improvement in the scores on a Graves orbitopathy-specific quality-of-life questionnaire ($p<0.001$ compared with placebo) in a recent European study, the improvements in clinical assessment were modest, with a median reduction of 2 and 3 mm in eyelid aperture, [slight improvement] in soft tissue signs, and no improvement in eye muscle motility [Marcocci C et al. *N Engl J Med* 2011]. No adverse events occurred. Dr. Bahn noted that selenium levels are marginally decreased in most areas of Europe and were not determined in the study. Thus, further evaluation of a selenium-sufficient US population is needed. She said that selenium can be discussed with patients who have mild Graves eye disease but added that clinicians should not "oversell any possible benefit."

Moderate-to-Severe Disease

According to a 2008 European Group on Graves Orbitopathy (EUGOGO) consensus statement, pulses of intravenous glucocorticoids is the treatment of choice for moderate-to-severe Graves eye disease, defined as a CAS≥3/7 [Bartalena L et al. *Thyroid* 2008]. Dr. Bahn said that she uses the Kahaly regimen (500 mg weekly x 6 plus 250 mg weekly x 6) [Kahaly GJ et al. *JCEM* 2005] and tends to reserve treatment for patients with a slightly higher clinical score than the EUGOGO group recommends (CAS≥4/7).

Rituximab is being studied as a potential treatment for moderate-to-severe disease, and the drug has been beneficial in several uncontrolled series. Two parallel randomized controlled trials are currently underway, one of which Dr. Bahn is conducting with colleagues at the Mayo Clinic. Dr. Bahn feels that "the jury is still out" on rituximab for the treatment of Graves eye disease but doubts it will be a "blockbuster." She added that it may be beneficial only for specific subsets of patients and would not be appropriate for milder cases, especially because of the risk of potentially serious side effects. Until the results or more studies are available, rituximab should be used only as part of a randomized controlled trial or under expert supervision in selected patients for whom other therapies have failed.

Managing Graves Disease in Children

For children with Graves disease, medical therapy (antithyroid medications) is the firstline approach for more than 95% of children, to "buy time with the hope of remission," said Catherine Anne Dinauer, MD, Yale University School of Medicine, New Haven, Connecticut, USA. However, a durable remission is achieved in only a small percentage of children, making definitive treatment (radioactive iodine [RAI] or surgery) necessary for most children at some point. Dr. Dinauer said that controversies surround each treatment option, primarily related to the associated risks and benefits and the timing of definitive therapy.

Medical Therapy

Methimazole (MMI) and propylthiouracil have been the most commonly used antithyroid medications. However, an unacceptable risk of severe liver injury in children has been reported with propylthiouracil, and a black box warning on the label became required in April 2010. The drug should never be used as firstline therapy, said Dr. Dinauer. MMI is thus the drug of choice.

According to recently published guidelines for the management of hyperthyroidism [Bahn R et al. *Thyroid* 2011], the recommended initial dose of MMI for children is 0.2–0.5 mg/kg/day (range, 0.1–1.0 mg/kg/day). A general dosing schema, based on age can be used:

- Infants: 1.25 mg/day
- 1 to 5 years: 2.5 to 5 mg/day
- 5 to 10 years: 5 to 10 mg/day
- 10 to 18 years: 10 to 20 mg/day

Dr. Dinauer said that clinicians should use the lowest dose possible to achieve euthyroidism, with the dose titrated down once the free T4 or total T4 level becomes normal. The block-and-replace approach should not be used. The side effect profile of MMI is safer than propylthiouracil, but rare, serious side effects, such as Stevens-Johnson syndrome, can occur. Adverse events have been reported in about 19% of children, with approximately 90% of events occurring within the first 6 months of treatment.

Treatment is usually recommended for 1–2 years and can continue beyond 2 years if there is no treatment-related toxicity, thyromegaly is not worsening, and the patient is compliant and not ready for definitive treatment. Dr. Dinauer pointed out that remission rates among children are lower than those among adults. The remission rate is 25% (compared with 49% to 75% of adults) after treatment for less than 2 years and is 15% to 30% after treatment for 2 years or longer.

Definitive Therapy: RAI Versus Surgery

The evidence does not support many long-term risks that have been thought to be associated with RAI in children. For example, Dr. Dinauer noted that studies have failed to demonstrate an increased risk of congenital anomalies in the offspring of individuals who have been treated with RAI in childhood or an increased risk of thyroid cancer when recommended doses have been used. In addition, there is no evidence to date that the use of RAI in childhood increases the risk of a nonthyroid malignancy; however, a large sample of children aged ≤10 years is needed to detect a small risk. Theoretical projections indicate a slight risk of cancer for children aged <5 years at the time of RAI treatment. Because of this, RAI should not be used for children aged <5 years.

The RAI dose should be calculated according to the size of the thyroid size, with a dose >150 µCi of RAI/g of thyroid tissue and a dose of 200–300 µCi of RAI/g for thyroids that are 50–80 g. For children aged 5 to 10 years, the dose should be <10 mCi; if the calculated dose is higher, surgery or medical therapy should be considered rather than reducing the dose on the basis of age. Dr. Dinauer said that there are no outcome data on the use of fixed doses versus calculated doses in children but that a fixed dose may be higher than the calculated dose and thus expose the child to higher-than-necessary radiation.

There are several indications for surgery as definitive treatment: a thyroid that is larger than 80 g, patient age <5 years, noncompliance with medical or RAI safety regimens, a suspicious nodule or known cancer, need for immediate control of disease, and obstructive or compressive symptoms. Total or near-total thyroidectomy is the procedure of choice, as relapse rates are lower than for subtotal resection. Dr. Dinauer cautioned that while the rate of overall complications after thyroidectomy is similar for both children and adults, the rate of endocrine complications is higher for children, especially the youngest patients. Studies have shown that the complication rate, length of stay, and cost are lower when thyroidectomy is done by a high-volume surgeon (one who performs more than 30 endocrine procedures per year).

Dr. Dinauer noted that there is no one "right" treatment path for children with Graves disease, and a stratified approach should be taken (Table 2). For each child, clinicians should consider the age, clinical factors, and the risks of treatment options to determine the best course of action. She also urged clinicians to review and follow recently published management guidelines [Bahn R et al. *Thyroid* 2011].

Table 2. Stratified Approach to Management of Graves Disease in Children.

Age of Patient	Treatment
<5 years	• Initial: MMI—may need prolonged course • Definitive: surgery if <5 years; consider RAI if >5 years
6 to 10 years	• Initial: MMI; if age ~10 years, RAI can be considered if likelihood of remission is low • Definitive: RAI, if dose <10 µCi or surgery
>10 years	• Initial: MMI or RAI, depending on prognostic factors • Definitive: RAI or surgery

Rivkees SA et al. *Horm Res Paediatr* 2010.; MMI=methimazole; RAI=radioactive iodine.