



Published: October 31, 2023

Citation: Reyes DR, Rodriguez IV, et al., 2023. Graves' Disease in Children: A Comprehensive Review on Diagnosis, Treatment, and Long-Term Considerations, Medical Research Archives, [online] 11(10).

<https://doi.org/10.18103/mra.v11i10.4549>

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DOI

<https://doi.org/10.18103/mra.v11i10.4549>

ISSN: 2375-1924

REVIEW ARTICLE

Graves' Disease in Children: A Comprehensive Review on Diagnosis, Treatment, and Long-Term Considerations

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ABSTRACT

This comprehensive review of Graves' Disease (GD) addresses some of the challenges in diagnosing the condition and with the techniques utilized. Focus is given to the relevant clinical manifestations, management options, complications and long-term effects, and future directions in treatment. It highlights the critical role of thyroid function tests (TFTs) in confirming thyrotoxicosis, and the role of thyroid autoantibodies in distinguishing GD from other thyroid disorders. It discusses the role of antithyroid medications, radioactive iodine therapy, and surgical interventions in the management of GD in children. It sheds light on the risks and benefits associated with each approach. The paper also studies the impact of GD on growth, development, and ophthalmic complications in the pediatric population. Promising advancements in treatment such as B-lymphocyte depletion, CD40 blockage, and small molecule TSH-receptor antagonists are also explored. Lastly, the importance of risk factor assessment, screening programs, and increased research are underscored with an attempt to enhance the understanding and management of GD in children.

Keywords: thyrotoxicosis; Grave's; children; thyroid; surgery

Aims and Objectives

This study seeks to offer a comprehensive exploration on the challenges and nuances of diagnosing and managing Graves' Disease in pediatric patients. It is set to be accomplished by an extensive comprehensive literary review of the disease. The paper provides a thorough examination of various diagnostic approaches, management options, and future directions. Its aim was to consolidate existing knowledge on the topic and present it in a cohesive way. To provide an overview of GD in pediatrics focusing on its epidemiology, clinical manifestations, and diagnostic challenges was among our objectives. Also, to evaluate various diagnostic methods, to discuss management options, to investigate the long-term effects of GD, and to explore recent advancements and directions of the condition. Another important objective is to identify risk factors and predisposing elements associated with GD in children. We want to propose potential strategies for early detection and screenings for at-risk children. Lastly, we aim to emphasize gaps in the current research and areas that require further attention.

Introduction

Graves' disease, also known as Basedow's disease or exophthalmic goiter, is the most common cause of hyperthyroidism and is characterized by a diffuse hyperfunctional goiter accompanied by distinct clinical features. First described by Karl von Basedow in 1840 and later named after Robert Graves, the underlying mechanism of Graves' disease remained elusive for a long time, but it is now widely accepted to be an autoimmune disorder involving the production of autoantibodies that stimulate thyroid growth and hormone secretion.^{1,2} This condition is different from thyrotoxicosis caused by vesicular contents released in an inflammatory cytolytic process associated with drug or radiation therapy. Graves' disease is considered a form of autoimmune hyperthyroidism, primarily characterized by thyroid hyperfunction rather than thyrotoxicosis. However, despite these general definitions, there are still uncertainties and challenges in accurately defining and diagnosing the disease, particularly in cases without goiters or with extrathyroidal manifestations such as isolated Graves' orbitopathy and nodular variants. Achieving a consensus and developing standardized criteria for diagnosis and management are ongoing endeavors in the field of Graves' disease research.³

Causes and Risk Factors

Graves' disease is a rare autoimmune disorder that

affects the thyroid gland and it is characterized by the production of anti-TSH-receptor (TRAb) autoantibodies. The disease can occur at different stages of life, with variations in severity and prevalence. In children under 5 years of age, Graves' disease is more severe, as indicated by elevated TRAb levels. The incidence of Graves' disease increases with age, from 0.1/100,000 patient-years in children to 3/100,000 in adolescents. The prevalence among 10 to 19-year-olds in the United States is reported to be 106.9/100,000. In Hong Kong, where iodine intake is increased, the incidence of Graves' disease in childhood is high and continues to rise, particularly in girls.^{4,5}

The pathogenesis of Graves' disease involves a breakdown of immune tolerance towards thyroid structures, leading to the production of TRAb by B-cell clones infiltrating the thyroid gland. These antibodies target the extracellular domain of the TSH receptor, exerting a predominantly stimulating action. The majority of cases result in unregulated thyroid hyperfunctioning. Genetic factors play a significant role in the development of Graves' disease, with an estimated 75-80% contribution compared to 20-25% for environmental factors. In fact, genetic susceptibility may explain the variations in disease prevalence among different ethnic groups. Moreover, the involvement of immunomodulatory genes, such as the major histocompatibility complex (MHC), CTLA4, PTPN22, CD40, CD25, FOXP3, and FCRL3, has been implicated in the pathogenesis of Graves' disease. Additionally, thyroid-specific genes, including thyroglobulin and the TSH receptor, have also been associated with the disease. Further research is needed to confirm the role of these genes and their mechanisms in Graves' disease.⁶

Clinical Presentation and Symptoms

Graves' disease (GD) is an autoimmune disorder that affects the thyroid gland, causing hyperthyroidism and thyrotoxicosis. This article aims to provide an overview of GD, including its pathophysiology, diagnosis, and treatment. It draws from reviews and guidelines from the American Thyroid Association (ATA), European Thyroid Association (ETA), and Japan Thyroid Association/Japan Endocrine Society.

Hyperthyroidism, a characteristic feature of GD, is associated with an increased metabolic rate. This results in a higher energy expenditure by the body, leading to weight loss. Patients with GD often experience unintentional and significant weight loss despite having an increased appetite. This symptom

is an important clinical marker for diagnosing hyperthyroidism.

Individuals with GD commonly report heat intolerance and excessive sweating. The elevated levels of thyroid hormones in the body due to hyperthyroidism disrupt the normal temperature regulation mechanisms. As a result, patients feel more sensitive to warm temperatures and may experience excessive sweating even in mild conditions. This symptom can significantly impact a patient's quality of life.

Another prominent manifestation of GD is a rapid heart rate and palpitations. The excess thyroid hormones circulating in the body can increase cardiac output and heart rate. Patients may feel their heart beating faster than normal or experience a sensation of palpitations, where they are aware of their own heartbeat. This symptom often necessitates further evaluation and monitoring of the patient's cardiovascular health.

In summary, GD is characterized by a range of clinical features, including increased metabolic rate and weight loss, heat intolerance and excessive sweating, as well as rapid heart rate and palpitations. These symptoms serve as important indicators for the diagnosis of GD and can guide the appropriate management and treatment strategies for affected individuals.⁷

Graves' disease, a thyroid disorder, is characterized by a set of classical signs and symptoms known as the "Merseburger triad." These include hyperthyroidism, diffuse goiter, and ophthalmopathy, also referred to as thyroid eye disease. Ophthalmopathy associated with Graves' disease presents a significant challenge in terms of treatment and imposes a considerable burden on patients. Exophthalmos, which refers to the protrusion of eyeballs, is one of the notable manifestations of this condition. Additionally, ocular irritation, dryness, double vision, and eye muscle weakness are commonly observed in individuals with Graves' ophthalmopathy.

Thyroid eye disease is prevalent in 25-50% of Graves' disease cases, manifesting as gritty eyes, photophobia, chemosis, and clear exophthalmos. However, even subclinical changes can be detected in nearly all cases of Graves' disease. It is important to note that the occurrence of eye signs may not always coincide with hyperthyroidism and goiter.

The precise pathogenesis of thyroid eye disease remains unclear, hindering the development of effective medical treatments. However, studies

have focused on the immune system's self-reactivity to antigens in retro-orbital tissues, considering the close connection between eye disease and Graves' disease. Early immune theories explored the anatomical connection between the lymphatic systems of the eyes and thyroid, proposing a retrograde flow from the thyroid to the orbits involving thyroid antigens, such as thyroglobulin. Additionally, antibodies to striated muscle cells were detected in the serum of patients with thyroid eye disease. However, it is believed that these antibodies are more likely a consequence rather than the cause of the inflammatory reaction in retro-orbital muscles.

In the 1980s, a theory based on the recognition of autoantibodies to the thyroid-stimulating hormone receptor (TSH-R) emerged. While this theory expanded the concept of receptor antibodies to include eye components, subsequent studies disproved the notion that TSH-R-related antibodies primarily stimulate orbital fibroblasts as the main cause of thyroid eye disease.

Orbital fibroblasts, which differentiate into mature adipocytes, are believed to play a crucial role in thyroid eye disease. These fibroblasts express the full, functional TSH-R to a significant extent and can also trigger autoreactive immune reactions.

In addition, recent research indicates that the cytokines interferon-gamma (IFN- γ) and interleukin-4 (IL-4) can enhance the production of hyaluronan from orbital fibroblasts stimulated by IL-1 β . Hyaluronan is a glycosaminoglycan molecule involved in the edematous reaction of retrobulbar tissues in Graves' disease.⁸

In summary, Graves' ophthalmopathy, as part of the Merseburger triad, encompasses a range of manifestations including exophthalmos, ocular irritation, dryness, double vision, and eye muscle weakness. While the exact pathogenesis remains elusive, studies have explored the immune system's reactivity to retro-orbital tissue antigens, particularly the involvement of orbital fibroblasts and the interplay of various cytokines. Understanding the complex immune mechanisms underlying thyroid eye disease is crucial for developing effective treatment strategies.⁹

While the most common extrathyroidal manifestation of GD is ophthalmopathy, dermatopathy is also observed, typically occurring in the pretibial area. Dermopathy is commonly seen in conjunction with ophthalmopathy and, in severe cases, with acropachy. The pathogenesis of these extrathyroidal manifestations involves a common antigen, likely the TSH receptor, present in the skin

and eyes. Dermopathy and acropachy serve as indicators of the severity of the autoimmune process. Local corticosteroid application is the standard therapy for dermopathy, with variable response rates depending on the severity of the condition. Trials are underway to investigate immune modulators and biotherapies for the treatment of ophthalmopathy, which may offer potential future treatment options for dermopathy. Some manifestation of Grave's dermopathy includes:

1. **Skin Changes:** Graves dermopathy is characterized by notable skin changes, including a warm and flushed appearance. The affected skin in the pretibial area exhibits localized thickening, often resembling orange peel or pigskin texture. Hyperkeratosis, acanthosis, and papillomatosis may develop in advanced cases.
2. **Fine Hair and Hair Loss:** In addition to skin changes, Graves dermopathy may also manifest with fine hair and hair loss. The underlying mechanisms contributing to these hair abnormalities in dermopathy require further investigation.
3. **Onycholysis:** Onycholysis, which refers to the separation of the nail from the nail bed, is another manifestation observed in Graves dermopathy.
4. **Thyroid acropachy:** Thyroid acropachy, found in about 20% of dermopathy cases, involves clubbing of the fingers and digits. Severe cases may exhibit swollen fingers. It is usually bilateral and symmetrical, but single digit involvement can occur. Joints are unaffected, and increased skin temperature is absent. Radiographs show bilateral periosteal reactions in the hands and feet. Bone scans reveal increased uptake in the periosteum, occasionally affecting long bones. Tobacco use is common in acropachy cases. Management is similar to dermopathy, with pain management for extremity pain.¹⁰

Graves' disease (GD) is known to affect the growth and puberty development of children and adolescents. In a cross-sectional study analyzing newly diagnosed GD cases, it was observed that the average age at initial diagnosis was 8.9 ± 2.9 years. Most cases (64.7%) experienced symptoms before puberty, while 35.3% had symptoms during puberty. Goiter, a characteristic feature of GD, was detected in 94.6% of cases. Exophthalmos, another common manifestation, was present in 68.6% of cases, with 21.4% exhibiting infiltrative exophthalmos. GD can have diverse clinical manifestations, and some children and adolescents may present with atypical symptoms such as

vomiting, fainting, and headache. These hypermetabolic symptoms and emotional changes are often overlooked, leading to delayed diagnosis. Additionally, GD can have an impact on various organ systems, including the cardiovascular, gastrointestinal, and hepatic systems. Liver dysfunction was observed in 26.5% of the studied population. Considering the influence of GD on growth, puberty, and overall health, it is important to raise awareness among parents and healthcare professionals to facilitate early diagnosis and appropriate management.¹¹

Psychiatric symptoms such as mood and anxiety disorders are frequently observed in patients with Graves' hyperthyroidism. However, distinguishing between Graves' disease and hyperthyroidism from other causes based on the available literature is often unclear. The induction of adrenergic nervous system hyperactivity by Graves' hyperthyroidism is thought to contribute to these psychiatric manifestations. Despite successful treatment of hyperthyroidism, a significant proportion of patients continue to experience altered mental states, suggesting the involvement of mechanisms beyond hyperthyroidism alone, including the autoimmune process associated with Graves' disease and ophthalmopathy. The primary treatments for Graves' hyperthyroidism and its psychiatric manifestations involve antithyroid drugs combined with β -adrenoceptor antagonists. However, in cases where psychiatric symptoms persist even after restoration of euthyroidism and treatment with β -adrenoceptor antagonists, specific treatment targeting the psychiatric symptoms, such as psychotropic drugs, may be necessary. Further research is needed to gain a better understanding of the pathophysiology of psychiatric symptoms in Graves' disease and to optimize treatment strategies for these patients.¹²

Diagnosing Graves' Disease in Children

Diagnosing Graves' disease (GD) in pediatric patients can be challenging due to its rare incidence in this age group and accompanying wide range of symptoms. Children with GD may exhibit a variety of behavioral changes, including irritability, nervousness, anxiety, fatigue, emotional lability, and a decline in academic performance. Of note is the overlap of some of these symptoms with attention-deficit/hyperactivity disorder, which further complicates the diagnosis. In addition to behavioral signs, physical symptoms may include headaches, tachycardia, tremors, palpitations, excessive perspiration, weight changes, sleep disturbances, polyuria, and increased stool

frequency. Around 40% of children and adolescents with GD present ophthalmologic changes, typically those of proptosis and eyelid retraction, but tend to be much milder when compared to adult patients. In addition, growth acceleration and bone age advancement may be observed in children, while fatigue is more common in adolescents.¹³

During physical examination, the size of the thyroid gland may vary greatly but is typically symmetrically enlarged, firm, and non-tender. In some cases of thyrotoxicosis, a thyroid bruit may be detected during examination. In addition, although rare in children, a true thyroid storm is a severe complication of Graves' disease. Its hallmark features include fever and an acutely ill appearance accompanied by stark symptoms of thyrotoxicosis such as rapid heartbeat, high blood pressure, precordial thrill, shortness of breath, and abdominal pain. Thyroid storm is diagnosed based on multiple clinical factors and scoring systems, rather than the degree of elevation of thyroid hormone levels.¹⁴

Thyroid function tests (TFTs) are a set of common endocrine blood tests used to evaluate the functioning of the thyroid gland. TFTs assess the level of hormones produced by the thyroid gland and are essential in the diagnosis and management of thyroid disorders. The variety of TFTs include assessment of thyroid-stimulating hormone (TSH), free thyroxine and triiodothyronine (FT4 and FT3, respectively), total thyroxine and triiodothyronine (TT4 and TT3, respectively), thyroglobulin (Tg), and thyroid antibodies, such as thyroid peroxidase antibodies (TPO-Ab), TSH receptor antibodies (TRAb), and thyroid-stimulating immunoglobulin (TSI). The TFTs commonly used to assess the functional status of the thyroid include TSH, FT4, and FT3, while TPO-Ab and TRAb testing is useful in the diagnosis of Hashimoto's thyroiditis and Graves' disease, respectively. Thyroid function tests may also examine calcitonin levels, an important tumor marker in the management of medullary thyroid carcinoma.

As mentioned, thyroid autoantibodies are evaluated in thyroid function tests. The immune system produces these antibodies that mistakenly target components of the thyroid gland and are common findings of autoimmune conditions like Graves' disease and Hashimoto's thyroiditis. There are three main types of thyroid autoantibodies which include thyroid peroxidase antibodies (TPO-Ab), thyroglobulin antibodies (TgAb), and TSH receptor antibodies (TRAb). TPO-Abs target the enzyme thyroid peroxidase, a crucial mediator of thyroid hormone production, and are found in 5-

20% of the general population; they are nearly always elevated in Hashimoto's thyroiditis.¹⁵ On the other hand, TgAb targets thyroglobulin, a glycoprotein produced by thyroid follicular cells essential in thyroid hormone synthesis. Interestingly, TgAb is elevated in serum in 10% of the general population, especially in women, and it shows less sensitivity and specificity as a biomarker when compared to TPO-Ab or TRAb. TgAb is mainly used as a tumor marker for differentiated thyroid cancers (DTCs). Lastly, TRAb binds to TSH receptors, resulting in the overstimulation of the thyroid gland and excess thyroid hormone production. This autoantibody can be measured with a thyroid-stimulating immunoglobulin (TSI) assay which solely identifies stimulating TRAb, as there are also blocking or neutral TSH receptor antibodies. Therefore, TSI levels are essential in determining the presence of stimulating TRAb. Importantly, these antibodies are specific for the diagnosis of Graves' disease, given their absence from the general population.

In pediatric patients with GD, a diagnosis of thyrotoxicosis is confirmed by the results of TFTs. Patients will present with suppressed TSH levels ($<0.3\text{mIU/L}$) and most will also have very high free and total T4 and T3 serum concentrations. However, it is important to note that some patients may principally present an elevation in T3 levels, a condition labeled T3 toxicosis. Once this diagnosis is established, the medical history and physical examination are essential in determining the etiology. For example, a patient showing an enlarged thyroid accompanied by orbitopathy most likely has Graves' disease, while a patient with mild enlargement of the thyroid gland who lacks ophthalmologic findings requires distinction between GD and Hashitoxicosis, the transient thyrotoxic phase of Hashimoto thyroiditis. In cases like the latter, TFTs measuring thyroid antibodies become pertinent. A test of TSH receptor antibody levels, including TSI, can aid in differentiating the conditions since they present greater specificity for GD in comparison to thyroid peroxidase antibody titers, for example, which may show positive results in both GD and Hashitoxicosis. Nevertheless, antibody positivity overlap may still be observed in both diseases, which calls for diagnostic tools in nuclear medicine and ultrasonography, as discussed later.¹⁵

Ultrasonography of the thyroid gland is a valuable imaging technique for the anatomical assessment of the thyroid, but it is unable to distinguish between conditions like GD and Hashitoxicosis. It provides information on size, nodularity, vascularity, and echotexture, but no diagnostically distinguishing

parameter. For example, although thyroid size tends to be markedly increased in Graves' disease than in Hashitoxicosis, there is a significant degree of variability which means we lack a size criterion to distinguish them. Similarly, increased blood flow is a nonspecific finding, even when the thyroid gland is usually hypervascular in GD; it is not unique to this disease. However, ultrasonography continues to be useful because it is a non-invasive procedure which is generally used to diagnose thyroid nodules, evaluate goiters, monitor thyroid disorders, guide fine needle aspiration biopsies, and assess congenital thyroid abnormalities.

In cases of diagnostic indetermination, such as antibody positivity overlap in both GD and Hashitoxicosis, a thyroid radionuclide scintigraphy study becomes helpful. This test, commonly known as a thyroid nuclear scan or thyroid uptake scan, involves the administration of a small amount of radioactive tracer, like iodine 123 (I-123) or technetium 99m pertechnetate (Tc-99m), and the subsequent assessment of gamma radiation emitted by the thyroid. The normal thyroid gland has a characteristic scintigraphic pattern for both I-123 and Tc-99m, but only I-123 uptake can be quantified. Therefore, although a Tc-99m scan is more cost effective and less time consuming, it does not allow quantitative assessment of iodine uptake and therefore does not aid in differentiating between GD and Hashitoxicosis. Moreover, thyroid diseases often produce characteristic abnormal scintigraphic patterns that can be described as focal or diffuse, heterogeneous or homogeneous, and increased or decreased.

The radioactive iodine uptake (RAIU) normally ranges from 5% to 15% at 4 hours to 15%-30% at 24 hours, where peak activity is observed. These values depend on the population being tested and the laboratory conducting the test, although an I-123 uptake of 65% at 4 hours is markedly increased and suggestive of GD, for example.²¹ Additionally, the thyroid gland should have smooth contours and a homogeneous radiotracer pattern. In Graves' disease, Tc-99m imaging usually reveals a "hot" thyroid gland, as described when an area or nodule within the gland exhibits a concentrated tracer uptake, suggesting overactive thyroid cells and hormone overproduction. The thyroid scintigraphy also provides information on blood flow, which is increased in GD.

Graves' disease, the most common form of hyperthyroidism, has been linked to an increased risk of developing papillary thyroid carcinoma (PTC). A meta-analysis of 33 studies analyzing surgically-resected specimens revealed that the

event rate of thyroid carcinoma in Graves' disease was 0.07 (95% CI 0.04 to 0.12). Among thyroid carcinomas in Graves' disease, papillary carcinoma accounted for 88% of cases, with solitary papillary microcarcinoma (tumors ≤ 10 mm in diameter) comprising 23% of all detected thyroid carcinomas. This suggests a significant association between Graves' disease and PTC. Clinicians should be aware of this relationship and consider appropriate screening measures for nodules in Graves' disease patients while remaining cautious about the potential over-diagnosis and treatment of clinically insignificant papillary microcarcinomas.¹⁶

Antithyroid Medication

Antithyroid medications, such as propylthiouracil (PTU) and methimazole (MMI), are commonly used in the medical management of pediatric GD. However, PTU is generally avoided in children due to the risk of hepatic failure. Thionamides, including MMI and its active metabolite carbimazole (CBZ), act by inhibiting thyroid hormone synthesis. A preference is given to a prolonged course of MMI or CBZ treatment, with dose titration to achieve euthyroidism. Regular monitoring of thyroid function tests is necessary during treatment to assess the response and adjust the dosage accordingly.¹⁷

Radioactive Iodine Therapy

Radioactive iodine therapy (RAI) is an alternative treatment modality for pediatric GD. It involves the administration of radioactive iodine, which selectively destroys the hyperactive thyroid tissue. The mechanism of action involves the emission of beta radiation that damages the thyroid follicular cells. RAI is generally not recommended for children under 10 years of age but may be considered in patients with large goiters. Special considerations, including the potential long-term effects on growth and development, should be taken into account when considering RAI in pediatric patients.¹⁸

Surgical Intervention

Thyroidectomy, the surgical removal of the thyroid gland, is another treatment option for pediatric GD. It is usually reserved for cases where antithyroid medications and RAI are contraindicated or have failed to achieve adequate control of hyperthyroidism. Thyroidectomy aims to provide definitive treatment by completely removing the thyroid tissue. The procedure carries potential advantages, such as rapid control of hyperthyroidism and avoidance of long-term medication. However, it is also associated with potential complications, including surgical risks, the need for lifelong thyroid hormone replacement, and the risk of hypoparathyroidism.¹⁹

This scientific publication focuses on the outcomes of pediatric thyroidectomy, a relatively uncommon procedure associated with potential complications. The study utilized data from the National Surgical Quality Improvement Program (NSQIP) database and analyzed cases between January 2014 and November 2015. Of the 344 patients who underwent thyroidectomy, 2.9% experienced complications, with readmission, surgical site infections, and wound disruption being the most common. Pediatric otolaryngology had a higher percentage of complications compared to pediatric surgery. Hypocalcemia was identified as the main reason for readmission.

The study emphasizes the overall low incidence of adverse events following pediatric thyroidectomy. The findings provide reassurance regarding the safety of the procedure for families. However, efforts to reduce complications, particularly hypocalcemia, should be encouraged. The analysis also highlights the association between surgical specialties and postoperative complications. Pediatric otolaryngology had a significantly higher number of complications compared to pediatric surgery, although confounding factors and the low complication rate make this finding difficult to interpret.²⁰

Total thyroidectomy in children (≤ 18 years of age) was examined in a study to determine the incidence and risk factors of hypocalcemia and hypoparathyroidism. The analysis included 106 children who underwent the procedure for various indications such as Graves' disease, Multiple Endocrine Neoplasia type-2, multinodular goiter, and follicular/papillary thyroid carcinoma. Around 59.4% of the children experienced hypocalcemia within 24 hours after surgery, and approximately 49.3% were discharged with calcium supplementation. After 6 months, hypoparathyroidism persisted in 21.7% of the children. Notably, the study found that having fewer than four parathyroid glands remaining in situ was associated with higher rates of both hypocalcemia and hypoparathyroidism. These findings emphasize the importance of preserving the parathyroid glands during surgery to minimize complications and ensure favorable outcomes for pediatric patients undergoing total thyroidectomy.

The study sheds light on the significant incidence of hypocalcemia and hypoparathyroidism in children undergoing total thyroidectomy. The preservation of the parathyroid glands during surgery emerges as a critical factor in reducing the risk of these complications. Therefore, it is imperative to exercise

caution and adopt meticulous techniques to identify and protect the parathyroid glands, particularly in pediatric patients. By doing so, surgeons can optimize surgical outcomes and mitigate long-term complications associated with imbalances in calcium levels. Moving forward, further research and clinical attention should be directed towards developing strategies that improve preservation techniques and minimize the occurrence of postoperative calcium-related morbidities in pediatric patients undergoing total thyroidectomy.²¹

Postoperative complications following total thyroidectomy pose a potential threat to patient well-being and overall quality of life. Among these complications, hypocalcemia and vocal cord paralysis are particularly concerning due to their impact on morbidity. Notably, the occurrence of complications appears to be more prevalent in patients with tumors, lymph node involvement, or those undergoing a second thyroid procedure with neck dissection. However, it is worth noting that the overall risk of postoperative complications stands at a modest 2%. In our series, we employed a management approach that involved the administration of oral calcium carbonate supplementation at a dosage of 2400mg per day, along with vitamin D in the form of calcitriol (0.5). This comprehensive strategy resulted in a notable reduction in the incidence of postoperative hypocalcemia, thus demonstrating its efficacy in mitigating such complications.

This retrospective study aimed to assess weight gain in pediatric patients after total thyroidectomy and identify predictors of weight gain. The study reviewed charts of patients aged 3-17 years who underwent total thyroidectomy at a tertiary healthcare facility from 2014 to 2020. Body Mass Index z-scores (BMIz) at the time of thyroidectomy and at 1- and 2-year post-operation intervals were analyzed. Patient demographic information, comorbidities, pre- and postoperative thyroid stimulating hormone levels, and postoperative free T4 levels were also examined. Patients with known endocrine abnormalities, chronic kidney disease, or inadequate follow-up were excluded. A total of 56 patients (17 with Graves' disease, 39 with presumed cancer) met the inclusion criteria. Over the first year, significant increases in average BMIz were observed in patients with Graves' disease, Hispanic ethnicity, Medicaid/no insurance coverage, age < 13 years at thyroidectomy, and persistent postoperative hypothyroidism. These changes remained significant after the second year. Age at thyroidectomy negatively correlated with BMIz changes only after the first year. Regression analysis identified age at thyroidectomy as a

significant predictor of BMIz changes after the first year, while Hispanic ethnicity was a significant predictor after the second year. These findings suggest that younger age at thyroidectomy and Hispanic ethnicity may be associated with increased weight gain in the first two years following total thyroidectomy in pediatric patients.²²

Temporary hypocalcemia is a frequent complication following total thyroidectomy, leading to prolonged hospital stays and unpleasant symptoms. The routine postoperative administration of vitamin D and calcium has been suggested as a preventive measure to reduce the incidence of symptomatic hypocalcemia. In this systematic review, four randomized controlled trials involving 706 patients were analyzed. The calcitriol group (n=346) received vitamin D and calcium, the oral calcium group (n=288) received calcium alone, and the control group (n=72) received no treatment. The rates of hypocalcemia symptoms were 4%, 19%, and 31% in the calcitriol, oral calcium, and control groups, respectively.

The odds ratio for the comparison between the calcitriol + calcium group and the no treatment group was 0.32 (95% CI, 0.13–0.79), indicating a significant reduction in the incidence of symptomatic hypocalcemia with the prophylactic administration of vitamin D and calcium. Similarly, the odds ratio for the comparison between the calcitriol + calcium group and the exclusive calcium group was 0.31 (95% CI, 0.14–0.70), further supporting the effectiveness of the combined treatment. These findings highlight the potential benefits of routine administration of vitamin D or its metabolites in conjunction with calcium to decrease the occurrence of symptomatic hypocalcemia following total thyroidectomy.²³

This underscores the low incidence of complications in pediatric thyroidectomy cases. The most common complications observed were readmission, surgical site infections, and wound disruption. Pediatric otolaryngology exhibited a higher complication rate than pediatric surgery, but further research is needed to fully understand the underlying factors. The results of this analysis contribute to the understanding of outcomes and can guide efforts to improve patient care and reduce complications in pediatric thyroidectomy procedures.²⁴

Supportive Care

Supportive care plays a crucial role in the management of pediatric GD. It includes the use of beta-blockers, such as propranolol or atenolol, for symptom relief and to manage thyrotoxicosis-related cardiovascular symptoms. Nutritional

counseling and weight management are essential to address potential weight gain and ensure proper nutrition. Emotional support and psychological interventions are important to address the psychological impact of the disease, especially in children and adolescents.^{25,26}

The management of pediatric Graves' disease requires a comprehensive approach that takes into account the risks and benefits of different treatment modalities. Antithyroid medications, radioactive iodine therapy, and surgical intervention each have their advantages and considerations in the pediatric population. Supportive care, including the use of beta-blockers, nutritional counseling, and emotional support, is crucial to optimize patient outcomes. Individualized treatment plans should be formulated in collaboration with pediatric endocrinologists to ensure the best possible care for children with GD.^{27,28}

Long Term Effect in Growth and Development

In discussing pediatric Graves' disease, it is important to assess its long-term effects and prognosis on a variety of health aspects. Although the impact of GD on bone health is prevalently studied in adults, it may also affect children. Given the crucial role of thyroid hormones on bone development and maturation, excessive levels may disrupt typical development and variably present among patients. For example, prepubertal children with GD most prominently experience accelerated bone maturation leading to premature closure of epiphyseal plates and diminished adult height potential. In other words, the processes of intramembranous and endochondral ossification are accelerated, ultimately resulting in early bone growth cessation.²⁹

Another essential aspect in the discussion of long-term effects concerns intellectual and cognitive impairments in pediatric GD patients. The state of thyrotoxicosis leads to an apparent increase in sympathetic nervous system activation, which manifests in young patients as hyperactivity, palpitations, tremors, sweating, and anxiety³⁶. In fact, this is the frequently reported neurobehavioral presentation, along with poor academic achievement, difficulties with attention, and cognitive deterioration. Moreover, Hamed et al. (2021) found high frequencies of patients with active GD having high total scoring of the Anxious/Depressed, Withdrawn/Depressed, Somatic Complaints, and Thought and Attention Problems subscales of the Child Behavior Checklist (CBCL)³⁰. The same study also noted that the

prominent behavioral manifestations during both active and euthyroid states were anxiety and inattention, showing that behavioral problems are seemingly independent from the severity of GD.

Ophthalmic Complications

Graves' disease may also produce ophthalmologic changes in pediatric patients, a condition termed thyroid-associated ophthalmopathy (TAO), thyroid eye disease (TED), or Graves' ophthalmopathy (GO). Pediatric GO tends to be less severe than the adult manifestations of the condition, although the risk of children developing this manifestation of GD is similar to that in adults.³¹ Interestingly, pediatric GO constitutes one-third of the cases of pediatric Graves' disease, and mostly manifests in children who have a family history of autoimmune thyroid disease. The complications of GO arise as the extraocular muscles (EOM) and orbital soft tissue become edematous in response to inflammatory drivers. As the condition progresses, TSH-receptor antibodies stimulate these receptors in orbital fibroblasts, which produce cytokines and glycosaminoglycans, to trigger lymphocyte and myofibroblast proliferation.³² Then, as edema progresses, a patient may present with proptosis, movement restriction, and peribulbar swelling. However, pediatric patients tend to have more soft-tissue involvement than EOM implications.

When it comes to treating eye-related issues in pediatric Graves' disease, most physicians adopt a "wait-and-see" policy to assess disease progression prior to active intervention. In cases of worsening symptoms or of no improvement once the patient has achieved a euthyroid state, glucocorticoids are recommended as first-line treatment. Nevertheless, the use of intravenous prednisone or methylprednisolone, for example, poses risks of immunosuppression, weight gain, and growth failure.⁴¹ Additionally, surgical approaches like orbital decompression may be considered in some cases of pediatric GO where proptosis-derived physical disfigurement is prominent and when quality of life is impacted.³³

Risk of Recurrence

The risk of recurrence in Graves' disease is influenced by various factors, including antibody levels, physical characteristics, behavioral aspects, and genetic determinants. High baseline levels of thyroid-stimulating antibody (TRAb) at the start of treatment are associated with an increased likelihood of disease relapse.⁴⁶ Larger goiter size and the presence of Graves' ophthalmopathy are also indicators of disease severity and correlate with a higher risk of relapse. Smoking is a

behavioral factor that contributes to relapse, particularly among adult patients, while in children, it may pose a greater risk during adolescence.³⁴

Genetic factors, such as human leukocyte antigen (HLA) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) genes, also play a role in the development and recurrence of Graves' disease. HLA genes regulate immune responses, and certain variants of HLA class II genes, including DQA1, DQB1, and DRB1, are believed to be predictive markers for GD development and recurrence.⁴⁷ CTLA-4 encodes a regulatory molecule involved in antigen presentation to T-cells, and single nucleotide polymorphisms of this gene are associated with GD susceptibility. However, these genetic markers are not reliable predictors of disease relapse.

In summary, monitoring TRAb levels, assessing goiter size and ophthalmic changes, advising smoking cessation, and evaluating genetic factors are important in identifying patients at risk for Graves' disease relapse. Healthcare providers can potentially reduce the likelihood of relapses by identifying and managing these risk factors in a timely manner.³⁵

Future Directions and Research

Conventional therapeutic approaches for Graves' disease have shown limited efficacy, necessitating the search for novel treatments. Promising advancements include B-lymphocyte depletion, blocking CD40 interactions, and small molecule TSH-receptor antagonists.

B-lymphocyte depletion therapies, such as rituximab (RTX), have been explored for treating Graves' hyperthyroidism. RTX, an anti-CD20 monoclonal antibody, induces B-cell depletion and has demonstrated efficacy in other autoimmune diseases. However, the extent of B-cell depletion does not consistently correlate with reduced thyroid-stimulating antibody levels or surpass traditional antithyroid medication effects.³⁶ Further investigation is required before routine use in adults can be supported. In a study involving pediatric patients, RTX combined with antithyroid drug treatment showed improved remission rates compared to the norm.³⁷

Blockade of CD40-receptor interactions is another therapeutic avenue. CD40 plays a crucial role in immune response coordination and antibody production in Graves' disease. Iscalimab, a monoclonal antibody targeting the CD40-CD154 pathway, has shown promise in reducing thyroid hormone levels and antibody concentrations. However, additional research is needed to evaluate

sustained remission potential and potential benefits for Graves' ophthalmopathy.

Small molecule compounds that stimulate or inhibit TSH-receptor signaling offer another treatment approach. Inverse agonists like ANTAG-3 have shown inhibitory effects on TSH-receptor function in laboratory tests. Other compounds, such as VA-K-14 and S37a, have also demonstrated inhibitory potential but require human testing.³⁸ Although these compounds hold promise, further research and clinical trials are necessary to establish their safety and efficacy.

Research on pediatric manifestations and treatment of Graves' disease is limited compared to adult patients, highlighting the need for increased investigation to improve assessment and treatment strategies for younger individuals.

Assessing and treating children with Graves' disease begins with adequate understanding of the risk factors that predispose the pediatric community to developing this condition. There is an interplay between environmental, genetic, and microbiome features we should be aware of in our identification of at-risk children. For example, environmental factors such as diet and bacterial and viral infections are thought to influence the rise in pediatric GD incidence. Specifically, deficiencies in vitamin D and selenium, as well as excess iodine uptake, are dietetic factors to take into consideration.³⁹ Moreover, data from familial studies points to genetic factors as important contributors in around 63% of GD cases. Immune-related genes like MHC and CTLA4, as well as thyroid-specific genes like TSHR and TG, represent genetic loci which have been associated with Graves' disease.³⁹ As mentioned, the microbiome is also suspected to influence the risk of developing GD. It has been hypothesized that gut microbial imbalance can influence cytokine production which contributes to the disruption of immune homeostasis. However, there is a need for ongoing investigation in this avenue to assess how well this parameter plays into GD risk factors.

Another important factor in identifying at-risk children are screening programs. Given the rarity of Graves' disease in children, there are no specific national or international screening programs exclusively dedicated to this effort. However, healthcare professionals may employ specific approaches to identify the conditions and its risk factors. During routine check-ups and physical examination, physicians should be on the lookout for any symptoms suggestive of GD, especially if there is a family history of the condition. If suspected, physicians may also order thyroid function tests and antibody testing to elucidate a diagnosis. Considering that screening for GD in children is not a widespread practice due to its low prevalence compared to adults, it is important to create awareness of the conditions so that both physicians and caregivers can recognize the warning signs.

Conclusion

In conclusion, this paper offers a comprehensive and insightful exploration of the diagnosis, management, and long-term implications of Graves' Disease in pediatric patients. While acknowledging the challenges in diagnosing this relatively rare condition in children, the paper meticulously details the array of symptoms, both behavioral and physical, that may manifest. The significance of thyroid function tests and thyroid autoantibodies in confirming thyrotoxicosis is underscored, providing a foundation for accurate diagnosis. The discussion further delves into various management options, ranging from antithyroid medications and radioactive iodine therapy to surgical intervention, shedding light on their respective merits and considerations. Additionally, the paper explores promising advancements in treatment approaches, such as B-lymphocyte depletion and TSH-receptor antagonists, hinting at a potentially transformative future in managing Graves' Disease. Ultimately, this manuscript constitutes a valuable contribution to the medical community, consolidating current understanding and paving the way for further research and advancements in the care and management of this condition.

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