Chapter

Graves' Disease in Childhood

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Abstract

Graves' Disease (GD) is an autoimmune disease caused by autoantibodies against thyroid stimulating hormone receptor (TSH-R), resulting in stimulation of thyroid gland and overproduction of thyroid hormones resulting in clinical manifestations. It is uncommon in children and is 6 times more prevalent in females. The symptomatology, clinical and biochemical severity are a function of age of onset of disease. Prepubertal children tend to present with weight loss and bowel frequency, associated with accelerated growth and bone maturation. Older children are more likely to present with the classical symptoms of thyrotoxicosis like palpitations, tremors and heat intolerance. Prepubertal children tend to have a more severe disease, longer duration of complaints and higher thyroid hormone levels at presentation than the pubertal and postpubertal children. The non-specificity of some of the symptoms in pediatric age group can lead to children being initially seen by other specialities before being referred to endocrinology. Management issues are decided based on patient's priorities and shared decision making between patient and treating physician. Radioactive Iodine Ablation is preferred when there is relatively higher value placed on Definitive control of hyperthyroidism, Avoidance of surgery, and potential side effects of ATDs. Similarly Antithyroid drugs are chosen when a relatively higher value is placed on possibility of remission and avoidance of lifelong thyroid hormone treatment, Avoidance of surgery, Avoidance of exposure to radioactivity. Surgery is preferred when access to a high-volume thyroid surgeon is available and a relatively higher value is on prompt and definitive control of hyperthyroidism, avoidance of exposure to radioactivity and avoidance of potential side effects of ATDs. Continental differences with regards to management do exist; radio-iodine ablation being preferred in North America while Anti-thyroid drug treatment remains the initial standard care in Europe.

Keywords: Graves, hyperthyroidism, radioactive iodine, antithyroid, thyrotoxicosis, children

1. Introduction

Graves' Disease (GD) is an autoimmune disease caused by autoantibodies against thyroid stimulating hormone receptor (TSH-R), resulting in stimulation of thyroid gland and overproduction of thyroid hormones resulting in clinical manifestations. GD is a relatively uncommon entity in pediatric age group, in contrast to adults, where prevalence ranges from 0.5–1%. Pediatric GD in the age group 0–15 years comprises of only 5–6% of the total number of Graves' thyrotoxic patients. It usually occurs in the context of a family history of autoimmune thyroid disease or in association with other autoimmune diseases like type 1 diabetes, Hashimoto's thyroiditis, rheumatoid arthritis or adrenal insufficiency. It is also found in association with

genetic syndromes like Down's syndrome and Turner's syndrome. However, GD is the most common cause of thyrotoxicosis in children, accounting for atleast 95% cases of hyperthyroidism and 10–15% of all childhood thyroid disorders [1]. Other rare causes of juvenile thyrotoxicosis include toxic adenoma (TA), toxic multinodular goitre (TMNG), McCune Albright syndrome (MAS), Hashimoto's thyroiditis and iatrogenic causes. In children, GD can occur at any age, but is most often diagnosed in adolescent age group, occurring more frequently in females than in males [2, 3].

The eye changes accompanying GD are termed thyroid-associated ophthalmopathy (TAO) or Graves' ophthalmopathy (GO). The symptoms of GO can run an independent course from the clinical course of thyrotoxicosis and often require specific treatment. Clinical characteristics of GO are often milder in children than in adults, nevertheless adversely affecting quality of life.

2. Epidemiology

Very few epidemiological studies are available to document the incidence of pediatric Graves' Disease in different populations, mostly involving Northern Europe and Hongkong. These have resulted in widely variable incidence rates, ranging from 0.79 to 6.5/100000 patient-years [4–9]. Iodine intake in populations could be one of the factors for differences observed in different populations, with higher incidence rates being observed in populations with higher iodine intake, particularly in studies from Hong-Kong compared to Caucasian children [7, 8].

GD, in concordance with other autoimmune disorders, is more common in females, particularly after 4 years of age. Female to male ratio has varied from 2.37–9.7 in various studies, depending on the age groups included [9]. The female preponderance becomes particularly marked in adolescent years, merging into the adult trends.

In one of the earliest nation-wide comprehensive studies, the incidence ratio of thyrotoxicosis was 0.79/100 000 person-years in Danish children under the age of 15 years between 1982 and 1988. The incidence was very low in age < 4 years, gradually increasing in both genders to peak incidence at 10–14 years of age. As with other autoimmune disorders, there was a female preponderance of 6.7: 1, but this difference was virtually non-existent in age group 0–4 years. The gender disparity widened gradually after early childhood to reach the maximum in the 10–14 year age group. Diffuse toxic goitre accounted for 96% of the cases, toxic adenoma and toxic multi-nodular goitre (MNG) were rare entities [4].

However, a more recent study in the Danish population spanning between 1998 and 2012 revealed a higher incidence rate of 1.58/100000 person-years [6], GD accounting for 86.8% of the cases. This increasing trend was consistent with rising incidences of other autoimmune disorders like type 1 diabetes and celiac disease. The authors postulated that environmental factors, including hygiene hypothesis, could play a key role in explaining the increasing trends in autoimmune disorders [6].

Similar trends of rising incidence rates have also been documented in studies from Hong-Kong as well. This could not be explained by the slight advancement in pubertal age or increasing disease awareness. The trends were primarily ascribed to the increasing iodine intake in the population, reflected by high urinary iodine concentration in the population [7, 8].

Similar to GD, GO is rare in pediatric age group. One of the earliest data about the incidence of pediatric GO came from the Olmsted County cohort study from Minnesota, USA. The study identified 120 incident cases of GO from 1976 to 1990. Peak incidence of GO had a bimodal distribution in the age groups 40–49 year and 60–69 years in both females and males, with a 5 year later presentation in males. The overall age-adjusted incidence rates per 100000 population were 16 and 2.9

cases in females and males respectively. On the other hand, GO was much less frequent in the pediatric age group. Incidence rates per 100000 population per year in the age groups 5–9, 10–14, and 15–19 years were 3.5, 1.8 and 3.3 and 0, 1.7 and 0, for females and males respectively. Only 6 out of the 120 incident cases of GO observed in this cohort study were in patients below the age of 20 years [10]. The prevalence of GO in different countries has also been seen to be directly related to the prevalence of smoking in teenage population in the respective countries, emphasising the importance of smoking as risk factor for development of GO [11].

3. Pathogenesis

GD is a classical autoimmune disorder, characterised by a complex interplay of genetic susceptibility and environmental factors. GD had long been recognized as having a genetic background in view of clustering of cases in families. Family H/O autoimmune thyroid disease (AITD) is apparent in nearly half of the affected patients. AITD also tends to occur in more than a third of siblings and thyroid autoantibodies occur in over half of asymptomatic children of affected patients. This was further confirmed by twin studies where concordance of AITD in monozygotic twins was 30–40%, as compared to less than 5% concordance in dizygotic twins. It has also been proposed that genetic anticipation may occur in successive generations leading to younger ages at onset of disease [12, 13].

The genetic predisposition to GD is polygenic in origin, with each individual gene conferring a modest increase in risk. The most commonly implicated genes are located in the HLA region in the short arm of chromosome 6, the odds ratio (OR) for GD ranging from 2 to 4. HLA DRB1*03 and DQA1*05 in Caucasian patients, and HLA DPB1*05:01 allele in Han Chinese populations have been found to confer 2–3 times increased risk of GD. Similarly HLA class I alleles C*07 and B*08 have also been implicated as risk factors, and DRB1*07, DRB1*12:02, DQB1*03:02, B*44, C*03, C*16 have been observed to have a protective effect in various populations.

Some of the other genes which confer a modest increase in risk of GD (OR ranging from 1.1–2) are Protein Tyrosine Phosphatase-22 (PTPN22), Cluster of Differentiation 40 (CD40), Cytotoxic T-lymphocyte-associated factor 4 (CTLA4), TSH-R, Thyroglobulin (Tg), FC-Receptor Like-3 (FCRL3), Secretoglobin 3A2 (SCGB3A2), Interleukin-2 receptor alpha (IL2RA) etc. Possible mechanisms postulated are variation in binding of self-antigens, defective regulation of thymic selection of autoreactive clones, regulation of T cell responses and effect of HLA class I molecules on natural killer cells.

Some studies have also observed genotype phenotype correlation. For example, several genes like interferon γ (IFN γ, TNF, IL-1A, IL-23R, IL-5, CTLA4, PTPN-12, ICAM-1 have been associated with development of Graves ophthalmopathy (GO). Similarly several candidate genes have been associated with clinical course of GD, including age of onset (HLA, ICAM-1, PTPN22, NFKB1, CD40), severity and remission/relapse rates of GD (CTLA4, CXCL10) [14].

With the concordance rate in monozygotic twins being clearly less than 100%, it highlights the importance of environmental factors for predisposing an individual for developing GD. Analysis of Danish twin studies in GD attributed 79% of liability to develop GD on genetic factors, whereas 21% could be explained by environmental factors not shared by the twins [15].

Stressful life events and post-partum periods can result in a dysregulated immune response, predisposing to autoimmunity. Smoking, radiation, excess iodine intake, dietary selenium deficiency, drugs like amiodarone, interferons, alemtuzumab have been associated with development of AITD. Recent evidence has

brought into light the role of Endocrine disrupting chemicals (EDCs), which are environmental toxicants that interfere with thyroid hormone production, metabolism and action. Most widely studied EDCs are polychlorinated biphenyls (PCBs), which have thyroid-disrupting effects and can have intrinsic thyroid hormone agonist action. Others chemicals like bisphenol A, phthalates, perflourinated chemicals and brominated flame retardants have also been shown to have thyroid-disrupting effects, predisposing to AITD [16, 17].

The thyroid gland typically demonstrates a non-homogenous lymphocytic infiltration and absence of follicular destruction. T-lymphocytes can cause local inflammation and cytokine release resulting in dysregulation of B- cells and production of autoantibodies. These TSH-R auto antibodies (TRAb) can bind to the TSH-R on thyroid follicular cells. These are of the IgG1 subclass and can have different functional implications of stimulation, blockade or neutral effects on the TSH-R. Thyroid stimulating antibodies (TSIs) act via G proteins like Gs and Gq to cause increased thyroid hormone production, secretion and modulation of cell proliferation respectively [2, 18].

Graves ophthalmopathy is a distinct pathological process that may precede or follow the hyperthyroid phase. Orbital fibroblasts are the target cells in the pathology. Plausible explanation for this cellular origin include antigen sharing with the TSH-R, enhanced expression of Thy-1 (CD90) and IGF-1 receptor, exaggerated inflammatory response to cytokines and hyaluronan synthesis. Environmental factors like smoking and radioiodine therapy play a major role in development of ophthalmopathy [19].

4. Clinical features

GD can present at any age, with peak prevalence occurring in adolescent years. Around 10% of cases can present in very young children less than 5 years of age. GD is clinically characterized by the triad of thyrotoxicosis, ophthalmopathy and dermopathy. GD in children often presents with classical symptoms and signs of thyrotoxicosis like in adults.

The frequency of the symptomatology, however, is variable across literature. Major presenting symptoms symptoms include goitre (19–99%), excessive sweating and heat intolerance (28–53%), fatigue or weakness (10–54%), irritability, nervousness or restlessness (17–47%), tremors (17–58%), ocular symptoms, ophthalmopathy or exophthalmos (10–43%), weight loss or no weight gain (28–63%), tachycardia (34–45%). Decreased academic performance can be seen in 1–24% of patients, whereas decreased athletic performance can be seen in upto 15% of patients. Other common complaints included behavioural changes (50%), headache (1–22%), increased bowel frequency (11–16%) and slight fever (10.5%) [5, 20–22]. Children can also present with ocular complaints like pain, foreign body sensation and grittiness, tearing, redness, photosensitivity, and rarely diplopia [23].

Children, like adults, can have low bone mass for age and increased fracture risk in the presence of untreated thyrotoxicosis, but this is often reversible once euthyroidism is restored for 2 years with treatment. Thyrotoxicosis may rarely be associated with choreiform movements in childhood and adolescence. This may manifest as involuntary, coordinated, rapid spastic movements like flexion and extension of fingers, raising and lowering of shoulders and grimacing. Thyrotoxicosis can also result in proximal muscle weakness and wasting syndrome, termed the thyrotoxic myopathy, which can mimic limb girdle muscular dystrophy. Importantly, these symptoms can even precede the more typical thyrotoxic symptoms. Another type of muscular weakness associated with thyrotoxicosis is thyrotoxic periodic paralysis,

characterized by recurrent transient episodes of muscular weakness, usually precipitated by a stressor event like exposure to cold, high carbohydrate meal, infections and stress. This phenomenon has been more commonly described in Asian populations in middle aged males. It is rare in pediatric age groups, and is virtually not reported in very young populations [24].

The symptomatology, clinical and biochemical severity are also a function of age of onset of disease. Prepubertal children tend to have a more severe disease, longer duration of complaints and higher thyroid hormone levels at presentation than the pubertal and postpubertal children. Prepubertal children tend to present with weight loss and bowel frequency, associated with accelerated growth and bone maturation. Older children are more likely to present with the classical symptoms of thyrotoxicosis like palpitations, tremors and heat intolerance [25].

The risk of developing GO in pediatric GD appears to be to be similar to or slightly higher than the risk in adult patients with GD. Female preponderance (87%) is also similar to that observed in adult patients (83%). However, pediatric GO tends to be less severe and debilitating as compared to adult manifestations. Soft tissue involvement, lid lag, proptosis and punctate corneal epithelial erosions are more commonly seen with pediatric GO, whereas the more severe manifestations like restricted ocular motility, severe strabismus and optic nerve affection are virtually never seen in pediatric GO. This has been attributed to the lower prevalence of smoking in children as compared to adults. Manifestations of GO tended to become similar to adults as adolescence approached in pediatric patients with GO in another study, likely due to increased prevalence of smoking in adolescent ages. Hence active or passive smoking seems to increase the risk and severity of GO in children as well as adults [11, 26, 27].

The non-specificity of some of the symptoms in pediatric age group can lead to children being initially seen by psychologists, gastroenterologists, neurologists, cardiologists and ophthalmologists, before being referred to endocrinology.

Examination may reveal tachycardia, increased blood pressure for age and raised pulse pressure. Skin may be warm and moist, thinning of hair, onycholysis and softening of nails can be present.Vitiligo and alopecia areata can be seen in patients with associated autoimmune disorders. Precordial pulsations may be prominent, accompanied by a apical systolic regurgitant murmur due to functional mitral insufficiency secondary to papillary muscle dysfunction. Tremors may be present, along with hyperactive deep tendon reflexes. Musculoskeletal examination may reveal proximal muscle weakness and wasting.

On local examination, size of the gland can be variable, with a large proportion of patients having none to small or moderate sized goitre, which may escape patient's and family's attention [28]. The thyroid gland is usually symmetrically enlarged, non-tender, smooth and having firm consistency, and may be associated with a palpable thrill and a thyroid bruit in upto one fourth of patients due to increased vascularity. A large goitre can cause tracheal compression and other compressive symptoms.

Lid retraction, especially of the upper eyelid, and a staring appearance may be evident in upto one-third of the cases. Lid retraction is a sign of adrenergic overactivity, and is not considered a sign of GO per se. Other common signs in pediatric GO are lagophthalmos or von Graefe's sign (9–74%), proptosis (4–91%), signs of soft tissue involvement (19–26%), including conjunctival injection (8–49%), chemosis (1–23%) and lid edema in around 10% of the patients. Corneal involvement can occur in the form of corneal punctate staining (12–34%), exposure keratitis and superior limbic keratitis. Extraocular muscle motility defects has been described in relatively fewer number of patients (2–11%), except in a study by Eha et al., where it was observed in 36% of the patients [23] (**Table 1**). Similarly, dysthyroid optic neuropathy (DON) can be seen very rarely in pediatric age groups.

Differences	Pediatric Graves	Adult Graves
Symptoms	Classic symptoms less common (Tachycardia is a reliable sign than blood pressure changes)	Classic
Ophthalmopathy	Less common Less severe	More common
Pretibial Myxedema	Rare	5% (15% in Graves' Disease with ophthalmopathy)
Thyroid storm	Rare	1–2%
Atrial fibrillation	Rare	10–15% (25% in age > 60 years)
Remission rate with ATD	<30% (Higher in Koreans) (Lower rates in prepubertal children ~17%)	40–60%
Surgery	Higher complication rates Requires experienced high-volume thyroid surgeon	Relatively safe and easy surgery
Cosmesis	Greater concern	Lesser concern
RAIA	Increased sensitivity to radiation Increased susceptibility to carcinogenic effects of radiation	Lesser sensitivity Negligible carcinogenic effects

Table 1.
Differences in Pediatric vs. Adult Graves' Disease.

Some of the key differences in the presentation of pediatric GD vis-à-vis adult GD are as follows:

- Weight loss is less common in children. Increased appetite with/without weight loss, or absence of weight gain during pubertal years can be an indicator of thyrotoxicosis. Growth charts can be pivotal in identifying trends for early detection. BMI SD scores have been reported to be particularly lower in younger children as compared to older children in few studies.

- Early symptoms like behavioural changes, emotional lability, fatigue, nervousness, palpitations, sleep disturbances with insomnia are particularly subtle and difficult to identify.

- Difficulty in concentrating, restlessness, hyperactivity, impaired scholastic performance can be the presenting complaints, especially in younger children. These can be commonly mistaken to be Attention deficit hyperactivity disorder (ADHD), leading to a delay in diagnosis and treatment.

- Untreated thyrotoxicosis can lead to increases in height velocity and advancement of skeletal age, which can be apparent as an increased height SDS in

growth charts. Increase in height SDS is seen more commonly in prepubertal children than pubertal and post-pubertal children. This may be explained by the fact that prepubertal bone maturation is driven by growth hormone (GH) and thyroid hormones, whereas pubertal bone growth is driven primarily by estradiol. Another plausible reason could be the delay in diagnosis in younger children. The effect on final height, however is variable across literature, where some studies show achievement of a normal height within target range, some showing increased final height [25, 29]

- Ophthalmic abnormalities are less severe. Soft tissue involvement, lagophthalmos, proptosis and punctate corneal erosions more common, extraocular muscle restriction and optic neuropathy are rare
- Pretibial myxedema is rare (0.9%)
- Atrial fibrillation is rare
- Thyroid storm is rare in children

Pediatric GD can commonly be associated with other conditions as follows [2, 30].

5. Differential diagnosis

GD is the most common cause of thyrotoxicosis in children. However, it has to be clinically differentiated from other causes of thyrotoxicosis in childhood. These include hyperthyroid disorders, associated with increased secretion of the thyroid hormones from the thyroid gland, or cases of thyroiditis, where symptoms occur due to thyroid follicular disruption leading to release of preformed causes. Some of the common differential diagnostic causes have been summarized in **Tables 2–4**.

Consumption of biotin as a part of management of metabolic or dermatological diseases can lead to surreptitious laboratory results of elevated thyroid hormones, suppressed TSH and positive thyroid receptor autoantibodies with immunoassays utilizing the streptavidin-biotin platforms. Hence, laboratory results must be reconsidered and rechecked in the absence of supportive clinical features of thyrotoxicosis [31].

Endocrine autoimmune disorders	Non-endocrine autoimmune disorders	Syndromic disorders
• Hashimoto's thyroiditis • Celiac disease • Type 1 diabetes • Primary adrenal insufficiency	• Vitiligo • Systemic lupus erythematosus (SLE) • Rheumatoid arthritis (RA) • Myasthenia gravis	• Down syndrome • Turner syndrome

Table 2.
Common associations of pediatric GD.

Differential diagnosis of GD	Remarks
TA	• Focal increase in uptake on nuclear scans with suppressed uptake in rest of the gland • Surgical excision preferred therapy
TMNG	• Multiple foci of increased uptake with suppressed uptake in remainder of the gland on nuclear scan • Surgery preferred modality
Germline activating mutations of TSH-R	• Familial or denovo forms • Can lead to simple or multinodular goitre
McCune Albright syndrome	• One-third can develop hyperthyroidism • Polyostotic fibrous dysplasia, café-au-lait spots, precocious puberty
TSH producing pituitary adenoma	• Rare • Elevated T4 with an inappropriately normal TSH • High serum alpha subunit concentration and alpha subunit to TSH ratio, little to no response to thyrotropin releasing hormone (TRH)
Resistance to thyroid hormone	• Autosomal dominant • Elevated T4 with a normal or elevated TSH • Generally euthyroid, clinical manifestations depend on the site of the defect in thyroid hormone receptor

Table 3.
Differential diagnosis of GD: Hyperthyroid disorders.

Acute suppurative thyroiditis	• Bacterial infection: Haemophilus influenza, Group A streptococci • Painful thyroid, fever, fistula can be present • Transient thyrotoxicosis • Associated with elevated ESR and WBC count, decreased uptake on nuclear scan (Tc-99 m or radioiodine)
Subacute granulomatous thyroiditis/ de Quervain disease	• Viral infection • Fever, painful thyroid, symptoms less severe than bacterial thyroiditis
Hashimoto's thyroiditis	• 5–10% of children can present with "Hashitoxicosis" • Transient thyrotoxicosis • Low or absent uptake in thyroid on nuclear scans
Thyroid injury	• H/O significant neck trauma or exposure to radiation
Thyrotoxicosis factitia	• Exogenous ingestion of thyroid hormones, particularly in the setting of adolescents trying to lose weight • Low or absent thyroid uptake in nuclear scans • Low serum thyroglobulin is diagnostic

Table 4.
Differential diagnosis of GD: Thyrotoxic disorders without hyperthyroidism.

6. Diagnosis

6.1 Biochemical diagnosis

6.1.1 Thyroid function tests

All patients with suspected thyrotoxicosis should undergo detailed thyroid function tests, including TSH, free thyroxine (FT4) and preferably total triiodothyronine (T3). Measurement of total T3 is preferred over free T3 (FT3) as the FT3 assays are less robust and less validated as compared to the FT4 assays. Measurement of free hormones makes the assay reports more reliable in the presence of conditions affecting the concentrations of thyroid binding globulin (TBG) like liver disease, nephrotic syndrome. Serum TSH is more sensitive the changes in thyroid hormone levels due to the log-linear relationship of TSH with the free thyroid hormone levels.

Assays have been constantly evolving from the older manual radioimmunoassays (RIA) to the modern day fully automated chemiluminescent immunoassay (CLIA) and electrochemiluminescent immunoassay (ECLIA) platforms. Results have to interpreted in the light of age and assay-specific reference ranges. Lack of consistency between biochemical reports and clinical presentation should alert the physician to consider assay interferences like presence of heterophile antibodies and excess biotin consumption.

Thyroid function tests typically reveal elevated free thyroxine (FT4) and T3 with a suppressed TSH in overt thyrotoxicosis. Patients with milder thyrotoxicosis may exhibit only elevated T3 values and suppressed TSH with normal T4 values, a state known as T3 toxicosis, a common presentation in pediatric age groups. Higher T3 values have been noted in prepubertal children as compared to post-pubertal children, and have been observed to be a negative predictor of the likelihood of remission in pediatric GD [25, 32].

6.1.2 Markers of thyroid autoimmunity

TRAbs are specific for GD, and are found in majority of the patients at diagnosis, with a reported prevalence of >70% in pediatric GD in some studies [33, 34]. TRAb levels can be higher in younger patients <5 years of age and in clinically severe disease [2].

Traditionally, TRAb concentrations were measured using either bioassays or receptor assays. Estimation of TRAb levels by bioassays was based on the ability of TRAbs to increase cyclic adenosine monophosphate (cAMP) production either directly from thyroid follicular cells in vitro, or indirectly via TSH-R transfected Chinese hamster ovary (CHO) cells. These also enabled detection of functional subtypes of TRAbs, including inhibitory TRAb antibodies. Receptor assays, on the other hand, provide an estimate of TRAb levels by measuring the ability of TRAb to inhibit the binding of labelled TSH to thyroid membranes, and provided enhanced sensitivity [1].

TRAb assays subsequently evolved with the advancements in immunoassays techniques. The "liquid phase" first generation immunoassays were competitive immunoassays based on inhibition of binding of radionuclide or enzyme labelled TSH. These provided excellent specificity of 97.5–100%, but suffered from a suboptimal sensitivity ranging from 52 to 94%. Subsequently, 2nd generation "solid phase" immunoassays utilized monoclonal antibodies and human or porcine TSH-R immobilized on a solid surface, improving the sensitivity to 87–100%. The 3rd generation immunoassays utilized a stimulating biotinylated monoclonal antibody

(M22) to bind to immobilized TSH-R. In recent years, fully automated platforms have been developed using the ECLIA and fluoroenzymatic immunoassay principles, with excellent sensitivity of 95–100% and specificity of 97–100% [35].

GD may also be associated with other anti-thyroid antibodies like thyroid peroxidase (TPO) autoantibodies, anti-thyroglobulin antibodies, as well as other autoantibodies like antimicrosomal antibodies (AMA) and antinuclear antibodies (ANA) [33].

6.2 Thyroid imaging

6.2.1 Thyroid scintigraphy

Thyroid scans utilize a gamma camera to provide a planar image, which provides anatomical information in addition to the functional status, whereas uptake scans are used to measure the % radioiodine uptake (RAIU), typically measured by placing a non-imaging gamma scintillation probe detector over the neck. Most commonly used radiopharmaceuticals for nuclear thyroid imaging are iodine-123 (I-123) and 99 m-technetium (Tc99m-pertechnetate). Drugs which can potentially interfere the tracer uptake like thionamides and sources of excess iodine have to be stopped atleast 3–7 days and 2–4 weeks prior to the study respectively. The doses for diagnostic imaging should be weight-based rather than fixed doses especially in children. The scintigraphic images and uptake studies are typically performed around 4 hours after I-123 intake, or 20 minutes after the iv injection of Tc-99 m pertechnetate. While technetium scans result in a low radiation exposure, they result in a high background noise and a low range of normal uptake in the thyroid gland [36].

GD is characterized by a homogenous increase in tracer uptake in the thyroid scans and an increased %RAIU on uptake studies. These studies are not done routinely for diagnosis in pediatric GD. Their primary role is in differential diagnosis of thyrotoxicosis in cases with inconclusive clinical and biochemical findings, and in assessing the radioiodine uptake in order to calculate the dose of therapeutic I-131 when radioiodine ablation is planned as therapy. However, germline TSH-R activating mutations can also give rise to a diffuse and homogenously increased uptake in the thyroid gland. On the other hand, McCune Albright syndrome, TA and TMNG are typically associated with focal increases in uptake with suppressed uptake in the remainder of the gland, whereas autoimmune thyroiditis, iodine excess and thyrotoxicosis factitia are associated with decreased to absent uptake in the thyroid gland [22, 37].

6.2.2 Thyroid ultrasonography

A thyroid ultrasound and doppler study provides a safe and non-invasive modality for differential diagnosis of thyrotoxicosis. Thyroid gland is classically diffusely enlarged in GD, and may display normal echogenicity or hypoechogenicity like in thyroiditis. GD is characterized by a diffuse increase in parenchymal vascularization, often referred to as a "thyroid inferno". Autoimmune thyroiditis may be associated with a lesser degree of increase in parenchymal vascularity as well. Quantitative measurements of the thyroidal blood flow can also be vital in diagnosing GD, with superior and inferior thyroidal artery's mean peak systolic velocities of more than 45–50 cm/second suggestive of a diagnosis of GD, providing a sensitivity and specificity of 81–83% and 92–96% respectively.

Ultrasound should also be performed in the case of thyroid asymmetry or a palpable nodule [2, 18, 38–40].

7. Management

The three cornerstones of management of pediatric GD are antithyroid drugs (ATDs), radioiodine (RAI) therapy and surgical management. Age of the patient, likelihood of remission, availability of expertise and facilities, patient preferences determine the choice of modality. The choice of initial therapy also depends on the prevailing practices in different geographic regions of the world. For instance, antithyroid drug therapy remains overwhelmingly the most popular choice in Japan, with >90% of children with newly diagnosed GD being instituted on ATDs, whereas the proportion is >80% in Europe, Asia, Oceania and South America. RAI therapy is more commonly used in the United States of America, with >70% of newly diagnosed pediatric GD patients being treated with I-131 previously. However, the use has been declining, with current estimates of 40% of patients being instituted on ATDs [22].

7.1 Medical management

Antithyroid medications still remain the modality of choice in most pediatric patients with GD, despite lower remission rates as compared to adults. Methimazole (MMI) or carbimazole (CBZ) are the drugs of choice, with the former used commonly in the United States and Japan, and the latter being used in Europe.

All the drugs act by inhibition of the critical enzyme thyroid peroxidase, effectively inhibiting the organification of iodine by inhibiting its binding to the tyrosyl residues on thyroglobulin. They also inhibit thyroglobulin synthesis, coupling of iodotyrosine residues, and secretion of thyroid hormones. PTU additionally inhibits type 1 deiodinase enzyme, decreasing the conversion of T4 to the peripherally active T3. Carbimazole is a prodrug and it get converted to methimazole completely after hepatic metabolism. 10 mg CBZ is equivalent to 7.5 mg MMI and 100 mg PTU. Besides the differences in potencies, the drugs differ in their pharmacokinetics, with MMI having a half-life of 6–8 hours, whereas PTU has a much shorter half-life of 30 minutes, necessitating 3 times a day dosing [22].

7.1.1 Dosing considerations

The starting dose of MMI is typically 0.2–0.5 mg/kg/day, ranging from 0.1-1 mg/kg/day. French guidelines suggest a dose of 0.4 mg/kg/day in moderate thyrotoxicosis (FT4 < 50 pmol/L), and doses of 0.8 mg/kg/day in severe thyrotoxicosis (FT > 70 pmol/L). As MMI is usually available in the form of 5 or 10 mg tablets, ATA guidelines also put forth a simplified guideline to ease administration, suggesting doses of 1.25 mg/day, 2.5–5 mg/day, 5–10 mg/day and 10–20 mg/day in the age groups of infancy, 1–5 years, 5–10 years and 10–18 years respectively, with dose escalation of 50–100% above the suggested doses in cases of severe hyperthyroidism. The doses are typically administered in a single dose or divided into two or three doses a day in the initial stages. Single dose therapy may result in better patient compliance.

PTU may be considered in doses of 2–7.5 mg/kg/day in three divided doses. But it is strictly avoided in pediatric patients due to concerns of severe hepatotoxicity, except in cases of thyroid storm and patients with adverse reactions to MMI requiring short-term control of thyrotoxicosis prior to definitive therapy. French guidelines contraindicate PTU use in children, and Japanese guidelines advocate caution with PTU use [22, 31, 36].

Symptoms of sympathetic overactivity including tremors, tachycardia, muscle weakness, neuropsychological disturbances are treated with beta blockers, propranolol at 1–2 mg/kg/day in 2–3 divided doses, or atenolol at 0.5–1.2 mg/kg/day as

a once daily dose. Selective beta blockers like atenolol and metoprolol are preferred in children with reactive airway disease [22, 31, 36].

7.1.2 Adverse effects

Most adverse reactions to antithyroid drugs emerge within 3 months of initiating treatment. PTU was widely used for medical management of pediatric GD until it fell out of favour in early 2000s, due to multiple reports of serious hepatotoxicity. PTU is associated with idiosyncratic hepatocellular necrosis, leading to hepatic dysfunction ranging from reversible injury to acute liver failure requiring transplantation, and rarely leading to death. PTU was the third most common cause of drug-induced liver failure, accounting for approximately 10% of drug-related liver transplantations in the United States [41].

The risk of hepatotoxicity is considerably higher in children than in adults, with children accounting for almost half of the patients in case reports of PTU-induced liver failure. Rivkees et al. estimated that the risk of reversible liver injury in children taking PTU was atleast 1 in 200, and the risk of liver failure requiring transplantation was atleast 1 in 2000–4000. It was also noted that PTU-induced liver failure was rapidly progressive and with low chances of reversibility, and there were no meaningful biochemical markers to predict the risk of hepatotoxicity [42]. FDA issued a boxed warning for PTU use in 2010, noting that 22 adult and 10 pediatric cases of serious liver injury were associated with PTU use, and limited its use to patients intolerant to other modalities and in first trimester of pregnancy [43].

MMI can also be associated with hepatotoxicity, although it is typically milder and of the cholestatic pattern. No cases of liver failure or transplantation have been reported in association with MMI use in children, in contrast to adults in whom hepatocellular toxicity has been described.

PTU is also associated with a 40 times higher risk of antineutrophil cytoplasmic antibody (ANCA) vasculitis than with MMI use. The positivity rate of ANCA in pediatric users is higher, approximately 64%, approximately 20% of whom can develop vasculitis. The antibodies tend to develop at or after 1 year of treatment. Usually asymptomatic, it can occasionally manifest as polyarthritis, dermatologic involvement in the form of purpuric skin lesions, pulmonary and renal involvement. There exist few case reports of renal failure in children due to vasculitis. Majority of the cases resolve with discontinuation of the offending medication, but severe involvement may require glucocorticoid and other immunosuppressive therapy.

MMI is more commonly associated with minor adverse events in upto 25% of the children being treated with MMI, most commonly involving mucocutaneous adverse events like urticaria, rash, oral ulcers and arthralgias, myalgias. The risk of agranulocytosis appears to be similar for MMI and PTU, affecting 0.3% of treated adults, with possibly lower prevalence in children. The risk appears to be dose-dependent with MMI use, with most of the cases occurring with daily MMI doses exceeding 20 mg/day.

Minor allergic reactions are usually managed with antihistamines, while continuing the drug under watchful guidance. On the other hand, occurrence of serious adverse reactions warrant drug discontinuation and consideration of alternative therapies. PTU and MMI exhibit significant cross-reactivity, hence use of either drugs should be avoided with the occurrence of a serious adverse reaction to the other drug [22, 31, 36].

7.1.3 Monitoring and dose titration

Patients should be monitored clinically for symptoms and signs of thyrotoxicosis. Weight and height should be checked periodically during clinic visits and

charted in appropriate growth charts. Parents should also be counselled about possible weight gain in the first few months of therapy, which can persist.

ATA guidelines suggest a complete hemogram and liver function testing prior to initiating ATDs. Routine monitoring of WBC counts and liver function tests is not advocated due to sudden onset of agranulocytosis and rapidly progressive nature of PTU-related hepatotoxicity. WBC counts should be ordered in the presence of febrile illnesses or pharyngitis. Similarly, liver functions should be obtained when patients develop symptoms of hepatotoxicity like jaundice, pruritus, anorexia, light-coloured stools or dark urine, drug should be discontinued if transaminases are elevated upto 2–3 times the upper limit of normal. Subsequently, liver function tests should be monitored till normalization. Japanese guidelines also advocate annual urinalysis and MPO-ANCA measurement for early detection of ANCA-associated vasculitis in children on PTU [22, 36].

Thyroid function tests should first be obtained after 2–6 weeks of initiation of therapy, every 4–6 weeks till dose is stabilized and every 3 months thereafter. MMI dose can be reduced by 50% once thyroid hormones normalize. The usual maintenance doses range from 5 mg every alternate day to 10 mg a day [22, 36].

Alternatively, "block and replace" strategy has been used, where replacement levothyroxine is added so that ATDs can be continued at higher doses. A 2010 metanalysis by Abraham et al. showed that block and replace regimens had similar efficacy to titration regimens, but had higher risk of treatment withdrawal due to adverse effects [44]. This is especially true for MMI as most adverse effects of MMI are dose-related. However, some authors attributed these findings to the unconventionally higher doses of MMI in the studies using block-and-replace regimens in the meta-analysis, and hence maintain that block-and-replace can be a worthwhile strategy, especially in patients who are sensitive to minor increases in doses of MMI and become hypothyroid [36, 45].

7.1.4 Duration of therapy

Multiple prognostic factors determine the response to antithyroid drugs. It is usually assessed by remission rates, defined as the proportion of patients who remain euthyroid 1 year after cessation of ATD. Remission rates in children after 1–2 years of ATD therapy are typically 20–30%, lower than in adults.

In contrast to older studies which suggested a 25% chance of remission for every 2 years of continued treatment, longer duration of therapy has not translated into significant improvements in remission rates in more recent studies. For example, treatment beyond 2 years has been seen to associated with remission rates of 23–37% after 4 years, and only 15% after 4–10 years of therapy. Relapse can occur in as many as 36–47% of patients after initial remission. Additionally, longer treatment durations carry the risk of non-compliance and drug toxicities. However, more recent studies have shown encouraging data on relapse rates. In a retrospective study involving 1138 pediatric GD patients by Ohye et al., remission rate was 46% after a median duration of 3.8 years of ATD therapy, with no significant predictors for remission identified. The cumulative rates of remission increased with duration of anti-thyroid medication till 5 years of therapy. Similar findings were seen in the prospective study by Leger et al., in which remission rates were 20, 37, 45 and 49% after 4, 6, 8 and 10 year of ATD therapy respectively, suggesting a plateau of remission after 8–10 years of ATD therapy [36, 46, 47].

Evidence for prognostic factors predicting remission and relapse in pediatric GD have been mostly derived from many retrospective and few prospective studies. Older age and pubertal onset of disease, higher BMI, lower levels of thyroid hormone levels at presentation, early achievement of euthyroidism within 3 months

of institution of ATDs and smaller goitres, have all been associated with early remission. Pre-pubertal children also tend to require longer duration of therapy to achieve remission vis-à-vis pubertal children [25, 32, 33, 48]. Non-Caucasian origin, higher TRAb levels additionally have also been associated with increased risk of relapse in treated patients [49]. In a study by Smith et al., TRAb antibodies decreased with duration of antithyroid therapy, but normalized only in 18% of children even after 24 months of therapy, with no further significant decreases with prolonged therapy. This points to a persistence of autoimmunity in pediatric age groups in contrast to adults, in whom TRAb levels tend to decline with anti-thyroid therapy, and may be used to guide decision-making for stopping anti-thyroid medication [50].

ATA guidelines suggest 1–2 years of ATD therapy before considering definitive modalities of RAI or surgery, depending on age of the child. Japanese guidelines suggest a duration of atleast 18–24 months, extending upto 5–10 years for better remission rates. They also suggest utility of TRAb assays in deciding duration of therapy.

7.1.5 Other drug therapies

Patients of thyrotoxicosis intolerant to MMI, awaiting surgery can be treated with inorganic iodine, either with 3–7 drops thrice a day of saturated solution of potassium iodide (SSKI) containing 50 mg iodide per drop, or 3–4 drops a day of Lugol's solution, containing 6.3 mg of iodine per drop, for 10 days prior to surgery. Inorganic iodine can also be used in the management of thyroid storm. It acts by inhibiting organification of iodine and thyroid hormone release, termed the "Wolff-Chaikoff effect". Caution has to be exercised for potential development of escape phenomenon, or exacerbation of thyrotoxicosis after drug withdrawal.

Alternatively, other drugs like lithium carbonate can be used, which acts by inhibiting the synthesis and release of thyroid hormones, but needs watchful care for any adverse effects. Some of the other medications that have been used are perchlorate, cholestyramine, corticosteroids and rituximab [22, 36].

7.2 Radioiodine therapy

The target of I-131 therapy is to achieve hypothyroidism by thyroid ablation with a single optimal dose of I-131 rather than euthyroidism. This is particularly relevant in pediatric age groups due to sensitivity of the thyroid gland to radiation.

The concerns over increased risk of malignancy with radioiodine were born after the Chernobyl incident, where increased risk of thyroid malignancies was attributed to low doses of I-131 and other radionuclides, in the presence of a dietary iodine deficiency in the population. Importantly, the maximum risk appeared to occur in children less than 5–6 years of age, decreasing gradually through 12 years of age. However, the highest risk of thyroid malignancy is seen with low levels of radiation exposure of about 0.09–30 μCi/g, and not with the higher activities administered in treatment of GD.

In a retrospective study by Read et al. involving 36 years follow up of 116 patients who had received RAI therapy between the ages of 3–19 years, there were no cases of thyroid malignancy or leukemia. There was also no increase in congenital anomalies in the offspring or rate of spontaneous abortions in the cohort [51]. Similarly, no significant increase in risk of non-thyroid malignancies has been observed in recipients of I-131 treatment.

Hence, ATA guidelines suggest avoiding RAI therapy in children less than 5 years of age, and considering RAI therapy in children between 5 and 10 years of age when the

required activity for treatment is <10 mCi, while emphasizing that these restrictions are based on theoretical concerns of malignancy [18, 22, 31, 36].

7.2.1 Preparation

ATA guidelines suggest achieving euthyroidism with anti-thyroid drugs and beta blockers in patients with total T4 > 20 μg/dl, and free T4 > 5 ng/dl prior to RAI therapy. Iodine intake has to be restricted atleast 1 week prior to I-131 therapy. Anti-thyroid medications are typically stopped 2–3 days prior to administering I-131. This is associated with potential risk of worsening thyrotoxicosis and precipitating thyroid storm after radioiodine therapy. Alternatively, 20% higher dose can be administered while patient is on anti-thyroid medication, minimizing the risk of thyroid storm. Either of these approaches have not been well studied in pediatric age groups.

ATDs are restarted only 1 week after RAI therapy to optimize the likelihood of successful ablation, although this is seldom required in children as thyroid hormone levels begin to decrease within one week after RAI treatment [18, 22, 31, 36].

7.2.2 Dosing considerations

The activity to be administered as fixed doses of about 15 mCi or calculated using the Quimby-Marinelli formula, or the modified version based on the 24-hour uptake values on RAIU scan. Estimation of total gland size can be done by physical examination or by ultrasound dimensions of the gland, and is particularly challenging in pediatric patients. In general, the total dose of I-131 should be atleast 150 μCi/g of thyroid tissue, resulting in hypothyroidism in >95% of cases. Increased doses of 200–300 μCi/g may be required in patients with large goitres and lower radioiodine uptake. There are no studies available to compare the two methods in children.

Radioiodine is retained in the thyroid for several days, and is also excreted in body fluids like saliva, tears, sweat, stool and urine. Appropriate local radiation safety precautions have to be observed by the patient and family members after RAI treatment [18, 22, 31, 36].

7.2.3 Complications

Pain in the gland can develop in the week after I-131 therapy in less than 10% of the patients. It can be managed by symptomatic treatment with analgesics for 1–2 days. There may be temporary exacerbation of thyrotoxicosis, requiring treatment with ATDs, glucocorticoids and iodine preparations. Long-term risks include the theoretical risk of secondary malignancies following radiation [36].

7.2.4 Monitoring

Patient has to be clinically monitored for signs and symptoms of hyperthyroidism as well as for development of hypothyroidism. Patients can experience an exacerbation in ophthalmopathy, which may require treatment with glucocorticoids.

Hypothyroidism is usually achieved at 1–3 months after an optimal dose of I-131, with occasional patients taking upto 6 months to achieve hypothyroidism. Thyroid function tests should be obtained 4 weeks after I-131, followed by periodic testing at 4–6 weeks till hypothyroidism is achieved, when thyroid hormone replacement can be initiated [22, 36].

7.2.5 Contraindications

RAI therapy is an absolute contraindication in children less than 5 years of age as per AT and French guidelines. The latter also mention it as a relative contraindication in pre-pubertal children. Japanese guidelines advocate "careful administration" in children younger than 18 years of age on account of risk of thyroid malignancy and gonadal injury post radiation.

RAI therapy can be considered in pediatric patients with GO in non-severe cases. The NO-SPEC severity classification and clinical activity score (CAS) have not been validated in pediatric population. RAI therapy may still be considered in the presence of more severe manifestations like corneal involvement, persistent lid retraction and chemosis with concomitant oral glucocorticoid therapy, beginning a day after RAI, and tapered over 1–3 months [22, 31, 36].

7.3 Surgery

Surgery should be considered in patients with large goitres, presence of compressive symptoms, coexisting differentiated thyroid cancer (DTC), patients wishing to achieve faster remission, patients who do not wish to use ATDs or have adverse effects or contraindications to use of ATDs. ATA guidelines recommend thyroidectomy in children younger than 5 years of age, in whom definitive therapy is indicated and have accessibility to surgical expertise.

The major limiting factor for choice of surgery as the modality is the access to a high volume thyroid surgeon, defined as performing more than 30 cervical endocrine procedures in a year. The surgical complication rates are inversely related to the annual number of procedures by the operating surgeon, rather than the training or surgical specialty per se. The centre should be capable of handling pediatric anesthestic challenges and post-operative intensive care requirements. In the presence of availability of expertise and infrastructure, surgery can be offered as equivalent to RAI therapy to the parents [18].

7.3.1 Preparation

Patient should be rendered euthyroid with medications prior to surgery (thionamides, inorganic iodide and beta blockers). Potassium iodide, containing 50 mg iodide/drop can be administered as 1–2 drops thrice a day, 7–10 days prior to surgery can alleviate thyrotoxicosis as well as decrease vascularity of the gland. Dexamethasone can also help in rapid control of thyrotoxicosis [22, 36].

7.3.2 Procedure

Total or a near-total thyroidectomy (with <3 g of residual thyroid tissue) are the procedures of choice for management of GD. Partial or subtotal thyroidectomies may result in recurrence rates of 10–15%. Intra-operative PTH monitoring can be valuable in predicting the occurrence of post-operative hypocalcemia.

7.3.3 Complications

Most common post-operative complications include transient hypoparathyroidism and recurrent laryngeal nerve palsy. These complications tend to occur at the rate of 10–20%, more frequent than in adults, and are particularly more common in younger children. Other severe complications like permanent hypoparathyroidism, hematoma, infection, recurrent laryngeal nerve palsy occur less

frequently. Significant bleeding occurs more frequently with large goitres, necessitating blood transfusions in children. Caution has to be exercised in handling of recurrent laryngeal nerves as they are thinner in children. Growth-related bone metabolism may make the patient prone for transient hypoparathyroidism post-operatively. Post-operative hypocalcemia requiring intravenous calcium correction occurs more frequently in children. Its risk can be decreased by preoperative calcitriol, usually started 3 days before surgery and weaned off over the first 2 weeks post-operatively.

Surgery offers the advantages of definitive therapy. This has to be weighed against the risks associated with an invasive procedure, and the requirement of life-long thyroxine replacement with appropriate monitoring after surgery [22, 31, 36].

7.4 Choice of modality

Anti-thyroid drugs are usually the first line of management, typically administered for atleast 1–2 years. Definitive therapy with RAI therapy or surgery should be considered if remission is not attained after 1–2 years of ATD therapy. Continued medical management with periodic biochemical monitoring is a viable option in patients who are not candidates for either of the two definitive modalities. They offer the advantages of ease of administration, availability, reasonable safety and avoidance of exposure to radioactivity and surgical procedure. These have to be weighed against long duration of therapy and associated followup, lower rates of remission, low rates of compliance, higher frequency of adverse effects.

Radioiodine therapy in sufficient doses results in achievement of hypothyroidism in majority of patients, and should be considered as the modality of choice for definitive therapy in children >10 years of age, and in children 5–10 years of age with calculated dose requirements of less than 10 mCi. This has to be balanced against the risks of temporary flare, radiation thyroiditis and concerns of malignancy, even if theoretical as per most studies.

Medical management	RAI therapy	Surgery

• First line of therapy in most patients
• Lack of access to definitive therapies
• Good compliance to medication and periodic followup
	• Risk factors for poor response to ATDs:
	  ○ Prepubertal
	  ○ Severe biochemical thyrotoxicosis and elevated TRAb at presentation
	  ○ Prolonged time to achieve euthyroidism
	  ○ Persistently elevated TRAb
	  ○ Large goitre
	• Adverse effects and poor compliance to ATDs
	• Contraindications or unwilling for surgery
	• Relapse after medical and surgical management
	• Avoidance of surgical scar and risks associated with surgery
		• Risk factors for poor response to ATDs as described
		• Children younger than 5 years of age
		• Large goitres more than twice the normal size for age or > 80 g
		• Compressive symptoms
		• Nodular goitre, suspicion of malignancy
		• Inability to comply with precautions and follow-up instructions after RAI therapy
		• Severe eye disease
		• Post-pubertal patients considering pregnancy

Table 5.
Clinical factors influencing choice of modality in pediatric GD.

Surgery offers immediate and definitive therapy. However, the need for hospitalization, associated complications, surgical scarring preclude its use as a first line therapy. It can be considered in patients requiring definitive therapy and not being suitable candidates for RAI ablation.

Clinical factors that can influence the choice of modality are summarized in **Table 5**.

8. Special considerations

8.1 Thyroid storm

Encephalopathy can occur in association with thyroid storm. Initial presentation can include mental status changes including behavioural abnormalities, agitation, confusion, anxiety and emotional lability. Patients can also present with seizures, which can range from generalized tonic clonic to complex partial to more focal seizures.

8.2 Neonatal GD

Neonatal GD, though rare, can be life-threatening with significant morbidity and mortality. Maternal transfer of thyroid-stimulating immunoglobulins (TSIs) to the fetus, can occur in 1 in 80 cases of maternal GD. The risk of neonatal GD is directly proportional to the magnitude of elevation of TSI levels, typically increased at levels 2–4 times the upper limit of normal. The fetal thyroid can respond to TSIs resulting in excessive production of thyroid hormones.

This can manifest as fetal thyrotoxicosis, especially in second half of gestation. The condition should be suspected in the presence of fetal tachycardia (heart rate > 160/min after 20 weeks of gestation), goitre on antenatal ultrasound. Uncontrolled fetal thyrotoxicosis can result in intrauterine growth retardation (IUGR), premature fusion of cranial sutures, advanced skeletal age, accelerated maturation of femoral ossification centre, learning disabilities and mental retardation.

Management consists of adequate control of maternal thyrotoxicosis with anti-thyroid drugs. Propylthiouracil (PTU) is often the first choice at the time of organogenesis. Methimazole (MMI) is avoided in first trimester due to risk of methimazole embryopathy (Odds ratio of 1.66 for developing birth defects). This can manifest as aplasia cutis congenita, omphalocele, choanal and esophageal atresia and other omphalomesenteric duct anomalies in the newborn [52, 53].

The condition usually resolves by 3–6 months of age, due to clearance of TSIs from the infant's circulation. Infants may meanwhile require medical management of thyrotoxicosis. This entails treatment with antithyroid medications (PTU 5–10 mg/kg/day or MMI 0.5–1 mg/kg/day) and propranolol (1 mg/kg/day). Rapid biochemical control may require administration of Lugol's solution or saturated solution of potassium iodide (SSKI) for 7–10 days. Thyroid hormones typically normalize after 2 weeks of medical therapy, and may necessitate addition of levothyroxine to prevent hypothyroidism. Anti-thyroid medication can usually be weaned by 3 months, guided by monitoring of infant's serum TSI levels.

9. Summary

Graves' Disease in children is a classic example of children not being small adults. There are differences in management and response to treatment in children with Graves' Disease. Nuances exist for the various modalities for children and requires

specialist pediatric endocrinology care. Therapeutic options need to be discussed with parents before deciding on choice of definitive therapy. Smooth transitioning to adult endocrinology clinic is important to continue quality medical care.

Abbreviations

EDCs	Endocrine-disrupting chemicals
GD	Graves' Disease
MAS	McCune Albright syndrome
TA	Toxic adenoma
TMNG	Toxic multinodular goitre

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