Treatment of childhood Graves' disease

A review with emphasis on radioiodine treatment

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■ Graves' disease is the most common form of hyperthyroidism in children. Because of complications with either thyroid surgery or antithyroid drug therapy, the authors prefer high-dose radioiodine as the initial treatment of choice. Long-term follow-up studies have not shown an increased incidence of malignancy in the patients or birth defects in their offspring.

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OF ALL patients with Graves' disease, 1%–5% are children. Childhood Graves' disease, in turn, accounts for 10%–15% of all childhood thyroid disorders.[1,2] Of 343 patients with Graves' disease studied from 1935 to 1967, Furszyfer et al[3] identified hyperthyroidism in 25 less than 20 years old and in one girl less than 10 years old. In three series consisting of 269 children with Graves' disease, the onset of hyperthyroidism was from birth to age five in 14%, from age six to 10 in 26%, and age 11 or more in 60%.[2,4,5] The female-to-male ratio in these patients was 4:1.

In children, thyrotoxic manifestations may include behavioral abnormalities, poor school performance, accelerated bone maturation, weight loss, diarrhea, and muscle weakness. To avoid prolonged morbidity during the developmental years, rapid control of hyperthyroidism is desirable. Since no current therapy is ideal, those advocating surgery,[6–9] antithyroid drug therapy,[2,4,5,10,11] or radioiodine ablation[12–15] have debated advantages and disadvantages during the last four decades. With antithyroid drug therapy, the usual remission rate varies from 30% to 60%[2,4,11,16] and increases with prolonged or high-dose therapy.[17,18] Toxic drug reactions such as agranulocytosis, granulocytopenia, skin rash, arthritis, vasculitis, collagen disease-like syndromes, and hepatitis do occur.[19–24] In a small percentage of patients, thyroid surgery is associated with hypoparathyroidism, recurrent laryngeal nerve injuries, postoperative bleeding, and keloid formation. Yet many physicians prefer antithyroid drug therapy or surgery, while cautiously awaiting further information from follow-up studies of patients with childhood Graves' disease who were treated with I-131.

Since the U.S. Atomic Energy Commission released I-131 for treatment of hyperthyroidism in 1946, more than one million adults have received radioiodine treatment.[25] An increased risk of leukemia, malignancy, or birth defects has not been identified in the offspring of patients treated with radioiodine for Graves' disease as children or adults.[7,12–15,26–32] At The Cleveland Clinic Foundation, we have maintained long-term follow-up studies of 208 patients who had childhood Graves' disease, as well as their progeny.[13,27,33,34] We recommend high-dose ablative radioiodine as the initial treatment of choice.

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HISTORY

In 1786, Parry[35] described a case in which hyperthyroidism developed in a 21-year-old woman shortly after

she experienced emotional stress due to being thrown out of a rapidly moving wheelchair. His initial description of the disease was published posthumously in 1825 without significant recognition. Graves[36] and, according to Werner,[37] von Basedow later recorded further details of a similar syndrome. Heiman[38] states that in 1851 Henoch-Romberg described the first child with "Graves' disease." Rehn performed the first subtotal thyroidectomy for Graves' disease in 1884.[37]

Thyroid surgery in the 19th century was associated with substantial morbidity and mortality. Of 70 thyroid operations performed before 1850, Halstead[39] estimated a surgical mortality rate of 41%. With the discovery of anesthesia in 1846, antisepsis in 1867, and the hemostat in 1879, surgical mortality decreased.[40] Coller and Boyden also stated that Kocher perfected the surgical procedure for thyroidectomy and identified the role of thyroid deficiency in postoperative myxedema. They reported that Kocher's surgical mortality rate gradually decreased from 21.1% of 146 patients from 1850 to 1877, to 6.9% of 43 patients in 1884, to 2.4% of 250 patients in 1889, and to an astonishingly low 0.18% of 560 patients in 1898.

Prior to 1923, childhood Graves' disease was an ominous illness with an estimated surgical mortality rate of 10%.[41] Since death from postoperative thyroid storm was common, superior thyroid artery ligation or injection of sclerosing agents into the thyroid gland was frequently performed prior to thyroidectomy to control hyperthyroidism. Of 19 children undergoing these alternative procedures at the Mayo Clinic from 1908 to 1921, four children died postoperatively and another child died after a second operation for persistent thyrotoxicosis.[42] Without treatment, seven of 12 patients with Graves' disease died during three and one half years of observation, White[43] reported. Early medical therapy included the use of arsenious acid, atropine, extract of ergot, digitalis, iron, and salicylate of soda, as well as bed rest for six to 10 weeks.[38,44] These were tried in some children, with variable results.

When Plummer[45] reported that orally administered iodide could prevent postoperative thyroid crisis, subtotal thyroidectomy became the treatment of choice for childhood Graves' disease.[42,46,47] Of 21 children with Graves' disease receiving iodine prior to thyroid surgery, Helmholtz[46] reported only one postoperative death secondary to thyroid crisis. In 1932, Dinsmore[47] reported two postoperative deaths in 43 children undergoing surgery at the Cleveland Clinic, although one had died before iodine was used. Of 196 children treated by subtotal thyroidectomy at the Mayo Clinic from 1908 to 1959, only four children died, all before 1934.[42]

In 1941, Mackenzie et al[48] discovered that sulfaguanidine may induce thyroid hyperplasia in rats. In 1943, the Mackenzies[49] and Astwood et al[50] independently discovered that sulfonamides and thiourea could inhibit the synthesis of thyroid hormone. After evaluation of 106 different compounds, Astwood[51,52] successfully controlled hyperthyroidism in three patients with thiourea and thiouracil. When further studies confirmed these findings in children, many physicians preferred antithyroid drug therapy over surgery.[10,11] On the other hand, advocates for surgical therapy noted that antithyroid drug therapy was often prolonged, drug reactions occurred, and the remission rate of hyperthyroidism was lower in children.[7]

The early history and use of radioiodine has been well summarized.[53] In 1941, a patient with Graves' disease received 1 mCi (37 MBq) of I-131, which in retrospect was a tracer dose.[54] Although Hertz and Roberts[55] treated 29 patients with I-131 from 1941 to 1943, the isolated effect of the radioisotope was unclear since stable iodine was also administered. In 1943, Chapman[53] successfully treated a patient with 30 mCi (1,110 MBq) of I-131 as a single agent. In a review of radioiodine therapy, Chapman and Maloof[54] concluded that radioiodine therapy was effective for hyperthyroidism, hypothyroidism was a common complication, fertility appeared to be unaffected, and I-131 should be used only for subjects more than 40 years old until the likelihood of a potential carcinogenic effect could be excluded. Early follow-up studies of children treated with I-131 revealed hypothyroidism as the only adverse effect, which could be easily corrected with thyroid-hormone replacement.[7,12,26,27]

CLINICAL MANIFESTATIONS

The major clinical manifestations in childhood Graves' disease include goiter (97%–100%), nervousness or restlessness (60%–92%), tachycardia (65%–91%), exophthalmos (55%–77%), tremor (40%–76%), increased appetite (40%–71%), weight loss (50%–67%), emotional disturbances (declining school performance, excessive crying, emotional lability, temper tantrums, and increased irritability) (40%–56%), and school problems (not related to "emotional disturbances") (40%–43%).[2,4,5] Most patients experience clinical symptoms of hyperthyroidism six to 12 months prior to the diagnosis of Graves' disease. However, a sudden appearance of clinical thyrotoxicosis may occur.

In children, exophthalmos is usually present, but less

severe than in adult Graves' disease.[42,57] Safa et al[13] reported 67 of 87 hyperthyroid children treated at the Cleveland Clinic had "eye" signs indicating Graves' disease. Following radioiodine therapy, such signs lessened in 60 (89.5%), did not change in five (7.5%), and worsened in two (3.0%) who subsequently required orbital decompression. In another study of 194 patients undergoing orbital decompression for Graves' ophthalmopathy,[58] less than 3% had undergone surgery before age 20. Also, no relationship between radioiodine or surgical therapy and the appearance of exophthalmos was found. According to Hayles and Zimmerman,[57] children with unilateral exophthalmos without thyrotoxicosis should be evaluated for a possible underlying neoplasm.

The height and bone age of hyperthyroid children are usually advanced at the time of diagnosis and are associated with a below-average weight that remains low after hyperthyroidism has been controlled.[42,59,60] Buckler et al[60] reported that the stature of 46 hyperthyroid children was 70% above the predicted values with respect to the parents' statures. Also, costochondral calcification is uncommonly observed in chest or abdominal radiographs of children, but increases with advancing age.[61] Senac et al[61] found 66% of 32 hyperthyroid children (between 13 and 15 years old) had costochondral calcification as shown on radiographs, compared with 12% of 600 controls. In neonatal thyrotoxicosis, craniosynostosis, advanced bone age, and mental retardation have been reported.[62] Rapid control of hyperthyroidism with the maintenance of a euthyroid state is indicated to avoid advanced skeletal maturation.

A number of coexisting illnesses are associated with childhood Graves' disease. In a study of 130 children with Graves' disease evaluated at the Mayo Clinic from 1965 to 1977, Howard and Hayles[56] reported diabetes in 4.6%; Down's syndrome in 2.3%; vitiligo in 1.5%; and rheumatoid arthritis, acute nephritis, hyperlipidemia, asthma, and sickle cell disease in 0.08%. In a survey of 203 of 224 patients with Graves' disease evaluated five to 31 years after initial radioiodine therapy at the Cleveland Clinic, diabetes mellitus occurred in 5.9%; asthma in 2.0%; vitiligo in 1.5%; systemic lupus erythematous, Still's disease, nephrolithiasis, and idiopathic thrombocytopenia purpura in 0.09%; and Addison's disease, McCune-Albright syndrome, Wegener's granulomatosis, sarcoidosis, and osteogenic sarcoma in 0.05%.[33] Diabetes is especially common and may appear before, after, or with the presentation of hyperthyroidism. In addition to polyuria, polydipsia, and weight loss, diabetes may present with secondary enuresis, which also may be the initial manifestation of hyperthyroidism alone.[63]

DIAGNOSIS

In children with classic symptoms, thyrotoxicosis is readily confirmed with an elevated thyroxine (T4) level, as well as triiodothyronine-resin uptake, which is required to exclude self-limited low-uptake hyperthyroidism,[64] and the thyroxine-binding index. The T3 concentration is invariably elevated, unless another severe systemic illness is present. A thyroid scan is not routinely performed.

The physician should be alerted to a number of euthyroid clinical conditions in which elevated thyroid function studies may be confused with hyperthyroidism in normal and healthy children. Fisher et al[65] reported elevated T4, T3, and thyroid-binding- globulin concentrations in younger children. Since the concentrations decline with age, T4 and T3 values in children should be compared with age-matched controls. In addition, T4 may also be elevated in peripheral thyroid hormone resistance with elevated concentration of serum thyroid-binding proteins and acute nonthyroidal illness without thyrotoxicosis.[66,67] The measurement of thyroid-stimulating hormone (TSH) by immunoradiometric assay, which is tenfold more sensitive than the usual TSH measurement by radioimmunoassay, may help identify which of these patients have hyperthyroidism.[68,69] When hyperthyroxinemia is secondary to Graves' hyperthyroidism, TSH concentration is suppressed and does not increase when thyroid-releasing hormone (TRH) is injected intravenously. When TSH increases in response to TRH testing, treatment for hyperthyroidism is not indicated. Further information regarding the details of clinical conditions with hyperthyroxinemia, which may be confused with Graves' disease, are discussed by Borst et al[66] and Weintraub et al.[67]

RADIOIODINE TREATMENT

We prefer to use a large initial dose of 100–200 μCi (3.7–7.4 MBq) of I-131 per gram of thyroid tissue according to the following formula[13]:

Thyroid tissue in grams x 100–200 μCi *of I-131 = dose in mCi of I-131 (fractional I-131 24-h uptake)* x 1,000.

In children with severe hyperthyroidism or large goiters, who require a larger dose of radioiodine, we admini-

ster 200 μCi (7.4 MBq) per estimated gram of thyroid tissue.[70,71] Children with other associated conditions, such as poorly controlled diabetes, where rapid control of hyperthyroidism is desirable also receive high-dose therapy. Less radioiodine is required for children with mild hyperthyroidism or small goiters. Two months after the initial I-131 therapy, a repeat I-131 uptake and thyroid-function studies are done. When significant hyperthyroidism persists, repeated treatment with I-131 is recommended.

Low-dose radioiodine therapy has been abandoned since persistent hyperthyroidism is common in the early years following therapy and is unavoidable in later years.[70,72,73] Rapoport et al[72] reported that when only 50 μCi (1.85 MBq) of radioiodine per estimated gram of thyroid tissue was used, 54% of patients had persistent hyperthyroidism one year later. McCullagh et al[73] wrote that hypothyroidism was present in 90% of adults with Graves' disease studied 17 years after receiving 3 mCi (111 MBq) or less of I-131. Safa et al[13] reported that hypothyroidism developed in 46% of 76 patients five to 24 years after initial radioiodine therapy. Of 15 patients evaluated 20 or more years after antithyroid drug therapy for Graves' disease, Wood and Ingbar[74] found elevated TSH levels in five patients and diminished thyroid reserve in four others.

Since hypothyroidism reflects the natural history of Graves' disease, there is a need to discuss life-long thyroxine replacement with the patient prior to I-131 therapy.[75] A summary letter is sent to the referring physician and family, reemphasizing the need for thyroxine replacement after therapy is completed. With continued physician and patient education, we try to avoid the unnecessary morbidity of untreated hypothyroidism.

Adjunctive therapy

Adjunctive therapy to alleviate severe symptoms of thyrotoxicosis is indicated while awaiting the definitive effects of radioiodine therapy. Potassium iodide, as a saturated solution of potassium iodide (SSKI) or Lugol's solution, interferes with the organification of intrathyroidal iodide (the Wolf-Chaikoff effect) and inhibits the release of thyroid hormone.[76,77] Since the irradiated thyroid is more sensitive to stable iodide, 2–10 drops of SSKI in water or orange juice administered once daily for seven days following radioiodine therapy may ameliorate thyrotoxicosis. Beta-adrenergic blockade therapy may improve symptoms of restlessness, tachycardia, tremor, anxiety, myopathy, and thyrotoxic periodic paralysis.[78,79] Although short-term propranolol therapy does not affect thyroid function, prolonged therapy inhibits T4-to-T3 conversion and thereby reduces the T3 concentration 10%–40%, with a 10% reduction in oxygen consumption.[79,80] The reduction of serum T3 levels occurs with nadolol, sotalol, and high-dose metoprolol therapy, but not with atenolol, oxprenolol, or acebutolol.[79] In children who require symptomatic relief of severe thyrotoxicosis, we recommend propranolol (2.5–10.5 mg/kg/d, administered orally) in divided doses or an equivalent dose of nadolol.[81,82] Beta blockers should be avoided in children with insulin-dependent diabetes mellitus, congestive heart failure, asthma, or Raynaud's phenomenon.[78,79]

Treatment with antithyroid drugs is not indicated prior to radioiodine therapy, since little thyroid hormone is stored in the thyroid gland of a patient with Graves' disease.[83] At the Cleveland Clinic, more than 7,000 patients with Graves' disease have been treated with radioiodine without a single case of associated thyroid storm.[84]

Long-term effects

Several long-term follow-up studies, including 60,000 patients reported by Pochin,[28] 32,000 patients described by Werner et al,[30] and 21,000 patients reported by Saenger et al[29] have not demonstrated an increased incidence of leukemia, thyroid cancer, or other malignancies following I-131 therapy for Graves' disease. Of 4,557 patients treated with I-131, Holm[32] found no increase in thyroid malignancy. With radioiodine therapy for Graves' disease, the usual radiation dose of 5,000–20,000 rad (50–200 Gy) ablates most thyroid cells and impairs their ability to undergo malignant transformation.[85,86] On the other hand, low-dose external irradiation does not destroy the thyroid cells' ability to proliferate, thus the subsequent risk of thyroid carcinoma is increased.[87]

Adverse genetic effects have not been identified in the progeny of children treated with I-131 for Graves' disease.[7,12–15,26,27,33,34] The radiation dose to the gonads has been estimated to be 1–2 rad (0.1–0.2 Gy), which is no greater than the amount of radiation exposure associated with a barium-enema examination or intravenous pyelography.[88] In 217 offspring of 208 patients who had had childhood Graves' disease and were treated with radioiodine at the Cleveland Clinic, four congenital malformations (clubfoot in two; tracheoesophageal fistula in one; and patent ductus arteriosus in one, which spontaneously closed at seven years of age) were reported. Other significant associated illnesses in the progeny included two with diabetes mellitus, hypothyroidism, and asthma and one each with cystic fibrosis, leukemia, nephrotic

syndrome, petit mal epilepsy, and congenital deafness.[34] An association of autoimmune illnesses is expected in these children and the other problems have been attributed to chance. In addition, karyotypes of 114 progeny of patients treated with radioiodine at the Cleveland Clinic were reviewed. Mild chromosomal instability was identified four times, without the aberrations associated with ionizing radiation. Of 33 children treated with 80–691 mCi (2.96–25.567 GBq) of I-131 (mean dose, 196 mCi [7.252 GBq]) for thyroid carcinoma, the subsequent birth histories have been normal, without an increase in congenital anomalies.[89] As further evidence, subjects exposed to large doses of gonadal radiation at Hiroshima and Nagasaki have not had an increase in birth defects.[90] Thus, children exposed to radioiodine for Graves' disease or thyroid cancer have normal reproductive histories.[13–15,33,34,89,91]

On the other hand, women with hyperthyroidism during pregnancy do have an increased incidence of congenital malformations, fetal loss, and maternal morbidity.[92,93] Momotani et al[93] found the risk of congenital malformations was increased when maternal hyperthyroidism was present in the first trimester, which was unrelated to the use of methimazole. They also reported that six percent of 50 infants of hyperthyroid mothers not using methimazole had congenital malformations compared with 1.7% of 117 infants of hyperthyroid mothers using methimazole. On the other hand, when the mother was euthyroid in the first trimester, 0.3% of 350 malformed infants developed in mothers not using methimazole and no malformations were found in 126 infants of mothers using methimazole.

Although a causal relationship between external radiation and hyperparathyroidism exists, no association has been identified in adults treated with radioiodine for Graves' disease.[94,95] However, two children who received I-131 therapy before age 13 had surgically proved hyperparathyroidism,[33,96] suggesting a relationship between I-131 therapy for childhood Graves' disease and hyperparathyroidism. On the other hand, Parfitt and Dent[97] suggested an association between hyperparathyroidism and Graves' disease in patients who were not exposed to radioiodine. Further follow-up of children treated with radioiodine will be required.

ANTITHYROID DRUG THERAPY

Methimazole and propylthiouracil are the currently recommended antithyroid drugs for treatment of childhood Graves' disease. Although the enzymatic blockade of thyroid hormone synthesis is rapid, several weeks elapse before the stored thyroid hormone is depleted. Propylthiouracil, which inhibits the conversion of thyroxine to triiodothyronine, is used more frequently in the United States,[98] and is preferred for pregnant or lactating women since it is tightly bound to plasma proteins and less likely to cross into the fetal circulation.[24] Methimazole, which is a more potent antithyroid drug with a longer half life, controls hyperthyroidism sooner and has a longer inhibitory effect on organification of iodide in the thyroid.[98,99]

Therapy is usually started with propylthiouracil (5–7 mg/kg/d) or methimazole (0.5–0.7 mg/kg/d) in divided doses every eight hours.[57] The initial total daily dosage may reach 600 mg a day for propylthiouracil or 60 mg a day for methimazole.[56] Within seven to eight days, clinical improvement occurs and the dosage may be tapered to the lowest effective therapy to control hyperthyroidism.[56]

Antithyroid drug therapy is more likely to fail in children with large goiters, a history of previous relapse, thyroxine levels greater than 20 μg/dL, or ophthalmopathy.[100] Takamatsu et al[101] found 18% of patients had elevated T3 and normal T4 concentration after three months of antithyroid drug therapy with a T3-T4 ratio greater than 20. In these patients with "T3-predominant Graves' disease," relapse of hyperthyroidism was common. The enhanced T4-to-T3 conversion in these patients has been attributed to elevated levels of thyroid-stimulating immunoglobulins and an enhanced iodine metabolism in the thyroid gland.[101,102]

With antithyroid drug therapy, the usual remission rate of childhood hyperthyroidism varies from 30% to 61%.[2,4,11,16] Factors affecting the remission rate include the dietary intake of iodine and the duration and dosage of antithyroid drug therapy. In 1973, Wartofsky[103] reported 17.1% of 35 hyperthyroid patients treated with antithyroid drugs for one year or more achieved remission. He noted a similar decline in remission rates in other series, corresponding to an increased iodine content in the American diet. In 1987, antithyroid drug therapy resulted in remission of hyperthyroidism in 50.7% of 69 patients with Graves' disease treated at the same clinic.[104] The enhanced therapeutic response coincided with a parallel decline in the estimated daily iodine intake in the average diet. For 67 children, Barnes and Blizzard[2] reported a remission rate of 77% for those treated with a single course of thionamide therapy from 1946 to 1962, but only 53% for those treated between 1962 and 1975. Prolonged or high-dose therapy increases the remission rate and may be related to an immunosup-

pressive property of the antithyroid drugs.[105] In 63 hyperthyroid children treated with antithyroid drugs, Lippe et al[18] predicted 25% would achieve remission in 2.3±0.3 years, 50% in 4.3±1.5 years, and 75% in 10.9±2.3 years. A major limitation of antithyroid drug therapy is the prolonged treatment required to control hyperthyroidism and prevent relapse. Poor compliance is another problem.

Adverse reactions to antithyroid drugs are more common in children. Vasily and Tyler[106] report cutaneous reactions in 3%–5% of adults and up to 18% of children treated with antithyroid drugs. In one review, Cooper[24] reported only 1%–5% of patients experienced an adverse reaction to antithyroid drugs. However, Hayles and Zimmerman[57] reviewed six series consisting of 329 hyperthyroid children treated with antithyroid drugs and found 80 (24%) experienced an adverse reaction. Buckingham et al[16] reported serious drug-related complications in 14% of 107 children treated with antithyroid drugs. Major adverse reactions to antithyroid drug therapy include agranulocytosis; collagen vascular disease syndromes, including systemic lupus erythematosus and vasculitis; toxic hepatitis; erythema multiforme; and nephrotic syndrome.[2,19–24,106]

THYROID SURGERY

Most surgeons prefer a subtotal thyroidectomy to treat childhood Graves' disease,[6–8] while others advocate a total thyroidectomy.[107,108] The incidence of recurrent hyperthyroidism or the occurrence of postoperative hypothyroidism has been related to the size of the remaining thyroid tissue.[109–111] Preoperative therapy is indicated to prevent postoperative exacerbation of hyperthyroidism and reduce blood loss. With the standard approach, hyperthyroidism is controlled with antithyroid drugs followed by Lugol's solution or SSKI 10–14 days prior to surgery. Iodide therapy reduces thyroid vascularity and may acutely lower T4 and T3 levels. Although short-term iodide therapy alone is usually effective for thyrotoxicosis, prolonged iodide therapy may exacerbate hyperthyroidism.[112]

Beta-adrenergic-blockade therapy may acutely curtail thyrotoxic symptoms in hyperthyroid patients requiring urgent or nonthyroidal surgery.[79,113] Advocates for beta-adrenergic therapy as the sole preoperative therapy for Graves' disease note that prolonged preoperative therapy is not required, the timing of surgery is more flexible, and operative blood loss is reduced.[79,111,113]

Adequate beta-adrenergic blockade may be determined by a 25% reduction in exercise-induced tachycardia.[79] The resting heart rate is a less reliable indicator because it is regulated by the parasympathetic nervous system, sympathetic stimulation is decreased at rest, and some adrenergic blockers have a beta-agonist effect.[114] Since the metabolism of propranolol is increased in children and severely thyrotoxic patients, doses larger than 160 mg/day may be required to achieve adequate beta-adrenergic blockade.[115,116]

Beta-blockade therapy should be administered on the day of surgery and continued for five to 10 days afterward, since the half-life of thyroxine is six to seven days.[79,111,113] In a review of almost 1,000 hyperthyroid patients treated with beta-blockade therapy prior to surgery, 3% had exaggerated thyrotoxic symptoms.[79] Since thyroid storm has been reported in patients treated with beta-adrenergic blockade alone, preoperative iodide therapy has been recommended in children[56] and adults.[117,118] The traditional preoperative therapy of antithyroid drugs followed by orally administered iodide is favored in severely thyrotoxic children.[56]

The widespread use of radioiodine for Graves' disease has limited the opportunity for young surgeons to develop and maintain their expertise in thyroid surgery.[25] Crile[119] has noted that thyroid surgery is more difficult in children because of the smaller and softer larynxes. Of 62 children undergoing thyroid surgery, Ching et al[120] found the postoperative complication rate was 30% in 20 hyperthyroid patients and 0% in 42 euthyroid patients. Thus, thyroid surgery in children is more difficult for hyperthyroidism than for nodular goiter in cases of suspected carcinoma. In a summary of six series totaling 411 children undergoing thyroid surgery for Graves' disease, transient hypocalcemia occurred in 10%, hypoparathyroidism in 2%, recurrent laryngeal nerve injury in 1%, and temporary tracheostomy in 0.7%.[57] The surgical morbidity and potential mortality may be reduced but unfortunatley not eliminated with an experienced surgeon.

NEONATAL GRAVES' DISEASE

Neonatal thyrotoxicosis is usually a transient disorder attributed to the transplacental passage of thyroid-stimulating immunoglobulins.[121] The prevalence of Graves' disease with pregnancy is about 0.2%.[122] Approximately 1.4% of these cases will result in overt neonatal thyrotoxicosis.[123] When thyroid-stimulating immunoglobulins are 500% greater than normal in the third trimester, neonatal thyrotoxicosis is likely.[121] Neonatal Graves'

disease has been reported involving mothers with no known thyroid disease, as well as those with Hashimoto's thyroiditis or those who had Graves' disease previously but were not afflicted at the time of their pregnancy.[121,124–126] Normally, the mean fetal heart rate is 143±6 at 24 to 32 weeks and 132±8 from 36 to 40 weeks of gestation.[127] But when that heart rate is greater than 160 in the third trimester, mothers with elevated levels of thyroid-stimulating immunoglobulins should be treated with 150/300 mg/day of propylthiouracil in divided dosages.[128] Since high-dose propylthiouracil may induce fetal goiter and transient fetal hypothyroidism,[129] the lowest possible dose should be used and tapered to 50–150 mg at term.[126,128]

Neonatal Graves' disease is a life-threatening disorder with a mortality rate of 16%.[124] Clinical manifestations include goiter, exophthalmos, tachycardia, irritability, nervousness, diarrhea, excessive weight loss, and hypertension.[130,131] Prematurity, intrauterine death, craniosynostosis, advanced bone maturation, and impaired intellectual development have also been described.[61,124,132] Thyrotoxicosis usually appears in the first few days of life, but may present seven to 10 days after delivery in mothers treated with antithyroid drugs.[133] Clinical manifestations usually resolve in several months, corresponding to the half-life of thyroid-stimulating immunoglobulins.[121]

TREATMENT

The treatment for neonatal Graves' disease is 5–10 mg/kg/day of propylthiouracil in divided doses and one drop of potassium iodide or Lugol's solution, as part of a solution consisting of 126 mg of iodine per milliliter, administered every eight hours.[134] In the normal newborn, the T3 concentration abruptly increases three to six times in the first four hours of life,[135] secondary to increased T4 5'-monodeiodinating enzyme activity that converts T4 to T3.[136] Iodide therapy, including sodium ipodate, which inhibits T4 to T3 conversion, may acutely lower T4 and T3 levels in the thyrotoxic neonate.[137] In addition, propranolol (1–2 mg/kg/day) may alleviate symptoms of sympathetic stimulation. In a study by Hollingsworth and Mabry,[124] congenital hyperthyroidism persisted in 13% of 75 patients after one year. Radioiodine therapy is contraindicated in very young children, since they usually have self-limited disease.

SUMMARY

In the 1950s, radioiodine therapy was reserved for children who had persistent or recurrent hyperthyroidism following antithyroid drug therapy, surgery, or both. In addition, many patients received I-131 following toxic antithyroid drug reactions, including rash, agranulocytosis, or the onset of systemic lupus erythematosus. The only morbidity shown by the early follow-up of children treated with radioiodine was hypothyroidism, which was easily corrected with thyroid-hormone replacement.[27]

Presently, definite complications of antithyroid drug therapy and surgery exist. With antithyroid drugs, prolonged and high-dose therapy is often required for control of hyperthyroidism. Compliance may be more difficult for children with thyrotoxicosis and school performance may decline. Also, drug reactions are more common in children. Alternatively, since less thyroid surgery is now performed, fewer surgeons are able to develop and maintain their skills. Consequently, radioiodine remains optimal for treatment of childhood Graves' disease at the Cleveland Clinic.

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