Introduction

Graves' disease is a common endocrine disorder in adults. It also accounts for most cases of hyperthyroidism in children and adolescents. The incidence increases with age and peaks during adolescence. It seems that Hong Kong children have more Graves’ disease than Caucasian children with the incidence of 6.5/100000/year and 0.79 to 2/100000/year respectively, (1-6) and the incidence seems to be increasing.7 Girls are usually affected 4-5 times more frequently than boys. In a local series, the female to male ratio was up to 9.7.7

Graves’ disease is characterised by diffuse goitre, hyperthyroidism and ophthalmopathy.

In Graves’ disease there is spontaneous development of thyroid stimulating antibodies (TSAbs) which mimic TSH action, and lead to the excessive production and release of thyroid hormones. The main clinical presentations of Graves’ disease in children are similar to those in adults, including weight loss, sweatiness, palpitation, enlarged goitre and proptosis. Sometimes children might present as deterioration in school performance due to poor attention and hyperactivity. Typical clinical features and biochemical hyperthyroidism can confirm the diagnosis in most of the cases. In doubtful cases, TSAbs can be of help since it is elevated in most cases.8

Current Treatment Modalities

Medication

Antithyroid medications, surgery and radioactive iodine are the currently used modalities to manage Graves’ disease either in adults or in children. Antithyroid drugs are still the commonest used choice. It was introduced in early 1940s by Astwood. Current therapies include the thioamide derivatives: Propylthiouracil (PTU), Methimazole and Carbimazole. They reduce the thyroid hormone synthesis by inhibiting the oxidation of iodide and block the coupling of iodotyrosyl residues in thyroglobulin. Furthermore, PTU inhibits the peripheral conversion of T4 to T3. The recommended doses for PTU is 5-10 mg/kg/day, and for Carbimazole and Methimazole is 0.5-1.0 mg/kg/day. Because of its shorter half-life, PTU is better given as twice a day especially in the early treatment course. The maximal clinical responses occur after about 4-6 weeks. Before that, the signs and symptoms can be controlled by beta blockers such as propranolol. Saturated potassium iodide (Lugol’s solution) blocks the release of thyroid hormones and is usually used prior to surgery to reduce the vascularity of the thyroid gland.

The remission rate for antithyroid drugs ranged from 21-42% according to different studies.9-13 Dr. Raza and Brook in Great Ormond Street Hospital analysed 76 paediatric patients with thyrotoxicosis and showed a remission rate of 38% after drug therapy for a mean period of 3.3 years.14 Two large series involving nearly 200 children each done by Hamburger JJ et al and Glaser NS et al showed that only 20% and 30% achieved remissions lasting more than 2 years respectively.9 The remission rate had been shown to be even lower in prepubertal kids (17%) than pubertal kids (30%).15 Data from adult patients showed that the remission rate is inversely related with serum level of TSAbs and goitre size15-19. Furthermore long-term remission rate is less likely also if hyperthyroidism persists after short term (4-6 months) of drug treatment.20,21

It has been reported that 20-30% of patients will develop complications such as mildly increased liver enzymes, mild leucopenia, skin rash and agranulocytosis.9,22 Some respond well with switching to the other thioamide derivatives while others require discontinuation of all thionamide drugs.

Surgery

Surgery is an alternative, especially in those who failed the medical treatment. Subtotal thyroidectomy is the older form of therapy which has been described in 1909. Total thyroidectomy is increasingly recommended to reduce the risk of recurrent hyperthyroidism. The success rate largely depends on the skills and experience of the surgeon. Long-term cure rate after subtotal thyroidectomy is shown to be 80%. 60% of them developed hypothyroidism and 10-15% remained hyperthyroidism.22,23 Apart from pain, transient hypocalcaemia (10%), keloid formation (2.8%), permanent hypopara-thyroidism (2%) and vocal cord paralysis (2%) are the main complications associated with thyroidectomy. (24,25 incidence shown in the brackets.)

Radioactive iodine

Radioactive iodine was first introduced in 1942 at the Massachusetts General Hospital. After iodine-131 has been taken orally, most of it is localised in the thyroid gland. It is the beta radiation which destroys the follicular cells. There would be epithelial swelling,
necrosis, oedema and leukocyte infiltration of the thyroid gland following the irradiation. At the end, the thyroid gland becomes fibrotic. The dose of iodine-131 is usually from 50 to 200 microCi per gram of thyroid tissue calculated according to the formula below.

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\text{Dose (mCi)} = 50 - 200 \times \frac{\text{microCi of I-131}}{\text{gm of thyroid X estimated thyroid weight}}
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It has been suggested that doses delivering 10,000-20,000 C Gy may result in complete or partial destruction of the thyroid. Usually, a dose of 150 microCi/g of thyroid tissue yields radiation doses of 12,000 C Gy to the thyroid. Symptoms of hyperthyroidism may appear 4-10 days after iodine-131 administration because more thyroid hormone is released from degenerating follicular cells. It can be controlled by beta-blockers or Lugol’s solution.

The long term cure rate has been reported in different studies. Hyperthyroidism persists in 25-40% if a dose of 50-100 microCi/g thyroid tissue is given. It would be only 5-20% if 150-200 microCi/g thyroid tissue is administered. In the later group, 60-90% of the patients become hypothyroid. In adults, the main short term side effects which include nausea, thyroid storm and transient ophthalmopathy, another potential side effect of iodine-131 treatment in adults, however, has not been well studied or reported in paediatric age group.

In children, the risk of thyroid cancer and the other cancers are the main worries for iodine-131 therapy. It has been shown that when used diagnostically, a dose of 60 microCi (6.5 Gy) iodine-131 resulted in no increased risk of thyroid or nonthyroid cancers in adults. But there is an increased risk of thyroid neoplasia when the thyroid gland is exposed to 20-2000 cGy. Most of our experiences for radiation induced malignancy came from nuclear weapon use in world war II, radiation leakage or disaster. After the atomic bomb explosions in Japan, there is 3-10 fold increase in the rates of both benign and malignant thyroid neoplasms. And the estimated dose received from the bomb explosion is about 150 cGy for adults, about 700-1400 cGy for children. The Chernobyl disaster also resulted in an increased rate of thyroid cancer, with children under 10 years old being affected most. CTSG(Collaborative Thyrotoxicosis Study Group) has performed a large scale epidemiological survey involving more than 36,000 patients in USA. They reported that when the thyroid gland was exposed to high levels of radiation, rates of thyroid cancer were not increased. Follow up studies done by the same group of people for children showed that the incidence of thyroid neoplasms was not increased when the children were treated with high doses of iodine-131 (100-200 microCi/g). In other reports, children were followed up from less than 5 years to 15 years after iodine-131 treatment. They have not found increased risk of thyroid malignancy. There are several studies which showed that the risk of leukemia and breast cancer does not differ significantly from control populations. It has been reported that the risk of stomach cancer was slightly higher (1.14 relative risk) in adults. CTSG follow-up studies in adults showed that non-thyroid cancer mortality after iodine-131 therapy was not significantly elevated.

Up to year 2004, only four cases of thyroid malignancy in children treated with iodine-131 were reported. They were all treated with low to moderate doses of iodine-131. The use of high dose was further justified by Ron et al. It is because when a high dose is used, it totally ablates the thyroid gland. When there is no thyroid tissue remains, there would be no chance to develop thyroid cancer.

The radiation to the gonads is comparable to that from barium enema. Data showed that the incidence of congenital anomalies among the offspring of patients who had received iodine-131 did not differ from the general population.

**Summary**

Childhood Graves’ disease is a rather common disease in our locality. There are different preferences among paediatricians for the choice of treatment. Although the remission rate after antithyroid drug alone is lower when compared to the adult population, it remains the first line of treatment in almost all clinical centres. However, surgical treatment under experienced hands should be considered when medical treatment fails and the patient has a large goitre (>80g) or in those with severe thyroid eye diseases. With more and more promising long term data coming out, radioactive iodine aiming at thyroid ablation should also be one of the treatment choice in older children above 12-15 years, especially for those who could not tolerate antithyroid drugs.

**References**


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