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Treatment of hyperthyroidism in young people

Graves' disease is rare in childhood but occurs with increasing frequency into adolescence and young adult life. There is a strong familial predisposition but the precipitating cause is not known. Stimulation of the thyroid stimulating hormone (TSH) receptor by autoantibodies causes excessive thyroid hormone production and secretion, and diffuse enlargement of the thyroid. Other systems may be involved, notably the eyes with proptosis. In children the early symptoms of hyperthyroidism are non-specific and may be of gradual onset; unless there is an obvious goitre, a psychological or behavioural disorder is often suspected. Once considered, the diagnosis is readily confirmed biochemically by raised concentrations of circulating thyroid hormones and suppression of TSH.

The aim of treatment is to restore and maintain permanent euthyroidism as safely, quickly, and conveniently as possible. Especially in young people, there is no consensus on how this is best achieved and in this annotation we shall consider the options.

Initial management

The symptoms of hyperthyroidism may be distressing and can be relieved promptly to a great extent by blocking the peripheral effects of the excess thyroid hormones. A β blocking agent such as propranolol, 1 mg/kg/day in divided doses, is effective and useful to tide the patient over until the disease is controlled.

An antithyroid drug can be started at the same time. The thionamide drugs block the synthesis of thyroid hormones and also have ill understood immunosuppressive effects in Graves' disease.[1] Carbimazole is more widely used in Europe and propylthiouracil in the United States; although their actions and side effect profiles are slightly different, in practice they are interchangeable. Carbimazole 0.5 to 1.0 mg/kg/day or propylthiouracil 5 to 10 mg/kg/day in divided doses brings the hyperthyroidism of Graves' disease under control in four to eight weeks.

If there is urgent need to cure the disease as soon as possible, it is then safe to proceed to thyroidectomy but most clinicians favour a trial of medical treatment in the hope that a long term remission will occur. This entails treatment with an antithyroid drug for 18 months to two years under regular supervision. When the circulating thyroid hormones are restored to the normal range, treatment can be reduced to a single daily dose and titrated against regular thyroid function tests to maintain euthyroidism. A more convenient approach is to continue the antithyroid drug unchanged and add thyroxine 100 μg/m^2/day in a "block and replace" regimen.[2] Although there is continued exposure to the antithyroid drug in full dosage, less monitoring is needed and euthyroidism is more reliably maintained.

As with any long term treatment, many patients and their families find it remarkably difficult to remember to take the drugs regularly. Some 2–5% of patients develop a rash or other minor side effects with an antithyroid drug (usually nausea, headache, or arthralgia). If mild, the symptoms generally prove transient but if they persist the patient can be changed to the other major agent, as cross sensitivity is unusual. Serious side effects are rare, especially in young patients, but include neutropenia, agranulocytosis (which is nearly always reversible), and hepatotoxicity.[3 4] If such effects occur they usually do so in the first few months of treatment. They cannot be predicted by frequent monitoring, so patients and parents must be warned to report promptly any episode of significant fever, sore throat, or other symptoms. It is our practice to request a blood count whenever checking on thyroid function but not to order tests otherwise.

At the end of the course of medical treatment the drugs are withdrawn and the child is observed for recurrent hyperthyroidism. Relapse is more likely in children than in adults, and in those with a low body mass index and a large goitre at presentation.[5 6] The remission rate of children in the USA is reported to be 25% after each of repeated two year courses of medical treatment,[7] with remission rates around 50–65% reported in adult studies.[5 8] Of the wide variety of biochemical markers and dynamic tests that have been investigated in the hope of finding a method of predicting relapse, none has proved reliable. Hashizume and colleagues[9] reported that giving thyroxine during and after treatment with antithyroid drugs greatly improved the remission rate, perhaps by reducing antigen presentation, but recent studies have not confirmed their findings.[10 11] Relapse generally occurs within the first few months after treatment is withdrawn but can be long delayed. Patients in remission from Graves' disease are also at increased risk of becoming hypothyroid in the future, so a case can be made for continued infrequent checks on thyroid function.

If relapse occurs, there are three options: (1) to resume antithyroid drug treatment; (2) to proceed to thyroidectomy; (3) to treat the child with radioiodine. Here there is a transatlantic divide in approach. In Europe subtotal or total thyroidectomy has in general been the only option offered for definitive treatment.[2] Some American units continue to report excellent surgical results[12] but in many centres[13–15] radioiodine treatment is preferred in all age groups.

Further medical treatment

If medical treatment was well tolerated and regular supervision with thyroid function testing did not prove a burden, some patients and their families will prefer to resume antithyroid drug treatment. This could be for a further full course with the hope of remission at the end—which may be expected in up to 25% of those who have relapsed after the first course of treatment—or for a shorter time, with definitive treatment planned at a convenient moment.

Thyroidectomy

Surgery provides one definitive therapeutic option. In the past, partial thyroidectomy was favoured with the hope of leaving sufficient thyroid tissue for the child to remain euthyroid. Too conservative an operation resulted in a high rate of recurrent hyperthyroidism and too radical a thyroidectomy in hypothyroidism; either of these problems could occur unpredictably many years later.[16–18] Most surgeons now aim to render the child hypothyroid at the first operation by removing essentially all the gland. As soon as hypothyroidism is confirmed, thyroxine replacement can be started. Although compliance with replacement treatment does remain a concern, thyroxine dose adjustment through the years of growth and development is straightforward and no further changes are necessary once the patient is fully grown. Many areas in the United Kingdom now keep thyroid registers, and patients can be followed up by their general practitioners without the need for continuing hospital review.

A short hospital stay is needed and potential problems include the discomfort of the operation, the scar (which may form keloid), the small but appreciable risk of general anaesthetic and surgical complications, the specific risks of damage to the recurrent laryngeal nerves, and transient or permanent hypoparathyroidism. All these risks are reduced in the hands of expert thyroid surgeons, but such expertise is rare now that hyperthyroidism in adults is generally treated with radioiodine.

Radioiodine

This elegant form of treatment was first used 50 years ago and it has earned a remarkable safety record.[19] Radioiodine can be given with the aim of leaving the patient euthyroid, or in a higher dose with the specific intention of ablating the gland and accepting permanent hypothyroidism. Adjustment of the dose in relation to the size and uptake of the gland may result in the temporary restoration of euthyroidism but eventual progression to hypothyroidism is likely at some stage. Since a primary objective of definitive treatment is to relieve the patient of the need for long term monitoring,[17 20] many centres have now adopted the policy of ablating the thyroid and accepting the need for thyroxine replacement[21]; this is particularly appropriate in children.

There has been concern that radioiodine treatment may aggravate Graves' ophthalmopathy, and steroid cover has been recommended to prevent this complication.[22 23] In our own experience and that of others this effect has not proved a problem; eye disease need not be considered a contraindication to radioiodine treatment.[23]

In the past in many centres the use of radioiodine was restricted to patients beyond their reproductive age. With increasing confidence in its safety it is now used throughout adult life but still often denied to children and adolescents because of lingering concerns about the possibility of long term adverse effects. These concerns are entirely appropriate but after 50 years use of radioiodine, there is no evidence that they are justified.

External irradiation is well known to cause thyroid cancer[24] and carcinogenesis may also result from exposure to low doses of ^{131}I, as seen after the Chernobyl accident in the former Soviet Union.[25 26] Fortunately the risk of future thyroid cancer can be removed by ablating the gland and this provides a strong additional argument in favour of using this approach when treating young patients.[27 28] There is no evidence of an increase in the incidence of leukaemia,[29] or of reduced fertility or germ cell damage[13 30] after therapeutic radioiodine. In a large group of patients, mainly adults, who received a mean dose of 506 Mbq and were followed for a mean of 15 years there was no overall increase in cancer,[28] although a small excess of stomach cancer was observed in this one study only.

Although it is conceivable that greatly delayed adverse effects of radioiodine in young people might yet emerge, many clinicians now consider radioiodine a treatment of first choice in young patients with Graves' disease who relapse after medical treatment. Radioiodine has become an even more acceptable option since it has become apparent that lifelong thyroxine replacement is also needed after surgery.

In the past 10 years we have treated eight young patients with radioiodine. They were given an initial dose of 300 Mbq of ^{131}I with the intention of ablating the gland. Medical treatment was resumed for six months and then withdrawn. Four patients became hypothyroid after a single dose of radioiodine, but four needed a second dose. All became hypothyroid within two years. No adverse effects were observed, in particular there was no deterioration of the eye disease in any patient.

Some precautions are necessary after radioiodine treatment. Close and prolonged physical contact with others should be avoided for three days and we recommend that children stay away from school for two weeks.[31] For older girls the importance of avoiding pregnancy for least six months should be stressed.[32]

Conclusions

Once diagnosed, Graves' disease can readily be controlled, but there is no ideal form of treatment for young people. Detailed discussion of the advantages, disadvantages, and risks of each of the different forms of treatment is important so that a therapeutic plan can take into account the needs and wishes of the patient and family.

Unless there are compelling reasons to seek a rapid cure, an initial trial of medical treatment using a "block and replace" regimen for 18 to 24 months is recommended. For the majority who relapse when antithyroid drug treatment is withdrawn, medical treatment can be resumed but definitive treatment should be considered. If excellent surgical services are available, total thyroidectomy with subsequent thyroxine replacement provides a definitive solution with low risk. Treatment with radioiodine offers a simple alternative without short term risks and with an excellent long term safety record which justifies its use in young patients. Given the choice, many will opt for this form of treatment and our experience suggests that a dose of 400 mbq of ^{131}I will reduce the number of patients requiring a second dose. We recommend an approach in which the gland is ablated and the need for thyroxine replacement is accepted.

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