Juvenile thyrotoxicosis—a South Island, New Zealand experience with long-term outcome

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Abstract

**Aim** To assess our experience in the management of juvenile thyrotoxicosis.

**Method** Retrospective review of thyroid clinic records of juvenile (<16y) thyrotoxic (JT) patients treated at thyroid clinic between 1972 and 1999. Long-term (>8y) treatment outcome was assessed.

**Results** During the 28-year period, 34 JT patients were diagnosed and treated—30 girls and 4 boys, median age 13 years (5.6–15.9 y). Thirty-two children had Graves’ disease and two had toxic nodular goitre. All patients were initially treated with carbimazole, and no major adverse reactions occurred. One Graves’ disease child later developed severe ophthalmopathy. During long-term follow-up, 12 of the 32 Graves’ patients remain in remission after antithyroid drug treatment alone, but 4 of these 12 patients are currently receiving thyroxine replacement. Fifteen patients were surgically treated (median age 16 y), and six patients received radioiodine therapy (median age 18 y) including one patient with post-thyroidectomy relapse. The two patients with toxic nodular goitre were treated by thyroidectomy.

**Conclusion** Juvenile thyrotoxicosis is relatively rare and not always due to Graves’ disease. More than a third of children with Graves’ disease achieved long-term remission following antithyroid drug therapy, and remaining patients required definitive therapy.

Thyrotoxicosis is uncommon in childhood and is usually due to Graves’ disease, which is an autoimmune disease with the hyperthyroidism caused by antibodies stimulating the TSH receptor. Accurate incidence figures are sparse but a nationwide study from Denmark reported an annual incidence of 0.8 per 100,000 for children under 15 years of age, with 96% of thyrotoxicosis due to Graves’ disease. A report from Hong Kong however showed a five-fold greater thyrotoxicosis incidence in Chinese children, which may relate to environmental and genetic factors.

These incidence figures for juvenile thyrotoxicosis can be compared with the overall annual incidence for all age groups in New Zealand of 26 per 100,000, with the calculated incidence of Graves’ disease 15 per 100,000. More recent studies report increasing thyrotoxic incidence in both adults and children.

The choice of treatment for thyrotoxicosis in childhood remains the subject of much debate. In most countries, initial treatment is thionamide antithyroid medication for 1–2 years, with definitive treatment by thyroidectomy or radioiodine reserved for patients with persistent or relapsing disease, or for patients with serious adverse reactions to antithyroid drugs.
In contrast, North American clinicians are more likely to recommend relatively early treatment with radioactive iodine (RAI). There is now more than 40 years follow up of RAI-treated adolescents from the USA showing no subsequent adverse obstetric outcomes or increased cancer risk.

In this paper, a regional New Zealand experience of 34 patients with juvenile thyrotoxicosis (JT) is reported. These patients were diagnosed over a 28-year period (1972–99), and all patients have at least 8y follow-up. Infants with neonatal transient hyperthyroidism are not included in this report.

**Patients and Methods**

Thyrotoxic patients aged <16y at diagnosis between January 1972 and December 1999 were identified from Christchurch Hospital thyroid clinic records. The thyroid clinic is a regional clinic for the Canterbury and West Coast districts of the New Zealand South Island with an estimated average paediatric population (< 16y) of 100,000 using New Zealand census figures between 1971 and 1996. During this 28-year period, 34 children with thyrotoxicosis were investigated and treated at thyroid clinic; 2 of these children had been diagnosed some weeks prior to moving into our district. An additional two children seen in consultation but not managed at thyroid clinic were excluded from this report—a 3y Māori girl with diffuse thyroid hyperplasia, and an 8y girl with McCune-Albright syndrome.

The clinical diagnosis of thyrotoxicosis was confirmed by Christchurch Hospital laboratory investigations including: total serum thyroxine (T\textsubscript{4}: normal range 55–140 nmol/L), free thyroxine index (FT\textsubscript{4}I: normal range 55–160) and total serum triiodothyronine (T\textsubscript{3}: normal range 1.2–2.8 nmol/L) by radioimmunoassay and since 1987 by sensitive thyrotropin (TSH) by IRMA, 99m Tc pertechnetate thyroid scintiscans using a gamma camera, and thyroid antibodies (microsomal (TPO) and thyroglobulin) were measured by haemagglutination (Fujizoki kit).

**Results**

**Investigations**

Before treatment, all patients had elevated thyroid hormone levels and those diagnosed since 1987 had TSH suppressed to <0.1 mU/L. The median total T\textsubscript{4} was 247 (range 147–>350), FT\textsubscript{4}I 524 (177–885), and total serum T\textsubscript{3} 6.5 (3.7–>16).

Christchurch Hospital laboratory pre-treatment results were available for 29/34 patients, and the remaining patients had thyroid function tests from private laboratories.

Thyroid scintiscans were available for 32 of the 34 children and one patient had a thyroid ultrasound. Thirty two of the 34 patients had diffuse thyroid hyperplasia consistent with Graves’ disease, and in 2 girls the scintiscan showed toxic nodular goitre—a large autonomous nodule, and an ‘autonomous lobe with non-homogeneous tracer uptake’. Thyroid antibody testing in patients with diffuse hyperplasia showed 25/32 (78%) to have positive anti-microsomal (TPO) antibody results.

**Clinical**

**Age and gender distribution**—The 34 JT children were Caucasian, except for one Chinese girl with Graves’ disease. The age at presentation ranged from 5 years 7 months to 15 years 10 months (median age 13y), with only 5 patients less than 10y at diagnosis. There were 30 girls and four boys giving a female: male ratio of 7.5:1. In
the 28y period there was on average one new thyrotoxic child per year for the estimated juvenile population of 100,000.

Children with previously diagnosed medical conditions included: one boy with Down’s syndrome, one girl with Type 1 diabetes, a girl with McCune-Albright syndrome (‘toxic nodular lobe’), one boy with deaf mutism secondary to congenital rubella and one girl with surgically treated cardiac septal defect.

**Clinical features**—Emotional lability was the most prevalent symptom with other common symptoms including lethargy, heat intolerance, increase in appetite, weight loss, and tremor. In some patients the emotional changes caused problems with schooling. From case records it was difficult to assess the duration of symptoms but in some children symptoms had been present for at least 12 months. All children had palpable thyroid glands with 5 of the 32 with Graves’ disease having large diffuse goitres. One child presented with diabetic ketoacidosis and concurrent new Graves’ disease.

Fifty percent of the 32 Graves’ disease patients had thyroid eye signs—mild exophthalmos in 25% and lid retraction in 25%. The eye symptoms at presentation were mild, with no patient needing ophthalmological referral. However an 8.5y girl with initially mild exophthalmos developed severe exophthalmos with bilateral orbital nerve compression 4 years later. High-dose oral prednisone 60mg/d successfully preserved vision with the prednisone gradually withdrawn over 3 months, and total thyroidectomy was then performed. The exophthalmos was treated surgically by bilateral orbital decompression 5 years later (patient aged 18y) with an excellent cosmetic outcome.

The two girls with toxic nodular goitre were both diagnosed when seen for other medical problems—the first aged 15y during hospitalisation with asthma when an asymmetric goitre with tracheal deviation was noted and scintiscanning showed a toxic nodule; the second was diagnosed during follow up for McCune-Albright syndrome.

**Family history**—A family history of thyroid disease was initially noted in 44% of the total JT patient group: the 2 girls with toxic nodular goitre both had a family history of goitre, and 7 of the 32 children with Graves’ disease had a family history of thyrotoxicosis, including 2 mothers (one had thyroidectomy for JT) and 1 father.

Three mothers developed thyrotoxicosis some years after their children were treated—including a mother with thyrotoxicosis facticia, which was diagnosed during hospitalisation for medication-resistant thyrotoxicosis, when her son’s thyroxine bottle was discovered in her toilet bag. This occurred 10 years after her son’s thyroidectomy and she was noted to have an abnormally close mother-son relationship.

**Medical treatment**

All patients were initially treated with carbimazole with the dosage tailored to body weight and severity of thyrotoxicosis assessed by FT₄I and T₃ levels. Most patients were initially treated with carbimazole 10–20 mg daily (range: 5–45 mg) with tablets taken twice daily until euthyroidism was obtained—most children were euthyroid after 4–8 weeks treatment.
The carbimazole dosage was then reduced and changed to once daily administration. Three Graves’ patients were later prescribed thyroxine with carbimazole to avoid fluctuations in thyroid function, with a subsequent reduction in need for venepunctures. Four patients were switched from carbimazole to propylthiouracil because of rash or urticaria. No patient suffered a serious adverse reaction to antithyroid medication.

The initial treatment plan for the 32 patients with juvenile Graves’ disease was to continue antithyroid drug (ATD) treatment for 12–24 months in the hope that the underlying autoimmune disease process would remit. However 5 patients remained inadequately controlled after 6–9 months’ treatment and early definitive treatment with surgery or radioiodine was recommended. The subsequent management of the Graves’ patients is summarised in Figure 1.

**Figure 1. Treatment outcome for 32 children with Graves’ disease**

The majority of Graves’ disease patients completed a satisfactory course of ATD, and were given a ‘trial off’ medication when they had been euthyroid for some months on low dose carbimazole (2.5–5 mg daily). The median duration of medication was 18 months. Clinical and biochemical assessments were made 6 weeks after cessation of treatment, 6 months later then annually. The thyrotoxicosis relapsed in many patients—mostly within 12 months of stopping medication, and only one patient relapsed later (after 3.5y).
All patients were followed into adulthood, with only one patient lost to follow up (after 8y). Twelve of the 32 Graves’ patients (38%) have achieved long-term remission following ATD alone—7 after one course, and 5 after repeated ATD courses. These 12 patients include 2 of the 5 children <10y at diagnosis. The median follow-up of the patients in remission is 19y (range: 8–36y).

At most recent follow up, four of the 12 patients in remission have been commenced on thyroxine replacement therapy many years after the initial diagnosis of thyrotoxicosis—8, 16, 17, and 22y later. Two patients have subsequently developed associated autoimmune diseases—one type 1 diabetes after three years (aged 8.5y), and one coeliac disease after 25 years (aged 34y).

**Surgical treatment**

Fifteen Graves’ disease patients (14 female and 1 male) were treated by thyroidectomy following failed medical treatment, and both girls with toxic nodular goitre were also surgically treated. Eight Graves’ patients had early thyroidectomy, as did seven further patients following relapse after courses of ATD (See Figure 1). The median interval between diagnosis and thyroidectomy was 3y (range: 0.5–5y) and the median age at time of thyroidectomy was 16y (range: 8–20y, with only one child < 12y).

In earlier years the thyroidectomies were performed by senior general surgeons, and more recently by an endocrine surgeon with specialist thyroidectomy training. Most patients were treated by bilateral subtotal thyroidectomy, but four were treated by total thyroidectomy. The weight of the thyroidectomy specimens was >60 g in 7 of the 15, including 2 very large goitres weighing 154 and 373 g.

There were no major postoperative complications, with no recurrent laryngeal nerve injuries, but two of the earlier patients have needed long-term treatment for hypoparathyroidism. The median follow-up period post-thyroidectomy was 17y (5–26y) with all subtotal thyroidectomy patients having more than 10y follow up. Thyroidectomy has successfully treated all but 1 of the 15 patients—this patient, treated by less radical thyroidectomy, relapsed 3 years later and was treated with $^{131}$I.

A second subtotal thyroidectomy patient had postpartum thyrotoxicosis 12 years after surgery and required 6 months’ carbimazole treatment. Currently 5/11 subtotal thyroidectomy patients remain euthyroid without medication, and the remaining surgically treated patients are taking thyroxine replacement.

The two girls with toxic nodular goitre had persistent thyrotoxicosis, and were treated by hemithyroidectomy. The initial (1986) pathology report for the toxic nodule patient was a minimally invasive follicular carcinoma, but on more recent review it has been reclassified as a benign follicular adenoma. The McCune-Albright syndrome patient had very mild thyrotoxicosis, and the surgical specimen was a benign multinodular lobe with cystic changes.

**Radioactive iodine (RAI) treatment**

Six Graves’ disease patients were treated with radioiodine ($^{131}$I)—the 16-year-old deaf-mute boy after 11 months of suboptimal medical control, 4 patients relapsing following courses of carbimazole, and the post-thyroidectomy relapse patient (noted
above). The median interval between initial diagnosis and RAI was 9 years (range: 0.9–11y), and the median age at time of RAI was 18 y (range: 16–23y). The $^{131}$I dosage was adjusted for goitre size and severity of thyrotoxicosis—the median initial $^{131}$I dose was 8mCi (296MBq) with range 5–10mCi (175–370MBq). Two patients needed a second $^{131}$I treatment (total dosages 13 and 20mCi). Five of the six RAI patients became hypothyroid within 2 years of treatment, and one patient remains euthyroid 15y later.

**Discussion**

The present series of 34 children with thyrotoxicosis was accumulated over 28 years with an average of one new thyrotoxic child per year. Our population is largely Caucasian and our incidence is consistent with the nationwide Danish figures. In older reports it was estimated that up to 5% of thyrotoxic patients may be in the paediatric age group, but in our experience around 1% of thyrotoxic patients initially present when <16 years of age. This 1% figure has been calculated from our recent thyroid clinic database—over a 12y period, 11 children (<16y) were treated from a total of 1119 new Graves’ patients.

Most children in our series were female, and in the 12–16y age group which is comparable to other reports. A family history of thyrotoxicosis was noted in 20% of our juvenile Graves’ patients, which is the same as found in our adult patients. However the genetic effect seems stronger in our children with a higher proportion of first degree relatives—especially mothers. The mother with thyrotoxicosis facticia has been our only patient with this disorder.

Graves’ ophthalmopathy infrequently causes clinical problems in children with Graves’ disease. Recent reviews however suggest that the incidence of ophthalmopathy in juvenile Graves’ is similar to that seen in adults but it is less severe and more likely to remit completely. Our patient with optic nerve compression was an exceptional patient and her exophthalmos led to significant psychological and schooling problems.

Graves’ disease patients are more prone to other autoimmune diseases and three of our 32 juvenile Graves’ patients developed Type 1 diabetes during childhood. This association with diabetes has been previously documented. No other autoimmune diseases developed in our children, but during long-term follow-up one patient in her fourth decade was diagnosed with coeliac disease.

Our conservative management plan for juvenile Graves’ disease is similar to that followed in most European centres. All patients were initially treated with carbimazole with the dosage titrated to keep thyroid hormone levels in the normal range. However in some centres all JT patients are treated with carbimazole plus thyroxine therapy (‘block and replace’) which may have the advantage of a reduced need for follow-up venesections.

A small number of our patients suffered antithyroid drug side effects, but no major adverse reactions occurred. Some earlier series reported that children were more prone to serious adverse reactions; up to 14% of children in one series. This was possibly due to the greater use of propylthiouracil in the past.
In our study more than a third of juvenile Graves’ patients remain in remission following ATD therapy alone. This remission rate is similar to that reported in a recent similar series with long-term follow-up but comparison with some larger series is difficult because they include older adolescents aged 16–20y. Some studies have shown that younger children may be less likely to achieve remission, but this was not noted in our small series.

The optimal duration of ATD is uncertain but it is generally agreed that children need a longer course of treatment than in adults. Some authors have advocated very prolonged ATD in children and have claimed 25% remission for every 2 years’ treatment, but the predictions have not been confirmed by subsequent reports.

Long term follow-up of our juvenile Graves’ patients who remitted after ATD therapy has unexpectedly shown that four of the 12 patients are now on thyroxine replacement therapy. This spontaneous swing to hypothyroidism has been noted in some previous JT series, but this has not been emphasised. In adult Graves’ patients the evolution to spontaneous hypothyroidism is better documented, occurring in about 10% of patients, and is thought to be due to either destructive autoimmune thyroiditis or TSH receptor blocking antibodies.

The choice of definitive therapy for Graves’ patients remains the subject of much debate, and recent reviews have advanced strong opposing arguments for the more liberal use of radioiodine or thyroidectomy. It has been our practice to persevere with ATD medication until the mid-teenage years with the patient contributing to discussions. The choice of definitive treatment should be individualised with surgery recommended for patients with large goitres.

Almost half of our juvenile Graves’ patients have been treated by thyroidectomy. The bias towards surgery was in part due to physician preference, but many families were fearful of radiation—fears heightened by the New Zealand Government’s adoption of an ‘anti-nuclear’ stance in 1985.

The surgical management of Graves’ disease has changed since the 1970s, when the aim was to achieve euthyroidism, to more radical resection to minimise post-thyroidectomy relapse. Patients should be referred to a surgeon with specialist training to minimise surgical complications, and the risks of hypoparathyroidism or recurrent nerve injury should be around 2%.

A minority of our juvenile Graves’ patients have been treated with radioiodine. In earlier years conservative doses were prescribed, but recently higher doses have been used to reduce the need for retreatment. Some North American units have treated very young children with high-dose radioiodine to ablate all thyroid tissue but this is associated with a higher total body radiation dose.

Currently most units avoid radioiodine in children as the thyroid in young children is more sensitive to radiation. The increase in thyroid cancer incidence following the Chernobyl disaster has been most marked in children <10y at the time of radioiodine exposure.

Our series included two children with toxic nodular goitre. In many of the published series there has been no thyroid imaging or measurement of TSH receptor binding antibodies, and it seems likely that not all included cases had Graves’ disease. In our
series, one patient had a toxic autonomous nodule, which is 3% of our cohort and similar to the Danish study.\(^1\)

The treatment of choice for toxic nodules under the age of 20y is hemithyroidectomy to provide histology, and radioiodine is best avoided as many patients are left with a residual nodule, and there may be concerns about subsequent new nodules many years later.\(^2\) Toxic multinodular goitre is rare in the paediatric age group and is usually found in the context of McCune-Albright syndrome due to activating mutations.\(^2\)\(^6\), \(^2\)\(^7\)

This report describes our experience in the management of children with thyrotoxicosis. The relative rarity of this disorder (incidence approximately 1/100,000 children) explains the small size of our series. After long-term follow-up more than one-third of our Graves’ patients remain in remission following antithyroid medication, and remaining patients had ablative treatment.

Better documentation of treatment outcomes requires prospective multicentre studies of larger cohorts.\(^2\)\(^8\) Future advances in genetic and immunological research may lead to new treatments for Graves’ disease and reduce the need for thyroid ablation.

**Addendum**

Recently 1 of the 12 Graves’ patients in long-term remission after ATD treatment has been diagnosed with recurrent thyrotoxicosis—after a 16y remission.

**Competing interests:** None known (this research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector).

**Acknowledgments:** We thank Professor EA Espiner (endocrinologist) as well as RT Caseley and the late GD Abbott (paediatricians). We are also grateful to Sue Moran for data collection and Bridget Ginley for manuscript preparation.

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