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Review Article

Managing paediatric Graves' disease

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ABSTRACT

Graves' disease is the most common cause of hyperthyroidism in children. Anti-thyroid drug treatment with carbimazole or its active metabolite methimazole is offered as first line initial treatment but it induces remission in only 30%of children. Propylthiouracil is not recommended in children because of its association with severe hepatic toxicity. For those who relapse after ATD, radioactive iodine can be offered as definitive therapy except in cases with severe Graves' ophthalmopathy or patients with large goitre who are the candidates for surgery. Total (or near total) thyroidectomy is the surgical procedure of choice for treating paediatric patients with Graves' disease as it reduces the risk of recurrent hyperthyroidism which was seen in patients undergoing subtotal or partial thyroidectomy.

Keywords: Hyperthyroidism, Anti-thyroid drugs, Radioactive iodine, Thyroidectomy

INTRODUCTION

Graves' disease is the most common cause of hyperthyroidism in children, adolescents and adults.[1] Graves 'disease accounts for 10-15% of all childhood thyroid diseases. As in adults, Graves' disease occurs more frequently in female subjects. It may occur at any age during childhood, but it increases in frequency with age[.3.] The incidence is 0.1 per 100,000 person per year in young children to 3 per 100,000 person per year in adolescents.[3] Graves' disease occur more frequently in children who are suffering from other autoimmune diseases like rheumatoid arthritis, SLE, Pernicious anaemia and type 1 diabetes.[4]

CAUSES OF HYPERTHYROIDISM IN CHILDREN

Primary hyperthyroidism

- Graves` disease
- Toxic adenoma
- Autoimmune neonatal hyperthyroidism(passage of maternal TRAbs from placenta)
- Iodine induced hyperthyroidism (iodine, radio contrast agents)
- Activating mutations of TSH receptor gene.
- Somatic activating mutation of Gsα (McCune Albright syndrome)

Secondary hyperthyroidism

- TSH secreting pituitary adenoma
- Thyroid hormone resistance syndrome

Thyrotoxicosis without hyperthyroidism

- Sub-acute thyroiditis
- Silent thyroiditis
- Thyrotoxicosis facticia (ingestion of excess thyroid hormone or tissue)

PATHOPHYSIOLOGY OF GRAVES' DISEASE

A complex interaction of genetic, environmental and immune factors play an important role in the

pathogenesis of Graves' disease. Polymorphism in human leucocytes antigen HLA-DR, cytotoxic T lymphocyte antigen 4 (CLTA 4) and lymphoid protein tyrosine phosphatise (PTPN22 - a T cell regulatory gene) contribute to increased susceptibility to Graves`disease.[5]

The thyroid gland typically shows diffuse infiltration of lymphocytes with T lymphocyte abnormality .Activated T cell invade the thyroid ,produce local inflammation by producing and releasing cytokines. There is over production of antibodies in Graves' disease, the predominant antibodies are directed against the TSH R (TRAb). The TRAb's are heterogeneous and can either stimulate or inhibit thyroid hormone secretion.[6] The hyperthyroidism in Graves' disease is caused by TSI (Thyroid stimulating immunoglobulin) which binds to stimulate the TSH receptor on the cell membrane of thyroid gland leading onto increased vascularity and growth of follicular cells which in turn causes excessive synthesis and secretion of thyroid hormones.

CLINICAL PRESENTATION OF GRAVES`DISEASE IN CHILDREN

The signs and symptoms of Graves' disease are similar to those seen in adults. The symptoms develop insidiously and sometimes the diagnosis may be delayed .Initially, it may present with increased appetite, fatigability, mood changes, emotional labiality and attention deficit hyperactivity disorder. Prepubertal children commonly present with poor weight gain and frequent defecation whereas adolescent children present with fatigability, tremulousness, heat intolerance and goitre.

SIGNS AND SYMPTOMS OF GRAVES' DISEASE

Table 1: Signs and symptoms of Graves' disease.

Signs	Symptoms
• Goitre • Tachycardia • Tremors • Myopathy • Moist skin • Ophthalmopathy (proptosis) - Lid lag - Lid retraction	• Increased appetite with weight loss • Heat intolerance • Palpitations • Irritability • Increased frequency of stools • Hyperactivity • Decremental school performance

LABORATORY EVALUATION

The initial test advised is TSH level and if, it is found to be suppressed we do FT_3 and FT_4 levels. With this workup, if the biochemical data reveals presence of hyperthyroidism, we do a radio iodine uptake and scan. RAIU is useful to distinguish between sub-acute thyroiditis, toxic nodule and toxic multi nodular goitre. A thyroid ultrasound and colour Doppler is also performed to determine whether a nodule is present. If present, the same can be subjected to FNAC. In adult literature, cases of Graves' disease with co-existing differentiated thyroid cancer have been reported. At our centre, we came across two cases of papillary thyroid cancer presenting with Graves' disease. Niedziela M has also reported a case of thyroid cancer in a fourteen year boy with Graves`disease.[7]

TREATMENT OPTIONS

As in adults, the three conventional methods of treatment for childhood Graves' disease are

1. Antithyroid drugs
2. Radioactive iodine
3. Surgery (thyroidectomy)

All though ATD are associated with side effects and a very high relapse rate, they are still considered the first line of therapy for childhood Graves' disease.[8-10] Radioactive iodine therapy is offered in cases which relapse after ATD administration.

There is an on-going debate world over as to which is the most suitable mode of therapy for Graves' disease in paediatric patients.[9] ATD Which are commonly used as first line therapy cause long term remission in 20-30 %cases of pubertal age group and 15% of prepubertal age group.[9] Therefore either surgery or radioactive iodine is required for definitive treatment of most paediatric Graves' disease patients.

ANTI-THYROID DRUGS

Anti-thyroid drug therapy is offered as the initial treatment for hyperthyroidism in children and adolescents at our centre. Apart from this, patients with relapse who ultimately have to be given definitive therapy (in form of surgery/RAI) are also initially stabilised on ATD.

The most commonly used ATD are:

- Carbimazole or its active metabolite methimazole
- Prothyl thio uracil

These drugs inhibit the thyroid hormone synthesis by inhibiting the function of thyroid peroxidise and thereby reducing iodination of tyrosine residues in thyroglobulin.[10]

Carbimazole is administered in the dosage of 0.5-0.7mg/kg/day and methimazole is given in the dosage of 0.1 -1.0 mg/kg/day. With the recent association of PTU with hepatic failure, the US FDA has issued a black box warning against the drug. So it is not the first choice anti-thyroid medications for children in our centre. A beta blocker such as propranolol is added (except where it is contraindicated as in bronchial asthma, congestive

cardiac failure etc.) to provide relief to symptoms of palpitations and tremulousness.

Follow up is done with TFT at six weeks after initiation of therapy and repeated after two or three months once appropriate dose has been determined. The appropriate dose is one that achieves and maintains euthyroid state which is important for the well-being of the patient. TSH may remain suppressed for months and so dose adjustments are made on the basis of FT3 and FT4 levels.

The common side effects of anti-thyroid drugs are rash, urticaria, arthralgia, fever (1-5%). Major but rare side effects include agranulocytosis (≤ 1%), hepatitis and SLE like syndrome. At our centre we warn our patients in writing about the possible symptoms of agranulocytosis like fever, sore throat or mouth ulcer. Once these symptoms develop the patient should stop the anti-thyroid drugs and do a total leucocytes count to confirm agranulocytosis. It is not a usual practice to monitor blood counts at regular intervals because the onset of agranulocytosis is idiosyncratic. Growing children should also be treated with calcium and vitamin D supplementation as Graves' disease is associated with negative calcium metabolism.

A recent (2013) retrospective study performed by Ohye H et al. evaluated the outcome and side effects of long term anti-thyroid medication in children. The overall incidence of side effects associated with methimazole and propylthiouracil were 21.4% and 18.8% respectively. The cumulative remission rate increased with the duration of ATD until five years and the authors concluded that long term ATD treatment can be a useful treatment option for Graves' disease in children.[11]

Another study by Leger J et al. suggests that children with Graves ' disease, who do not experience adverse effects with anti-thyroid drugs and are compliant, can be offered medical treatment with carbimazole or methimazole up to 8-10 years before a definitive treatment can be planned.[12]

RADIOACTINE IODINE TREATMENT

Radioactive iodine was introduced for the treatment of Graves' disease more than fifty years ago and at present it is the treatment of choice for adult Graves' disease in our country and across the globe. It is safe, inexpensive, effective and has relatively fewer side effects.

Radioactive iodine causes progressive destruction of thyroid cells and thereby decreases the synthesis of thyroid hormones. In North America it is offered as the first line therapy for treatment for Graves' disease. In the United States, approximately 70% of patients are treated with RAI at the initial presentation and an additional fraction of arguably 10-15% treated with RAI after failure of anti-thyroid drugs or surgery.[13] These days younger patients are also offered radioactive iodine earlier in the course of their disease because evidence suggests that onset of Graves' disease at a younger age is associated with increased likelihood of relapse after anti thyroid medication. Even in children, radioactive iodine is very effective and most children are successfully treated with a single oral dose.[14]

Hypothyroidism inevitably occurs following after radioactive iodine administration in dosage ranging between 185MBq (5 mci) to 555MBq (15 mci) which is managed by lifelong levothyroxine replacement therapy.[15] Few patients who show evidence of persistent thyrotoxicosis six months after radioactive iodine may be considered for a second dose of I^{131}.

Some patients prefer radioactive iodine therapy over thyroidectomy in order to avoid the cosmetically disfiguring surgical scar. The only long term concern in administering radioactive iodine in children is the potential risk of developing secondary malignancy. In a study performed by Read et al where they followed up paediatric patients for thirty six years after radioactive treatment and found no evidence of increase in malignancy above the general population.[16]

There has been one case report of paediatric patient developing thyroid storm after administration of I^{131} which the authors attribute to the withdrawal of anti-thyroid drugs prior to giving radioactive iodine.[17]

SURGICAL TREATMENT

Total (or near total thyroidectomy) is the surgical procedure of choice for treating paediatric Graves' disease patients as it reduces the risk of recurrent hyperthyroidism which was seen in patients undergoing subtotal or partial thyroidectomy.[18] To reduce the risk of anaesthesia, all patients should be restored to euthyroid state by using anti thyroid medication. A seven to ten day course of potassium iodide can also be initiated before surgery to reduce the vascularity of the gland.

The major complications following surgery are hypothyroidism, vocal cord palsy due to damage to recurrent laryngeal nerve, laryngeal oedema and bleeding. The risk of developing these complications are minimal if the procedure is performed by an experienced surgeon. Surgery should be performed in a hospital capable of providing good post-operative care to the children. Availability of paediatric anaesthetist in such places is highly recommended.

Surgery is considered as a definitive option for children also have a large goitre and also those suffering from ophthalmopathy. Clear indications for surgery are suspected or confirmed malignancy, co-existing pathology that demands surgical treatment, large goitre, goitre with signs and symptoms of compression and active ophthalmopathy[19] (Table 2).

Table 2: Indications of surgery in childhood Graves' disease.

Indications
• Confirmed or suspected malignancy. • Huge goitre size (volume >80 ml). • Severe ophthalmopathy. • Retrosternal goitre.

FOLLOW UP AND LONG TERM TREATMENT OUTCOME OF PEDRIATRIC PATIENTS WITH GRAVES' DISEASE: APPROPRIATE TIMING FOR DEFINITIVE TREATMENT

Once a paediatric patient is diagnosed with Graves' disease, the most reasonable practise is to start anti thyroid drugs. Starting ATD immediately at the diagnosis gives prompt relief to the patients by decreasing the severity of symptoms in a relatively short period of time .ATD used should be carbimazole or its active metabolite methimazole. They have low incidence of side effects and are generally well tolerated. Considering the risk of hepatotoxicity with the use of PTU in children it should be avoided all together.[20,21]

Radioactive iodine therapy may be required in young children in situations like if a child is allergic to ATD or is not a fit candidate for surgery. When surgery is offered as a definitive treatment option for Graves' disease, total thyroidectomy should be performed to reduce the risk of relapse. Surgery should be performed by an experienced endocrine surgeon. whenever a definitive treatment option is planned, long term follow up is needed which will include physical examination of the gland and measurement of thyroid hormone levels to detect the development of hypothyroidism and its treatment with levothyroxine replacement.

CONCLUSION

Choosing a definitive treatment option for Graves' disease in children should be a combined decision of the treating physician and the family of the patient. All the risk and benefits of the treatment should be correctly informed to the patients and his/her family and a consensus decision for treatment should emerge out of it. At present, all the available and above mentioned treatment modalities aim at decreasing the thyroid hormone synthesis but none is aimed at modulating the underlying autoimmune disease process. Future efforts need to be focussed on development of newer modalities of treatment which aim at modulating the underlying disease process rather than just stopping thyroid hormone overproduction.

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REFERENCES

1. Rivkees SA. Pediatric Graves' disease: controversies in management. Horm Res Paediatr. 2010;74:305-11.
2. Bauer AJ. Approach to the pediatric patientwith Graves' disease: when is definitive therapy warranted. Clin Endocrinol Metab. 2011;96(3):580-8.
3. LovardL, Ranlov L, Perrild H, Anderson O, Jacobsen BB. Incidence of juvenile thyrotoxicosis in Denmark 1982-1988. A Nationwide study. Eur J Endocrinol. 1994;130:565-8.
4. Mizokami T, Yamauchi A, Sato Y, Toyonaga M, Imoto H, Kojima H, Saji H, Nunoi K. Simultaneous occurrence of type 1 diabetes mellitus and Graves' disease: a report of two cases and review of literature. Intern Med. 2013;52(22):2537-43.
5. BrixTH, Kyvik KO, Hegedus L. What is the evidence of genetic factors in the etiology of Graves' disease: a brief review. Thyroid. 1998;8:729-34.
6. BrixTH, Kyvik KO, Hegedus L, Christensen K. Evidence for a major role of heredity in Graves' disease: a population based study of two Danish twin cohorts. J Clin Endocrinol Metab. 2001;86:930-4.
7. Niedziela M, Korman E. Thyroid carcinoma in a fourteen year boy with Graves' disease. Med Pediatr Oncol. 2002;38;325-9.
8. Cooper DS. Anti-thyroid drugs. N Engl J Med. 2005;352:905-17.
9. Kaguelidou F, Alberti C, Castanet M, Guittany M A, Czernichow P, Leger J. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of anti-thyroid drug treatment. J Clin Endocrinol Metab. 2008;93:3817-26.
10. Cooper DS. Anti-thyroid drugs in the management of patients with Graves' disease: an evidence based approach to therapeutic controversies. J Clin Endocrinol Metab. 2003;88:3474-81.
11. Ohye H, Minagawa A, Noh JY, Mukasa K, Kunii Y, Watanabe N. Anti-thyroid drug treatment for Graves' disease in children: a long term retrospective study at a single institution. Thyroid. 2014 Feb;24(2):200-7.
12. Leger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C. Positive impact of long term anti-thyroid drug treatment on the outcome of children with Graves' disease: national long term cohort study. J Clin Endocrinol Metab. 2012;97:110-9.
13. Wartofsky L. Radio iodine therapy for Graves' disease: case selection and restrictions recommended to patients in North America. Thyroid 1997;7(2);213-6.
14. Allahahadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for Graves' hyperthyroidism. J Clin Endocrinol Metab. 2000;85:1038-42.

15. Leger J, Carel JC. Hyperthyroidism in childhood: causes, when and how to treat. J Clin Res Pediatr Endocrinol. 2013;5(Suppl 1):50-6.
16. Read JR, Tansey MJ, Menday Y. A 36 year retrospective analysis of the efficacy and safety of radioactive iodine in treating young Graves' disease patients. J Clin Endocrinol Metab. 2004;89:4229-33.
17. Kadmon PM, Noto RB, Bone CM, Goodwin G, Gruppuso PA. Thyroid storm in a child following radioactive iodine therapy: a consequence of RAI versus withdrawal of anti-thyroid medication. J Clin Endocrinol Metab. 2001;86:1865-7.
18. Lee JA, Grumbach MM, Clark OH. The optimal treatment of paediatric Graves' disease is surgery. J Clin Endocrinol Metab. 2007;92:801-3.
19. Jukic T, Slancic J, Petri CV, Kusic Z. Radioactive iodine versus surgery in the treatment of Graves' hyperthyroidism. Lijec Viesn. 2010;132:355-60.
20. Rivkess SA, Mattison DR. Ending propyl thiouracil-induced liver failure in children. N Engl J Med. 2009;360:1584-7.
21. Rivkess SA. 63 years and 715 days to the boxed warning: unmasking of the propyl thiouracil problem. Int J Pediatr Endocrinol. 2010;2010:PMC2913555.

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