Review article

http://dx.doi.org/10.6065/apem.2014.19.3.122
Ann Pediatr Endocrinol Metab 2014;19:122-126

Annals of Pediatric Endocrinology & Metabolism
apem

The treatment of Graves' disease in children and adolescents

Hae Sang Lee, MD,
Jin Soon Hwang, MD, PhD

Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, Suwon, Korea

Graves' disease (GD) accounts for 10%–15% of thyroid disorders in children and adolescents. The use of antithyroid drugs as the initial treatment option in GD is well accepted. An average two years remission is achieved in about 30% of children treated with antithyroid drugs. However, the optimal treatment duration and the predictive marker of remission after antithyroid drug therapy are still controversial. Additionally, ^{131}I therapy and surgery are considered the option for treatment in children and adolescents with GD. We review the treatment options for pediatric GD and the possible determinants of remission and relapse on antithyroid drug treatment in children and adolescents.

Keywords: Hyperthyroidism, Graves' disease, Antithyroid agents

Introduction

Graves' disease (GD) occurs less frequently in childhood than in adults, affecting from 0.1 per 100,000 children and 3.0 per 100,000 adolescents per year. However, it is the most common cause of hyperthyroidism in children and adolescents[1,2]. GD is an autoimmune disease associated with thyroid-stimulating hormone (TSH) receptor-stimulating antibodies that stimulate the synthesis and secretion of thyroid hormone[3]. Treatment for GD aims at restoring normal thyroid function and avoiding the recurrence of hyperthyroidism. Three treatment options are currently available for the management of pediatric Graves' disease. These include medication, surgery and radioiodine[4]. Most patients are initially treated with antithyroid drugs (ATD). Subtotoal or near total thyroidectomy and radioiodine therapy (RAI) are considered on relapse. However, the optimal treatment option for GD in children and adolescents remains an important controversy because of the high rate of relapse when ATD are used, and the duration of ATD therapy for the induction of remission has yet to be established.

This review focuses on the treatment of GD, and the reliable predictors of remission and relapse on ATD treatment in children and adolescents.

Antithyroid drugs

Thionamide derivatives such as propylthiouracil (PTU), methimazole (MMI), and carbimazole are commonly used as initial ATD therapy. These drugs inhibit thyroid hormone synthesis by disturbing the thyroid peroxidase-mediated iodination of tyrosine residues in thyroglobulin[5]. ATD may also have an immunosuppressive effect on the thyroid gland, including apoptosis of intrathyroidal lymphocytes, although conflicting data is reported[6,7].

PTU and MMI are former long standing first-line treat-ments in children and adolescents. PTU, unlike MMI additionally inhibits peripheral conversion of thyroxine (T4) to triiodothyronine (T3). However, PTU can cause severe, rapid onset and progressive hepatotoxicity, requiring liver transplantation[8,9]. MMI may be taken once daily because of its

Received: 15 September, 2014
Accepted: 17 September, 2014

Address for correspondence:
Jin Soon Hwang, MD, PhD
Department of Pediatrics, Ajou University Hospital, Ajou University School of Medicine, 164 World cup-ro, Yeongtong-gu, Suwon 443-380, Korea
Tel: +82-31-219-5166
Fax: +82-31-219-5169
E-mail: pedhwang@ajou.ac.kr

ISSN: 2287-1012(Print)
ISSN: 2287-1292(Online)

longer half-life and 10 to 20 folds higher potency than PTU[5]. Furthermore, MMI improves serum concentrations of T4 and T3 more rapidly. Some studies report that MMI has greater efficacy and fewer side effects[5,10]. The current American Thyroid Association (ATA) and American Association of Clinical Endocrinologists (AACE) guidelines recommend that MMI should be used in every pediatric patient as the initial treatment choice for hyperthyroidism[11].

Major adverse effects of ATD include agranulocytosis (a granulocyte count <500 cells/cm^3), mild leukopenia, rash, hepatitis, jaundice, and urticaria[12]. Aganulocytosis is the most severe side effect of ATD and occurs in 0.2%–0.5% of treated patients[13,14]. However, most of the side effects are rare and many are minor and transient.

The usual starting dose of MMI is 0.2 to 0.5 mg/kg/day, with a range from 0.1 to 1 mg/kg/day[4]. Improvement of most symptoms generally occurs within 3 to 4 weeks after the initiation of ATD[5]. The dose of ATD is required to be adjusted to normalize the serum levels of T4 and T3 and eventually to maintain normal serum thyrotropin levels. Most cases are usually managed with 5 to 10 mg of MMI. Follow-up thyroid function test should be assessed every 2 to 4 weeks upon ATD initiation, until patients are euthyroid. Thereafter, follow-up intervals can be increased to every 3 to 6 months. The two possible ATD therapeutic approaches are "the titration method" and "the block and replace method"[15]. The titration method represents an initial high dose of MMI (e.g., 20–30 mg) followed by a gradually reduction, enough to maintain normal thyroid hormone levels. On the other hand, the block and replace method consists of continuous higher doses of ATD administered combined with levothyroxine at sufficient doses to maintain euthryoid levels. Higher doses of ATD possibly reduce the autoimmunity and help in the remission of GD. However, on systematic review, the block and replace method has a higher rate of side effects and was not advantageous, as compared to the titration method[16,17]. Recent ATA and AACE guidelines therefore recommend that the block and replace method should be avoided[11].

Remission rate and optimal duration of ATD treatment in children and adolescents

The appropriate duration of ATD therapy in children and adolescents remains controversial and elusive. Recent systematic, evidence-based review in adults states that if remission does not occur after 12–18 months of therapy, there is little chance of remission on long-term therapy[17]. Although remission in adults is 40%–60%, less than 30% of children treated with ATD for an average of 2 years achieve remission, defined as normal thyroid function maintained for at least 1 year after termination of treatment in children and adolescents[18-22]. More prolonged use of ATD in children than in adults may be required to achieve remission. Some studies report that the remission rate increases by 25% for every additional 2 years of ATD treatment[20,23]. In one recent study on 154 children with GD, remission for at least for 18 months after completion of ATD had increasing rates with time i.e., 20% after 4 years, 37% after 6 years, 45% after 8 years, and 49% after 10 years of follow-up[24]. Another study shows that only 17% of prepubertal children treated for 5.9±2.8 years compared with 30% of pubertal subjects treated for 2.8±1.1 years achieve a 1-year remission after cessation of antithyroid treatment[25].

The remission rate varies between geographical areas. Remission rates are approximately 50% to 60% in Korean children and adolescents with GD. Lee et al.[26] show that of 64 subjects with GD, remission rates increased with time and were 6.3%, 16.4%, 29.4%, and 55.8% after 3-, 4-, 5-, and 6-year follow-up, respectively. Another study indicates that 56.6% were in remission after a mean 4.3±2.9 years of ATD therapy[27]. However, Kim and Hwang[28] report that of 41 children with GD, only 5 (12.2%) were in remission during the follow-up period (mean, 3.6±2.3 years).

Predictors of relapse after discontinuation of ATD treatment

Factors that are associated with relapse and remission in children and adolescents with GD are reported by several earlier studies. The results from studies on the development of more effective ATD treatment strategies have heterogeneous and conflicting results. Younger age, large goiter size, low body mass index, and higher initial thyroid hormone concentrations are independently and significantly associated with a higher probability of relapse[19,20,23,25,29]. Thyroid stimulating hormone receptor antibodies (TRAb) titers at the onset and end of treatment is one of the predictive markers of relapse[22,30]. Some studies have failed to assess these findings. A meta-analysis in adults reports that TRAb is not an effective predictor of relapse post-ATD treatment[31]. A recent review cites the variability in assay methodology, population characteristics, and study design in published data, as reasons why TRAb titers are insufficient predictors of relapse[32].

The findings on the risk of relapse are also inconclusive and variable in Korean studies. The predictive markers of GD relapse are age at diagnosis, serum thyrotropin concentration at presentation, and rapid achievement of TRAb normalization in Korean children and adolescents [26-28,33].

Radioiodine therapy

Radioiodine therapy (RAI) is an effective nonsurgical option for the definitive therapy for GD. Most clinical RAI experience is in children and adolescents from the United States, while it is still very uncommon in other geographic areas[34]. The goal of RAI is to prevent the recurrence of GD by inducing hypothyroidism, rather than euthyroidism. ^{131}I doses are typically calculated to deliver radiation based on the estimated amount of the thyroid gland and the 24-hour uptake (50 to 200 μCi radioiodine per gram of thyroid tissue), although some researchers deliver a fixed dose of radioiodine

without measuring uptake[35,36]. The risk of thyroid cancer and nodules is greater with exposure to low level thyroid irradiation, and not with the higher doses used to treat pediatric GD[37,38]. Furthermore, low administered activities of ^{131}I result in a high relapse rate[39]. Larger doses (usually >150 μCi of ^{131}I per gram of thyroid tissue) are hence preferred over smaller doses of radioiodine[40]. Hypothyroidism is achieved in approximately 60%–95% patients with a dose of radioiodine 150–200 μCi/g of thyroid[41,42]. The thyroid gland begins to shrink at 6–8 weeks after RAI, and hypothyroidism typically develops by 2–3 months posttreatment[39].

The most common adverse effects of RAI include vomiting and radiation-induced thyroiditis, characterized by anterior neck pain[43]. No serious complications occur for as long as 23 years on follow-up, according to a recent review on RAI in children and adolescents[44]. Although the major concern of RAI is the long-term risk of malignancy, there is no increased incidence of cancer in adults treated with radioiodine in childhood or adolescence[45]. However, RAI should be avoided in very young children (<5 years) because of an increased risk of neoplasia[11]. RAI causes new or worsening of Graves' opthalmopathy in about 15%–20% of adult patients, although there are rare reports of pediatric patients with worsening Graves' opthalmopathy after RAI[46].

Surgery

Surgery is a valid and acceptable treatment option of GD in children and adolescents, but is selected less often than ATD and RAI because of the risks of surgery. Thyroidectomy is indicated in patients with a large goiter causing compressive symptoms, relapse of hyperthyroidism after ATD, low uptake of radioacitve iodine, or when associated cancer is suspected[47].

Total or near-total thyroidectomy is the recommended procedure, since subtotal thyroidectomy increases the risk of relapse of hyperthyroidism more than total or near-total thyroidectomy[48]. Furthermore, near-total or total thyroidectomy does not increase the complication rate[49]. Surgical complication rates are higher in children than in adults, with higher rates in younger than older children. Transient hypocalcemia occurs in 10% of patients and permanent hypothyroidism in 2% of children[41]. Furthermore, hypoparathyroidism, palsy of the recurrent laryngeal nerve and wound infections can occur after thyroidectomy[47].

Conclusions

GD is the most leading cause of autoimmune hyperthyroidism in the pediatric population. ATD is considered the first-line therapy of pediatric GD. MMI should be selected for the treatment of GD in children and adolescents, because PTU can cause severe hepatotoxicity. The optimal duration of ATD treatment to remission, and the predictive factors for remission are not established. Children and adolescents may require more prolonged ATD treatment than adults. While there is no single marker that provides 100% predictability, there are several markers that are associated with a decreased likelihood of achieving and maintaining remission, such as high TRAb titers, large thyroid gland size, and younger age. Surgery and RAI are considered as the treatment option for GD. However, many patients and their guardians have an extreme fear of radiation and surgery, hence RAI and thyroidectomy is rarely used in Korea.

Prospective, multicenter studies are needed to identify the long-term risks and benefits of therapeutic options including ATD, RAI and surgery and also, to determine the appropriate duration of ATD and the predictive markers with high sensitivity and specificity.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

References

1. Metso S, Jaatinen P, Salmi J. Graves' disease. N Engl J Med 2008;359:1408-9.
2. Cooper DS. Hyperthyroidism. Lancet 2003;362:459-68.
3. Weetman AP. Graves' disease. N Engl J Med 2000;343:1236-48.
4. Dotsch J, Rascher W, Dorr HG. Graves disease in childhood: a review of the options for diagnosis and treatment. Paediatr Drugs 2003;5:95-102.
5. Cooper DS. Antithyroid drugs. N Engl J Med 2005;352:905-17.
6. Wilson R, Buchanan L, Fraser WD, Jenkins C, Smith WE, Reglinski J, et al. Evidence for carbimazole as an antioxidant? Autoimmunity 1998;27:149-53.
7. Weetman AP. How antithyroid drugs work in Graves' disease. Clin Endocrinol (Oxf) 1992;37:317-8.
8. Karras S, Memi E, Kintiraki E, Krassas GE. Pathogenesis of propylthiouracil-related hepatotoxicity in children: present concepts. J Pediatr Endocrinol Metab 2012;25:623-30.
9. Rivkees SA, Szarfman A. Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab 2010;95:3260-7.
10. Nakamura H, Noh JY, Itoh K, Fukata S, Miyauchi A, Hamada N. Comparison of methimazole and propylthiouracil in patients with hyperthyroidism caused by Graves' disease. J Clin Endocrinol Metab 2007;92:2157-62.
11. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 2011;21:593-646.
12. Streetman DD, Khanderia U. Diagnosis and treatment of

Graves disease. Ann Pharmacother 2003;37:1100-9.
13. Tajiri J, Noguchi S. Antithyroid drug-induced agranulocytosis: special reference to normal white blood cell count agranulocytosis. Thyroid 2004;14:459-62.
14. Tajiri J, Noguchi S, Murakami T, Murakami N. Antithyroid drug-induced agranulocytosis. The usefulness of routine white blood cell count monitoring. Arch Intern Med 1990;150:621-4.
15. Muldoon BT, Mai VQ, Burch HB. Management of Graves' disease: an overview and comparison of clinical practice guidelines with actual practice trends. Endocrinol Metab Clin North Am 2014;43:495-516.
16. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev 2010;(1):CD003420.
17. Abraham P, Avenell A, Watson WA, Park CM, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev 2004;(2):CD003420.
18. Kaguelidou F, Alberti C, Castanet M, Guitteny MA, Czernichow P, Leger J, et al. Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 2008;93:3817-26.
19. Glaser NS, Styne DM; Organization of Pediatric Endocrinologists of Northern California Collaborative Graves' Disease Study Group. Predicting the likelihood of remission in children with Graves' disease: a prospective, multicenter study. Pediatrics 2008;121:e481-8.
20. Glaser NS, Styne DM. Predictors of early remission of hyperthyroidism in children. J Clin Endocrinol Metab 1997;82:1719-26.
21. Hamburger JI. Management of hyperthyroidism in children and adolescents. J Clin Endocrinol Metab 1985;60:1019-24.
22. Gastaldi R, Poggi E, Mussa A, Weber G, Vigone MC, Salerno M, et al. Graves disease in children: thyroid-stimulating hormone receptor antibodies as remission markers. J Pediatr 2014;164:1189-94.e1.
23. Lippe BM, Landaw EM, Kaplan SA. Hyperthyroidism in children treated with long term medical therapy: twenty-five percent remission every two years. J Clin Endocrinol Metab 1987;64:1241-5.
24. Leger J, Gelwane G, Kaguelidou F, Benmerad M, Alberti C; French Childhood Graves' Disease Study Group. Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab 2012;97:110-9.
25. Shulman DI, Muhar I, Jorgensen EV, Diamond FB, Bercu BB, Root AW. Autoimmune hyperthyroidism in prepubertal children and adolescents: comparison of clinical and biochemical features at diagnosis and responses to medical therapy. Thyroid 1997;7:755-60.
26. Lee SH, Lee SY, Chung HR, Kim JH, Kim JH, Lee YA, et al. Remission rate and remission predictors of Graves disease in children and adolescents. Korean J Pediatr 2009;52:1021-8.
27. Song SM, Youn JS, Ko JM, Cheon CK, Choi JH, Yoo HW. The natural history and prognostic factors of Graves' disease in Korean children and adolescents. Korean J Pediatr 2010;53:585-91.
28. Kim SM, Hwang JS. Remission predictors of Graves' disease in children. J Korean Soc Pediatr Endocrinol 2010;15:100-5.
29. Mussa GC, Corrias A, Silvestro L, Battan E, Mostert M, Mussa F, et al. Factors at onset predictive of lasting remission in pediatric patients with Graves' disease followed for at least three years. J Pediatr Endocrinol Metab 1999;12:537-41.
30. Shibayama K, Ohyama Y, Yokota Y, Ohtsu S, Takubo N, Matsuura N. Assays for thyroid-stimulating antibodies and thyrotropin-binding inhibitory immunoglobulins in children with Graves' disease. Endocr J 2005;52:505-10.
31. Feldt-Rasmussen U, Schleusener H, Carayon P. Meta-analysis evaluation of the impact of thyrotropin receptor antibodies on long term remission after medical therapy of Graves' disease. J Clin Endocrinol Metab 1994;78:98-102.
32. Kamath C, Adlan MA, Premawardhana LD. The role of thyrotrophin receptor antibody assays in graves' disease. J Thyroid Res 2012;2012:525936.
33. Kim WK, Ahn BH, Han HS. The clinical course and prognostic factors to medical treatment of Graves' disease in children and adolescents. Ann Pediatr Endocrinol Metab 2012;17:33-8.
34. Ma C, Kuang A, Xie J, Liu G. Radioiodine treatment for pediatric Graves' disease. Cochrane Database Syst Rev 2008;(3):CD006294.
35. Rivkees SA, Cornelius EA. Influence of iodine-131 dose on the outcome of hyperthyroidism in children. Pediatrics 2003;111(4 Pt 1):745-9.
36. Nebesio TD, Siddiqui AR, Pescovitz OH, Eugster EA. Time course to hypothyroidism after fixed-dose radioablation therapy of Graves' disease in children. J Pediatr 2002;141:99-103.
37. Boice JD Jr. Thyroid disease 60 years after Hiroshima and 20 years after Chernobyl. JAMA 2006;295:1060-2.
38. Boice JD Jr. Radiation and thyroid cancer: what more can be learned? Acta Oncol 1998;37:321-4.
39. Chao M, Jiawei X, Guoming W, Jianbin L, Wanxia L, Driedger A, et al. Radioiodine treatment for pediatric hyperthyroid Grave's disease. Eur J Pediatr 2009;168:1165-9.
40. Rivkees SA. The management of hyperthyroidism in children with emphasis on the use of radioactive iodine. Pediatr Endocrinol Rev 2003;1 Suppl 2:212-21.
41. Rivkees SA, Sklar C, Freemark M. Clinical review 99: the management of Graves' disease in children, with special emphasis on radioiodine treatment. J Clin Endocrinol Metab 1998;83:3767-76.
42. Levy WJ, Schumacher OP, Gupta M. Treatment of childhood Graves' disease. A review with emphasis on radioiodine treatment. Cleve Clin J Med 1988;55:373-82.

43. Rivkees SA. Pediatric Graves' disease: management in the post-propylthiouracil Era. Int J Pediatr Endocrinol 2014;2014:10.
44. Clark JD, Gelfand MJ, Elgazzar AH. Iodine-131 therapy of hyperthyroidism in pediatric patients. J Nucl Med 1995;36:442-5.
45. Rivkees SA, Dinauer C. An optimal treatment for pediatric Graves' disease is radioiodine. J Clin Endocrinol Metab 2007;92:797-800.
46. Acharya SH, Avenell A, Philip S, Burr J, Bevan JS, Abraham P. Radioiodine therapy (RAI) for Graves' disease (GD) and the effect on ophthalmopathy: a systematic review. Clin Endocrinol (Oxf) 2008;69:943-50.
47. Sinha CK, Decoppi P, Pierro A, Brain C, Hindmarsh P, Butler G, et al. Thyroid surgery in children: clinical outcomes. Eur J Pediatr Surg 2014 Aug 21 [Epub]. http://dx.doi.org/10.1055/s-0034-1384649.
48. Palit TK, Miller CC 3rd, Miltenburg DM. The efficacy of thyroidectomy for Graves' disease: a meta-analysis. J Surg Res 2000;90:161-5.
49. Annerbo M, Stalberg P, Hellman P. Management of Grave's disease is improved by total thyroidectomy. World J Surg 2012;36:1943-6.