CASE REPORT

Journal of the ASEAN Federation of Endocrine Societies

Oscillation between Hyperthyroidism and Hypothyroidism in an Adolescent Female with Graves' Disease

Yee Lin Lee

Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Serdang, Selangor, Malaysia

Abstract

Graves' disease (GD) presenting as fluctuations between hyperthyroidism and hypothyroidism is a rare phenomenon and poses a diagnostic challenge. A 14-year-old female with GD, initially thought to have Hashimoto's thyroiditis presented with a goiter and oscillating thyroid function over the course of 4 years. This case depicts a case of GD with oscillating thyroid function and stresses the importance of TSH receptor antibodies (TRAb) in the evaluation of patients with hyperthyroidism without Graves' ophthalmopathy.

Key words: Graves' disease, hyperthyroidism, hypothyroidism

INTRODUCTION

Autoimmune thyroid disease is the most common autoimmune disorder and has a prevalence of 2% in the female population.[1] It occurs more commonly in adults, but it is also the most common cause of thyroid dysfunction in children and adolescents, with a peak age prevalence in the early to mid-puberty.[2] Autoimmune thyroid disease encompasses autoimmune thyroiditis and Graves' disease (GD), which are two thyroid disorders at different ends of the clinical spectrum. In autoimmune thyroiditis, there is T lymphocytic infiltration of the thyroid gland with formation of antithyroid peroxidase (anti TPO Ab) and antithyroglobulin antibodies (anti TG Ab) leading to antibody-dependent cell-mediated lysis of thyroid cells and subsequent hypothyroidism.[3] This entity includes atrophic thyroiditis (non-goitrous form) and Hashimoto's thyroiditis (goitrous form).[3] In contrast, in GD, lymphocytic infiltration of the thyroid gland results in activation of TSH receptor antibody (TRAb) producing B cells leading to hyperthyroidism.[3]

Patients with GD present with hyperthyroidism but may become euthyroid or even hypothyroid in later years.[4] Those with Hashimoto's thyroiditis can also have a transient phase of hyperthyroidism that is usually mild termed 'Hashitoxicosis,' before they progress into hypothyroidism.[3] Graves' disease with alternating thyroid status has been reported albeit rare.[4-8] We present a case of GD in an adolescent female with fluctuating thyroid status, initially presenting with transient hyperthyroidism, followed by a 2-year duration of hypothyroidism before evolving back to a state of hyperthyroidism.

CASE

A 14-year-old female initially presented at our clinic for evaluation of thyroid swelling that had been present since 8 years of age but gradually increasing in size for the past 2 years. She had symptoms of palpitations, emotional lability and heat intolerance. Clinically, she had a diffuse smooth goiter, more prominent on the right side, with an appreciable bruit. There was a family history of thyroid disease in her paternal grandmother and uncle, but the exact nature of the thyroid disease was not known. She was slightly tachycardic (pulse rate 104 beats/min) but was normotensive. Fine tremor was noted. Weight and height were on the 50th-75th percentile. No proptosis or lid lag was seen. Initial thyroid function test showed suppressed thyroid stimulating hormone (TSH) <0.01 mIU/L (0.47-4) and slightly raised free thyroxine (FT4) 19.38 pmol/L (10-17.6) and free triiodothyronine (FT3) 7.81 pmol/L (2.63-5.7). The patient's anti TPO Ab and anti TG Ab were both positive, 600 IU/ml (0-34) and 4000 IU/ml (0-115) respectively. Thyroid ultrasound showed a diffusely heterogenous and enlarged thyroid gland with markedly raised Doppler signal. There were no thyroid nodules.

She was started on low dose carbimazole of 5 mg daily and propranolol due to persistent symptoms of palpitations. However, she became biochemically hypothyroid three months after commencement of carbimazole. A provisional diagnosis of Hashimoto's thyroiditis with Hashitoxicosis was made due to the findings of mild hyperthyroidism before progression to hypothyroidism, supported by positive anti TPO Ab and anti TG Ab and absence of ophthalmopathy. She remained hypothyroid despite

eISSN 2308-118x (Online)
Printed in the Philippines

Received: July 24, 2024. Accepted: August 26, 2024.
Published online first: April 25, 2025.
https://doi.org/10.15605/jafes.040.01.07

Corresponding author: Yee Lin Lee, MBBS
Department of Paediatrics, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400, Serdang, Selangor, Malaysia
E-mail: yeelin@upm.edu.my
ORCiD: https://orcid.org/0000-0002-6111-2669

stopping carbimazole and required daily replacement of thyroxine 100 mcg. Subsequently, she became clinically and biochemically euthyroid for one year while on thyroxine replacement therapy. However, she was detected to be hyperthyroid again at 17 years of age during serial thyroid function monitoring and her hyperthyroid status persisted despite withholding thyroxine. She also had significant weight loss, heat intolerance and palpitations. An increase in goiter size with bruit, fine tremors and tachycardia were observed. The patient's diagnosis was revisited, and further work-up for hyperthyroidism was done, yielding a positive TRAb at 30.45 IU/L (normal <1.75). Anti TPO Ab and anti TG Ab remained positive; >600 IU/ml (normal <35); 966 IU/ml (normal <64) respectively.

Repeat thyroid ultrasound showed similar findings of enlarged bilateral thyroid lobes with heterogenous echogenicity and increased thyroid vascularity (Figure 1). In view of the unusual clinical picture of oscillating thyroid status, a radionuclide Tc-99m pertechnetate thyroid scintigraphy was also performed. It revealed bilateral diffuse homogenous tracer uptake of the thyroid gland with no hot or cold nodule seen, suggestive of a hyperfunctioning thyroid gland consistent with GD (Figure 2). Carbimazole 10 mg daily and propranolol were restarted. Serial FT4 and TSH trends are shown in Figure 3.

DISCUSSION

Graves' disease presenting as oscillating hyperthyroidism and hypothyroidism is a rare phenomenon and poses a diagnostic challenge. There are several case reports on the conversion of hyperthyroidism to hypothyroidism and vice versa, but only a few reported in children.[5-9] The alternating thyroid status in an individual with GD can be explained by the concurrent presence of two different types of TRAb i.e., TSAb and TBAb.[10] The hyperthyroid state is caused by TSAb whereas hypothyroidism is caused by TBAb.[10]

Previous studies of oscillating thyroid status in patients with GD have reported the co-existence of both TSAb and TBAb, whereby the clinical status is determined by the predominance of one antibody over the other.[5-10] The switch between TSAb and TBAb is more commonly

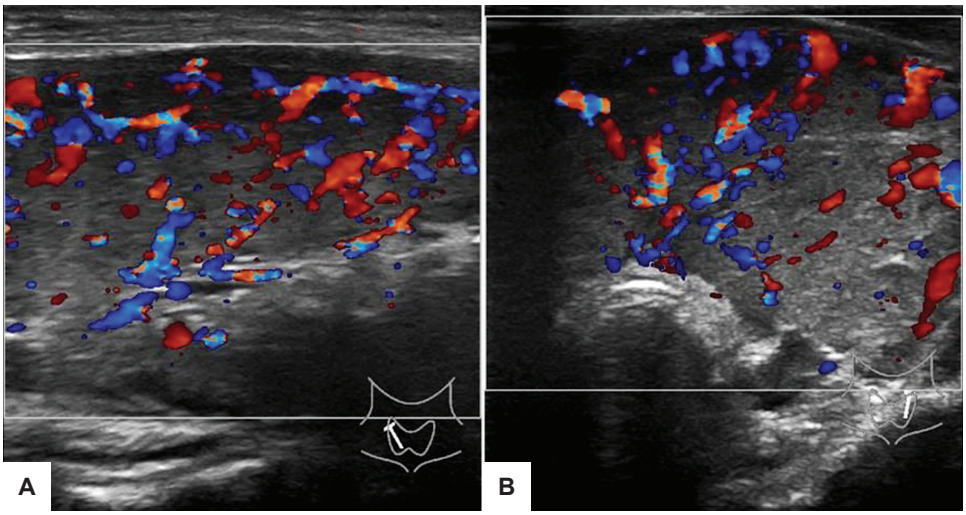

Figure 1. Ultrasound color Doppler thyroid gland showing heterogenous echogenicity and increased thyroid vascularity of right **(A)** and left **(B)** lobes.

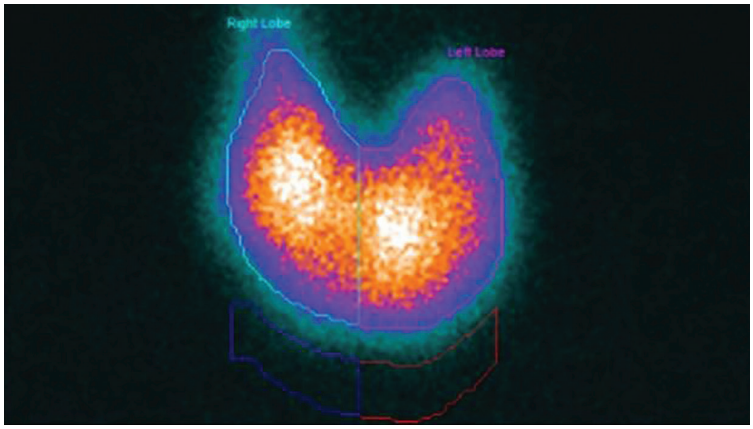

Figure 2. Radionuclide Tc99m thyroid scintigraphy showing bilateral diffuse homogenous tracer uptake 20.4%, (normal 5-15%), suggesting hyperfunctioning thyroid gland in Graves' disease.

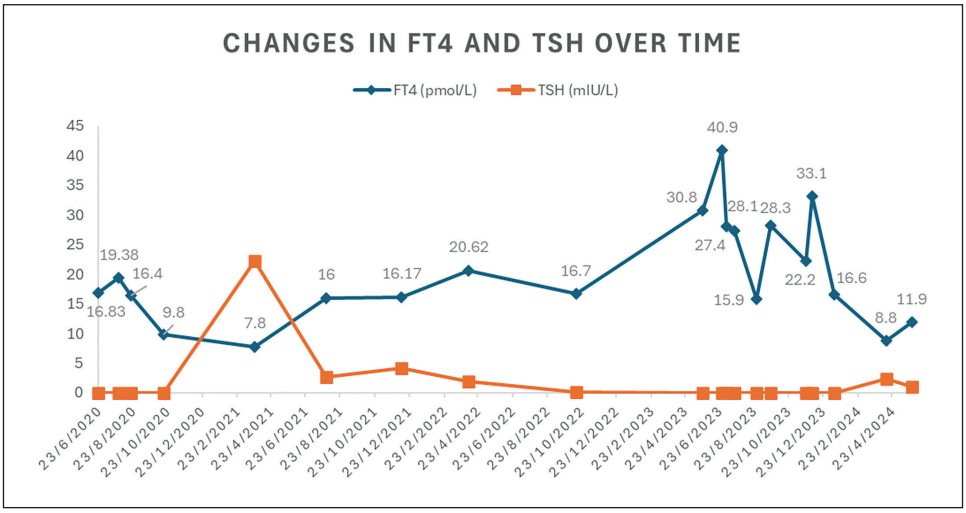

Figure 3. Serial FT4 and TSH trends

found in females.[7] It has been postulated that the use of levothyroxine could inhibit the T regulatory cells and enhance the expression of costimulatory molecules by dendritic cells, causing an increase in the TSAb and conversion to the hyperthyroid state.[5,8,11,12] Conversely, the use of antithyroid drugs reduces thyroid autoimmunity and TSAb synthesis, causing a switch to the hypothyroid state.[5,8,11,12] This may explain the underlying mechanism contributing to the change in thyroid status in our patient as she had reverted from hyperthyroidism to hypothyroidism shortly after initiation of carbimazole. Subsequently two years later, she switched back to hyperthyroidism while on thyroxine replacement.

Oscillating thyroid status has been more commonly reported in adults and its presentation is similar to that of children and adolescents.[5-10] In a study by Takasu et al conducted amongst adult men and women, 34 patients with hypothyroidism who were TBAb-positive and 98 patients with Graves' hyperthyroidism who were TSAb-positive were evaluated over a 10- year period.[10] Out of the 34 TBAb-positive patients, 17 had persistence of the TBAb and remained hypothyroid. Fifteen out of the 34 TBAb-positive patients had disappearance of the TBAb and resolution of hypothyroidism. Two out of the 34 TBAb- positive patients developed TSAb and Graves' hyperthyroidism. Amongst the 98 patients with Graves' disease who were TSAb positive, TSAb persisted in 10 patients who continued to have Graves' hyperthyroidism. Thyroid stimulating antibodies (TSAb) disappeared in 73 patients with 60 having remission of GD. Two of the 98 patients developed TBAb and reverted to hypothyroidism. Case reports describing such changes in TSAb and TBAb levels resulting in alternating thyroid status between hyperthyroidism and hypothyroidism have also been reported in adults.[13,14]

A second hypothesis to explain the oscillating thyroid status in this patient is the fact that both Graves' disease and Hashimoto's thyroiditis are manifestations of the same disease spectrum whereby thyroid-reactive T lymphocytes are formed and infiltrate the thyroid gland with an overlap of anti TPO Ab, anti TG Ab and TRAb in both conditions. Graves' disease with hyperthyroidism may occur in patients whose thyroid glands histologically show either Hashimoto's thyroiditis alone or a mixture of both parenchymatous hypertrophy of Graves' disease and extensive lymphocytic infiltrations.[15] Therefore, these patients present with hyperthyroidism and evolve into a hypothyroid state over a few months' time, resembling "Hashitoxicosis."[15] The hyperthyroid status may be due to the presence of TSAb associated with GD co-existing with the destruction of thyroid follicles. The spontaneous disappearance of the TSAb, with the underlying thyroid inflammation allows the Hashimoto's thyroiditis phenotype to predominate. Recurrent hyperthyroidism may be due to reemergence of the TSAb. In a review of 69 children with Hashimoto's thyroiditis, 11.69% were diagnosed with Hashitoxicosis with the duration of hyperthyroidism ranging from one to four months before evolving into hypothyroidism or euthyroidism.[16]

In this patient, the enlarged thyroid gland and marked increase in Doppler signal in her thyroid ultrasound pointed more to GD.[17] In Hashimoto's thyroiditis, the chronic inflammation leads to a reduction in thyroid gland volume with a normal or reduced vascularization on ultrasound Doppler.[17] An important discerning feature between Hashimoto's thyroiditis and GD is the presence of TRAb predominantly in the latter. In a review by Saravanan and Dayan, TRAb was positive in 70-100% of patients with GD but it was only positive in 2-6% of patients with Hashimoto's thyroiditis.[1] Anti TG Ab and anti TPO Ab are present in both Hashimoto's thyroiditis and GD and cannot be used to differentiate both conditions (anti TG Ab 35-60% and anti TPO Ab 80-99% in Hashimoto's thyroiditis versus anti TG Ab 12-30% and anti TPO Ab 45-80% in GD).[1] The diagnosis of GD in this patient was further supported by the demonstration of homogenous increase in radiotracer uptake in thyroid scintigraphy as it would be expected to be normal or reduced in Hashimoto's thyroiditis.[17]

Management of GD with fluctuating thyroid function is challenging. The management options proposed are radioactive iodine ablation, thyroidectomy and pharmacological therapy.[5-7,9] Pharmacological treatment may involve the combined use of thyroxine and antithyroid therapy in cases of rapidly changing thyroid function to achieve euthyroid status.[4] The thyroid status of our patient is currently still manageable with a single agent. However, she requires more frequent thyroid function monitoring to detect possible switching of thyroid status. Due to the unpredictability of the clinical course, a reasonable definitive management option to consider in her case is radioactive iodine ablation during hyperthyroid phase or thyroidectomy.

CONCLUSION

Graves' disease with oscillating hyperthyroidism and hypothyroidism is a rare phenomenon that can be explained by co-existence of both TSAb and TBAb. It may be confused with Hashimoto's thyroiditis in patients who present with only transient mild hyperthyroidism before switching to hypothyroidism. Thyroid stimulating hormone receptor antibody is an important diagnostic tool to differentiate between Hashimoto's thyroiditis and GD in patients with hyperthyroidism without Graves' ophthalmopathy. Thyroid scintigraphy is also invaluable in cases of diagnostic uncertainty. Management of GD with oscillating thyroid status includes close monitoring of thyroid function with consideration of radioactive iodine ablation or thyroidectomy.

Ethical Consideration
Patient consent form was obtained from the parents of the patient before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
YLL: Conceptualization, Formal analysis, Investigation, Resources, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration.

Author Disclosure
The author declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

Funding Source
None.

References

1. Saravanan P, Dayan CM. Thyroid autoantibodies. Endocrinol Metab Clinics North Am. 2001;30(2):315–37. PMID: 11444165 DOI: 10.1016/s0889-8529(05)70189-4
2. Hunter I, Greene SA, MacDonald TM, Morris AD. Prevalence and aetiology of hypothyroidism in the young, Arch Dis Child. 2000;83(3):207–10. PMID: 10952634 PMCID: PMC1718463 DOI: 10.1136/adc.83.3.207
3. Cappa M, Bizzarri C, Crea F. Autoimmune thyroid diseases in children. J Thyroid Res. 2010;2011:675703. PMID: 21209713 PMCID: PMC3010678 DOI: 10.4061/2011/675703
4. Wood LC, Ingbar SH. Hypothyroidism as a late sequela in patients with Graves' disease treated with antithyroid agents. J Clin Invest. 1979;64(5):1429-36. PMID: 91625 PMCID: PMC371292 DOI: 10.1172/JCI109601
5. Martins LC, Coutinho AR, Jerónimo M, et al. Autoimmune alternating hyper- and hypo-thyroidism: A rare condition in pediatrics. Endocrinol Diabetes Metab Case Rep. 2016;2016:150131. PMID: 26925233 PMCID: PMC4768072 DOI: 10.1530/EDM-15-0131
6. Solaimanzadeh I, Hossain MR, Shiferaw-Deribe Z, Sandhu H. Alternating thyroid status between thyrotoxicosis and hypothyroidism in a patient with varying antithyroid antibodies. AACE Clin Case Rep. 2018;5(2):e112-8. PMID: 31967014 PMCID: PMC6873863 DOI: 10.4158/ACCR-2018-0167
7. Wong M, Inder WJ. Alternating hyperthyroidism and hypothyroidism in Graves' disease. Clin Case Rep. 2018;6(9):1684-8. PMID: 30214742 PMCID: PMC6132101 DOI: 10.1002/ccr3.1700
8. McLachlan SM, Rapoport B. Thyrotropin-blocking autoantibodies and thyroid-stimulating autoantibodies: Potential mechanisms involved in the pendulum swinging from hypothyroidism to hyperthyroidism or vice versa. Thyroid. 2013; 23(1):14-24. PMID: 23025526 PMCID: PMC3539254 DOI: 10.1089/thy.2012.0374
9. Mathew RP, Moore DJ. Autoimmune alternating hypo- and hyperthyroidism in children. Clin Pediatr (Phila). 2011;50(11):1040-4. PMID: 21700620 PMCID: PMC3556509 DOI: 10.1177/0009922811412583
10. Takasu N, Matsushita M. Changes of TSH-Stimulation Blocking Antibody (TSBAb) and Thyroid Stimulating Antibody (TSAb) over 10 years in 34 TSBAb-positive patients with hypothyroidism and in 98 TSAb-positive Graves' patients with hyperthyroidism: Reevaluation of TSBAb and TSAb in TSH-Receptor-Antibody (TRAb)-positive patients. J Thyroid Res. 2012;2012:182176. PMID: 22655217 PMCID: PMC3359712 DOI: 10.1155/2012/182176
11. Furqan S, Haque NU, Islam N. Conversion of autoimmune hypothyroidism to hyperthyroidism. BMC Res Notes. 2014;7:489. PMID: 25086829 PMCID: PMC4126907 DOI: 10.1186/1756-0500-7-489
12. Fan WQ, Tandon P, Krishnamurthy M. Oscillating hypothyroidism and hyperthyroidism – a case-based review. J Community Hosp Intern Med Perspect. 2014;4(5):25734. PMID: 25432652 PMCID: PMC4246140 DOI: 10.3402/jchimp.v4.25734
13. Kasagi K, Hidaka A, Endo K, et al. Fluctuating thyroid function depending on the balance between stimulating and blocking types of TSH receptor antibodies: A case report. Thyroid. 1993;3(4):315-8. PMID: 7906975 DOI: 10.1089/thy.1993.3.315
14. Kraiem Z, Baron E, Kahana L, Sadeh O, Sheinfeld M. Changes in stimulating and blocking TSH receptor antibodies in a patient undergoing three cycles of transition from hypo to hyper-thyroidism and back to hypothyroidism. Clin Endocrinol (Oxf). 1992;36(2):211-4. PMID: 1637398 DOI: 10.1111/j.1365-2265.1992.tb00960.x
15. Fatourechi V, McConahey WM, Woolner LB. Hyperthyroidism associated with histologic Hashimoto's thyroiditis. Mayo Clinic Proc. 1971;46(10):682-9. PMID: 5171000
16. Nabhan ZM, Kreher NC, Eugster EA. Hashitoxicosis in children: Clinical features and natural history, J Pediatr. 2005;146(4):533–6. PMID: 15812459 DOI: 10.1016/j.jpeds.2004.10.070
17. Igor AH, Eckhart GH, Deike S. Thyroid disorders: Hashitoxicosis – Three cases and a review of the literature. European Endocrinology. 2008;4:70-2. https://www.touchendocrinology.com/wp-content/uploads/sites/5/2015/07/harsch_1.pdf