Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Case Series

Case series of Euthyroid Graves' Ophthalmopathy in patients seronegative for TSH receptor autoantibody (TRAb) & developed Hyperthyroidism in follow-up visits

Avijit Saha[1,*], **Somnath Chowdhury**[2]

[1]*Dept. of General Medicine, Malda Medical College & Hospital, Malda, West Bengal, India*
[2]*Dept. of Ophthalmology, Malda Medical College & Hospital, Maida, West Bengal, India*

ARTICLE INFO

Article history:
Received 18-12-2021
Accepted 19-03-2022
Available online 29-06-2022

Keywords:
Graves' ophthalmopathy
Thyroid receptor Antibody(TRAb)

ABSTRACT

We reported cases of Graves' ophthalmopathy who presented solely with symptoms of the eyes and normal thyroid function tests, negative TSH receptor autoantibody (TRAb). These cases were referred to our hospital for unilateral or bilateral eye swelling with painful eye movements, with or without double vision, without any signs or symptoms of hyper- or hypothyroidism. Serum thyroid function tests and 99mTc uptake studies were within the normal range. Anti-thyroid autoantibodies (TRAb) were negative in all the cases. Since orbital CT scan and MRI gave typical results compatible with Graves' ophthalmopathy and after exclusion of other possibilities, these patients were treated with corticosteroid pulse therapy and orbital radiation therapy, leading to a partial improvement of the symptoms. We followed up those cases with serial thyroid profile testing and TRAb estimation and they were subsequently developed clinical & biochemical hyperthyroidism within the next 18 months follow-up. At that time, they also became TRAb positive. These cases give us insight into the potential pathophysiologic mechanism underlying Graves' ophthalmopathy and cast light upon the difficulties of establishing the diagnosis in biochemically euthyroid & thyroid autoantibody negative cases. Clinicians should be aware of the variable temporal relationship between the clinical expression of thyroid dysfunction and orbital disease in the natural course of Graves' disease.

1. Introduction

Graves' ophthalmopathy (GO) is a chronic inflammatory disease of the orbital cavity with the potential of sight threatening complications, generally accompanied by hyperthyroidism associated with Graves' disease.[1] But 5–10% of patients have hypothyroidism or normal thyroid function.[2] Individuals with GO and normal thyroid status aresaid to have euthyroid Graves' ophthalmopathy (EGO), the diagnosis of which is supported by the presence of one or more thyroid-specific antibodies namely antibodies to thyroid peroxidase (TPOAb) and the TSH receptor(TRAb).[3] TRAbs, the pathological hallmark of Graves' disease, are present in almost every patient with the disease.[4] Thus, the occurrence of GO in the absence of thyroid dysfunction and thyroid antibodies is a cause of diagnostic uncertainty and are rarely reported. So, we report a case series of 3 patients with GO without thyroid dysfunction or thyroid specific antibodies at initial presentation who subsequently developed thyroid dysfunction in the form of overt hyperthyroidism during follow up between 6 and 18 months after the initial presentation.

* *Corresponding author*.
E-mail address: sahaavijit46@gmail.com (A. Saha).

https://doi.org/10.18231/j.ijceo.2022.058

2. Case Presentations

A 45year old female presented with a 5-month history of double vision, excessive tearing, sticky feeling in the eyes, and orbital pain in all directions of gaze. She had no symptoms of thyroid dysfunction, did not smoke, and denied any personal or family history of thyroid disease. She was clinically euthyroid and had no palpable goiter. Her visual acuity was 6/6 in both the eyes. She had fullness of her eyelids on the right side. She had right eye proptosis, upper eyelid retraction and diplopia on vertical gaze but no lid lag on voluntary eye movement. Her intraocular pressure was normal and the optic discs were normal in both eyes. At this point, a differential diagnosis of right inferior rectus mass or thyroid eye disease was considered. Thyroid function test was normal: TSH 2.25 μIU/ml (reference range 0.27–4.2), FT4 1.28ng/dl (reference range 0.93-1.7), and FT3 2.80 pg/ml (reference range 2.0–4.2). We then performed tests for anti TSH receptor antibody (TRAb) and thyroid peroxidase antibody (TPOAb) which were negative (Table 1) and thyroid ultrasound scan showed a normal-sized gland with normal blood flow pattern & no evidence of any thyroid disease. TRAb measurement was performed using a commercial third-generation ELISA kit that detects both thyroid stimulating (TSAbs) and -blocking antibodies (TBAbs) with manufacturer specificity and sensitivity of 100 and 95%, respectively. A CT scan of the orbit showed bilateral asymmetrical enlargement of the inferior rectus, more marked on the right eye than the left, and was highly suggestive of GO inflammation. MRI orbit also confirmed inflammation in keeping with GO. There was no evidence of structural or other inflammatory lesions on imaging. Serum calcium and angiotensin-converting enzyme (ACE) levels were normal. So, this case was clinically diagnosed as TRAb-negative euthyroid Grave's ophthalmopathy.

36 year old male patient (Figure 1) was referred to our Medical College with a three-month history of ocular focusing deficit without any history of weight loss, palpitation, tremulousness of limbs or frequent bowel movements. Past history and family history did not reveal the presence of any thyroid-related diseases. He had not been taking any medication but had a history of consuming 20 cigarettes a day for 20 years. Ophthalmological examination revealed double vision on upward gaze with minimal restriction in upward movement of the left eye, eyelid retraction, and exophthalmos of the left eye. Intraocular pressure and visual acuity were normal. The exophthalmoses on the right and left eyes were 15mm and 19mm by Hertel exophthalmometer (normal range: 10~15mm). Clinical activity score (CAS) of the ophthalmopathy was 2 with redness and swelling of the eyelid. Although no physical sign of thyroid dysfunction was observed, thyroid function tests were performed since Graves' ophthalmopathy was suspected. Plasma FT3, FT4,and TSH levels were as 3.5pg/mL, 1.34ng/dL, and 1.55μIU/ mL, respectively and were within the normal range(Table 1). Thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and TSH receptor autoantibodies (TRAb) were all negative. TSAb test could not be done due to financial constraints. Ultrasonography of the thyroid gland was performed and showed a normal-sized gland with slightly enhanced blood flow (Figure 2). To directly measure thyroid activity in vivo, 99mTc scintigraphy was then performed. The result was again negative with 99mTc uptake of 0.50%for the right lobe 0.39% for the left lobe and total 0.89% (normal <5% in total). These serological and imaging studies of the thyroid had scarcely given positive evidence for the diagnosis of Graves' disease in this patient. We next performed imaging analysis of the orbital cavity. CT scan showed obvious enlargement of the inferior rectus muscle of the left eye. MRI images of the orbit again showed inferior rectus muscle swelling of the left eye (Figure 3 a,b). Fat-suppression T2-weighted images showed a slight increase in the MR intensity of the muscle involved suggesting active inflammation of the extraocular muscle. No tumorous lesion was detected within the orbital cavity. Based on the insidious onset, absence of ocular pain, predominance of inferior rectus muscle swelling, and apparent muscular swelling with minimally swollen tendons, we diagnosed this case as TRAb negative euthyroid Graves' ophthalmopathy.

A 55 years old male attended eye OPD with complaint of prominence of both eyes for last 5months followed by swelling and pain for last 15days.It was associated with mild discomfort and grittiness of the eyes followed by development of progressive pain & swelling of both upper and lower eyelids. The pain was localized, non radiating, present both at rest and with movements of eyes. There was no doubling of vision. The patient denied any loss of weight in spite of good appetite, sweating, tremors or palpitation. There was no history of trauma. The patient also denied any skin discoloration, neck swelling or exposure to radiation therapy or chemotherapy. There was no history of dysphagia, dysphonia, easy fatigability or drooping of eyelids. The patient was nondiabetic but was hypertensive and on regular medication for the last 8years. He was a chronic smoker. On ocular examination, he had a staring look. His best corrected visual acuity was 6/18 right eye and 6/24 left eye. He had bilateral axial proptosis, periorbital edema around the lids; conjunctiva was congested nasally and temporally, with mild chemosis, pupil was 4 mm in diameter and reacting briskly to light. There was upper lid lag on down gaze with upper eyelid retraction. Convergence insufficiency was note in both eyes. No variation of proptosis was observed with bending forwards or stooping and with Valsalva's manoeuvre. No thrill or pulsation felt. Proptosis was measured by Hertel exophthalmometer, 20 mm of proptosis was found in right eye and 22 mm in left eye. On applanation tonometry, IOP was 19 mm Hg in right

eye and 18 mm Hg in left eye in primary gaze. The patient was advised thyroid function tests. Serum levels of free Tri iodothyronine, free Thyroxine and Thyroid stimulating hormone levels were 3.2 pg/mL (2.0-4.4), 0.98 ng/dL (0.93-1.7) and 1.12 μIU/ml(0.27-4.2) respectively and his TSH receptor antibody (TRAb) level was negative. We suggested thyroid stimulating antibody (TSAb) test and patient was able to do the test despite the high costand it was turned out to be positive (240%; reference range <120%) by Bioassay technique (Table 1). Then, CECT orbit was done which revealed outward protrusion of left eyeball with fusiform swelling of all recti muscles of left orbit and superior and lateral rectus muscle of right side with sparing of tendinous insertion. Retro orbital fatty tissue and optic nerve sheath complex were normal. There was no evidence of intra or extraocular mass lesions. CECT Brain was done which was normal. With these tests results, he was finally diagnosed to have euthyroid Grave's Ophthalmopathy.

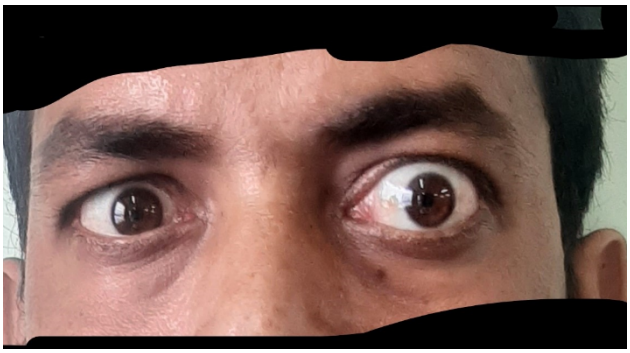

Fig. 1:

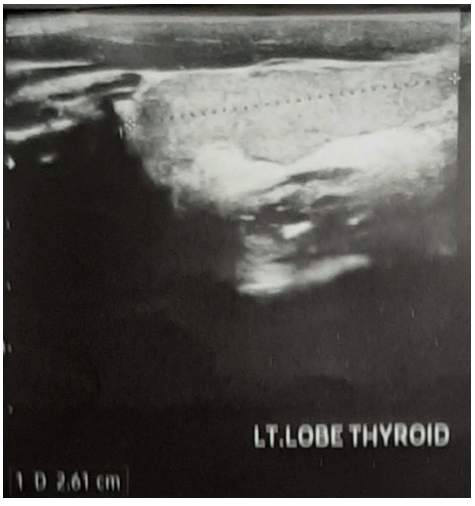

Fig. 2:

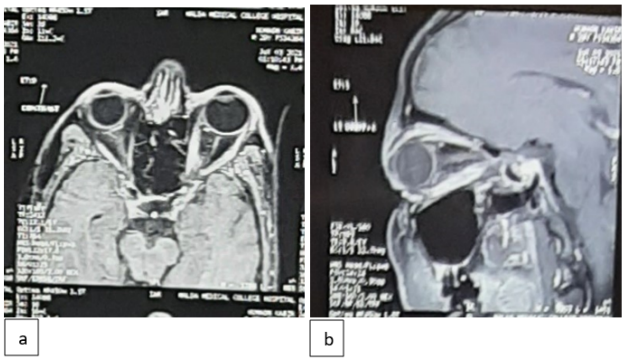

Fig. 3:

3. Treatment & Follow-up of Cases

The first case was treated symptomatically with topical lubricants, fitted with corrective prism & was advised for surgical resection of inferior rectus which the patient declined.

The second & third cases were managed with a combination of corticosteroid pulse therapy and radiation therapy of the orbit. Intravenous administrations of methylprednisolone 1000mg/day for 3 days followed by oral prescription of prednisolone 30mg/day for 4 days. They were also unwilling for surgical treatment. We followed up these cases at 6month intervals with serial testing of thyroid function & thyroid receptor antibody. Our cases started developing the usual symptoms of hyperthyroidism & typical low TSH(<0.01μIU/ml) with elevated FT4 or FT3 or both with TRAb positivity after 8^{th}, 10^{th}, 16^{th} months of initial presentation respectively. Then they were started on carbimazole therapy, and they responded satisfactorily with significant clinical & biochemical resolution.

4. Discussion

Here we reported three cases who presented with symptoms, signs and imaging results typical of Graves' ophthalmopathy but with normal thyroid profile & negative TRAb at the time of presentations. This kind of presentations can occur in approximately 5% of the cases of GO and are termed as Euthyroid Grave's ophthalmopathy. Patients with EGO typically have relatively mild disease, characterized by unilateral or asymmetrical disease and lesser degrees of soft tissue inflammation and muscle involvement than patients with overt hyperthyroidism.[5] For patients with established hyperthyroidism, TRAb estimation is not essential for the recognition or management of GO.[6] However, a patient with orbital symptoms in the absence of thyroid disease or autoantibodies presents a diagnostic dilemma and the clinician may be tempted to attribute such cases to nonthyroid causes. Our reports illustrate the importance of a thorough clinical and radiological evaluation and close monitoring of long-

Table 1: Clinical features & thyroid profile of cases at the time of presentation

Cases	Clinical status	FT4 (ng/dl)	FT3 (pg/ml)	TSH(μIU/ml)	TRAb (IU/L)	Anti TPO Ab(IU/ml)	TSAb (%)	AT Follow-up
Case 1	Rt eye swelling	1.28	2.8	2.25	1.37	21.11	——	
Case 2	Lt eye swelling	1.34	3.5	1.55	0.89	16.45	——	
Case 3	B/L eye swelling without goiter	0.98	3.2	1.12	1.67	13.47	240%	

(Reference ranges: FT4:0.93-1.7ng/dl; FT3:2.0-4.4pg/ml;TSH:0.27-4.2 μIU/ml; TRAb(ECLIA):<1.75IU/L; AntiTPOAb(ECLIA):<34IU/ml; TSAb:<120%)

term thyroid status in such individuals. As we can see from these cases, CT or MRI imaging of the orbit is essential in excluding other causes of orbital disease including meningiomas, lymphomas, cavernous carotid fistula, orbital cellulitis, Cushing's disease, sarcoidosis, pseudotumor cerebri, and primary and metastatic tumors.[7] In our cases, the differential diagnosis was be as follows:(1) Intraorbital malignancies, (2) Granulomatous diseases such as Wegener's granulomatosis or sarcoidosis, and (3) Idiopathic orbital inflammatory disease. No involvement of the other organs or tissues, e.g., uveitis, hilar lymph node swelling, heart, lung, kidney, or skin lesions in these cases argue against the diagnosis of Wegener's granulomatosis or sarcoidosis. Malignant tumor has not been suggested because the imaging studies showed isolated swelling of extra ocular muscles especially the inferior rectus muscle without any intraorbital space occupying lesion. As we observed from our cases, imaging of the orbits is of paramount importance. CT or MRI will also detect bilateral disease that may not be clinically apparent, as some patients with asymmetric bilateral disease may present with unilateral symptoms and signs. Biopsy of the orbital tissue may be useful to differentiate EGO from other inflammatory or infiltrating diseases.

Serum TRAb play a central role in development of Grave's ophthalmopathy as it cross reacts with TSH receptors on orbital fibroblasts and preadipocytes, leading to activation and production of hydrophilic glycosaminoglycans (GAG) which in turn cause the orbital expansion seen in GO.[8] There are two types of TSH receptor antibodies (TRAb):thyroid stimulating antibody (TSAb) and TSH-stimulation blocking antibody (TSBAb).[9] TSAb stimulates the thyroid and causes Graves' hyperthyroidism. TSBAb blocks TSH-stimulation of the thyroid and causes hypothyroidism. To know whether TRAb is either stimulatoryor inhibitory, TSAb and TSBAb have been measured. TSAb is measured as a bioassay, using porcine thyroid cells and is an expensive test, not used in routine clinical practice. So, we have to rely upon only TRAb assay in doubtful cases. TRAb could be negative if the used assay technique has lower sensitivity or if the patient has very low titre of antibody during initial presentation of the disease. Some authors have described mild degree of hyperthyroidism in the form of smaller goiters and lower levels of radioactive iodine uptake might have very low, undetectable TRAb titre.[9] It has also been suggested that antibody-negative individuals may harbor intrathyroidal TRAbs, which donot spill into the circulation.[10] Furthermore, TRAb is unlikely to be the sole pathogenetic agent in GO. Insulin like growth factor 1 receptor (IGF1R) which is present on the surface of orbital fibroblasts, is another auto antigen that has been implicated in the pathogenesis of GO.[11] Once the disease is fully evolved we would expect classical clinical features of hyperthyroidism coupled with very low TSH (<0.01 μIU/ml) and high FT3or FT4 or both. If we perform TRAb estimation, it would eventually be positive. In a series by Khoo and coworkers, 25% of patients with EGO developed thyroid dysfunction within 4 years of follow-up.[12]

After initiation of appropriate therapy with antithyroid medication TRAb level will be undetectable.[13] Our patients ultimately developed features of overt hyperthyroidism with TRAb positivity. This emphasizes the need for long-term follow-up and continued patient and physician vigilance in patients who have been suspected of having EGO.

5. Conclusion

Clinicians should be aware of the variable temporal relationship between the clinical expression of thyroid dysfunction and orbital disease in the natural course of Graves' disease. Patients with suggestive symptoms of ophthalmopathy should be carefully evaluated & followed up for Grave's ophthalmopathy with imaging studies even when thyroid function and auto antibodies are normal.

6. Source of Funding

None.

7. Conflict of Interest

None.

References

1. Bartalena L, Tanda ML. Clinical practice. Graves' ophthalmopathy. *N Engl J Med*. 2009;360(10):994–1001.
2. Bahn RS. Graves' ophthalmopathy. *N Engl J Med*. 2010;362(8):726–38.

3. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol*. 1996;121(3):284–90.
4. Cakir M. Euthyroid Graves' ophthalmopathy with negative autoantibodies. *J Natl Med Assoc*. 2005;97(11):1547–9.
5. Smith BR, Bolton J, Young S, Collyer A, Weeden A, Bradbury J, et al. A new assay for thyrotropin receptor autoantibodies. *Thyroid*. 2004;14(10):830–5.
6. Kamath C, Adlan MA, Premawardhana LD. The role of thyrotrophin receptor antibody assays in Graves' disease. *J Thyroid Res*. 2012;2012:525936. doi:10.1155/2012/525936.
7. Eckstein AK, Lösch C, Glowacka D, Schott M, Mann K, Esser J, et al. Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves' ophthalmopathy. *Br J Ophthalmol*. 2009;93(8):1052–6.
8. Chen DY, Schneider PF, Zhang XS, Luo XY. He ZM & Chen TH 2014 Changes in Graves' ophthalmopathy after radioiodine and antithyroid drug treatment of Graves' disease from 2 prospective, randomized, open-label, blinded end point studies. *Exp Clin Endocrinol Diabetes*. 2014;122(1):1–6.
9. Mallika P, Tan AK, Aziz S, Alwi SS, Chong MS, Vanitha R, et al. Thyroid associated ophthalmopathy - a review. *Malays Fam Physician*. 2009;4(1):8–14.
10. García-Rojas L, Ocampo GA, Alexánderson E, Tovilla-Canales JL. 18-Fluorodeoxyglucose Uptake by Positron Emission Tomography in Extraocular Muscles of Patients with and without Graves' Ophthalmology. *J Ophthalmol*. 2013;2013:529187. doi:10.1155/2013/529187.
11. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab*. 2006;91(9):3464–70.
12. Theodoraki A, Jones G, Parker J, Woolman E, Martin N, Perera S, et al. Performance of a third-generation TSH-receptor antibody in a UK clinic. *Clin Endocrinol (Oxf)*. 2011;75(1):127–33.
13. Weetman AP, Byfield PG, Black C, Reimer CB. IgG heavy chain subclass restriction of thyrotropin-binding inhibitory immunoglobulins in Graves' disease. *Eur J Clin Invest*. 1990;20(4):406–10.

Author biography

Avijit Saha, Associate Professor https://orcid.org/0000-0002-8956-0834

Somnath Chowdhury, Assistant Professor

Cite this article: Saha A, Chowdhury S. Case series of Euthyroid Graves' Ophthalmopathy in patients seronegative for TSH receptor autoantibody (TRAb) & developed Hyperthyroidism in follow-up visits. *Indian J Clin Exp Ophthalmol* 2022;8(2):290-294.