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A Case of Delayed Diagnosis of Graves' Orbitopathy Presenting as Bilateral Cranial Nerve VI Palsy

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Abstract

Graves' Orbitopathy (GO) is reported in nearly half of Graves' hyperthyroidism cases. This eye disease often develops simultaneously or within 18 months of demonstrated thyroid autoimmunity. In this case report, we will discuss a young female patient presenting with ophthalmopathy associated with bilateral cranial nerve VI palsy and asymptomatic hyperthyroidism with very unusual features for Graves' disease. Her atypical presentation of Graves' orbitopathy led to a comprehensive medical approach which included the use of several diagnostic tests and resources that resulted in delay in diagnosis and prolonged hospitalization.

Keywords: Graves'; Orbitopathy; Cranial nerve palsy; Hyperthyroidism; Diplopia

Introduction

Graves' Orbitopathy (GO), also known as thyroid eye disease, is an autoimmune condition characterized by inflammation of the orbital tissues that is closely associated with Graves' disease *i.e.* [1]. A key aspect of these clinically and temporally related diseases is the production of autoantibodies to the thyrotropin receptor (TSH-R), primarily expressed in the epithelial cells of thyroid follicles, but also distributed in a variety of extrathyroidal tissues, including adipocytes and fibroblasts [2,3]. In Graves' disease, activated lymphocytes within the thyroid release TSH-R-Stimulating Immunoglobulins (TSI) which act as unregulated agonists stimulating the TSH-receptor and consequently driving thyroid hormone production, hormone release, and thyrocyte proliferation leading to the features of hyperthyroidism [4,5]. Common clinical manifestations of Graves' disease include anxiety, nervousness, tremors, weight loss, tachyarrhythmia, increased sweating, heat intolerance, goiter and Graves' orbitopathy [6].

Graves' orbitopathy is reported in nearly half of patients with Graves' hyperthyroidism [3]. This eye disease usually develops during the same period that thyroid autoimmunity is demonstrated, with hyperthyroidism and ocular symptoms occurring simultaneously or within 18 months of each other [3,7]. In some instances, GO may occur years prior to or after the initial onset of hyperthyroidism [7]. In addition, approximately 5% of GO cases present as euthyroid or hypothyroid with low titers of thyroid receptor antibodies detected [8].

Frequently, GO presents with bilateral and symmetric ocular involvement [8]. Symptoms of GO include dry and gritty foreign object sensation, excessive tearing, photophobia, retroocular pressure or pain, blurred vision and diplopia [3]. Additional physical findings of GO include exophthalmos, lid retraction, periorbital swelling, diplopia, and chemosis [8]. Severe forms of the disease occur in approximately 3% to 5% of cases and can result in vision loss, extreme pain, or compressive optic neuropathy [9]. The changes associated with GO are graded and described by several classification systems, such as the seven-point clinical activity score and Werner's NOSPECS. This score incorporates the signs of inflammation, proptosis, eyelid abnormalities, corneal damage, and loss of vision related to optic nerve compression.

Currently, the most accepted pathogenesis of Graves' orbitopathy postulates the activation of orbital fibroblast and adipocyte thyrotropin receptors and IGF-1 receptors by TSH-R autoantibodies and activated T cells [10]. These interactions stimulate fibroblast proliferation and adipogenesis along with concomitant orbital inflammation. Hydrophilic Glycos Amino Glycans (GAG) released by the activated fibroblasts amass in Extra Ocular Muscles (EOMs), along with inflammatory infiltrate, leading to fluid accumulation and subsequent swelling [3,11]. Together, retrobulbar adipogenesis, EOM GAG accumulation,

and extraocular inflammation increase the volume of the orbital tissues, explaining many of the presenting signs and symptoms of GO [12]. MRI and CT imaging of GO classically reveals smooth-bordered, fusiform enlargement of >4mm in the extraocular muscles with sparing of the tendons and increased retrobulbar fat volume. When these image findings appear preferentially in the rectus inferior followed by the medial rectus, superior rectus, and lateral rectus, they represent a Graves' pattern of EOM involvement specific for GO [8]. In a study analyzing 116 CT scans of patients with Graves' disease, Dr. Enzman et al. found that 40% of patients without clinical manifestations of Graves' orbitopathy still demonstrated characteristic muscle enlargement on orbital CT. Other studies measuring orbital soft-tissue volume that included hyperthyroid patients with Graves' disease with no ocular symptoms also showed a higher frequency of abnormal measurements, up to 70% [13]. Although proptosis, orbital inflammation, and serum levels of thyroid antibodies positively correlate with one another and serve as measures of GO therapeutic outcomes, a study of 210 patients with GO and diplopia found that diplopia negatively correlated with these signs of autoimmune activation [14]. In contrast, GO positively correlated with restriction of eye motility and asymmetrical orbital involvement. The researchers hypothesized that a modest restriction of a single muscle could produce severe diplopia due to overcompensation of the opposing muscles with deviation of the opposite eye as a result of coupled innervation of the external eye muscles [14]. In this case report and other studies of patients with confirmed autoimmune thyroid disease, diplopia without clinically evident exophthalmos can present as the predominant sign of GO and mimic cranial nerve III, IV, or VI palsies [15]. This presentation may lead to initial investigations directed at uncovering neurological etiologies, particular in cases with minimal signs and symptoms of thyrotoxicosis. The use of imaging contrast containing significant amounts of iodine during the evaluation of cranial neuropathies may later complicate or delay the subsequent use of Radioactive Iodine Uptake (RAIU) and scan for the diagnosis of Graves' disease and orbitopathy.

Case Report

A 36-year-old African American female non-smoker, recently diagnosed with hypertension, with no significant family history, presented to ophthalmology clinic due to a 3-day history of new-onset binocular diplopia. Her eye exam demonstrated increasing medial deviation of her right eye secondary to suspected cranial nerve VI palsy. The patient was referred to the ED for further testing. During the evaluation, the patient reported double vision. She denied any preceding causal events or trauma, headaches, fevers, vision loss, tinnitus, retroorbital or EOM pain, fatigue, ptosis, weakness, or paresthesia. She endorsed a viral upper respiratory infection 3-weeks prior to symptoms. Vital signs in the ED were normal except for intermittent sinus tachycardia with the highest heart rate measured at 122 bpm. Neurological examination demonstrated bilateral esotropia more pronounced in the right eye during eye cover testing with medial deviation of the right eye at rest. Bilateral abduction deficits with limited upward gaze and decreased intorsion and suppression of the right eye were identified. The remainder of the neurological exam was unremarkable with no nystagmus or signs suggestive of additional neuropathy.

Due to a concern of bilateral cranial nerve VI palsy, workup for a central etiology was initiated to rule out causes of increased intracranial pressure, cavernous sinus involvement, microvascular ischemic changes, neurosarcoidosis, other inflammatory causes, infection, ischemic events, or aneurysms. Radiologic evaluations, including CT Head without contrast and CT angiogram of the head and neck, were performed and did not identify any acute intracranial abnormalities. All blood vessels were found to be patent without signs of AV malformations, fistulas, or aneurysms. The head CT also revealed normal ventricles, sulci, and cisterns without concerning fluid collections, and the orbits appeared normal. A follow-up MRI of the brain with and without contrast also identified no concerning intracranial anomalies. The chest X-ray was unremarkable without manifestations suggestive of sarcoidosis.

Laboratories, including CMP, CBC, lipid profile, B12, and HbA1c, were unrevealing with values within reference ranges. Immunoglobulin G levels, ACE levels, and a Myasthenia Gravis panel were normal. A beta-hCG test was negative for pregnancy, and a RPR titer was nonreactive. Inflammatory markers were elevated with an ESR of 60 mm/h and CRP measuring 2.23 mg/dL.

TSH levels were low at 0.01 mU/mL with elevated free T4 (2.35 ng/dL) and Total T3 (2.64 ng/dL). These values, combined with restricted eye movements in multiple directions raised concerns for possible thyroid eye disease and an endocrinology consultation was placed. During the consultation, the patient denied any personal or family history of thyroid disease, and a review of systems was negative for any signs or symptoms of hyperthyroidism. During the endocrinology exam, tachycardia and a diffuse symmetric goiter was noted. No obvious exophthalmos, lid retraction, lid lag, dermopathy, or tremors were identified. Further work up revealed no detected Thyroglobulin antibodies (<1 IU/mL) or thyroid microsomal antibodies (<3.00 IU/mL). A high level of Thyroglobulin (247.2 ng/mL) was reported. Thyroid Stimulating Immunoglobulin (TSI) was ordered and pending through discharge. Prior contrast imaging did not permit the use of Radioactive Iodine Uptake (RAIU) to aid in etiologic evaluation of hyperthyroidism. A thyroid ultrasound showed an enlarged thyroid gland (via, right lobe measured 6.5 x 3.4 x 2.7 cm and left lobe measured 6.4 × 3.3 × 2.7 cm) with a heterogenous echo pattern and no discrete nodules (Figure 1).

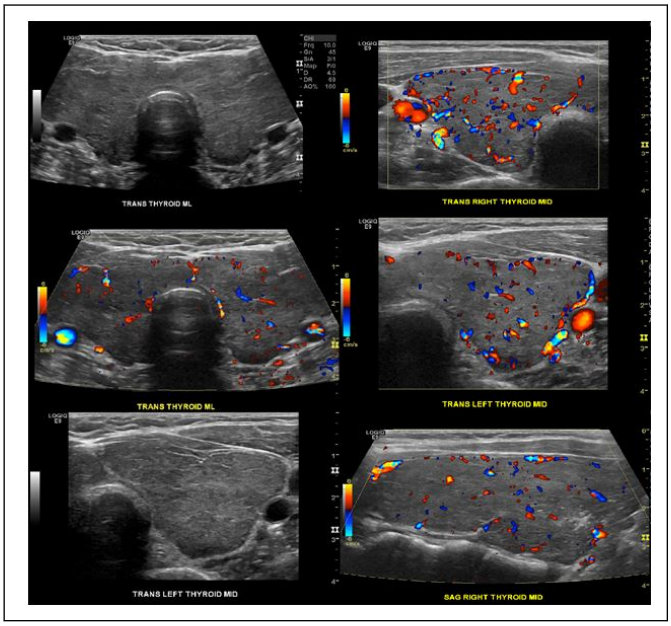

Figure 1: Thyroid US images. No significant increase in vascular flow noted.

The color flow Doppler pattern did not show the marked vascularity anticipated with Graves' disease. A peak systolic velocity of the inferior thyroid arteries was not obtained.

Following this evaluation, the clinical presentation, a thyroid ultrasound with color flow Doppler with a low vascularity, and elevated thyroglobulin increased the suspicion for possible subacute or painless thyroiditis.

After an inpatient ophthalmological evaluation, an MRI of the orbits was ordered and demonstrated bilateral orbital proptosis with the posterior sclera located beyond the limits of the interzygomatic line region. Bilateral extraocular muscles were within the reference normal size ranges and no increased retroorbital fat or orbital apex crowding abnormalities were identified. The optic chiasm, optics nerves, and nerve sheath appeared normal without signs of compression, correlating with the patient's normal visual acuity (Figure 2).

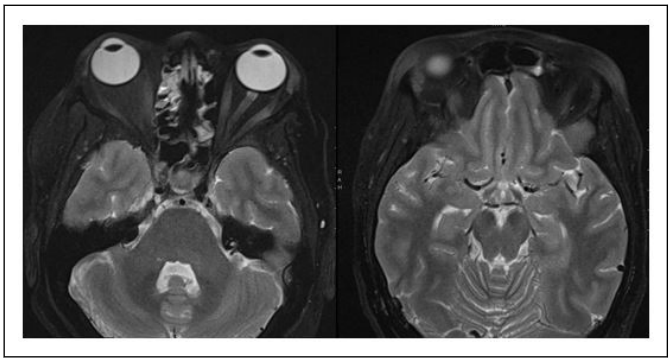

Figure 2: MR orbits w/wo contrast.

The neurology team performed a Lumbar Puncture (LP) to further investigate etiologies for the patient's apparent multiple cranial neuropathies. The LP showed normal opening pressure, and a subsequent, extensive Cerebrospinal Fluid (CSF) analysis including cytology, flow cytometry, ACE, IgG, protein, glucose, meningitis panel, oligoclonal banding, Lyme PCR, Gram stain, and culture did not suggest other etiologies. Following the normal LP results, a trial of pyridostigmine was attempted with no clinical improvement in the patient's diplopia. The patient did not receive additional therapy, such as corticosteroids or thioamides.

A repeated thyroid function test, 5-days after, showed improvement. A TSH value of < 0.01 mU/mL with a Total T3 level of 2.01 ng/dL (initially 2.64 ng/dL) and a Free T4 of 1.58 ng/dL (initially 2.35 ng/dL).

Since free T4 and total T3 levels decreased, subacute thyroiditis remained in the differential diagnosis, and the patient was discharged home. 1-week following discharge, TSI antibody levels returned elevated at 307 (reference range<140%), favoring the diagnosis of Graves' disease. The patient was started on Methimazole 2.5 mg daily with follow-up with ophthalmology to discuss further management of GO.

Discussion

The patient's history of a recent upper respiratory infection prior to presenting with biochemical thyrotoxicosis and the absence of classical findings of Graves' disease led to a differential diagnosis that included a possible inflammatory process such as Subacute Thyroiditis (SAT). The thyroid ultrasound showing some enlargement of the gland, but no evidence of the hypervascularity typically associated with Graves', further favored SAT. However, the orbital MRI with bilateral proptosis made it difficult to completely rule out Graves' orbitopathy as the cause of the patient's apparent cranial neuropathies. Unremarkable LP results and a lack of clinical improvement following a trial of pyridostigmine further narrowed the differential diagnosis of the patient's diplopia.

Graves' Orbitopathy (GO) presenting with diplopia and restricted extraocular movements may mimic cranial nerve III, IV and VI palsies without clinically evident proptosis or orbital inflammation [14-16]. Signs and symptoms of excess thyroid hormone often facilitate distinguishing GO from other causes of double vision and deconjugate gaze. However, when GO presents with diplopia and minimal characteristics of thyrotoxicosis, investigations of other etiologies for cranial neuropathies are frequently performed. Unfortunately, these investigations often involve the use of iodinated contrast to enhance computed tomography images which competes with iodine uptake diminishing the efficacy of RAIU in the diagnosis of Graves' disease. Testing of post-contrast 24-hour urinary iodine content can help establish if a patient is ready for RAIU. Practices differ in how long to wait prior to RAI use after contrast, but a prospective cohort study of patients undergoing contrast CT imaging showed a median time of 43 days for urinary iodine levels to normalize [17]. Within 60 days 75% of subject returned to baseline urine iodine levels, while 90% returned to normal levels within 75 days. In this patient with ophthalmoplegia and thyroid function tests indicative of hyperthyroidism following a recent upper respiratory tract infection, the inability to perform RAIU complicated her diagnosis and delayed her treatment. A retrospective chart

review of inpatient endocrinology consultations for patients with newly diagnosed thyrotoxicosis found that 45% of the patients referred for endocrinology evaluation had received iodinated contrast within 2 weeks of their presentation to the service [18]. Of these patients, the 43 receiving a contrast CT scan had a total of 7 patients with a resultant finding that potentially changed their inpatient management. Based on our case report and available literature, the presence of bilateral cranial neuropathies involving cranial nerves III, IV or VI might result in a timelier diagnosis and treatment of underlying Graves' orbitopathy if thyroid function tests and RAIU are performed prior to administering iodinated contrast.

As in this case, research has shown that Graves' orbitopathy may not always correlate with autoimmune activity within the orbits. Despite the patient's measured proptosis, her extraocular muscles and orbital adipose tissue did not show increased volume on orbital MR imaging. The closer association between GO and limited asymmetric muscle restriction, versus GO and autoimmune activity, demonstrates why a confirming RAIU may be particularly valuable when other image findings may not reveal classical signs of Graves' related orbital involvement [14]. While previous contrast use prevented this diagnostic approach in the current case, many studies have examined the efficacy of ultrasound as a tool in assessing Graves' thyroid disease. Doppler sonography in Graves' disease commonly reveals a pulsatile pattern of diffuse thyroid hypervascularity, not seen in normal euthyroid or other dysfunctional thyroid patients, referred to as a "thyroid inferno" [19]. Multiple thyroid blood flow parameters, such as thyroid volume and blood flow and intraparenchymal peak systolic velocity, likely resulting from increased TSH or TSH-receptor antibody stimulation of the thyroid, have demonstrated some reliability in differentiating Graves' disease from other thyroid conditions [20-23]. The present case did not demonstrate a clear pattern of increased intrathyroidal vascularity, despite the noted gland enlargement, further complicating the diagnosis and treatment of GO in this patient. Without ultrasound or orbital MRI and no ability to reliably conduct an RAIU, the patient in the present case continued to undergo additional, unnecessary testing and empiric treatments to rule out other etiologies of ocular nerve involvement, until her TSI antibody testing changed the treatment of her thyroid condition.

Although diplopia is a quite common outcome in moderate to severe Graves' orbitopathy, a lack of other signs of autoimmune activity within the orbit in combination with limited signs and symptoms of thyrotoxicosis can make the diagnosis challenging. Furthermore, a lack of thyroid hypervascularity on thyroid ultrasound may present an additional diagnostic challenge further confounded by previous contrast administration limiting the effectiveness of RAIU [14].

The role of hyperthyroidism treatment in Graves' orbitopathy continues to be controversial. Multiple observational and clinical studies have found that the severity of the thyroid dysfunction correlates with the degree of orbitopathy, suggesting that achieving control of thyroid function is important in the setting of thyroid eye disease [24]. However, other studies have found mild thyroid eye disease follows the expected course described in Rundle's curve independent of treatment status. After following 65 untreated patients with GO, Menconi et al. identified improvement in 50.8% of cases, stable GO in 33.8% of cases, and worsened GO in 15.4% of cases regardless of thyroid status or thyroid treatment [25]. Additional studies have also demonstrated no difference in GO outcome with the initiation of antithyroid medication. However, Martalena et al. conducted a large study following 443 patients with Graves' disease and mild or no ophthalmopathy. Patients were assigned randomly to treatment with methimazole, radioiodine with a 3-month prednisone course, or radioiodine alone and then followed at 1, 2 and 12-month intervals after initiation of treatment to evaluate for thyroid eye disease progression. They concluded radioiodine therapy is followed by worsening ophthalmopathy more often than treatment with methimazole. This outcome is usually transient and was noticed to be preventable with the addition of prednisone [26].

Initially, our assessment favored SAT over Graves' disease. Once the etiology of Graves' disease was confirmed by the presence of an elevated TSI antibody, we established with more clarity that the ophthalmopathy of our patient was secondary to Graves' disease, and treatment with thioamides was initiated. Our patient was started on Methimazole, but within a few days she developed a rash. We switched the patient to PTU, and no side effects have been reported. Ophthalmology started using patch and Fresnel prism. Subsequently, she was referred to an ophthalmologist specialized in thyroid eye disease for expert evaluation and consideration of Teprotumumab. Our patient was seen recently in the clinic and is feeling better. The double vision and ocular movements are improving, and she currently denies symptoms of hyperthyroidism. Thyroid function testing has not been completed by the patient at the time of the submission of this manuscript, and Teprotumumab has not been initiated yet due to some constraints with insurance.

Conclusion

We are reporting the unusual presentation of GO causing bilateral cranial nerve VI palsy. We review the current literature in an effort to provide better understanding of this condition.

References

1. Banga JP, Moshkelgosha S, Berchner-Pfannschmidt U, Eckstein A (2015) Modeling Graves' Orbitopathy in Experimental Graves' Disease. Horm Metab Res 47: 797-803.
2. Davies T, Marians R, Latif R (2002) The TSH receptor reveals itself. J Clin Invest 110: 161-164.
3. Bahn RS (2010) Graves' ophthalmopathy. N Engl J Med 362: 726-738.
4. McLachlan SM, Pegg CA, Atherton MC, Middleton SL, Clark F (1986) TSH receptor antibody synthesis by thyroid lymphocytes. Clin Endocrinol (Oxf) 24: 223-230.
5. Smith BR, Hall R (1974) Thyroid-stimulating immunoglobulins in Graves' disease. Lancet (London, England) 2: 427-431.
6. Hegazi MO, Ahmed S (2012) Atypical clinical manifestations of graves' disease: an analysis in depth. J Thyroid Res 768019.

7. Wiersinga WM, Smit T, Van der Gaag R, Koornneef L (1988) Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. J Endocrinol Invest 11, 615-619.

8. Boddu N, Jumani M, Wadhwa V, Bajaj G, Faas F, et al. (2017) Not All Orbitopathy Is Graves': Discussion of Cases and Review of Literature. Front Endocrinol 8: 184.

9. Wiersinga WM, Bartalena L (2002) Epidemiology and prevention of Graves' ophthalmopathy. Thyroid 12: 855-860.

10. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, et al. (2006) Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab 91: 3464-3470.

11. Forbes G, Gorman CA, Brennan MD, Gehring DG, Ilstrup DM, et al. (1986) Ophthalmopathy of Graves' disease: computerized volume measurements of the orbital fat and muscle. AJNR Am J Neuroradiol 7: 651-656.

12. Valyasevi RW, Erickson DZ, Harteneck DA, Dutton CM, Heufelder AE, et al. (1999) Differentiation of human orbital preadipocyte fibroblasts induces expression of functional thyrotropin receptor. J Clin Endocrinol Metab 84: 2557-2562.

13. Enzmann DR, Donaldson SS, Kriss JP (1979) Appearance of Graves' disease on orbital computed tomography. J Comput Assist Tomogr 3: 815-819.

14. Laurberg P, Berman DC, Pedersen IB, Andersen S, Carle A, et al. (2015) Double vision is a major manifestation in moderate to severe graves' orbitopathy, but it correlates negatively with inflammatory signs and proptosis. J Clin Endocrinol Metab 100: 2098-2105.

15. Appen RE, Wendelborn D, Nolten WE (1982) Diplopia in autoimmune thyroid disease. Arch Intern Med 142: 898-901.

16. Chen VM, Dagi LR (2008) Ocular misalignment in Graves' disease may mimic that of superior oblique palsy. J Neuroophthalmol 28: 302-304.

17. Nimmons GL, Funk GF, Graham MM, Pagedar NA (2013) Urinary iodine excretion after contrast computed tomography scan: implications for radioactive iodine use. JAMA Otolaryngol Head Neck Surg 139: 479-482.

18. Phillips BD, Hennessey JV (2009) Iodinated contrast prior to evaluation for thyrotoxicosis. J Hosp Med 4: 285-288.

19. Ralls PW, Mayekawa DS, Lee KP, Colletti PM, Radin DR, et al. (1988) Color-flow Doppler sonography in Graves' disease: "thyroid inferno". AJR Am J Roentgenol 150: 781-784.

20. Ota H, Amino N, Morita S, Kobayashi K, Kubota S, et al. (2007) Quantitative measurement of thyroid blood flow for differentiation of painless thyroiditis from Graves' disease. Clin Endocrinol 67: 41-45.

21. Bogazzi F, Bartalena L, Brogioni S, Burelli A, Manetti L, et al. (1999) Thyroid vascularity and blood flow are not dependent on serum thyroid hormone levels: studies in vivo by color flow Doppler sonography. Eur J Endocrinol 140: 452-456.

22. Saleh A, Cohnen M, Furst G, Godehardt E, Modder U, et al. (2002) Differential diagnosis of hyperthyroidism: Doppler sonographic quantification of thyroid blood flow distinguishes between Graves' disease and diffuse toxic goiter. Exp Clin Endocrinol Diabetes 110: 32-36.

23. Anjuman A, Fariduddin M, Sharmin J, Nusrat S, Mashfiqul H, et al. (2017) Can color Doppler ultrasonography differentiate thyrotoxicosis in Graves' disease from subacute thyroiditis? J Endocrinol Thyroid Res 2: 555600.

24. Prummel MF, Wiersinga WM, Mourits MP, Koornneef L, Berghout A, et al. (1990) Effect of abnormal thyroid function on the severity of Graves' ophthalmopathy. Arch Intern Med 150: 1098-1101.

25. Menconi F, Profilo MA, Leo M, Sisti E, Altea MA, et al. (2014) Spontaneous improvement of untreated mild Graves' ophthalmopathy: Rundle's curve revisited. Thyroid 24: 60-66.

26. Bart Alena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, et al. (1998) Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med 338: 73-78.