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Marine-Lenhart Syndrome Masquerading as Ocular Myasthenia Gravis: A Case Revealed by Isolated Unilateral Ptosis

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ABSTRACT

Graves' disease (GD) is the leading cause of hyperthyroidism, with ophthalmic involvement occurring in up to 50% of cases (Graves' orbitopathy, GO). Classical GO features include bilateral proptosis, lid retraction, and restrictive strabismus. Unilateral ptosis is an exceedingly uncommon presenting sign of Graves' disease and poses a significant diagnostic challenge, frequently leading clinicians to prioritize neurological etiologies before the underlying thyroid autoimmune process is identified.

We present a 34-year-old woman referred for progressive right-sided ptosis over six months, initially investigated for neurological causes. Ophthalmological assessment revealed mild right-sided proptosis and inferior scleral show contralateral to the ptotic lid, consistent with unilateral lid retraction masking asymmetric GO. Biochemical evaluation confirmed hyperthyroidism with a suppressed TSH, markedly elevated free T4 and T3, and positive thyroid-stimulating immunoglobulins (TSI) and thyrotropin receptor antibodies (TRAb). Thyroid ultrasound identified a diffusely enlarged gland with a 1.8 cm right lobe nodule. Tc-99m scintigraphy demonstrated diffusely increased uptake with a superimposed focus of relatively autonomous activity corresponding to the nodule, establishing the diagnosis of Marine–Lenhart syndrome the rare coexistence of Graves' disease with an autonomously functioning thyroid nodule. Orbital MRI revealed asymmetric extraocular muscle enlargement bilaterally, right greater than left, confirming Graves' orbitopathy as the cause of apparent unilateral ptosis.

This case highlights two converging diagnostic challenges: the misclassification of contralateral lid retraction as unilateral ptosis, and the recognition of Marine–Lenhart syndrome a rare overlap of Graves' hyperthyroidism with a coexisting autonomously functioning thyroid nodule (AFTN) found in fewer than 3% of Graves' patients. The presence of Marine–Lenhart syndrome critically modifies the management strategy, particularly regarding radioiodine dosing, surgical planning, and the assessment of post-treatment euthyroidism.

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KEYWORDS:

Marine–Lenhart syndrome; thyroid eye disease; unilateral ptosis; hyperthyroidism; TRAb; thyrotropin receptor antibodies; thyrotoxicosis.

INTRODUCTION

Graves' disease (GD) is an autoimmune thyroid disorder driven by thyrotropin receptor antibodies (TRAb), which stimulate thyroid follicular cells, resulting in autonomous thyroid hormone overproduction and diffuse goiter. It accounts for 60–80% of all cases of hyperthyroidism in iodine-sufficient regions, with a female-to-male predominance of approximately 5–8:1 and peak incidence between the third and fifth decades.

Graves' orbitopathy (GO) also termed thyroid-associated ophthalmopathy (TAO) or thyroid eye disease (TED) is the most clinically significant extrathyroidal manifestation of GD, occurring in 25–50% of patients. The orbital fibroblast is the central target of the autoimmune process: TRAb cross-react with IGF-1 receptors and TSH receptors on orbital

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fibroblasts, triggering glycosaminoglycan accumulation, adipogenesis, and fibrosis. This leads to expansion of extraocular muscles (EOMs) and orbital fat, causing the hallmark clinical triad of proptosis, restrictive myopathy, and upper eyelid retraction.

Lid retraction defined as an upper lid margin resting at or above the superior limbus is the most frequent periocular sign of GO, present in up to 90% of affected patients. It results from sympathetic overstimulation of Müller's muscle in the context of thyrotoxicosis, and from fibrotic changes and inferior rectus contracture in chronic GO. When lid retraction occurs asymmetrically, the contralateral eye may appear frankly ptotic by comparison, creating a diagnostic trap.

True ptosis is rarely a feature of GO; its occurrence should prompt systematic exclusion of concurrent conditions including myasthenia gravis (which coexists with GD in 0.2–0.5% of cases due to shared autoimmune susceptibility), third cranial nerve palsy, Horner syndrome, and levator dehiscence. Failure to recognize that apparent ptosis may reflect contralateral lid retraction in the context of GD leads to unnecessary neuroimaging, misdiagnosis, and delayed treatment of the underlying thyrotoxicosis.

We present this case to highlight a structured endocrinological approach to unilateral ptosis revealing Marine– Lenhart syndrome.

CASE PRESENTATION

A 34-year-old female, office worker and non-smoker presented with a 6-month history of progressive right-sided eyelid drooping. The patient first noticed asymmetry of her eyelids six months prior, with the right lid appearing progressively lower. She was initially referred to neurology, where CT brain, MRI brain with gadolinium, and acetylcholine receptor antibody testing were all unremarkable. Neostigmine test was negative. Given the exclusion of primary neurological causes, the patient was referred to endocrinology.The patient reported a 4month history of heat intolerance, palpitations, and a weight loss of approximately 5 kg without dietary change. She described increased stool frequency (3–4 times daily), mild hand tremor, and subjective anxiety. She denied neck swelling, dysphagia, or voice change. She had no prior history of thyroid disease and was taking no regular medications. Oligomenorrhea was reported over the past 3 months. No prior pregnancies. No recent iodinecontrast exposure or amiodarone use.

Upon physical examination, the patient exhibited an anxious appearance with a fine resting tremor in both hands. Her vital signs revealed a regular tachycardia with a heart rate of 118 beats per minute and a blood pressure of 128/78 mmHg. Her weight was 54 kg, corresponding to a BMI of 20.1 kg/m², which noted a significant weight loss down from 59 kg six months prior. On neck examination, a diffuse, smooth goiter approximately twice the normal size was palpable, with no audible bruit on auscultation. Her skin was characteristically warm and moist, though no pretibial myxedema was observed. Neurological assessment was notable for generalized bilateral hyperreflexia.

Parameter	Patient Value	Reference Range
TSH (3rd generation)	**< 0.005 mIU/L**	0.4–4.0 mIU/L
Free T4 (FT4)	**42.1 pmol/L**	12–22 pmol/L
Free T3 (FT3)	**18.4 pmol/L**	3.1–6.8 pmol/L
TRAb (TSH receptor Ab)	**18.2 IU/L**	< 1.75 IU/L
TSI (Thyroid-stimulating Ig)	**Positive (420%)**	< 140%
Anti-TPO antibodies	**892 IU/mL**	< 34 IU/mL
Anti-Tg antibodies	64 IU/mL	< 115 IU/mL
CBC	Normal	—
Liver function (ALT/AST)	Normal	—
AChR antibodies	Negative	< 0.4 nmol/L
Serum calcium	Normal	2.1–2.6 mmol/L

Detailed neuro-ophthalmological evaluation revealed significant ocular asymmetry. On the right side, the upper lid position demonstrated an apparent ptosis.

Thyroid ultrasound demonstrated a diffusely enlarged gland with heterogeneous, coarsely echogenic parenchyma and markedly increased vascularity on Doppler interrogation, consistent with Graves' disease. A well-defined, solid, isoechoic nodule measuring 1.8 x 1.4 cm with a peripheral halo and internal vascularity on color Doppler was identified in the right thyroid lobe. No cervical lymphadenopathy was detected.

Technetium-99m (Tc-99m) pertechnetate scintigraphy was critical to the definitive diagnosis. It demonstrated diffusely and homogeneously increased radiotracer uptake throughout the gland, consistent with Graves' disease. Crucially, a superimposed focus of relatively increased autonomous activity was identified in the right lobe corresponding to the sonographic nodule. Unlike a classical toxic adenoma, the extranodular parenchyma was not suppressed: both the gland and the nodule showed elevated uptake, the nodule appearing as a hot focus within a hot gland.This scintigraphic pattern established the diagnosis of Marine–Lenhart.

Antithyroid therapy was initiated with methimazole (thiamazole) 30 mg/day, using a titration regimen to achieve euthyroidism over 6 to 8 weeks, alongside propranolol 40 mg twice daily for symptomatic control of tachycardia and tremor, to be tapered once euthyroid. Baseline liver function tests, a complete blood count, were obtained prior to initiation, and the patient received agranulocytosis counseling. The treatment target is to bring free T4 within the normal range within 4 to 6 weeks to proceeded to a total thyroidectomy.

Discussion:

Pathophysiology of Marine–Lenhart Syndrome:

Marine–Lenhart syndrome (MLS) occupies a unique position in thyroid pathophysiology as the overlap between two competing mechanisms of hyperthyroidism: TSH-receptor antibody-driven diffuse stimulation (Graves' disease) and TSH-independent autonomous nodule function (toxic adenoma).[1] Its prevalence of 0.8–3% among Graves' patients makes it rare enough to be missed if scintigraphy is not routinely performed or carefully reviewed.[1,2]

The pathogenesis of MLS is incompletely understood.[2] Somatic activating mutations in the TSH receptor gene (TSHR) or GNAS gene are found in the autonomous nodule, as in classic toxic adenoma.[3] The Graves' component is driven by TRAb, which independently stimulate TSH receptors throughout the gland.[4] The two processes coexist rather than being causally related, though some hypothesize that chronic TSH-receptor stimulation by TRAb may accelerate the growth of pre-existing autonomous clones.[5]

The scintigraphic diagnosis of MLS is nuanced.[2] In a classic toxic adenoma, the autonomous nodule concentrates iodine with full suppression of the extranodular parenchyma.[6] In MLS, TRAb stimulation maintains uptake in the surrounding Graves' tissue, so the nodule appears as a focus of relatively higher uptake within an already hyperactive gland — the "hot nodule within a hot gland" pattern.[1,2] This distinction is critical: without scintigraphy, the nodule may be entirely missed on biochemistry alone (both components contribute to hyperthyroidism), and ultrasound alone cannot determine functional autonomy.[2,7] **Lid Retraction, Ptosis, and Orbital Manifestations in Graves' Disease:**

Lid retraction in Graves' disease occurs through two mechanisms: adrenergic hyperstimulation of Müller's smooth muscle in the upper lid, reversible with beta-blockade and achievement of euthyroidism; and fibrotic restriction of the levator-superior rectus complex in chronic, inactive Graves' orbitopathy (GO).[8,9]

True ptosis in a Graves' patient should trigger evaluation for myasthenia gravis (MG).[10] The co-occurrence of Graves' disease (GD) and MG, while rare, is immunologically plausible: both are antibody-mediated disorders with shared HLA associations (HLA-DR3).[10,11] AChR antibody testing and a pharmacological challenge should be part of the workup of any Graves' patient with documented MRD1 reduction.[10] **Role of TRAb, Disease Classification, and Activity Assessment:**

Thyrotropin receptor antibodies (TRAb) serve a dual role in Graves' disease: diagnostic confirmation and disease monitoring.[4,12] In the context of GO, TRAb also correlates with orbitopathy severity and activity.[12,13]

The European Group on Graves' Orbitopathy (EUGOGO) classification guides treatment by stratifying severity into three tiers: mild disease (CAS < 3, minimal quality-of-life impact), managed with watchful waiting, selenium, lubricants, and smoking cessation; moderate-to-severe disease (CAS ≥ 3, no immediate sight threat), requiring intravenous glucocorticoids (IVGC), or orbital radiotherapy/rituximab if refractory; and sightthreatening disease (dysthyroid optic neuropathy or corneal breakdown), demanding emergency IVGC or surgical decompression within 24–48 hours.[13,14]

Definitive Treatment: RAI, Thyroidectomy, and Biologic Therapy:

Radio-iodine therapy (RAI) is a highly effective definitive treatment for Graves' hyperthyroidism but carries a well-established risk of new-onset or worsening orbitopathy, particularly in active GO, in smokers, and in patients with elevated TRAb.[15,16] The mechanism involves the acute rise in thyroid antigen release post-RAI stimulating an exacerbation of the orbital autoimmune response.[15] The EUGOGO consensus and ATA guidelines both classify active moderate-to-severe GO as a relative contraindication to RAI without concomitant corticosteroid

prophylaxis.[13,17] In patients with vision-threatening GO (dysthyroid optic neuropathy, corneal breakdown), RAI is absolutely contraindicated until the ophthalmic emergency is resolved.[13,17] Thyroidectomy is the preferred definitive modality in patients with active severe GO, as it rapidly reduces antigen load and TRAb levels.[13,17,18]

Antithyroid drugs (ATDs) effectively control hyperthyroidism from both the Graves' and autonomous components, making them an appropriate first-line bridging therapy regardless of an MLS diagnosis.[2,19] While RAI is challenging in MLS due to competing dose requirements — the autonomous nodule demands ablative doses while the Graves' component responds to lower doses — it is also relatively contraindicated in the context of active thyroid eye disease (GO).[1,2,15] Consequently, total thyroidectomy is the preferred definitive treatment for MLS with active moderate-to-severe GO, as a single intervention simultaneously eliminates the autonomous nodule and the Graves' autoimmune source, leading to a rapid reduction in TRAb levels that favorably alters the GO trajectory.[13,17,18] Following treatment, strict post-therapy surveillance with TSH monitoring at 3 to 6-month intervals after ATD discontinuation is mandatory; if ATD therapy achieves remission of the Graves' component, the autonomous nodule may become functionally unmasked as TRAb-driven background stimulation wanes, potentially causing persistent subclinical or overt hyperthyroidism.[2,19] Teprotumumab, an FDA-approved anti-IGF-1R monoclonal antibody for active thyroid eye disease (TED), significantly reduces proptosis, CAS scores, and diplopia based on Phase III trials (OPTIC/OPTIC-X).[20,21] Though not yet EMA-approved, it is used in Europe via compassionate access, with case series suggesting benefit for asymmetric Graves' ophthalmopathy with pseudo-ptosis.[21,22] However, its high cost, 24-week infusion regimen (8 doses), and side-effect profile — notably hearing loss (~10%), hyperglycemia, and muscle cramps — require careful patient counseling.[20,21] **Conclusion:** Unilateral ptosis as the presenting manifestation of Graves' disease represents a diagnostically challenging scenario that demands a structured, multidisciplinary approach. The central lesson of this case is that apparent unilateral ptosis in the thyrotoxic patient must be systematically evaluated for contralateral lid retraction before neurological or structural etiologies are pursued. Measurement of MRD1 bilaterally, combined with Hertel exophthalmometry and orbital MRI, provides the anatomical clarity needed to make this distinction.

The additional finding of Marine–Lenhart syndrome in this case underscores the importance of routine thyroid scintigraphy in the workup of Graves' disease, particularly when nodular disease is detected on ultrasound. Scintigraphy is indispensable for establishing functional autonomy, guiding RAI dosing decisions, and identifying patients who will require additional post-ATD surveillance for unmasked nodular hyperthyroidism.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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