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THE CONCURRENT GRAVES' OPHTHALMOPATHY AND OCULAR MYASTHENIA GRAVIS: A RARE CASE

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ABSTRACT

Background: To raise awareness of clinicians about the possibilities of Graves' ophthalmopathy and ocular myasthenia gravis (MG).

Case Presentation: A 49-year-old female showed ptosis and proptosis at the same time. It was preceded with systemic manifestation of hyperthyroidism, so she was treated with thyrozol and Propylthiouracil. *Harvey-Masland* test revealed positive myasthenia gravis, so she was given pyridostigmine. Ophthalmological examinations revealed eye lid retraction and ptosis on right eye, and proptosis on left eye. Right eye movements were restricted to all direction beside up gaze and down gaze. Left eye movements were restricted to superior, inferior, supero-temporal, infero-temporal, and medial. Diplopia was confirmed by WFDT. Orbital MRI without contrast showed there were thickening of right ocular medial rectus muscle belly and left superior and inferior rectus muscle, without tendinous insertion involvement. Anti-acetylcholine receptor binding and acetylcholine receptor blocking autoantibody were in normal level. Methylprednisolone 48 mg/day was given initially and tapered off into 16 mg/day. At the moment, she only consumed pyridostigmine, methylprednisolone, and celecoxib which were given by the neurologist to control her myasthenia gravis.

Conclusion: A strong suspicion of myasthenia gravis should be considered while dealing with parallel scenarios. Restriction of extraocular eye muscles and diplopia were caused by Graves' ophthalmopathy and ocular MG. The coexistence of both diseases has prognostic relevance in mild expression of MG. The association of both diseases needs further immunological and genetic studies to verify the hypotheses of immunological interaction and genetic.

Keywords: Graves' ophthalmopathy, ocular myasthenia gravis

BACKGROUND

Autoimmune disease is defined as an altered immune response in which it targets host tissue due to lack of self-tolerance and resulting in pathological state of host tissue damage.[1] Autoimmune disease is a product of complex interaction between genetic susceptibilities and various environmental factors and they arise more often in women than men.[2] Manifestation of autoimmune diseases vary and may arise in a specific organ such as in autoimmune thyroid disease and in myasthenia gravis or in multiple organs where it is considered as a systemic disease.[3]

Myasthenia gravis (MG) is an autoimmune disease that caused by autoantibodies directed towards neuromuscular junction proteins. The incidence of MG is rare, about 0.24 to 2.00 per 100.000 per year.[4]Majority of MG expresses autoantibodies against the nicotinic acetylcholine receptor (AChR) while a small subset of MG expresses antibodies against the muscle specific tyrosine kinase (MuSK) or the low-density lipoprotein receptor-related protein 4 (LRP4).[5] Features of this disease includes weakness of affected muscle groups with specific distribution with specific characteristic, in which muscle weakness tends to worsen with activities and improved upon resting.[6] Most of the cases of MG only showed ocular symptoms like ptosis and diplopia, and it can take several years to progress into systemic symptoms.[7]

Autoimmune thyroid disease (ATD) comprises of three major groups of disease: Graves' Disease, Hashimoto Thyroiditis and patients tested positive for anti-thyroid autoantibodies.[8] Graves' disease is characterized by diffuse goiter and thyrotoxicosis due to production of autoantibodies against the thyroid stimulating hormone receptor (TSHR) (TSHR Abs) and behave as thyroid-stimulating antibodies.[9]The annual incidence of Graves's disease worldwide is estimated at about 5 per 10.000 people.[9,10]About 40% of Graves' disease patient shows ocular manifestation that was known as Graves' ophthalmopathy, it may present as ocular myopathy and exophthalmos.[11]

The challenge of diagnosing autoimmune diseases lies in their various signs and symptoms, not just between one illness with another, but also within the same spectrum of disease. Several autoimmune diseases share some common pathophysiology and mechanism which resulted in tissue damage; therefore, it is of no surprise that an individual may have more than one autoimmune disease. Screening for other autoimmune disease in patient with autoimmune thyroid disease when the patient has nonspecific symptoms become crucial.[10]

About 5-7.5% of ATD patients showed the co-existence with MG patients.[12] Rennie et al.[13] had discovered the association between ATD and MG since 1908. MG had been known to be associated with various autoimmune disorders, depending on the type of MG involved. Ocular MG, a subset of MG, had been found to produce thyroid-related antibodies and among patients with thyroid eye disease, a small subset of patients also produce antibodies against AChR.[14,15] Two studies performed by Mao ZF et al.[16] and Bollaert et al.[17] further provided the link between connection of MG and other autoimmune disorder, and also ATD with other autoimmune disease.

The aim of this case study to raise the awareness of clinicians about the possibilities of other autoimmune disease when presented with ATD, like Graves' ophthalmopathy, ocular MG. Therefore, proper examination and early treatment can be accomplished in this rare case.

CASE PRESENTATION

A 49-year-old female complained her right eyelid start dropping, following protruding eye since a year ago. Around four months before her eyes problem significantly altered, she got easily fatigue, felt weak, and sometimes faint. These symptoms were fluctuated, but not specifically worse later in the day. Palpitation, difficulty in sleeping, get easily sweating, unexplained weight gain or loss, tremors, or sensitive to temperature were denied. General practitioner in private hospital told that symptoms were related to exhaustion and stress because she recently lost her family member and encountered difficult time. As faint frequently happening, she was referred to internist to do further examination. The laboratory result showed high FT4 (2.52 ng/dl) and low TSH (<0.01). She was diagnosed with thyroid disease and treated with thyrozol 1x25 mg and Propylthiouracil (PTU).

Following the time, her right eyelid started drooping, followed slight proptosis of the left eye. She admitted diplopia and her eyes look deviated occasionally. She denied pain on and blurry vision during her eye movement. The internist in private hospital diagnosed her with bell's palsy and treated her with electric-muscle stimulation (electrotherapy). As there was no improvement, the patient went to another private hospital for second opinion. The neurologist there conducted electromyography (EMG) and *Harvey-Masland* test, one of clinical EMG to diagnose myasthenia gravis that involves percutaneously stimulating accessible motor neurons with supramaximal shocks during

any specified frequency and monitoring the action potentials of the related muscles. The test was interpreted positive in this patient towards ocular myasthenia gravis, as electrically detected muscle potentials decreased. Then, she was treated with pyridostigmine 3 x 60 mg. After consuming it for three months, she admitted there was a little improvement after consuming it. Internist in the first private hospital confirmed that there were no intracranial abnormalities such as infarction, hemorrhage or tumor causing these symptoms by conducting Brain MRI in October.

Figure 1. Ophthalmological examinations in *Cipto Mangunkusumo Kirana* Hospital in January 2019 revealed the left eye showed slight proptosis with vertical palpebral fissure about 15 mm. Right eye showed ptosis with vertical palpebral fissure about 10 mm and lower eyelid retratction. ocular alignment was orthophoria.

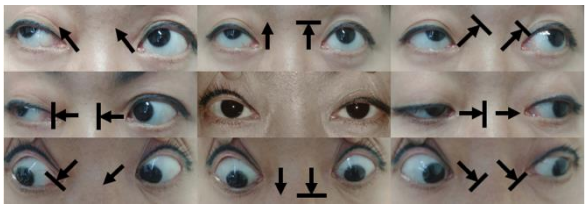

Figure 2. Extraocular movements were restricted during visit visit in *Cipto Mangukusumo Kirana* Hostpital (January 2019). Right eye movements were restricted to all direction beside up gaze and down gaze. Left eye movements were restricted to superior, inferior, supero-temporal, infero-temporal, and medial.

After eight months of these symptoms, the patient sought a second opinion from an ophthalmologist at a private eye hospital. The ophthalmologist explained her about the disease and referred her to Neuro-ophthalmology division, *Cipto Mangunkusumo Kirana* Hospital. She was given methylprednisolone 1x16 mg, but she did not feel any improvement from that drug.

Patient went to *Cipto Mangukusumo Kirana* Hospital in January 2019. Her ophthalmological examination showed both of her visual acuity may reach 6/6 with correction. Her ocular alignment was orthophoria and intra-ocular pressure both eyes were normal. Her right eye showed ptosis and lower eyelid retraction, while her left eye slight proptosis (Figure 1). Both eyes showed restriction during eye movement (Figure 2). Right eye movements were restricted to all direction beside up gaze and down gaze. Left eye movements were restricted to superior, inferior, supero-temporal, infero-temporal, and medial. The anterior and posterior segment showed normal findings. Worth-four-light-dot test (WFDT) revealed there was horizontal diplopia. Crossed diplopia was occurred during her left gaze and uncrossed diplopia during her right gaze. The patient was diagnosed with Graves' ophthalmopathy and ocular myasthenia gravis. methylprednisolone 1 x 48 mg/day was given (0.8 mg/BW) immediately after internist confirmed there was no contraindication. Her other drugs were also continued. Ancillary examinations were planned to support diagnosis and treatment.

Orbital MRI without contrast (Figure 3) showed there were thickening of right ocular medial rectus muscle belly and left superior and inferior rectus muscle, without tendinous insertion involvement. Bilateral retrobulbar fat involvement caused bilateral proptosis in this patient with differential diagnosis thyroid associated orbitopathy. Thoracal CT scan with and without contrast revealed there was no thymoma. Anti-acetylcholine receptor binding and acetylcholine receptor blocking autoantibody were negative (<0.25 nmol/L and <15%, respectively).

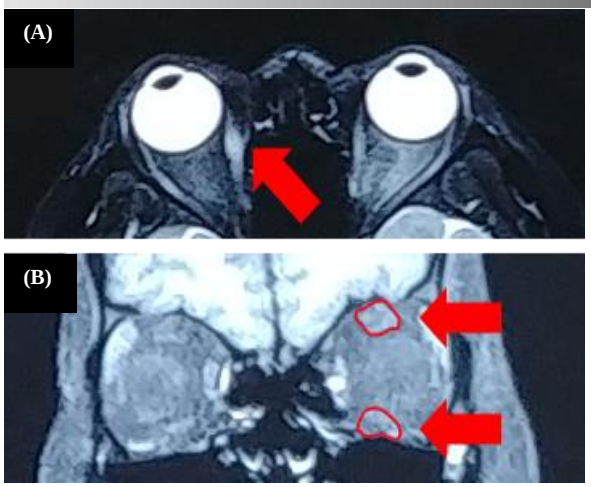

Figure 3. Orbital MRI with axial view (A) and coronal view (B) showed thickening of right ocular medial rectus muscle belly (red arrow) and left superior and inferior rectus muscle (red arrow and circle), without tendinous insertion involvement.

After two weeks control in *Cipto Mangunkusumo Kirana* Hospital, she complained to have difficulty in swallowing. She was referred to the neurologist to find out whether the symptoms related to generalized myasthenia gravis. On the fourth week in *Cipto Mangunkusumo Kirana* Hospital, the patient said diplopia was diminished although her eyelid still showed ptosis on the right eye and proptosis on the left eye. The recent TSH had reached therapeutic goal in normal range 1.49 mU/l. The patient was treated with methylprednisolone tapering weekly from 40 mg/day till reach 16 mg/day. After a month, the ocular conditions were steady and stable, so there was no further treatment from ophthalmologist. The patient was referred to observe the ocular signs and symptoms and focus on her myasthenia gravis in neurology department. Recently, the patient only consumed pyridostigmine 3x60 mg, methylprednisolone 1x16 mg/day, and celecoxib 1x200 mg/day. The sign and symptoms remained stable.

DISCUSSION

Complex interaction between genetic predisposition, environmental, and endogenous factors may lead to defect in immune system. Graves' disease is characterized by the production of autoantibodies that specifically recognize the thyroid stimulating hormone (TSH) receptor on thyroid follicular cells. It results in uncontrolled thyroid hormone production.[18]The laboratory results (high FT4, low TSH) in this patient showed hyperthyroidism followed by classical symptoms such as fatigue, muscle weakness, palpitation, insomnia, and sweating, in which around 80-95% of the cases Extreme emotional factors could trigger this. However, genetic susceptibility could not be excluded prior to further testing such as HLA gene testing.[20]

Graves' disease affects not only thyroid, but also eyes and skin.[21] About 50% of Graves' disease patients show symptoms of Graves' ophthalmopathy,[19] a self-limiting autoimmune disease associated with hyperthyroidism. Although often associated with hyperthyroidism,[22] Graves' ophthalmopathy still develops into euthyroid or hypothyroidism. Therefore, ocular symptoms do not have to occur simultaneously with Graves' disease and may develop hyperthyroidism signs before or after system. Graves' ophthalmopathy generally occurs 18 months after hyperthyroidism.[21,23]

Thyroid and orbital tissue are hypothesized to have a common antigen which might explain the ocular involvement in Graves' disease.[11] Autoantibodies activate heterogenous orbital fibroblasts that can differentiate into adipocytes and myofibroblasts. This process also releases chemokines that allow invasion of T-lymphocytes into orbit and further stimulates fibroblast production. These mechanisms lead to pathological findings found in Graves' ophthalmopathy such as glycosaminoglycan deposition, fibrosis on extraocular muscles and orbital adipogenesis.[11] Proptosis in this case might be due to muscle enlargement and orbital fat

invasion which were found in 70% Graves' ophthalmopathy cases.[24]Based on clinical activity score (CAS) from European Group of Graves' Orbitopathy (EUGOGO),[25] this patient was classified as mild Graves' ophthalmopathy in inactive state. There was no spontaneous pain on eye movement, soft-tissue involvement, and decreased visual acuity. Moreover, as ptosis is generally not seen in Graves' ophthalmopathy, the finding of this symptom led to suspicion of other underlying disease in this case.

Myasthenia gravis is an immune-mediated disorder that manifests in muscle weakness. Autoantibodies prevent Acetylcholine (ACh) molecules in the neuro-muscular junction to bind to acetylcholine receptor (AChR) and thus disturb muscle contraction.[26] Extraocular muscles (EOMs) are prone to be affected in myasthenia gravis because twitch fibers allow faster tension and higher frequency of synaptic firing, therefore causing EOMs to be easily exhausted. Lack of AChR in EOM also causes the fatigue to be more clinically prominent. Unilateral ptosis associated with orbicularis weakness and contralateral eyelid retraction can manifest in ocular myasthenia gravis which might confuse the clinician. Weakness of superior levator palpebral muscle stimulates the increase of eyelid innervation and causes the contralateral eyelid (due to Hearing's law) to be overreacted and presented with lid retraction. However, the patient presented with proptosis in this case, rather than eyelid retraction only. This finding made the clinician can suspect the patient to have other disease.

Graves' ophthalmopathy and myasthenia gravis are related to autoimmune thyroid disease. About 70% cases of ocular myasthenia gravis is preceded by hyperthyroidism. Graves' disease frequently occurs together with ocular myasthenia gravis rather than generalized myasthenia gravis.[27]Based on epidemiological studies, only 0.2% of patients with AITD suffer from MG.[12] This data emphasizes that the coincidence of Graves' disease and MG is a rare findings. The association of Graves' disease and ocular myasthenia gravis is still elusive. Several hypotheses were made, such as immunological cross-reactivity against autoantigens shared by thyroid and eye muscle and genetic factor.[28]Th17 cell and MuSK antibody were found in ocular myasthenia gravis and Graves' disease.[29]Human-leukocyte antigen -B8 and -DR3 have been reported to be found in both disorders.[28] However, the possibility that the occurrence of Graves' ophthalmopathy and ocular myasthenia gravis in this case was not correlated still could not be excluded.[28]

From this case, there were overlapping symptoms of either Graves' ophthalmopathy and ocular myasthenia gravis that might confuse clinicians. Proptosis in this case is specific to Graves' ophthalmopathy. Diplopia might occur due to restriction of ocular motility or ocular muscle weakness.[24]In Graves' ophthalmopathy, inferior and medial rectus are the most susceptible muscle to be involved.MRI findings in this case supported the muscle involvement of Graves' ophthalmopathy. Therefore, the affected muscle restricted the elevation and abduction of EOMs. However, other restriction of eye motilities might be due to ocular myasthenia gravis. Almog Y et al.[30] found that the most affected EOMs in ocular MG was inferior oblique (63.3%), lateral rectus (30%), superior rectus (13.3%), inferior rectus (20%), medial rectus (13.3%), and superior oblique (10%) muscles. Restriction of EOM movement is not typical in myasthenia gravis. The initial signs of myasthenia gravis are ptosis and diplopia (50% of cases).[26] These findings might suggest that there were two disease entities in this patient.

Grave's ophthalmopathy can be diagnosed based on its clinical features, thyroid auto-immunity status, and exclusion

of other diseases. The disease activity and severity are determined by clinical assessment and imaging techniques.[31] Tortora et al.[32]suggested that clinical score should be supported with imaging modalities for diagnosis and treatment. This was supported by Sas et al.[31]where they suggested that imaging assessment of all orbital structures were imperative in every patient with Graves' ophthalmopathy. A study showed that while 50-75% patient only shows can unilateral symptoms clinically, bilateral orbital involvement was discovered by orbital imaging.[33]Moreover, Kirsch EC et al.[33] found that the majority of Grave's ophthalmopathy were bilateral and only 15% cases were unilateral. Therefore, orbital MRI was deemed appropriate and reasonable to be conducted in this case.

Orbital MRI may reveal mild to severe alteration of orbit and inflammation in the extraocular muscle, such as protrusion, muscle thickening or optic nerve edema. Meanwhile, computed tomography (CT) scans help to determine and distinguish orbital components which have different attenuation values. CT-scan can help to plan or determine a surgical decompression of the orbit in the future. However, this imaging has a high risk of radiation and cannot identify inflamed muscle in active stage.[11,34]

In this case, the diagnosis of ocular myasthenia gravis was established based on the clinical manifestation and the positive result of *Harvey-Masland* test (repetitive nerve stimulation) result. The negative serological findings did not exclude ocular myasthenia gravis. AChR-Abs can be found in almost all cases of generalized myasthenia (99%), while autoantibodies are detected in 40 – 77% of ocular myasthenia gravis.[35,36] This might explained why no antibodies were detected in this case. Electrodiagnostic tests are useful in confirming the diagnosis of neuromuscular transmission disorders.[37]Lo YL et al.[38]found that repetitive nerve stimulation has a lower sensitivity compared to single fiber electromyography (SFEMG). However, SFEMG results can be influenced by multiple factors, for example diabetes mellitus, neuropathy, and myopathy. Meanwhile, tensilon test cannot identify well myasthenia gravis with slight symptoms. Clinical examination is the gold standard in diagnosing myasthenia gravis.[39]Ice pack test is a simple clinical test that can be used to evaluate the ptosis related to ocular myasthenia gravis. The sensitivity and specificity of the test is 76.9% and 98.3%, respectively. Resolution of ptosis (elevates at least 2 mm) after applying ice pack for two minutes in the suspected eye might indicate ocular myasthenia gravis.[40]

Restoration of thyroid status into euthyroid state might affect the myasthenia gravis. It is known that myasthenic symptoms improve significantly when hyperthyroidism is treated.[12]Therefore, co-existence of Graves' ophthalmopathy and ocular MG can be managed by restoring and stabilizing thyroid function of the patient.[12] In this case, the patient has reached euthyroid state by consuming PTU and thyrozol for approximately one year.

To date, there is yet an optimal therapy to control the progression of ocular myasthenia gravis. Pyridostigmine is an acetylcholinesterase inhibitor that is commonly used. It has been known to be safe and has been recommended as the first line therapy for myasthenia gravis for over 50 years. Pyridostigmine improves ptosis but is not effective to resolve diplopia. Kupersmith MJ et al.[41] reported that coadministration of pyridostigmine and corticosteroid (prednisone) reduced diplopia and ocular motor dysfunction. Corticosteroid regimen in the study was safe and effective in controlling ocular myasthenia gravis in 73% patients. Oral methylprednisolone in myasthenia gravis help to increase decremental response, reduce twitch tension and lower maximum contraction strength. Corticosteroids provide spontaneous release of Ach in myasthenia

gravis that can improve ptosis and ocular immobility in ocular myasthenia gravis.[42] The patient in this case did not show significant improvement of signs and symptoms. Kupersmith MJ et al.[41]suggested to taper corticosteroid gradually to maintain ocular motor and lid function. Large daily or alternate-day doses of corticosteroids in ocular myasthenia gravis should be further studied, as it has been shown to be effective in generalized myasthenia gravis. Immunomodulator also should be considered as it helps to prevent deterioration of ocular myasthenia gravis into generalized myasthenia gravis. [41]

EUGOGO suggests to administer immunosuppressive therapy in the active stage or moderate to severe Graves' ophthalmopathy, where the lymphocytes and inflammation play a significant role.[25]Oral corticosteroids result in a favorable response in about 30-60% of patients with recent onset eye muscle involvement.[43]In inactive stages, these treatment methods should be avoided due to the side effects of glucocorticoids.[22]In this case, the patient was in inactive and mild stage of Graves' ophthalmopathy but was treated with methylprednisolone. Mourits et al.[44] reported that patients who were evaluated with CAS and presented with mild stages still showed significant response to immunosuppressive treatment. Although EUGOGO guideline is acceptable and widely used, Tachibana S et al.[45]reported that CAS alone could not adequately detect active Graves' ophthalmopathy. Tu X et al.[22] conducted a systematic review and meta-analysis to find out that non-surgical therapies such as radiotherapy, colchicine, immunoglobulin, somatostatin rituximab, MMF, and cyclosporine, were inferior to corticosteroids. Therefore, the methylprednisolone in this case was given not only to treat myasthenia gravis but also Graves' ophthalmopathy.

Early diagnosis and prompt treatment of Graves' ophthalmopathy would therefore lead to at least partial remission in up to 65% of cases. Graves' ophthalmopathy can cause permanent physical disfigurement and functional disability that negatively impact quality life of patient.[46]In addition, untreated ocular myasthenia gravis can cause psychological disturbance due to visible ptosis and diplopia.[47] Ocular myasthenia gravis relapses occur more frequently (41.5%) in single ptosis or diplopia rather than in patients with co-existence of diplopia and ptosis (28.6%).[29]Marinó et al.[28] studied that patients with AITD showed milder expression of myasthenia gravis compared to patients without AITD. The patients had lower thymus abnormalities and AChR-abs. They might provide favourable prognostic factors as generalized myasthenia gravis was less frequent in myasthenia gravis related to AITD.[27]However, if in this case the ocular myasthenia gravis was not associated with Graves' disease, the clinical findings of ptosis or diplopia could serve as potential predictors for generalized myasthenia gravis.[29]About 50% of the patients who showed ptosis and diplopia in ocular myasthenia gravis progresses to generalized myasthenia gravis within two years.[7]

CONCLUSION

The coincidence between Graves' ophthalmopathy and ocular myasthenia gravis is rare, but caution should be made to avoid misdiagnose. Accurate and early diagnosis in such circumstances is a challenge to the clinicians. A strong suspicion of myasthenia gravis should be considered while dealing with parallel scenarios.Most cases of Graves' ophthalmopathy was later followed by ocular myasthenia gravis. Clinical manifestations of both diseases play an important role in establishing the diagnosis. In this case, the keywords of the co-existence two diseases are proptosis, eyelid retraction, diplopia and ptosis. Imaging tests like orbital MRI,

serological tests for AChR-abs and thyroid status, electrodiagnostic tests such as repetitive muscle stimulation/*Harvey-Masland* test used in this case were helpful to confirm the diagnosis. Ice pack test is suggested to be routinely conducted in clinical setting as it is a simple and reliable test to confirm the myasthenic ptosis.

The target management of coexisting Graves' ophthalmopathy and ocular myasthenia gravis is to achieve euthyroid state; therefore, collaboration with other departments is needed. Internists help to treat thyroid disease, meanwhile neurologist should take part to control myasthenia gravis. Corticosteroids is helpful in both diseases by aiding in Ach release in myasthenia gravis that leads to clinical improvement. In the early stages of disease, it is useful to inhibit the inflammation and to obtain Graves' ophthalmopathy remission.

The coexistence of MG with thyroid auto immunity might have prognostic relevance in the identification of a subgroup of MG patients with a mild form of the disease. The association of both diseases needs further immunological and genetic studies to confirm the hypotheses of the interaction between immunological and genetic factors.

REFERENCES

1. Rosenblum MD, Remedios KA, Abbas AK. Mechanisms of human autoimmunity. J Clin Invest.2015;125:2228–33.
2. Desai MK, Brinton RD. Autoimmune Disease in Women: Endocrine Transition and Risk Across the Lifespan. Front Endocrinol. 2019;10:265.
3. Wang L, Wang FS, Gershwin ME. Human autoimmune diseases: a comprehensive update. J Intern Med . 2015;278:369–95.
4. Kubiszewska J, Szyluk B, Szczudlik P, Bartoszewicz Z, Dutkiewicz M, Bielecki M, et al. Prevalence and impact of autoimmune thyroid disease on myasthenia gravis course. Brain Behav. 2016;6:e00537.
5. McGrogan A, Sneddon S, de Vries CS. The Incidence of Myasthenia Gravis: A Systematic Literature Review. Neuroepidemiology. 2010;34:171–83.
6. Gilhus NE. Myasthenia Gravis. N Engl J Med. 2016;375:2570–81.
7. Lin CW, Chen TC, Jou JR, Woung LC. Update on ocular myasthenia gravis in Taiwan. Taiwan J Ophthalmol. 2018;8:67–73.
8. Lin YP, Iqbal U, Nguyen PA, Islam MM, Atique S, Jian WS. The Concomitant Association of Thyroid Disorders and Myasthenia Gravis. Transl Neurosci. 2017;8:27–30.
9. Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev. 2015;14:174–80.
10. Iddah MA, Macharia BN. Autoimmune thyroid disorders. ISRN Endocrinol. 2013;2013:509764.
11. Maheshwari R, Weis E. Thyroid associated orbitopathy. Indian J Ophthalmo. 2012;60:87–93.
12. Chhabra S, Pruthvi BC. Ocular myasthenia gravis in a setting of thyrotoxicosis. Indian J Endocrinol Metab. 2013;17:341–3.
13. Rennie. Exophthalmic goiter combined with myasthenia gravis. J Nerv Ment Dis. 1921;53.
14. H N, Usa T, Motomura M, Ichikawa T, Nakao K, Kawasaki E. Prevalence of interrelated autoantibodies in thyroid diseases and autoimmune disorders. J Endocrinol Invest. 2008;31:861–5.
15. Nacu A, Andersen JB, Lisnic V, Owe JF, Gilhus NE. Complicating autoimmune diseases in myasthenia gravis: a review. J Autoimmun. 2015;48:362–8.
16. Mao ZF, Yang LX, Mo XA, Qin C, Lai YR, He NY. Frequency of Autoimmune Diseases in Myasthenia Gravis: A Systematic Review. Int J Neurosci. 2011;121:121–9.
17. Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM. Prevalence and Relative Risk of Other Autoimmune Diseases in Subjects with Autoimmune Thyroid Disease. Am J Med. 2010;123:183.
18. Bahn RS. Pathophysiology of Graves' Ophthalmopathy: The Cycle of Disease. J Clin Endocrinol Metab. 2003;88:1939–46.
19. Girgis CM, Champion BL, Wall JR. Current concepts in graves' disease. Ther Adv Endocrinol Metab. 2011;2:135–44.
20. Płoski R, Szymański K, Bednarczuk T. The genetic basis of graves' disease. Curr Genomics. 2011;12:542–63.
21. Bahn RS. Graves' ophthalmopathy. N Engl J Med. 2010;362:726–38.
22. Tu X, Dong Y, Zhang H, Su Q.

Corticosteroids for Graves' Ophthalmopathy: Systematic Review and Meta-Analysis. Biomed Res Int. 2018;2018:1–9.
23. Gillespie EF, Smith TJ, Douglas RS. Thyroid eye disease: towards an evidence base for treatment in the 21st century. Curr Neurol Neurosci Rep. 2012;12:318–24.
24. Laurberg P, Berman DC, Pedersen IB, Andersen S, Carlé A. 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. 2015;100:2098–105.
25. Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velázquez-Villoria Á, Galofré JC. Graves' Ophthalmopathy: VISA versus EUGOGO Classification, Assessment, and Management. J Ophthalmol. 2015/08/17. 2015;2015:249125.
26. Nair AG, Patil-Chhablani P, Venkatramani D V, Gandhi RA. Ocular myasthenia gravis: a review. Indian J Ophthalmol. 2014;62:985–91.
27. Masood I, Yasir M, Aiman A, Kudyar RP. Autoimmune thyroid disease with myasthenia gravis in a 28-year-old male: a case report. Cases J. 2009;2:8766.
28. Marinó M, Ricciardi R, Pinchera A, Barbesino G, Manetti L, Chiovato L. Mild Clinical Expression of Myasthenia Gravis Associated with Autoimmune Thyroid Diseases. J Clin Endocrinol Metab. 1997;82:438–43.
29. Wang L-L, Zhang Y, He M-L. Clinical Features and Prognosis of Ocular Myasthenia Gravis Patients with Different Phenotypes. Chin Med J . 2015;128:2682–4.
30. Almog Y, Ben-David M, Nemet AY. Inferior oblique muscle paresis as a sign of myasthenia gravis. J Clin Neurosci [Internet]. 2016;25:50–3.
31. Sas TN, Camen GC, Stefanescu A, Gheonea IA. Imaging Evaluation of the Orbit in Graves Ophthalmopathy. Curr Heal Sci J. 2015;41:285–7.
32. Tortora F, Cirillo M, Ferrara M, Belfiore MP, Carella C, Caranci F. Disease activity in Graves' ophthalmopathy: diagnosis with orbital MR imaging and correlation with clinical score. Neuroradiol J.2013;26:555–64.
33. Kirsch E, Kaim A, Oliveira M, Arx G. Correlation of signal intensity ratio on orbital MRI-TIRM and clinical activity score as a possible predictor of therapy response in Graves' orbitopathy-a pilot study at 1.5 T. Neuroradiology. 2009;52:91–7.
34. Daubner D, Spieth S, Engellandt K, von Kummer R. Diagnosis and differential diagnosis of Graves' orbitopathy in MRI. Radiologe. 2012;52:550–9.
35. Extraocular muscles: relationship of structure and function to disease. Aust N Z J Ophthalmol [Internet]. 1999;27:369–70.
36. Selvan C, Dutta D, Maisnam I, Thukral A, Chakraborthy PP, Roy A. Thyroid associated orbitopathy with ocular myasthenia in primary hypothyroidism: Keep those eyes open. Indian J Endocrinol Metab. 2013;17:S657–9.
37. Howard JF, Sanders DB, Massey JM. The Electrodiagnosis of Myasthenia Gravis and the Lambert-Eaton Myasthenic Syndrome. Neurol Clin. 1994;12:305–30.
38. Lo Y-L, Dan Y-F, Leoh T-H, Tan Y-E, Nurjannah S, Ratnagopal P. Effect of Exercise on Repetitive Nerve Stimulation Studies: New Appraisal of an Old Technique. J Clin Neurophysiol. 2004;21:110–3.
39. Lo YL, Najjar RP, Teo KY, Tow SL, Loo JL, Milea D. A reappraisal of diagnostic tests for myasthenia gravis in a large Asian cohort. J Neurol Sci. 2017;376:153–8.
40. Chatzistefanou KI, Kouris T, Iliakis E, Piaditis G, Tagaris G, Katsikeris N. The Ice Pack Test in the Differential Diagnosis of Myasthenic Diplopia. J Ophthalmol. 2009;116:2236–43.
41. Kupersmith MJ, Ying G. Ocular motor dysfunction and ptosis in ocular myasthenia gravis: effects of treatment. Br J Ophthalmol. 2005;89:1330–4.
42. Homiyama A, Arai H, Kijima M, Hirayama K. Extraocular muscle responses to high dose intravenous methylprednisolone in myasthenia gravis. J Neurol Neurosurg Psychiatry. 2000;68:214–7.
43. Yang DD, Gonzalez MO, Durairaj VD. Medical management of thyroid eye disease. Saudi J Ophthalmol Off J Saudi Ophthalmol Soc. 2011;25:3–13.
44. Mourits M. Graves' orbitopathy: A multidisciplinary approach. Karger. 2007;66–77.
45. Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for Graves’ ophthalmopathy. Endocr J. 2010;57:853–61.
46. Yeatts RP. Quality of life in patients with Graves ophthalmopathy. Trans Am Ophthalmol Soc. 2005;103:368–411.

47. Jeong A, Min J-H, Kang YK, Kim J, Choi M, Seok JM, et al. Factors associated with quality of life of people with Myasthenia Gravis. PLoS One. 2018;13:e0206754.