IMMUNOLOGIC BASIS OF MYASTHENIA GRAVIS WITH SUBSEQUENT PREMATURE OVARIAN INSUFFICIENCY: A CASE REPORT

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CASE

A 25-year old nulligravid had regularly occurring menstrual cycles until she noted amenorrhea 2 years after presenting with lower extremity weakness.

In 2014, she experienced lower extremity weakness which spontaneously resolved after one month. In 2016, the diagnosis of MG was made. A month into starting immunomodulating therapy, she had myasthenic crisis occurring during menses. Oligomenorrhea was reported for three months which eventually progressed to amenorrhea. She underwent thymectomy in 2018 and reported good control of symptoms post-operatively.

She had adult secondary sexual characteristics and normal pelvic examination. Pregnancy test was negative. The diagnosis of POI was made after two measurements of serum follicle stimulating hormone (FSH) were found in the menopausal range. Except for positive acetylcholine receptor antibodies, the rest of the work-up were unremarkable (Table 1). Transvaginal ultrasound showed a small-sized uterus with linear endometrium and atrophic ovaries. Dual energy x-ray absorptiometry showed a lumbar spine T score of -4.5, equivalent to osteoporosis. Lipid profile and fasting glucose level were normal.

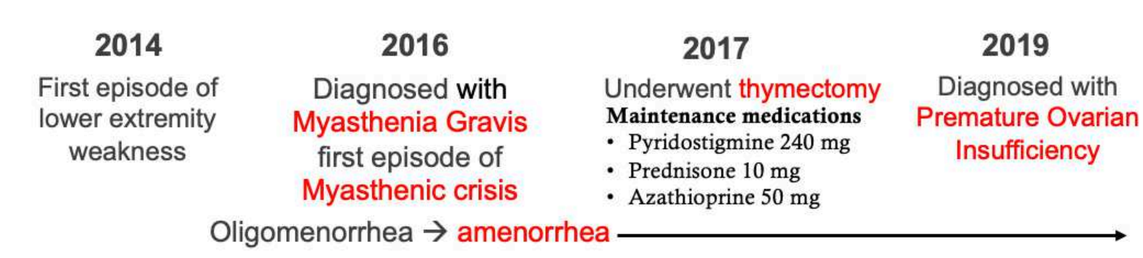


Table 1. Results of Diagnostic Tests

Diagnostics	Results
Electromyography	**Decrements of action muscle potential**
Acetylcholine receptor antibody	**289 nmol/L** (*high*)
Follicle stimulating hormone	**1st: 85.63 mIU/mL** *(high)* **2nd: 67.57 mIU/mL** *(high)*
Estradiol	**43 pg/mL** *(low)*
TSH	1.957 IU/mL
Prolactin	26.26 ng/mL
Karyotyping	46, XX
Fragile X mental retardation 1 (FMR1) gene premutation screening	Negative
Anti-ovarian antibodies	2.19 RU/ mL
Thyroid peroxidase antibodies	0.23 IU/mL
Steroid cell/ adrenocortical antibodies	Not available

OUTCOME

The patient was monitored monthly for 3 months until a maintenance dose of HRT was established, and regular menses resumed. She is on her second year of follow-up. The patient is compliant and tolerates her medications. MG maintenance medications were down-titrated every 3 months. No exacerbations were noted. Thereafter, symptom control and complication screening have been done annually.

DISCUSSION

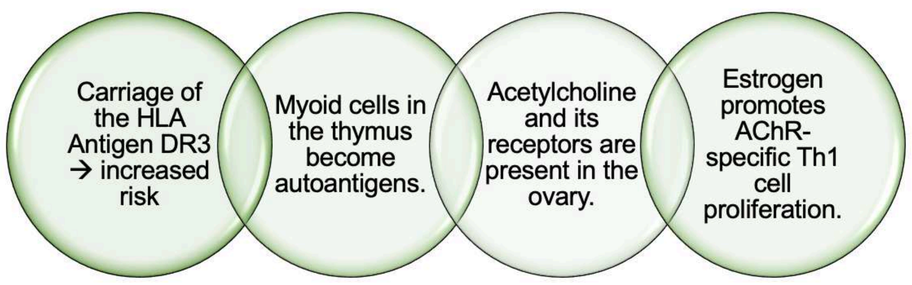
Patients who have POI with MG are fewer than 1%.(1) There is ovarian resistance to endogenous or exogenous hormonal activation as the autoantibodies competitively antagonize FSH or luteinizing hormone (LH). Uncontrolled thymic expression of antigens specific to the ovaries may contribute to the ovarian autoimmune disease.(2)

There are 8 documented cases of MG accompanied by POI and are summarized in Table 2.(3) The women were in the first decade of their reproductive debut with ages ranging from 15-27 years all presenting with symptoms of MG. Fifty percent manifested with symptoms of MG first followed by POI after several years. Six of the cases (75%) were positive with AChR Ab. Other antibodies seen were anti-leutinizing hormone antibody (12.5%), AOA (12.5%), and thyroglobulin antibody (12.5%), each occurring solely in 3 separate cases. Only one case underwent ovarian biopsy and it showed lymphoid oophoritis, but it is not recommended for the confirmation of autoimmune POI.(2) Majority (75%) of the reported cases of MG with POI were from Asia.

Table 2. *Summary of the Cases with Myasthenia Gravis with POI. (Adapted from Liu, et. al., 2018)[2]*

Patient profile	Year of Study							
	1981 (Kuki et. al., 1981)[11]	1993 (Chung et. al., 1993)[12]	2004 (Ryan et. al., 2004)[13]	2010 (Li et. al., 2010)[8]	2010 (Dong et. al., 2010)[14]	2011 (Cakir et. al., 2011)[4]	2018 (Liu et. al., 2018)[2]	2021 (Agbayani and Habana, 2021)
Age at Onset	19	26	27	19	15	18	23	21
Clinical presentation	Diplopia Fluctuating weakness Bulbar muscle weakness	Ptosis Easy fatigability Upper extremity weakness	Difficulty with fine motor on the right hand Bulbar muscle weakness	Ptosis Easy fatigability Limb muscle weakness Respiratory muscle weakness	Generalized myasthenia gravis	Generalized myasthenia gravis	Ptosis Dysarthria Dysphagia Easy fatigability	Generalized myasthenia gravis
Temporal relationship the two diseases	POI occurring 2 years after MG	Diagnosed with MG followed by POI shortly	POI occurring 12 years before MG	Simultaneous occurrence	POI occurring 3 years earlier than MG	POI occurring 3 years after MG	POI occurring 1 year earlier than MG	POI occurring 2 years after MG
Hormonal Assays	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol	Elevated FSH Reduced serum estradiol
Auto-antibody screening MG	N/A	N/A	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab	(+) AChR Ab
POI	Anti-LH Ab (+)	N/A	N/A	(+) AOA	N/A	(-) AOA (-) TGAb (-) TMA (-) Anti-21-hydroxylase enzyme Ab	(-) ANA (+) TGAb (+) TMA	(-) AOA (-) AntiTPO Ab
Ovarian biopsy	N/A	N/A	(+) lymphoid oophoritis	N/A	N/A	N/A	N/A	N/A

The co-existence of MG and POI represents a disorder of impaired immunoregulation involving the thymus gland, AChRs, and estrogen. Carriage of the HLA antigen DR3 result in over-reactivity of T cells. Myoid cells in the thymus express AChRs and trigger an autoimmune reaction. ACh and its receptors are also found in the ovary and are attacked by AChR Ab.(2) Estrogen promotes AChR-specific Th1 cell expansion and autoreactive B cells.(9)



Women with MG and POI are in a pathologic state of estrogen deficiency.

The goals of therapy require a multi-specialty approach and are as follows: to control MG, to relieve menopausal symptoms, to protect against cardiovascular diseases, stroke, cognitive decline and osteoporosis, and to improve quality of life. HRT should be continued until at least at age 52 years.(5,3) Immunomodulating therapy for MG also help to restore menses. Future pregnancies are achieved through in-vitro fertilization using donor oocytes or embryos.(5) Psychological support is an integral part of the management.(3) Monitoring for the long-term sequelae of POI should be done annually.(5)

Future research should be aimed at identifying the autoimmune link, reversing or slowing down the destructive effects of AI to ovarian function, and identifying women with MG who are at most risk for autoimmune POI. Longer follow-ups will allow monitoring of the two diseases' progression and interplay.

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