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Myasthenia gravis and premature ovarian failure — a causal link

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To the Editors:

Myasthenia gravis (MG) is a well-recognised autoimmune disease of the postsynaptic neuromuscular junction resulting in fluctuating weakness and fatigue of the skeletal muscles. Autoantibodies against the acetylcholine receptor (AChR) are most commonly found in MG. Like other autoimmune conditions, MG has been reported in association with thyroiditis, pernicious anaemia and systemic lupus erythematosus [1]. Premature ovarian failure (POF) is defined as anovulation with amenorrhoea in females younger than 40 years with evidence of hypo-oestrogenic and hypergonadotropic serum levels [2]. Recognised as being of autoimmune aetiology, there have been, however, very few reports on POF in conjunction with MG. We herein describe two cases of MG with coexisting POF, and perform a brief literature review.

Case 1

A 24-year-old nulliparous woman presented with bilateral thigh weakness, ptosis and diplopia for the past two years. She had also been afflicted with amenorrhoea two years preceding the limb weakness. Attaining menarche at the age of 14, her menses had always been regular. On examination, she had normal secondary sexual characteristics and there were no features of hypothyroidism, hyperpigmentation or vitiligo. She had bilateral incomplete ptosis with a normal visual field. The muscle power of both hips was 3/5. Antibodies to the AChR were detected. Computed tomography (CT) of the chest revealed no thymic enlargement. Her single-fibre electromyography (SFEMG) showed prolonged jitter and repetitive nerve stimulation (RNS) revealed a significant decremental response. She had hypo-oestrogenemia with a post-menopausal range of follicle-stimulating hormone (FSH) and luteinising hormone (LH) levels. She was treated with pyridostigmine 60 mg four times a day and azathioprine 75 mg daily. She was referred to a gynaecologist, and after much deliberation oral contraceptives (OCPs) were prescribed as treatment. After six months of treatment, she remained asymptomatic of MG and her menses resumed. Her condition has been stable with pyridostigmine 60 mg once daily and azathioprine 75 mg daily since then. Her periods have been regular without OCPs in the last six months of follow up.

Case 2

A 35-year-old para 1 woman presented with bilateral ptosis at the end of each day of three months' duration. Cessation of menses had occurred seven months preceding the ptosis. Upon review, there was bilateral ptosis with fatigability. Antibodies to the AChR were positive. Her SFEMG showed prolonged jitter with positive RNS study. Her blood tests revealed hypo-oestrogenemia with a post-menopausal range of both FSH and LH levels. Her chest CT revealed a thymic mass, for which thymectomy was performed. The histology concluded that the resected tissue was follicular thymic hyperplasia. She regained menses 20 months after thymectomy, and her symptoms of MG were controlled with a low dose of pyridostigmine.

Human ovaries have long been recognised as a target for autoimmune attacks leading to ovarian dysfunction, especially premature ovarian failure (POF). POF is heterogeneous and

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Table 1. Summary of our case series and previously reported cases

	Case 1	Case 2	Williams on, 1980 (1) [6]	Williams on, 1980 (2) [6]	Kuki, 1981 [8]	Bateman, 1983 [5]	Chung, 1993 [11]	Ryan, 2004 [1]	Li, 2010 [7]	Çakir, 2011 [9]
Age at onset (MG)	24	35	19	17	23	21	27	41	19	15
Age at onset (POF)	22	35 (7 months preceding MG symptoms)	18	29	19	21	27	27	19	18
MG symptoms	Ptosis, diplopia, proximal lower limb weakness	Ptosis, fatigability	Muscle weakness	Muscle weakness	Diplopia, bulbar muscle weakness	Muscle weakness	Ptosis, fatigability, proximal muscle weakness	Diplopia, fatigability, difficulty with fine motor manipulations	Ptosis, fatigability, proximal muscle weakness, respiratory muscle weakness	Ptosis, muscle weakness
Anti-AChR Ab	+	+	N/A	N/A	N/A	N/A	N/A	+	+	+
Ab related to POF	N/A	N/A	AOA +	AOA +	Anti-LH Ab +	N/A	N/A	Anti-FSH Ab +	AOA +	AOA -
Ovarian biopsy	N/A	N/A	+	+	N/A	+	N/A	+	N/A	N/A
Treatment	Pyridostigmine, azathioprine	Thymectomy, pyridostigmine	Ambenonium, OCP	Thymectomy, pyridostigmine, prednisolone	Thymectomy, pyridostigmine, hormone	Thymectomy, PE	Thymectomy, pyridostigmine, HRT	Thymectomy, pyridostigmine, HRT	PE, pyridostigmine, prednisolone	Pyridostigmine, prednisolone, thymectomy
MG outcome	Good	Good	Partial response	Partial response	Partial response	Good	Good	Worse during menstruation Improved with thymectomy	Worse with HRT	Partial response
Resumption of menses	Yes	Yes	No	No	No	Yes	Spontaneous pregnancy	No	No	Yes

	Liu, 2018 [12]	Cao, 2019 (1) [13]	Cao, 2019 (2) [13]	AlAsiri, 2020 [14]
Age at onset (MG)	23	20	21	37
Age at onset (POF)	22	20	21	17
MG symptoms	Ptosis, fatigability, dysarthria, dysphagia	Unexplained exhaustion on walking short distances	Right eyelid ptosis, diplopia	Right eyelid ptosis, diplopia, easy fatigability, weakness in upper limbs
Anti-AChR Ab	+	+	+	+
Ab related to POF	N/A	N/A	N/A	-
Ovarian biopsy	N/A	N/A	N/A	N/A
Treatment	Pyridostigmine, thymectomy, methylprednisolone and IVIg	Pyridostigmine, methylprednisolone, mycophenolate mofetil	Pyridostigmine, thymectomy	Pyridostigmine, HRT
MG outcome	Worse with HRT Remitted after immunosuppressants	Good	Good	N/A
Resumption of menses	Yes	Yes	No	No

Ab — antibody; MG — myasthenia gravis; POF — premature ovarian failure; AChR — acetylcholine receptor; N/A — not available; AOA — anti-ovarian antibody; PE — plasma exchange; OCP — oral contraceptive pill; HRT — hormone replacement therapy; LH — luteinising hormone; FSH — follicle-stimulating hormone; IVIg — intravenous immunoglobulin

can be due to other causes such as environmental factors, genetic aberrations, and metabolic conditions. Up to 20% of patients with POF are reported to have concomitant autoimmune conditions such as adrenal insufficiency, thyroiditis, and/or diabetes mellitus [3].

POF is also well known as a part of autoimmune polyglandular syndrome. Myasthenia gravis (MG) is an autoimmune disorder with autoantibodies against the acetylcholine receptor (AChR) most commonly found. These autoantibodies are detected in up to 90% of MG patients. Other antibodies found in MG are directed to muscle-specific receptor tyrosine kinase (MuSK), which is a transmembrane component of the postsynaptic neuromuscular junction, and to lipoprotein-related protein 4 (LRP4), which is an agrin receptor needed for agrin-induced activation of MuSK and AChR clustering and neuromuscular junction formation. Only a minority of MG patients are seronegative. It has been reported that MG patients might have an increased number of oestrogen receptors α in thymocytes and peripheral T lymphocytes [4]. This finding could propagate the development of POF. It has been hypothesised that AChR could exist in the ovaries, and that cross-reactivity with antibodies to the muscles and AChR could explain POF associated with MG [5]. Autoimmunity is further strengthened by the presence of anti-ovarian antibodies (AOA) found in three patients with MG and POF [6, 7].

Interestingly, in our literature review, one patient was found to have autoantibodies directed to the follicle-stimulating hormone, and another patient had autoantibodies against the luteinising hormone [1, 8]. AOA were not tested in our two cases as the test is not available in our country, which is a limitation of our study. However, the significance of the presence of circulating AOA and their predictive value in diagnosing POF are matters for discussion.

Both our cases presented with secondary amenorrhoea preceding MG, with no other associated autoimmune condition. One of our patients resumed her menses after thymectomy, which accords with the cases published by Bateman and Çakir [5, 9]. This indicates that the thymus might play a role in the pathogenesis of both conditions, which are already known to be a source of driving autoimmunity. AChR autoantibodies are thought to originate from the hyperplastic germinal centres in the thymus. This could well explain why most of the reported cases, including our two, are AChR positive where a causal link is observed. Genetic factors may contribute to the pathophysiology of immune-mediated diseases, namely the human leukocyte antigen (HLA) types. For instance, HLA-DR3 is significantly associated with POF as well as with MG [10]. A summary of our patients and other published cases is appended to this article (Tab. 1).

In conclusion, there is a causal link between MG and POF, the occurrence of which is not purely coincidental. This is based upon the presence of autoantibodies, and the resolution of amenorrhoea after thymectomy or immunotherapy in some cases. Further large-scale studies are required in order to provide better insights into the pathogenesis of both these diseases.

Conflict of interest: *The authors declare that they have no conflict of interest.*

Ethical approval: *This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.*

Informed consent: *Informed consent was obtained from both patients in this study.*

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