

Is a presynaptic pattern in myasthenia gravis an overlap syndrome?

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Introduction

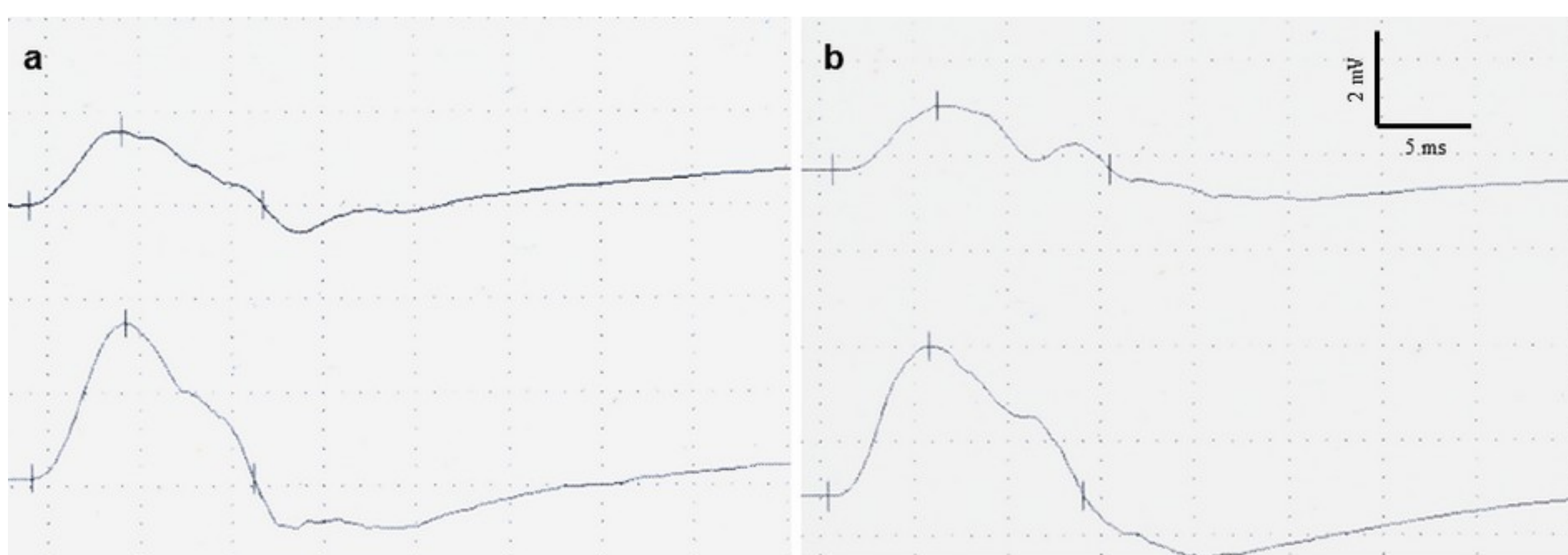
Myasthenia gravis (MG) and the Lambert-Eaton myasthenic syndrome (LEMS) are characterized by different clinical, neurophysiological and immunological features. Auto-antibodies (Abs) directed against post-synaptic membrane are detected in MG (acetylcholine receptor (AChR) in 85% of cases; muscle-specific kinase (MuSK) in 5-8% and lipoprotein receptor-related protein 4 (Lrp4) in a low proportion of cases); whereas in LEMS auto-Abs, directed against the voltage gated calcium channels (VGCC) of pre-synaptic membrane, are observed in large majority of cases (85-90%). Bulbar involvement is frequent in MG. Limb proximal weakness, hypo/areflexia, autonomic dysfunction and the association with small cell lung cancer (SCLC) are the main characteristics of LEMS.

We report two cases with a clinical diagnosis of MG and neurophysiological features consistent with a pre-synaptic defect of neuromuscular transmission. We reviewed English literature studies on co-existing features of MG and LEMS, and discuss diagnostic controversies.

Case reports

A 46 year-old woman and a 56 year-old man diagnosed with generalized MG were referred to our Institution. Both patients had weakness predominant in limb proximal muscles, electrophysiological studies showing a presynaptic pattern (+400% and +135% respectively) (Figure 1), no autonomic dysfunction, positive results on AChR Ab assay and undetectable VGCC Abs. Both patients improved on cholinesterase inhibitors (ChE-Is), 3,4-diaminopyridine (3,4-DAP) was ineffective; steroid treatment led to good control of symptoms. No associated tumours were found in the female patient during the 9-year follow up; whereas in the male patient, a PET/CT scan detected, at 21 months from the disease onset, an increased activity in the caecum (a biopsy revealed a carcinoma in situ).

Figure 1



Legend. Nerve conduction studies of peroneal nerve, recording from tibialis anterior, of male patient. Upper traces: CMAP at rest (1.4 mV for right nerve in a, and 1.3 mV for left nerve in b). Lower traces: CMAP after brief exercise (3.3 mV for right nerve in a, and 3.1 for left nerve in b). A significant increment of CMAP amplitude is shown (around 135% for both nerves).

Results

To date 36 patients (18 men and 18 women) with co-existing features of MG and LEMS have been described in the English literature. In 22 (61%) clinical and electrophysiological findings of MG and LEMS occurred simultaneously. Oculo-bulbar symptoms and limb weakness had the same frequency (in 35/36 patients, 97%). Tendon reflexes were hypo-evocable in 23 patients (64%); dysautonomia was reported in ten (28%). On electrophysiological studies, 33 cases (92%) had a pre-synaptic pattern; two a post-synaptic defect (SCLC was found in both cases); no neuro-muscular transmission defect was detected in one patient, (both AChR and VGCC Abs were present). AChR Abs were positive in 20/24 (83%) and VGCC Abs in 8/12 (66%) tested patients; both AChR and VGCC Abs were present in six patients; MuSK and VGCC Abs in a single case. Twenty-seven patients tried ChE-Is, with a definite improvement in 20 (88%); no patient responded to 3,4-DAP alone, but a combination of 3,4-DAP and ChE-Is was beneficial in four cases (Table 1). Five SCLCs and one thymoma were recorded.

Discussion and conclusion

The coexistence of MG and LEMS (overlap syndrome) is controversial. In earlier studies, this entity was diagnosed on the association of oculo-bulbar symptoms, response to ChE-Is, proximal limb weakness, reduced tendon reflexes and a presynaptic pattern on neurophysiological studies. Currently, the diagnosis of “true” overlap syndrome should be reserved to patients with immunological confirmation of both MG and LEMS, even though negative results on Abs assays do not exclude each single diagnosis (Figure 2). Whether a pre-synaptic pattern in MG patients represents an indication for tumour-screening as recommended in LEMS warrants further studies. This protocol proved very useful in our male patient in whom PET-CT scan detected a bowel carcinoma in situ. The distinction between MG with pre-synaptic pattern and overlap syndrome and the underlying mechanisms are still undefined.

References

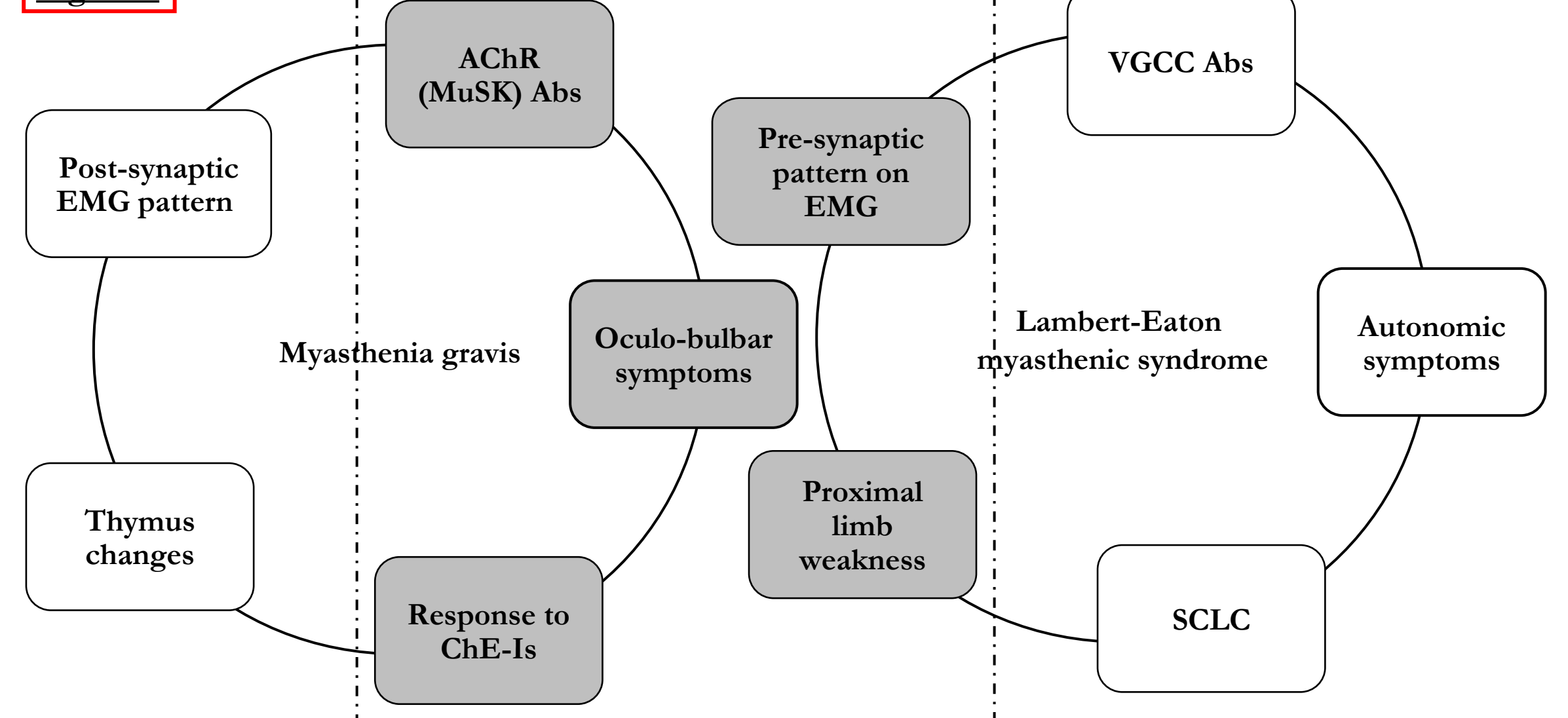
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Table 1

Studies	Age/ Gender	Weakness		Hypo/ areflexia	Autonomic dysfunction	Antibodies		EMG pattern	Response to	
		Oculo- bulbar	Limb			AChR	VGCC		ChE- Is	3,4- DAP
Takamori, 1972	33/F	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
	32/F	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
	33/M	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
	56/F	+	+	+	-	n.d.	n.d.	presynaptic	+	n.d.
Dahl, 1974	13/M	-	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
Oh, 1974	63/M	+	-	+	-	n.d.	n.d.	presynaptic	+	n.d.
Schwartz, 1975	47/F	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
Mori, 1976	50/M	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
Cherrington, 1976	43/M	+	+	-	-	n.d.	n.d.	presynaptic	+	n.d.
Fettel, 1978	58/M	+	+	+	+	+	n.d.	presynaptic	+	n.d.
Singer, 1981	58/F	+	+	-	-	+	n.d.	presynaptic	+	n.d.
Tabaa, 1986	42/M	+	+	+	+	+	n.d.	normal	-	n.d.
Sanders, 1987	77/M	+	+	+	-	+	n.r.	presynaptic	n.r.	n.d.
	41/F	+	+	-	-	+	n.r.	presynaptic	n.r.	n.d.
	51/F	+	+	-	-	n.r.	n.r.	presynaptic	n.r.	n.d.
	48/M	+	+	-	-	+	n.r.	presynaptic	n.r.	n.d.
	41/F	+	+	-	-	+	n.r.	presynaptic	n.r.	n.d.
	61/M	+	+	+	-	n.r.	n.r.	presynaptic*	n.r.	n.d.
55/M	+	+	+	-	n.r.	n.r.	postsynaptic	n.r.	n.d.	
Taphroon, 1988	80/F	+	+	+	-	+	n.r.	presynaptic	+	n.d.
Brenna, 1988	61/M	+	+	+	+	-	n.r.	presynaptic	-	n.d.
Newsom- Davis, 1991	59/M	+	+	+	+	+	+	presynaptic	+	+
	31/F	+	+	+	-	+	+	presynaptic	n.r.	n.r.
Katz, 1998	47/F	+	+	+	+	+	+	presynaptic	-	n.r.
	66/M	+	+	+	+	+	-	presynaptic	+	n.r.
Kanzato, 1999	57/M	+	+	+	-	+	+	presynaptic	+	+
Matsumoto, 1999	60/M	+	+	+	-	+	-	presynaptic	n.r.	n.r.
Patel, 2004	21/F	+	+	-	+	+	-	presynaptic	+	n.r.
Oh, 2005	26/F	+	+	+	-	+	+	presynaptic	+	n.r.
Roohi, 2006	70/F	+	+	+	-	+	+	postsynaptic	+	n.r.
Sha, 2007	18/F	+	+	+	-	+	n.r.	presynaptic	+	+
Basta, 2012	56/M	+	+	+	-	- (MuSK+)	+	presynaptic	+	n.r.
Iqbal, 2012	73/F	+	+	+	+	-	-	presynaptic	+	+
Kim, 2012	48/F	+	+	+	-	+	n.r.	presynaptic	+	n.r.
Lee, 2012	57/M	+	+	+	+	+	n.r.	presynaptic	+	n.r.
Kurt, 2013	52/F	+	+	+	+	-	+	presynaptic	+	n.r.
Our patients	46/F	+	+	+	-	+	-	presynaptic	+	-
	56/M	+	+	+	-	+	-	presynaptic	+	+

Legend. Shaded areas show patients with both MG and LEMS specific antibodies. *EMG pattern changed into post-synaptic after cancer treatment

Figure 2



Legend. The dashed box collects the main characteristics of reviewed patients with MG and LEMS features