Recognition and Treatment of Concurrent Amyotrophic Lateral Sclerosis and Myasthenia Gravis

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a motor neuron disorder presenting with progressive weakness with both lower and upper motor neuron findings. Myasthenia Gravis (MG) is an autoimmune neuromuscular junction (NMJ) disorder, which presents with fatigable weakness, nasal speech, fluctuating ophthalmoparesis and ptosis. Both cause skeletal muscle weakness, although ocular and eyelid weakness is typically not seen early in ALS. Clinical features of both, with appropriate interpretation of serological, electrodiagnostic, and clinical data, may indicate the rare co-occurrence of the two disorders.

CASE PRESENTATION

An 80-year-old patient was referred to our neuromuscular clinic with a three-year history of fatigable dysarthria. The character of the dysarthria was described as fluctuating and "slurred", and modest in severity. It was described as episodic and fatigable, and chewing fatigue was noted. Approximately six months prior, the patient developed dysphagia that progressively worsened, which prompted presentation to a neurologist. Dysphagia was noted to be primarily for liquids, affecting his pharyngeal swallow, without significant aspiration events. Hyponasal speech without nasal regurgitation, with slurring, was noted by speech language pathology. A mild bilateral ptosis was observed. The patient also developed a mild, fatigable (Medical Research Council scale 5/5 to 4/5) proximal upper and lower limb weakness, best in the morning and worsened over course of day. Given the patient's age and clinical presentation with fatigable bulbar and proximal limb weakness, generalized myasthenia gravis was the putative diagnosis and pyridostigmine 60 mg every six hours was trialed for symptom relief; however, this medication provided no benefit. No thymic hyperplasia or other pathology was observed on chest imaging of the patient. The patient subsequently developed symptomatic tachypnea with respiratory compromise and required hospitalization. He had marked improvement with intravenous immune globulin (IVIG) at a dose of 2 g/kg over five days with regards to respiration and dysphagia. He did not require intubation. Acetylcholine receptor (AChR) binding and modulating antibodies, and muscle specific kinase (MUSK) were sent (prior to IVIG administration), with AChR binding antibody resulting as a positive (0.21 nmol/L). MUSK antibody and AChR modulating antibodies resulted as negative. Creatine phosphokinase (CPK) level was normal (171 IU/L). He was discharged from the hospital in an improved state, with normal extraocular movements, improved proximal limb strength without fatigability, and 2+ patellar and biceps deep tendon reflexes with down going toes, although dysarthria remained.

In the subsequent four weeks post-hospitalization, the patient developed a progressive neck extensor weakness, sialorrhea, hyperreflexia including Hoffman signs and upgoing plantar reflexes bilaterally, as well as a jaw jerk reflex, and a worsened, mixed lingual/flaccid more than spastic dysarthria. The observed hyperreflexia and mixed speech dysfunction were not noted upon hospital discharge by the referring physician. Given significant symptom burden, and concern for respiratory compromise in the outpatient setting, he was given additional treatment with IVIG. Unfortunately, this repeat course of IVIG was not helpful.

An electromyogram (EMG), with accompanying nerve conduction study (NCS) with slow Repetitive Nerve Stimulation (RNS) demonstrated diffuse, ongoing and chronic denervation and reinnervation changes, involving the craniobulbar, cervical, thoracic, and lumbosacral bodily segments [**Table 1**], and >10% decrement in both the nasalis and the abductor digiti minimi muscles, more prominently abnormal at the nasalis [**Table 2**].

The patient's age and presenting symptoms of fatigable flaccid dysarthria and proximal bodily weakness prompted the initial putative diagnostic work-up of a generalized myasthenia gravis. The positive acetylcholine receptor binding antibody titer, followed by marked response to immune modulation with IVIG, bolstered this hypothesis. However, as the syndrome progressed, with development of more significant upper and lower motor neuron dysfunction, and lack of response to a second round of IVIG led to a change in diagnostic evaluation. The electrodiagnostic data from EMG met criteria for definite ALS via the El Escorial Criteria, as well a post-synaptic myasthenic syndrome, supporting

Table 1. Electromyogram Results

			Spontaneous					MUAP			Recruitment
Muscle	**Nerve**	**Roots**	**IA**	**Fib**	**PSW**	**Fasc**	**H.F.**	**Amp**	**Dur.**	**PPP**	**Pattern**
L. Biceps brachii	Musculocutaneous	C5-C6	2+	3+	3+	None	None	1+	1+	1+	Reduced
L. Triceps brachii	Radial	C6-C8	N	None	None	2+ (fast)	None	1+	1+	N	Reduced
L. Abductor digiti minimi (manus)	Ulnar	C8-T1	1+	1+	1+	1+	None	1+	1+	N	Reduced
L. First dorsal interosseous	Ulnar	C8-T1	1+	2+	2+	1+	None	2+	2+	N	Discrete
L. Flexor carpi radialis	Median	C6-C7	1+	2+	2+	1+	None	1+	1+	N	Discrete
L. Vastus medialis	Femoral	L2-L4	N	None	None	1+	None	1+	1+	1+	Reduced
L. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	N	None	Few	1+	None	1+	1+	N	Discrete
L. Gastrocnemius (Medial head)	Tibial	S1-S2	1+	2+	2+	1+	None	N	N	N	Reduced
L. Thoracic paraspinals	Spinal	T1-T12	1+	2+	2+	None	None	N	N	N	Reduced
L. Cervical paraspinals	Spinal	C4-C8	1+	2+	2+	None	None	1+	N	2+	Reduced
L. Geniogloss us	Hypoglossal	Medulla-	2+	3+	3+	None	None	N	N	N	N

Electromyogram demonstrating active and chronic denervation in bulbar, cervical, thoracic, and lumbar body regions, consistent with Revised El Escorial criteria for definite ALS.

Table 2. Repetitive Nerve Stimulation Results

Anatomy/Train	Rate Hz	Amp mV	4–1 %	Facilit %
L Nasalis				
Baseline	3	0.8	–4.9	100
Baseline 2	3	0.8	–15.1	106
Post exercise 10sec (technically lim)	3	0.4	57.6	49
Post exercise 10 sec	3	0.9	–10.7	119
1 min	3	0.9	–12.9	121
2 min	3	0.9	–12.3	121
4 min	3	0.9	–37.2	121

Repetitive Nerve Stimulation of the left nasalis muscle with evidence of >10% decrement from baseline, consistent with neuromuscular junction disorder.

co-morbid ALS and MG. He was treated symptomatically with prednisone and dietary modification. He elected not to start riluzole to slow the progression of ALS. He transitioned to hospice care and died two months after dual diagnosis, approximately three years after the onset of the initial myasthenic syndrome.

DISCUSSION

ALS and MG are both rare disorders that have different pathophysiology, prognosis, and treatment. Concurrence is very rare, though should be considered a possibility when clinical features of both are present.[1-3] In one Italian study, approximately 0.75% of incident ALS patients were also affected by MG, although the overall incidence of concurrence in this population was 1.87 per 10 million person-years.[4] Diagnostically, antibody testing against acetylcholine receptors (AChR), fatigable weakness, and significant (>10%) decrement on slow repetitive nerve stimulation (RNS) support a diagnosis of MG. However, significant decrement on slow RNS and/or abnormal jitter may also be seen in ALS sans MG, and up to 5% of ALS patients harbor AChR antibodies and 9.8% harbor LRP4 antibodies, which may suggest a degree of NMJ dysfunction and/or an autoimmune component in ALS; this patient's AChR binding titer was within limits of previously published titers for ALS sans MG.[5,6] As the diagnostic testing and clinical presentation may be similar in both ALS and MG, interpretation within the current clinical context is integral for appropriate diagnosis and subsequent treatment, as treatment and prognosis vary greatly between these two disorders.

Our patient had MG, responsive to immunotherapy, which progressed to a phenotype more consistent with ALS. The somewhat mild, fatigable bulbar symptoms with strong response to IVIG was most supportive of an initial diagnosis of MG, although his clinical phenotype, particularly in the ultimate three months of life, were most consistent with motor neuron disease. While both MG and ALS can present with bulbar weakness, ALS is not expected to respond to IVIG and our patient had a marked improvement of his symptoms following his initial course of IVIG. Subsequently, IVIG proved ineffective and thus required a broadening of the differential diagnosis, to include other diagnoses, such as motor neuron disease.

Electrodiagnostically, significant decrement was observed on slow RNS when he had begun to develop rapidly progressive upper and lower motor neuron signs. Notably, this finding can be seen in both myasthenic syndromes, such as MG, as well as ALS[5]; unfortunately, there was no prior RNS study with which to compare the results prior to development of upper and lower motor neuron dysfunction, which is a prime limitation in the interpretation of his mixed clinical picture. It is difficult to say if the electrodiagnostic NMJ

dysfunction was related to his MG or his ALS; however, the diffuse denervation changes on EMG would not be expected in MG, and thereby met criteria for definite ALS via the El Escorial Criteria. Given the rarity of this co-morbid combination, one may question if this case was solely bulbar ALS sans MG; however, the prolonged prodrome of fatigable dysarthria and primarily proximal weakness, with marked response to IVIG initially strengthens the interpretation of an inaugural MG followed by ALS. This case highlights the importance of recognition of rare clinical syndromes, the avoidance of anchoring bias to avoid misdiagnosis or under-diagnosis, and to diagnose rare combinations of disorders, when clinical data and supporting data dictate, in order to tailor appropriate treatment regimens for each stage of the overlap syndrome.[7]

Acknowledgment

We thank our patient and his loving family for allowing us to document this challenging and elucidating case. Although our patient's daughter did not wish to write a statement, she allowed me to relay her sentiments. In paraphrase from my discussion with her on 7/31/2024, about 2.5 years after the patient's passing: "We just noticed a few small things creeping up, but were just attributed to old age, like occasional trouble swallowing or occasional speaking issues, but I'm glad that he didn't experience this [referring to his dual diagnosis of ALS and MG] before, because he was living a good life. To see such a strong man deteriorate so fast was very sad."

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Disclosures

None

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