

Recognition and Treatment of Concurrent Amyotrophic Lateral Sclerosis and Multiple Sclerosis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are neurological disorders with different underlying pathophysiology but can share similar clinical features. Co-occurrence of both diseases is extremely rare with only 46 documented cases in literature to our knowledge. This case report relays the diagnosis of ALS in a patient with a decades'-long history of MS, and illustrates the importance of expanding the differential diagnosis and pursuing additional workup in a patient with overlapping progressive symptoms that can be caused by an alternate neurological etiology.

KEYWORDS: Amyotrophic lateral sclerosis; multiple sclerosis; co-morbidities

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) are both progressive neurological disorders that lead to a spectrum of motor, bulbar, and cognitive impairments despite having different pathophysiology.¹ ALS is a neurodegenerative disease affecting both upper and lower motor neurons, resulting in a progressive and insidious loss of motor function.² MS is an autoimmune disease characterized by inflammation and demyelinating plaques in the central nervous system and is one of the most common causes of neurologic disability within the young adult population.³ This case reports upon the rare and unfortunate co-occurrence of MS and ALS in a middle-aged woman, to our knowledge, representing only the 47th reporting of such a case in the literature.⁴

CASE REPORT

A 58-year-old woman with a history of secondary progressive MS (SPMS) and gastric bypass for obesity presented to her primary neurologist for

worsening weakness. The patient was initially diagnosed with relapsing and remitting MS (RRMS) at the age of 36, when she developed abnormal eye movements and facial paresthesia. She was started on interferon beta 1b and later transitioned to natalizumab. The patient remained on natalizumab for many years until further disease progression which manifested as dysmetria and worsening gait, approximately two years prior to current presentation, prompting a transition to ocrelizumab.

Following disease stability for the subsequent two years, the patient returned to clinic with a new, but gradual, distal left leg weakness. This was documented as Medical Research Council (MRC) 2 out of 5 strength in the proximal left leg, with 1 out of 5 strength in the distal left leg. She had 3+ patellar reflexes bilaterally. This was then followed by distal right leg weakness, over months, in a similar pattern. Magnetic Resonance Imaging (MRI) of the brain and spine with and without contrast was obtained to evaluate for MS progression but did not demonstrate corticospinal tractopathy, discrete enhancing lesions affecting the corticospinal tract, or new demyelinating lesions compared to prior MRIs [Figure 1]. Over the course of months, the patient developed worsened weakness at the distal left foot, now to MRC 0 out of 5, with marked hyperreflexia, including 4+ reflexes at the

Figure 1. MRI T2 FLAIR imaging [A] demonstrated global atrophy of the cerebral cortex and significant white matter lesions, and [B] T1 imaging with hypointense foci. No active contrast enhancement was observed (not pictured).

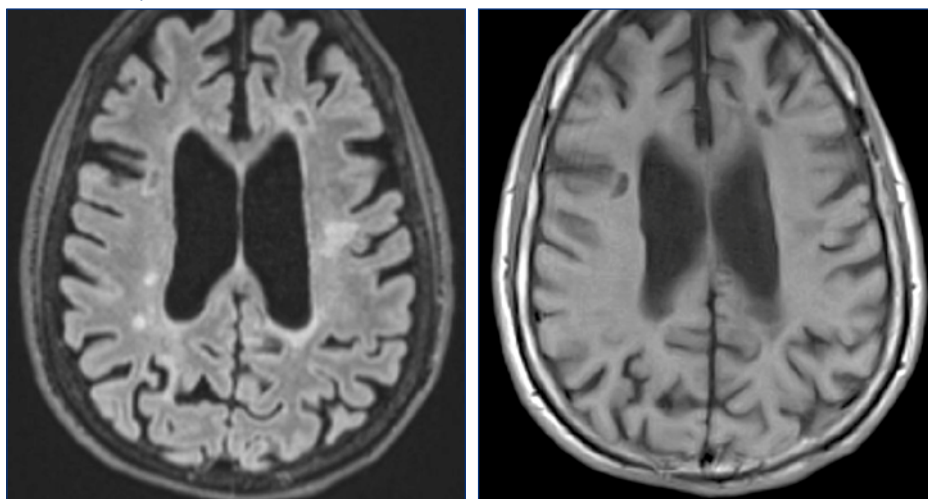


Figure 2. Nerve conduction studies [A,B] demonstrated an axonal motor-predominant neuropathy, and electromyogram [C] demonstrated marked ongoing denervation with chronic reinnervation changes in three bodily segments.

Sensory NCS									
Nerve / Sites	Rec. Site	Peak Lat ms	NP Amp μ V	PP Amp μ V	Segments	Distance cm	Velocity m/s	Temp C	
L Median - Digit II Ortho									
Digit II	Wrist	4.08	4.9	5.2	Digit II - Wrist	13	38.8		32
Ref.		3.50	10.0	10.0	Ref.				
L Ulnar - Digit V Ortho									
Digit V	Wrist	2.88	6.0	9.5	Digit V - Wrist	11	48.0		
Ref.		2.90	5.0	5.0	Ref.				
L Sural - Lat Mall									
Calf	Lat Mall	2.73	7.7	7.2	Calf - Lat Mall	14	67.2		
Ref.		4.20	5.0	5.0	Ref.				
R Sural - Lat Mall									
Calf	Lat Mall	2.79	8.8	10.9	Calf - Lat Mall	14	65.9		
Ref.		4.20	5.0	5.0	Ref.				

Motor NCS									
Nerve / Sites	Rec. Site	Lat ms	Amp mV	Rel Amp %	Segments	Dist cm	Velocity m/s	Area mVms	
L Median - APB									
Wrist	APB	5.38	3.5	100	Wrist - APB	6.5		13.3	
Ref.		4.40	4.2		Ref.				
Elbow		9.19	2.6	72.6	Elbow - Wrist	18.5	48.5	10.1	
Ref.			4.2		Ref.		49.0		
L Ulnar - ADM									
Wrist	ADM	2.65	7.3	100	Wrist - ADM	6.5		24.6	
Ref.		3.50	5.6		Ref.				
Below Elbow		5.54	7.1	96.5	Below Elbow - Wrist	18.5	63.9	23.7	
Ref.			5.6		Ref.		49.0		
Above Elbow		7.38	6.7	91.5	Above Elbow - Wrist	27.5	58.1	23.3	
Ref.			5.6		Ref.		49.0		
L Peroneal - EDB									
Ankle	EDB	4.25	0.2	100	Ankle - EDB	7.5		0.6	
Ref.		5.70	2.0		Ref.				
Fib Head		10.38	0.2	110	Fib Head - Ankle	29.5	48.2	0.8	
Ref.			2.0		Ref.		41.0		
Knee		11.92	0.2	111	Knee - Ankle	36	47.0	0.7	
Ref.			2.0		Ref.		41.0		
L Tibial - AH									
Ankle	AH	5.10	1.0	100	Ankle - AH	7.5		3.2	
Ref.		5.70	2.8		Ref.				
Knee		13.40	0.7	69.6	Knee - Ankle	37.5	45.2	4.3	
Ref.			2.8		Ref.		41.0		
L Peroneal - TA									
Fib Head	TA	4.06	0.4	100	Fib Head - TA	11.5		1.6	
Ref.			3.5		Ref.				
Knee		5.21	0.4	101	Knee - Fib Head	6.5	56.7	2.8	
Ref.			3.5		Ref.		41.0		
R Tibial - AH									
Ankle	AH	4.17	4.2	100	Ankle - AH	7.5		11.3	
Ref.		5.70	2.8		Ref.				
Knee		13.25	2.8	65.6	Knee - Ankle	39	42.9	6.2	
Ref.			2.8		Ref.		41.0		
R Peroneal - TA									
Fib Head	TA	4.96	1.8	100	Fib Head - TA	15		13.7	
Ref.			3.5		Ref.				
Knee		6.83	1.6	88	Knee - Fib Head	9.5	50.7	11.6	
Ref.			3.5		Ref.		41.0		

EMG Summary Table											
Muscle	Nerve	Roots	Spontaneous				H.F. / Other	MUAP			Recruitment Pattern
			IA	Fib	PSW	Fasc		Amp	Dur.	PPP	
L. Deltoid	Axillary	C5-C6	N	None	None	2+	None	1+	1+	N	Reduced
L. Biceps brachii	Musculocutaneous	C5-C6	N	None	None	1+	None	1+	1+	N	Reduced
L. Triceps brachii	Radial	C6-C8	N	None	None	1+	None	1+	1+	N	Reduced
L. First dorsal interosseous	Ulnar	C8-T1	N	None	None	1+	None	1+	1+	N	Reduced
L. Cervical paraspinals	Spinal	C4-C8	2+	2+	2+	None	None	1+	1+	N	Reduced
L. Vastus lateralis	Femoral	L2-L4	3+	3+	None	None	None	1+	1+	Incomplete activation.	
L. Tibialis anterior	Deep peroneal (Fibular)	L4-L5	3+	3+	3+	None	None	No motor unit potentials observed.			
L. Gastrocnemius (Medial head)	Tibial	S1-S2	3+	3+	3+	None	None	No motor unit potentials observed.			
L. Tensor fasciae latae	Superior gluteal	L4-S1	3+	3+	3+	None	None	1+	1+	N	Reduced
L. Lumbar paraspinals	Spinal	L1-L5	3+	3+	3+	None	None	1+	1+	1+	Reduced
L. Thoracic paraspinals	Spinal	T1-T12	3+	3+	3+	None	None	1+	1+	N	Reduced

multifocal leukoencephalopathy (PML). An inpatient nerve conduction study and electromyogram (NCS/EMG) was performed, and widespread active denervation in the cervical, lumbar, and thoracic segments, as well as a superimposed axonal sensorimotor neuropathy, was observed [Figure 2]. Based on the electrodiagnostic testing, she was diagnosed with ALS, meeting El Escorial Revised Criteria for definite ALS, with secondary diagnosis of axonal sensorimotor polyneuropathy due to malnutrition. Riluzole was initiated, but she did not meet candidacy criteria for edaravone, due to advanced ALS-Functional Rating Scale-Revised (ALS-FRS-R). Although she denied a family history of motor neuron diseases, genetic testing was offered and ultimately resulted negative for the most common genetic causes of ALS including C9orf72. Following diagnosis, weakness and bulbar symptoms progressed, now inclusive of significant neck extensor weakness (MRC 3 out of 5) and proximal arm weakness (MRC 4- out of 5) and the patient became wheelchair-dependent, aphonic, and markedly dysphagic. Seven months after development of foot drop, tongue fasciculations were observed with a present pathologic jaw jerk reflex. Ocrelizumab was discontinued in the interim due to malnutrition and the development of additional co-morbidities. Palliatively, she was treated with methylphenidate for her excess fatigue, baclofen for spasticity, and botulinum toxin for sialorrhea. She was eventually transitioned to hospice care and died approximately 27 months following onset of symptoms attributable to ALS, and 13 months after diagnosis.

DISCUSSION

Concomitance of ALS and MS, although previously documented, remains an extraordinarily rare finding, with this case possibly representing only the 47th documented case of co-occurrence. To date, no definitive genetic or mechanistic association has been identified between the two diseases,

left biceps with present Hoffman's sign, and upgoing plantar reflex (Babinski sign) on the right. Additionally, progressive dysphagia and burgeoning spastic dysarthria with limited word output, without frank tongue atrophy or fasciculations, was observed. Progressive dysphagia, in the context of her history of gastric bypass, led to severe protein calorie malnutrition requiring temporary total parenteral nutrition.

The patient was eventually admitted to the hospital for an expedited neurologic workup, as outpatient imaging did not support increasing MS disease burden or central nervous system (CNS) infection, such as progressive

though a combination of environmental and genetic factors, as well as inflammatory pathways have been explored.^{4,8} Although genetic testing was not always completed in previous cohorts with concurrent ALS and MS, only 5 of 33 reported cases in a literature review were found to carry a C9orf72 gene abnormality.⁵ Our patient had neither a family history of ALS, nor a de novo mutation in the most common ALS-causing genes.⁶ Some studies suggest a geographical north-south gradient of disease mortality in the ALS population, similar to that as seen in MS.⁸ In some cohorts, patients with ALS and MS patients had a higher frequency of PPMS compared to the standard MS population, and inaugural MS (i.e., MS presenting prior to ALS) appears to be the order in the majority of cases.^{4,5}

Most cases of MS present as RRMS, in which relapses are followed by gradual, and at times incomplete recovery.³ RRMS will classically develop into SPMS 10–15 years after initial onset and is characterized by a progression of disability without definitive clinical relapse, as was the case in our patient.³ Resumption of progression after initial stabilization on disease-modifying therapy in secondary progressive MS (SPMS) is not well-quantified but appears to occur with some frequency, reflecting the modest and variable treatment effects seen in this population. SPMS trials show only 20-25% relative reductions in disability progression, meaning most patients continue to progress, and treatment benefits are greatest in those with ongoing inflammatory activity that may diminish over time. In our case, a two-year period of stability followed by resumed progression likely reflects the exhaustion of the inflammatory component responsive to therapy with the non-inflammatory neurodegenerative mechanisms of SPMS becoming dominant; natural disease variability (as SPMS progression is not linear); or the modest treatment effect being overwhelmed by ongoing pathological processes not adequately addressed by current immunomodulatory therapies.

As demyelinating plaques often involve the brainstem and spinal cord, it is possible that clinical symptoms of SPMS can mask an underlying upper motor neuron-predominant neurodegenerative disorder. Of note, both conditions may result in corticospinal tractopathy, with MRI in ALS demonstrating a FLAIR hyperintense “Lateral Corticospinal Tract Sign” in the brain or spinal cord,⁹ whereas corticospinal tract lesions in MS tend to be discrete inflammatory lesions. Using diffusion tensor imaging (DTI) to determine characteristics of white matter tractopathies in these two disorders is a burgeoning field in radiologic research. Furthermore, given the chronic use of a B-cell suppressive agent, a CNS infection such as PML, or a process with positive mass effect (either tumefactive MS or neoplastic process) must be considered and ruled out.¹⁰

In this case, the patient was diagnosed with SPMS for over two decades prior to the onset of ALS based on imaging and clinical findings. ALS and SPMS can both present

as an insidious progression of upper motor neuron findings on examination (e.g., progressive hypertonicity, pathologic hyperreflexia, spastic weakness and gait dysfunction, particularly if corticospinal tract involvement is prominent); however, progressive sensory findings would not be expected in ALS, and marked lower motor neuron features such as ongoing and active denervation seen on EMG testing would not be expected in SPMS. Re-imaging, particularly with MRI with gadolinium contrast, and NCS/EMG testing, was critical in this patient to distinguish SPMS disease progression from ALS, as disease trajectory and treatment vary greatly. In this patient’s case, palliative treatments, such as anti-spasticity treatments and treatments against fatigue, can be shared between the two conditions. However, discovery of co-occurrence led to changes in management of the disease-modifying treatments, with discontinuation of the immunosuppressive MS medication ocrelizumab, and addition of the life-prolonging medication of riluzole. A unifying pathophysiologic principle such as a defined genetic basis or pertinent environmental trigger was not identified in this case, most likely indicating a random coincidence of disorders. Regardless, the rarity of this co-occurrence bears the importance of reporting.

CONCLUSION

In conclusion, as both SPMS and ALS may demonstrate similar clinical findings, a high index of suspicion for an alternative corticospinal tractopathy, such as ALS, is suggested, especially if new and insidiously progressive motor and bulbar features appear in a patient with SPMS. Prudence in re-assessing the diagnosis, and avoidance of anchoring on SPMS is advised, as treatment options and prognostic counseling, for both patient and family members, may change.

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