Amyotrophic Lateral Sclerosis and Multiple Sclerosis: More Evidence Suggesting a Link

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ABSTRACT

Objectives: Previous reports of the concurrence of multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) in the same patients suggest shared pathogenesis, with the *C9orf72* mutation as a possible shared genetic link.

Methods: Symptoms, neuroimaging, and laboratory data were summarized for patients with ALS and MS within our ALS registry. Using age adjusted MS prevalence rates, we calculated the expected co-occurrence using the binomial test.

Results: Clinical and demographic features of the five patients (four female, one male) with ALS and MS are described. Because ALS more frequently occurs in men, observing 4/5 female patients with concurrent ALS/MS showed a borderline expectation difference (P=0.073). The observed co-occurrence of ALS and MS was 5X times higher than the expected frequency of 0.98 (P <0.004). Four patients were found negative for *C9orf72*.

Discussion: Our results suggest a non-random association between MS and ALS, although shared genetic etiology was not found.

Keywords: *amyotrophic lateral sclerosis, central nervous system, gene, autoimmune disease, case report*

Introduction

Multiple sclerosis (MS) is a demyelinating central nervous system disease with an overall US reported prevalence of 309/100,000.[1] Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with a prevalence of 5.2/100,000.[2] If the MS/ALS association was random, their observed concurrence should be extremely rare (1.6 per 10 million).[3] However, the growing number of case reports suggests possible shared pathogenesis for these diseases. One-hundred sixty-eight cases of concomitant MS and ALS have been reported in the literature; however, only 25 patients have been described in clinical detail (summarized in Table 1).[3]

Genetic susceptibility for MS has been demonstrated.[4] The *C9orf72* mutation has been reported in patients with concurrent ALS and MS suggesting a possible shared genetic link; however, recent studies have not supported this.[1,4] Increased risk of developing ALS in patients with prior autoimmune disease has also been observed.[5] While immune dysregulation is known to be part of MS pathogenesis, ALS pathogenesis remains poorly characterized, but neuroinflammation and immune dysregulation may be disease mediators.[3] For this reason, various anti-inflammatory and immune-modulating therapies are currently being studied in ALS.

In this study, we describe five patients with concurrent MS and ALS and hypothesize this concurrence rate is greater than what would be expected by chance.

Methods

Data Collection

Two of our physicians at the Swedish Neuroscience Institute (KP and ME) had encountered six ALS patients with co-occurring MS diagnoses. Their medical charts were examined to confirm MS diagnoses using the MacDonald criteria. One patient was excluded due to inconclusive neuroimaging. To confirm our manual search, the Epic™ SlicerDicer program was used to collect aggregate counts of ICD-10 codes for MS within our ALS registry over the same timeframe. This computerized search yielded the same patients as our manual search. Finding identical results with two different strategies gave us confidence that we had not overlooked patients with MS/ALS dual diagnoses, nor had we extracted patients for whom strict MS and ALS criteria would not hold up to scrutiny.

We reviewed charts and characterized the demographic, clinical, and neurogenetic features of our patients with MS and ALS. The Swedish Institutional Review Board determined that this case report series as submitted does not meet the definition of human subjects' research and does not require IRB review as defined in the federal regulations. The fifth case report was not included prior to IRB consideration.

Data Analysis

Our calculations were based on the total number of ALS patients in our ALS clinic registry (N=213) from August 2016-July 2019 and the expected prevalence of MS within a similar age (55-64 years old) and region (Western US) matched cohort bases from data reported in 2019.[1] Averaging the high and low estimates for the 55-64 year old cohort in the Western US yielded an MS prevalence estimate of 461/100,000. That prevalence estimate was

Table 1. Demographic and clinical features of previously described patients with co-occurring MS/ALS diagnoses.

		Multiple Sclerosis			Amyotrophic Lateral Sclerosis	
Gender	**Cases**	**Mean Age of Onset (years)**	**Subtype**	**Mean Time Lapse Between Diagnoses (years)**	**Mean Age of Onset (years)**	**Site of Onset**
F	18	40.4	RRMS (7) PPMS (4) SPMS (4) Unk (3)	7.9	51.0	Bulbar (5) Limb (11) Unk (2)
M	7	34.0	RRMS (2) PPMS (2) SPMS (2) Unk (1)	4.3	51.1	Bulbar (4) Limb (3)

then used to calculate the probability of the observed result (5/213 with both conditions) using the binomial test. GraphPad QuickCalc was used to create these binomial calculations (https://www.graphpad.com/quickcalcs/binomial1/). $P<0.05$ was our significance criterion.

Case Reports

Patient 1 was a 68-year-old woman who developed right leg weakness. She was diagnosed with relapsing remitting MS (RRMS) and treated with glatiramer acetate. MRI brain revealed periventricular demyelination (Figure 1). Cerebrospinal fluid revealed oligoclonal bands. At age 70 she developed left leg weakness. Electromyography (EMG) demonstrated widespread active and chronic denervation. She was diagnosed with ALS and treated with riluzole. *C9orf72* testing was not completed. She died two years after ALS onset.

Patient 2 was a 72-year-old woman with longstanding RRMS, initially presenting with left-sided numbness and 10 months of bulbar weakness; treated with interferon beta-1a. Neuroimaging revealed stable demyelination (Figure 1). EMG demonstrated diffuse active and chronic denervation. She was diagnosed with ALS and treated with riluzole. *C9orf72* testing was negative. She expired within 6 months of diagnosis.

Patient 3 is a 54-year-old woman with longstanding MS, initially presenting with left-sided numbness, 2.5 years of bulbar weakness and treated with natalizumab and ocrelizumab. MRI brain revealed stable demyelinating changes (Figure 1). EMG confirmed ALS. *C9orf72* testing was negative. The patient is currently in hospice.

Patient 4 is a 49 year-old woman with a 9-month history of left leg and arm weakness. MRI demonstrated active demyelinating disease (Figure 1). Cerebrospinal fluid revealed no oligoclonal bands. EMG revealed widespread active and chronic denervation. She was diagnosed with MS and ALS simultaneously and treated with ocrelizumab and

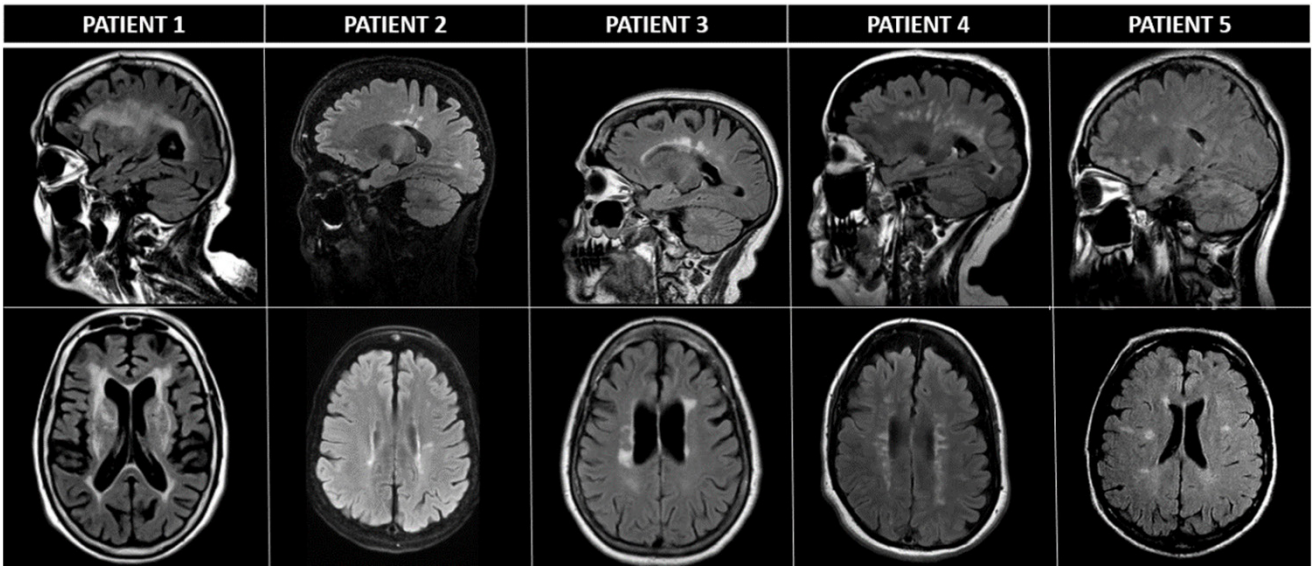

Figure 1. **MRI brain imaging demonstrating demyelinating white matter lesions for Patients 1 through 5.** Sagittal FLAIR sequences are displayed above their corresponding axial FLAIR images.

riluzole. She is currently wheelchair-bound and ventilator-dependent 1.5 years after ALS diagnosis.

Patient 5 is a 64-year-old man with a one-year history of dyspnea, weight loss, and left hand weakness. MRI demonstrated chronic demyelinating changes in the brain and cervical spine (Figure 1). EMG revealed widespread active and chronic denervation. He was diagnosed with ALS. *C9orf72* testing was negative. MS treatment was deferred to focus on supportive ALS care. Six months after ALS diagnosis, he is currently wheelchair-bound and ventilator-dependent.

Results

In our cohort we found that the observed prevalence of concurrent MS and ALS was five times greater than the expected frequency of 0.98 ($P < 0.004$). Given that the ratio of ALS cases in males to females is 1.6:1 (61% male predominance), the female predominance observed in our study at a ratio of 4:1 showed a borderline difference from expectation (P=0.073, binomial test).[2] Our patients' demographic, clinical, and neurogenetic features are summarized in Table 2.

Discussion

The concurrence of MS and ALS has now been reported in detail in 30 patients. The majority of our patients demonstrated sequential disease occurrence, with MS preceding ALS by an average of 6.6 years, similar to previous literature reports.[3] This finding is likely explained by the earlier age of onset and longer life expectancy observed in MS populations relative to ALS. In the now total 30 reported cases, there are none in which ALS onset precedes MS. We describe two patients in which MS and ALS were diagnosed simultaneously; however, neuroimaging revealed chronic demyelinating disease suggesting that subclinical MS predated ALS.

Most of our patients exhibited more aggressive subtypes of MS and ALS. The majority of our cohort developed progressive MS disease (SPMS or PPMS). Sixty percent of our patients developed either bulbar or respiratory-onset ALS, subtypes with worse outcomes.[6] The bulbar predominance in our report is consistent with Guennoc's findings, wherein 50% of patients developed non-limb disease onset.[3] The predominance of non-limb onset ALS in our cohort is striking, as limb-onset disease has been reported to represent up to 74% of cases.[10]

We did not find increased abnormal expansion of the *C9orf72* gene, consistent with previous literature. [4] The female predominance we observed in our study is consistent with the 72% female predominance observed in the 25 MS/ALS co-occurrence cases reported to date, a gender pattern similar to that observed in MS.[9,10] In contrast a recent Centers for Disease Control and Prevention survey of ALS prevalence in the US found 61% to be male.[2]

There are possible explanations for the observation of increased MS/ALS co-occurrence in our cohort. Improved MS therapies have resulted in longer life expectancies, allowing for this population to develop other diseases, including ALS. Additionally, we note that our average age at clinically evident MS/ALS co-occurrence was 61.0 years.

Table 2. **Demographic, clinical, and neurogenetic features of our patients with co-occurring MS/ALS diagnoses.** M = Male. F = Female. Unk = unknown. RRMS = Relapsing Remitting Multiple Sclerosis. SPMS = Secondary Progressive Multiple Sclerosis. PPMS = Primary Progressive Multiple Sclerosis. Neg = Negative. *Patients 3-5 are still living 60, 12, and 18 months later at the time of this report, respectively.

Multiple Sclerosis					Amyotrophic Lateral Sclerosis			
Patient	**Gender**	**Age at Diagnosis (years)**	**Subtype**	**Time Lapse Between Diagnoses (years)**	**Age at Onset**	**Site of Onset**	**Time from ALS symptom onset to death (months)**	**C9orf72 Status**
1	F	68	RRMS	2	70	Limb	24	Unk
2	F	49	RRMS	23	72	Bulbar	16	Neg
3	F	44	SPMS	8	51	Bulbar	≥60*	Neg
4	F	49	PPMS	0	49	Limb	≥12*	Neg
5	M	64	SPMS	0	63	Respiratory	≥18*	Neg
Mean		**54.8**		**6.6**	**61.0**			
SD		**9.4**		**8.7**	**9.5**			

If our patient sampling was truncated at 50 years old, we would have detected only 1/5 MS/ALS co-occurrences.

In summary, our observed prevalence of concurrent MS/ALS was five times higher than expected suggesting that a preceding autoimmune disease may increase ALS risk.[5] Of all autoimmune diseases reported associated with increased ALS risk, MS relative risk was one of the greatest (MS relative risk = 4.25).[5] It may be that the neurologic autoimmune process confers a greater effect compared to other systemic autoimmune diseases. The reasons for our observed MS/ALS concurrence deserves further investigation and may yield helpful clues into ALS pathogenesis.

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