Coexistence of amyotrophic lateral sclerosis and lymphoproliferative disorders – Analysis from a tertiary center

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Abstract

Background: The coexistence of motor neuron diseases (MNDs) and lymphoproliferative disorders (LPDs) has been documented historically in a few small retrospective studies but an update is lacking.

Objective: The goal of this study is to expand the database of patients with these coexisting diseases, and to describe the natural history and overall outcomes including presumed or identified cause of mortality (neurologic versus oncologic).

Materials and methods: A retrospective analysis of all patients within the Cleveland Clinic diagnosed with one or more LPDs between January 1, 2012 and June 30, 2021, was performed to identify patients with a diagnosis of MND.

Results: A total of 20 patients with one MND diagnosis and one coexisting LPD were included in the final analysis. Their clinical features are characterized. In 17 patients, the diagnosis of LPD was made prior to the MND diagnosis. Eighteen patients passed away with a mean survival of 49.1 (range: 6 to 128) months from the MND onset. In 16 patients, the cause of death was MND related. The incidence rates of MNDs and myasthenia gravis were examined in a group of 6,169 patients with LPDs. The incidence rate of MNDs in LPDs seems to be higher than those of the general population, appeared over-represented when comparing to the occurrence of myasthenia gravis in LPDs.

Conclusion: Coexisting MND and LPD continue to occur. There seems to be an over representation of MND in patients with LPDs.

Introduction

The association between neuromuscular diseases and malignant neoplastic disease has been reported since the 1960's.[1] Specifically, the coexistence of motor neuron diseases (MNDs) including amyotrophic lateral sclerosis (ALS), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and those of lymphoproliferative disorders (LPDs), including various subtypes of lymphoma, leukemia, multiple myeloma and Waldenström's macroglobulinemia, was described in a few small studies prior to the 20th century.[1-6] Gordon et al. reported the frequency of LPDs in patients with MND patients may range from 2% to 5%, depending on the methods of evaluation.[6] It remains unclear whether a potential association exists between MNDs and LPDs. Furthermore, significant updates on the epidemiology, clinical characteristics, or outcomes of patients with coexisting MNDs and LPDs have not been published since the late 1990s. In this study, we aim to analyze a group of patients who possesses both MND and LPDs in our tertiary center.

Materials and Methods

The following two in-house databases at our institution were reviewed: a database of 1,266 patients with MNDs (familial or sporadic ALS, PMA, PLS), and a hematology/oncology database of 6,169 patients diagnosed with LPDs (Hodgkin lymphoma, follicular lymphoma, non-follicular lymphoma including large B cell lymphoma and Burkitt lymphoma, T and natural killer cell lymphoma, Waldenström macroglobulinemia, multiple myeloma, lymphoid leukemia, myeloid leukemia, and monocytic leukemia). These two databases included selected patients seen in our institution between January 1, 2012 and June 30, 2024. A group of patients carrying simultaneous diagnoses of MNDs and LPDs were identified, based on the final conclusion of treating neuromuscular and hematological physicians. Only adult patients who age 18 years or greater were included. Detailed information regarding the neurologic diagnoses, oncologic diagnoses, presenting symptoms and neurologic exam features, electrodiagnostic findings, and survival were collected and summarized.

Results

A total of 20 patients were included in the final analysis. Their demographic information, diagnoses and selected clinical features are outlined in Table 1. Twelve (60.0%) were male and the average onset age of MND was 65.9 (range: 45 to 82) years.

The following MND diagnoses were encountered: ALS (N=17), PLS (N=2), and PMA (N=1). Onset regions of MND were as follows: lumbosacral (N=10), cervical (N=7) and craniobulbar (N=3). The following LPDs were encountered: lymphoma such as follicular lymphoma, diffuse large B cell lymphoma, marginal zone B cell lymphoma, Hodgkin's lymphoma and non-Hodgkin lymphoma (N=10), chronic lymphocytic leukemia (N=5), multiple myeloma (N=3), Waldenström's macroglobulinemia (N=1) and T cell large granular lymphocytic leukemia (N=1). In 17 (85.0%) patients, the diagnosis of LPD was established prior to the MND diagnosis. In the remaining 3 patients, the MND diagnosis was made earlier. The average interval between MND and LPD diagnoses were 63.0 (range: 0.5 to 189)

Table 1. Clinical features of 20 patients with coexisting motor neuron diseases and lymphoproliferative disorder

patient	Sex	MND diagnosis	MND onset age (years)	MND onset region	LPD diagnosis	First diagnosis	Interval between MND and LPD diagnosing (months)	Survival from MND onset (months)	Cause of death
1	M	ALS	70	cervical	lymphoplasmacytic lymphoma	LPD	2	77	unclear
2	M	ALS	76	craniobulbar	chronic lymphocytic leukemia	MND	0.5	14	MND related
3	M	ALS	63	craniobulbar	Hodgkin lymphoma	LPD	189	89	MND related
4	M	ALS	51	lumbosacral	chronic lymphocytic leukemia	MND	75	128	MND related
5	F	ALS	74	lumbosacral	extranodal marginal zone B-cell lymphoma	LPD	129	19	MND related
6	F	PMA	82	cervical	follicular lymphoma	LPD	66	6	MND related
7	F	ALS	54	lumbosacral	Waldenström macroglobulinemia	LPD	72	41	MND related
8	M	ALS	75	cervical	Chronic lymphocytic leukemia	MND	3	13	MND related
9	F	ALS	70	lumbosacral	Diffuse large B cell lymphoma	LPD	70	97	MND related
10	F	ALS	78	lumbosacral	follicular lymphoma	LPD	121	39	MND related
11	M	ALS	75	cervical	non-Hodgkin's lymphoma	LPD	29	65	MND related
12	M	ALS	66	lumbosacral	follicular lymphoma	LPD	2	19	MND related
13	M	PLS	63	lumbosacral	lymphoplasmacytic lymphoma	LPD	2	72	unclear
14	M	ALS	62	cervical	diffuse large B-cell lymphoma	LPD	79	29	MND related
15	M	ALS	65	lumbosacral	chronic lymphocytic leukemia	LPD	70	62	MND related
16	M	ALS	58	cervical	chronic lymphocytic leukemia	LPD	116	59	MND related
17	F	ALS	55	likely bulbar	multiple myeloma	LPD	100	24	MND related
18	F	ALS	72	lumbosacral	multiple myeloma	LPD	9	30	MND related
19	F	PLS	64	lumbosacral	T cell large granular lymphocytic leukemia	LPD	76	>197	alive
20	M	ALS	45	cervical	multiple myeloma	LPD	49	>110	alive

months.

Eight (40.0%) patients had cerebrospinal fluid (CSF) studies as a part of their workup. Of these, 5 (62.5%) patients had elevated CSF protein (mean 80 mg/dl, range: 51-109 mg/dl) and 1 patient had a unique oligoclonal band present in the CSF.

At the conclusion of this study, 18 (90%) of the included patients deceased, with an average survival from the onset of MND being 49.1 (range: 6 to 128) months. Two patients (one with ALS and multiple myeloma, the other with PLS and T cell large granular lymphocytic leukemia) remain alive following an MND course of 110 and 197 months respectively (Table 1). In 16 (88.9%) of 18 patients, the cause of mortality was MND related. In the remaining 2 patients, the cause of death was unknown.

We made a comparison of the incidence rates of various notable neuromuscular disorders based on patients exclusively from the hematology/oncology database of 6,169 patients. The following neuromuscular disorders were encountered: MND (N=6) and myasthenia gravis (N=6).

Discussion

The reported frequency of LPDs in patients with MND was 2-5%.[5,6] Louis et al. performed bone marrow examination in each of 161 patients MNDs, and found 4 (2.5%) cases of LPDs.[5] In the current study of 1,266 patients with MND, a total of 20 (1.6%) patients with coexisting LPDs were identified. Our incidence rate matches well with those of Louis et al., considering that bone marrow biopsy was not one of the inclusion criteria in our study. Mandatory bone marrow biopsy in all MND patients would certainly increase the diagnostic yield of LPDs.[5]

There has been no case control study to determine whether the frequency of MND in patients with LPDs is disproportionately greater, thus their coexistence remains possibly incidental. However, our current analysis seems to suggest that an association may exist between MNDs and LPDs. While the prevalence of MNDs in the United States is reported to be 11.8 per 100,000, this retrospective study identified 6 (97.3 per 100,000) out of 6,169 patients with LPDs carried a diagnosis of MND.[9] In comparison to MNDs, the prevalence rate of myasthenia gravis is higher at 37 per 100, 000 in the general US population, even a few fold higher in patients aged 50 years or older, an age hood when MND and LPD typically occurs.[8] However, we found an equal number of MG (N=6) and MND (N=6) in this large group of 6,169 patients with LPDs, implying a likely relative over-representation of MNDs.

In patients with coexisting LPDs and MNDs, the initial symptoms could belong to MND or LPD.[6] In 17 of 20 patients included in the current study, LPD diagnosis was made earlier than MND, raising the possibility that LPD or subsequent treatment could trigger the occurrence of MND secondary to neurotoxicity mediated by LPD or treatment. It has been suggested that lymphoma cells may result in a paraneoplastic mechanism by producing autoantibodies that binds to motor neurons resulting in neuronal dysfunction.[9] Alternatively, MND and LPD could share a common cause that can be neurotropic and oncogenic, and the onset of each syndrome is determined by a number of genetic and environmental factors that are unique to each individual. Increased frequency of paraproteinemia has been documented in patients with MND.[10] It was also previously shown that the presence of monoclonal paraproteinemia in MNDs increases the likelihood of LPDs.[2]

It is well known that MNDs associated with LPD is primarily of the lower motor neuron. However, MNDs associated with LPDs is not restricted to lower motor neuron. In one study, 88% of patients with MNDs and LPDs qualified for the diagnosis of ALS.[6] Cases of coexisting PLS and LPDs were described previously, as well as 2 patients from this study.[5] It was previously described that MNDs were responsible for death in all such cases and treatment such as radiation or immunosuppressive therapy had no effect on the progression of MND.[6,11] Observations from our study seem to be consistent with prior observations. In our study, the mean survival was approximately 4 years from the MND onset, and the majority of our patients died of MND related events.

The limitations to this study include the small sample size and the retrospective nature, which may have led to incomplete data analysis.

Conclusions

The overlap between MND sand LPDs has been historically reported. This retrospective study lends support that this overlap persists and may not be coincidental. Further studies should include population or case control studies to look for a causal relationship between these two categories of disorders. The clinical association between MNDs and LPDs has implications about elucidating possible disease pathology and major implications for management and treatment.

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Abbreviations: MND, motor neuron disease; LPD, lymphoproliferative disorder; M, male; ALS, amyotrophic lateral sclerosis; F, female; PMA, progressive muscular atrophy; PLS, primary lateral sclerosis