Venous thromboembolism in amyotrophic lateral sclerosis

A prospective study

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ABSTRACT

Objective: To prospectively assess the incidence of both symptomatic and asymptomatic venous thromboembolism (VTE) in patients with amyotrophic lateral sclerosis (ALS) and to identify risk factors.

Methods: Fifty outpatients with ALS were recruited consecutively and prospectively evaluated with bilateral venous duplex ultrasonography (VDU) of the proximal leg veins at enrollment and 6 and 12 months. The primary outcome measure was clinically important VTE, defined as asymptomatic proximal deep vein thrombosis (DVT) by screening VDU, symptomatically proven DVT or pulmonary embolism (PE), or fatal PE. For each patient, person-days of follow-up were recorded from enrollment until the date of VTE, death, loss to follow-up, or final 12-month visit.

Results: During the 1-year follow-up period, VTE was detected in 4 patients (1 symptomatic DVT, 1 symptomatic PE, and 2 asymptomatic DVTs) over 13,011 person-days of follow-up, representing an 11.2% 1-year incidence. Subjects with leg-onset ALS or significant leg weakness had a 1-year VTE incidence rate of 35.8% and 35.5%, respectively. VTE risk was significantly increased for those patients with decreased lower extremity Revised ALS Functional Rating Scale subscore ($p = 0.03$), decreased Lower Extremity Activity Scale score ($p = 0.02$), and decreased average lower limb Medical Research Council scale strength score ($p = 0.03$).

Conclusions: Our data suggest that clinically important VTE is common in patients with ALS, particularly those with leg weakness and reduced mobility. Given these results, the potential benefits of routine VTE screening and primary prophylaxis in high-risk patients with ALS with leg weakness should be explored in future studies. In the meantime, physicians should have a low threshold for considering VTE in patients with ALS with leg weakness. ***Neurology*® 2014;82:1674–1677**

GLOSSARY

ALS = amyotrophic lateral sclerosis; **ALSFRS-R** = Revised ALS Functional Rating Scale; **DVT** = deep vein thrombosis; **LEAS** = Lower Extremity Activity Scale; **MRC** = Medical Research Council; **PE** = pulmonary embolism; **VC** = vital capacity; **VDU** = venous duplex ultrasonography; **VTE** = venous thromboembolism.

Venous thromboembolism (VTE), consisting of deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common condition with substantial morbidity, mortality, and resource demands. Neurologic diseases that affect lower limb function are well-described risk factors for VTE.[1]

Patients with amyotrophic lateral sclerosis (ALS) have multiple risk factors for VTE, including reduced mobility, increased age, and progressive respiratory failure. Two retrospective studies have shown an increased incidence of symptomatic DVT[2,3]; however, there are currently no prospective studies assessing the rate of symptomatic and asymptomatic VTE in patients with ALS.

The aim of this study was to prospectively assess the incidence of clinically important VTE in patients with ALS and to identify potential risk factors.

METHODS

Subjects. Eligible patients from the ALS Clinic at the University of Toronto included El Escorial clinically definite or probable ALS, age >18 years, and capacity to provide informed consent and comply with study procedures. The exclusion criteria were as follows: anticoagulant therapy within 1 month prior to recruitment, major surgery within 3 months prior to recruitment, active cancer or chemotherapy treatment, current participation in an ALS clinical trial, and symptomatic VTE at enrollment. Fifty consecutive eligible subjects consented to the study. Assessments and ultrasounds were arranged at routine follow-up visits. Funding provided for an n = 50.

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Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the hospital research ethics board and all subjects provided informed consent.

Evaluation protocol. Patients were evaluated with bilateral venous duplex ultrasonography (VDU) of the proximal leg veins (popliteal to common iliac) at enrollment and 6 and 12 months. The primary outcome measure was clinically important VTE, defined as asymptomatic proximal DVT by screening VDU, symptomatic proven DVT or PE, or fatal PE. Asymptomatic proximal DVTs were deemed clinically important as most clinicians would initiate treatment in a high-risk patient. All VDU imaging studies were performed by a certified ultrasound technologist using either the Phillips iU22 (Phillips Healthcare, Cleveland, OH) or Toshiba Aplio XG (Toshiba, Tokyo, Japan) ultrasound systems and were interpreted by a board-certified radiologist with ultrasonography expertise.

Data of interest. Demographic and disease-specific data were collected at baseline. Additional clinical variables included the following: (1) Revised ALS Functional Rating Scale (ALSFRS-R), (2) Lower Extremity Activity Scale (LEAS), (3) Ashworth Scale of lower extremity spasticity, (4) lower extremity strength using the Medical Research Council (MRC) grading scale, and (5) vital capacity (VC). The ALSFRS-R is a well-validated tool that probes motor, respiratory, and bulbar function in ALS, scored out of 48, with lower scores indicating poorer function. Lower extremity strength was calculated by summing the MRC scores of the hip, knee, and ankle flexors and extensors, and averaging the values for both legs.

Table 1 Baseline demographics and clinical features (n = 50)

Characteristic	Mean ± SD (range) or n (%)
Age, y	59.5 ± 12.7 (40–85)
Sex, male/female	36 (72)/14 (28)
Disease duration (symptom onset), mo	40.6 ± 29.7 (10–147)
Region of disease onset	
Leg onset	20 (40)
Arm/bulbar onset	30 (60)
Ambulation status	
Ambulatory	30 (60)
Wheelchair-bound	20 (40)
ALSFRS-R total score	33.7 ± 8.3 (11–48)
Lower extremity subscore	6.9 ± 3.8 (0–12)
Upper extremity subscore	6.6 ± 3.7 (0–12)
Respiratory subscore	10.8 ± 2.0 (4–12)
Bulbar subscore	9.5 ± 2.9 (2–12)
LEAS score	7.0 ± 2.9 (2–11)
Average lower limb MRC scale strength score	17.5 ± 6.8 (0–25)
Lower limb spasticity	
Significantly spastic (≥2)	11 (23.4)
Not significantly spastic (<2)	36 (76.6)
Vital capacity, % predicted	79.5 ± 29.3 (16–130)

Abbreviations: ALSFRS-R = Revised ALS Functional Rating Scale (max score = 48); LEAS = Lower Extremity Activity Scale (max score = 12); MRC = Medical Research Council (average lower limb strength score, max = 25).
Significantly spastic defined as ≥2 on Ashworth Scale of spasticity at ankle.

Statistical analysis. For each patient, person-days of follow-up were recorded from date of enrollment to date of VTE, death, loss to follow-up, or the 12-month end-of-study visit. Descriptive statistics summarize demographic and clinical variables. Bivariate analyses (Mann-Whitney U test or χ^2 test, as appropriate) were performed to evaluate the association between variables of interest and incidence of VTE. A p value of < 0.05 was considered statistically significant. Analyses were conducted using SPSS Statistics, version 22 (IBM Corporation, New York, NY).

RESULTS

Fifty consecutive subjects (36 male, 14 female, mean age 59.5 ± 12.7 years) were screened and enrolled over a period of 14 months. The mean symptom duration was 40.6 ± 29.7 months, and 40% of patients had leg-onset disease (table 1).

Incidence of VTE. During the 1-year follow-up period, VTE was detected in 4 subjects. Two events were symptomatic (1 with bilateral PE and another with symptomatic nonocclusive DVT of the femoral and popliteal veins) and 2 were asymptomatic, detected only by screening VDU (both unilateral nonocclusive thrombus of the femoral veins). Of the 4 subjects with VTE, the average age was 68.5 ± 14.4 years (47–77). All 4 patients had leg-onset disease and 3 were wheelchair-bound, with an average total ALSFRS-R score of 30.2 ± 8.1 (24–42), LEAS score of 4.0 ± 1.8 (2–6), and an average lower limb MRC strength score of 10.2 ± 8.7 (1.5–18). For subjects without VTE, 25 completed the study to 12 months, 15 subjects died partway through the study, and 6 subjects withdrew (3 after baseline visit and 3 after the 3-month visit). None of the deaths was sudden, unexpected, or suggestive of fatal PE.

In total, there were 13,011 person-days (35.6 person-years) of follow-up. The 1-year incidence of VTE was 11.2% (4 per 35.6 person-years). For subjects with leg-onset ALS or significant leg weakness, as defined by LEAS scores of 6 or less at baseline, the 1-year VTE incidence increased to 35.8% (4 per 11.2 person-years) and 35.5% (4 per 11.3 person-years), respectively.

Baseline risk factors for VTE. Subjects with VTE were older and had longer disease duration ($p = 0.07$ and $p = 0.05$, respectively) (table 2). Four of 20 patients with leg-onset disease developed VTE, while none was detected in arm or bulbar-onset subjects ($p = 0.02$). Decreased lower extremity ALSFRS-R subscore ($p = 0.03$), decreased LEAS score ($p = 0.02$), and decreased average lower limb MRC strength score ($p = 0.03$) were all associated with VTE. Sex, total ALSFRS-R score, significant lower limb spasticity, and VC were not associated with VTE.

DISCUSSION

This prospective study of VTE in subjects with ALS demonstrated a 1-year incidence of clinically important VTE of 11.2%. For symptomatic cases only, we found a 5.6% incidence, which is

Table 2 Demographic and clinical comparisons of subjects with ALS with and without clinically significant VTE

Characteristic	VTE (n = 4)	No VTE (n = 46)	*p* Value
Age, y	68.5 ± 14.4	58.7 ± 12.7	0.070
Sex			
Male	3	33	0.690
Female	1	13	
Disease duration (symptom onset), mo	62.3 ± 36.9	38.7 ± 28.7	0.054
Region of disease onset			
Leg onset	4	16	0.021
Arm/bulbar onset	0	19	
Ambulation status			
Ambulatory	1[a]	29	0.170
Wheelchair-bound	3	17	
ALSFRS-R total score	30.2 ± 8.1	34.0 ± 8.4	0.166
Lower extremity subscore	3.2 ± 3.0	7.2 ± 3.8	0.028
Upper extremity subscore	4.0 ± 5.0	6.8 ± 3.6	0.122
Respiratory subscore	12 ± 0	10.6 ± 2.1	0.112
Bulbar subscore	11 ± 1.4	9.4 ± 3.0	0.176
LEAS score	4.0 ± 1.8	7.2 ± 2.8	0.017
Average lower limb MRC scale strength score	10.2 ± 8.7	18.2 ± 6.3	0.028
Lower limb spasticity			
Significantly spastic (≥2)	1	10	0.670
Not significantly spastic (<2)	3	33	
Vital capacity, % predicted	75.3 ± 31.6	79.7 ± 29.5	0.382

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = Revised ALS Functional Rating Scale (max score = 48); LEAS = Lower Extremity Activity Scale (max score = 12); MRC = Medical Research Council (average lower limb strength score, max = 25); VDU = venous duplex ultrasonography; VTE = venous thromboembolism.
Data are presented as mean ± SD (range) or n. Significantly spastic defined as ≥2 on Ashworth scale of spasticity at ankle.
[a] The single ambulatory VTE+ patient was found to have an asymptomatic DVT at 6-month VDU screening.

higher than the 2.7%[3] and 3.3%[2] previously reported in retrospective studies. The 1-year incidence of symptomatic VTE in this ALS cohort was almost 10-fold higher than the reported incidence of the oldest age group (85–89) in a large epidemiologic study (annual incidence rate 0.59%).[4]

Our data suggest that clinically important VTE is common in patients with ALS and may be undersuspected given the prevalence of leg swelling and pain. Respiratory muscle weakness and shortness of breath may also mask the symptoms of PE. The true incidence of VTE may be underestimated in this study as screening was limited to proximal leg DVT, ultrasound is less sensitive than venography, and autopsies were not performed.

Patients with leg-onset disease and leg weakness with reduced mobility (LEAS <6) had the highest 1-year VTE incidence rates of 35.8% (4 per 11.2 person-years) and 35.5% (4 per 11.3 person-years), respectively. These findings suggest an association between leg weakness and increased risk of VTE consistent with previous reports.[2,5] Increased age and disease duration were also found to be risk factors approaching significance.

VTE has been studied in other neurologic diseases that impair mobility, such as ischemic stroke[6] and spinal cord injury,[7] and short-term prophylactic anticoagulation is routinely employed in these conditions.[8,9] Given the results of the present prospective study and the availability of effective, safe, and inexpensive oral anticoagulants, the potential benefits and risks of primary prophylaxis in high-risk patients with ALS with leg weakness should be explored in future studies.

Limitations of the present study include the relatively small sample size and number of VTEs. In addition, follow-up was limited to 1 year and a substantial proportion of the cohort died prior to completion, which is typical of ALS studies and limits power. Forty percent of subjects had leg-onset disease, which is higher than expected[10] and may have resulted in an overestimation of VTE risk in the ALS population. Generalizability is limited to ALS outpatients receiving tertiary care. While there were more male than female participants, the sample size was too small to determine whether sex was a VTE risk factor. Although patients with active cancer or recent major surgery were excluded, other potential confounders such as hydration status, trauma from falls, or an occult malignancy may have contributed.

Further prospective studies are needed to determine the merits of routine screening for VTE and the potential benefits of short-term or long-term prophylactic anticoagulation. In the meantime, health care providers should have a low threshold for considering VTE in patients with ALS, particularly those with leg weakness.

AUTHOR CONTRIBUTIONS

Matthew Gladman contributed to analysis and interpretation of the data, drafting and revising the manuscript. Melanie DeHaan contributed to design and conceptualization of the study, drafting and revising the manuscript. Hanika Pinto contributed to drafting and revising the manuscript. William Geerts contributed to design and conceptualization of the study, drafting and revising the manuscript. Lorne Zinman contributed to design and conceptualization of the study, analysis and interpretation of the data, drafting and revising the manuscript.

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DISCLOSURE

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