SHORT REPORT

Prognosis of amyotrophic lateral sclerosis with respiratory onset

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Respiratory muscle involvement is a recognised, but often late, complication of amyotrophic lateral sclerosis (ALS). The clinical features and prognosis of 21 patients with respiratory onset ALS are reported here. On a retrospective chart review, it was found that 2.7% of patients with ALS presenting to a tertiary care specialty clinic have respiratory symptoms as their first clinical symptom of ALS. Only 14% of these individuals presented acutely and required emergency intubation. The mean survival time of the total group from symptom onset to death or permanent ventilation was 27.0 (14.9) months, which was not significantly different from the survival time in patients with bulbar onset ALS. Non-invasive positive pressure ventilation (NIPPV) significantly improved survival compared with those who did not use NIPPV. This study suggests that ALS with respiratory onset does not necessarily follow a rapidly progressive course.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder caused by progressive motor neurone loss. As the disease progresses, respiratory muscle weakness occurs eventually. In general, the presence of impaired respiratory function is a negative prognostic factor in ALS.[1 2] Although there are multiple case reports in the literature suggesting that ALS can present with severe respiratory insufficiency requiring emergency mechanical ventilation,[3–8] respiratory symptoms are regarded as an uncommon presenting feature of ALS. The literature does not highlight the fact that respiratory onset ALS can start more insidiously and can be diagnosed before requiring emergency intubation. The prognosis of respiratory onset ALS has not been assessed adequately, since previous reports discuss prognosis on the basis of a small number of patients.[9]

Several studies have shown that non-invasive positive pressure ventilation (NIPPV), most commonly in the form of bilevel NIPPV, improves the prognosis of individuals with ALS with significant respiratory insufficiency.[5 10 11] However, no study has described the impact of NIPPV in individuals with respiratory onset ALS.

In this paper, we review the clinical characteristics and prognosis of a cohort (n = 21) of patients with ALS with respiratory onset, and evaluate the effect of NIPPV on the prognosis of these individuals.

METHODS

All included patients eventually met the criteria for either definite or probable ALS (revised El Escorial criteria[12]). Subjects were defined as having respiratory onset ALS if their first symptom of neuromuscular weakness, as reported at the time of presentation to our clinic, was orthopnoea or dyspnoea at rest or with exertion. At the time of presentation, affected individuals could have weakness outside respiratory muscles, but the initial symptom had to be respiratory in nature in order to be counted as a respiratory-onset case.

We performed a retrospective analysis of all cases reviewed at the Motor Neuron Diseases Clinic at the London Health Sciences Centre (London, Ontario, Canada) from 1990 to 2005. All incident cases were entered into a database and indexed by several features including first clinical symptoms, time of first presentation to our clinic, findings at presentation and a final classification of disease by the El Escorial criteria. The database was searched for entries with respiratory onset. The clinic and hospital charts of these individuals were then searched to confirm the coding of respiratory onset ALS. The following data were then collected from the charts with confirmed ALS with respiratory onset: initial symptoms, age at onset, initial physical examination findings, time to diagnosis, survival, duration of disease, pattern of progression of disease, NIPPV usage and pulmonary function test (PFT) results.

The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects approved the protocol for this study.

RESULTS

Our clinic database held 791 clinical records for patients with probable or definite ALS seen between January 1990 and September 2005. Searching the database by first clinical symptom for respiratory symptoms yielded 29 clinical records, 21 of which were confirmed to be clearly respiratory onset. The majority of charts that were excluded were of patients who had respiratory symptoms at diagnosis but did not have respiratory symptoms as their first symptom of ALS.

The incidence of ALS with respiratory onset in a tertiary care ALS clinic was 21/791 (2.7%). Of the 21 charts determined to be respiratory onset, 16 belonged to men. Only two of the included individuals were alive at the time of this analysis. The mean (SD) age at symptom onset was 65.7 (7.1) years (median 68.5 years) and mean (SD) time to diagnosis was 15.3 (9.4) months (median 12 months). All individuals were assessed for underlying pulmonary and cardiac causes for their dyspnoea, and in all cases the primary cause for the dyspnoea was thought to be neuromuscular weakness. With the exception of one individual with a previous diagnosis of chronic bronchitis, the remainder of this cohort did not have an underlying primary pulmonary disease. Diagnosis of definite or probable ALS was confirmed at some point during the disease course, but not necessarily at the time of presentation to the clinic.

Descriptions of respiratory symptoms recorded at presentation to our clinic included dyspnoea on exertion (n = 21), dyspnoea at rest (n = 9), orthopnoea (n = 16), early morning

Abbreviations: ALS, amyotrophic lateral sclerosis; FVC, forced vital capacity; NIPPV, non-invasive positive pressure ventilation; PFT, pulmonary function test

Table 1 Prognosis of amyotrophic lateral sclerosis with respiratory onset

Mean survival time from	Mean (months)	SD
Symptom onset to death	30.6	20.1
Symptom onset to death or PAV	27	14.9
Diagnosis to death	13.4	16.7
Diagnosis to death or PAV	9.8	9.7
Symptom onset to death (NIPPV offered and tolerated)	36.4	16
Symptom onset to death (no NIPPV)	21.5	16
Onset to death/PAV if initial FVC was <50% (n = 6)	29.5	14.1
Onset to death/PAV if initial FVC was >50% (n = 15)	26	15.6

FVC, forced vital capacity; NIPPV, non-invasive positive pressure ventilation; PAV, permanent assisted ventilation.

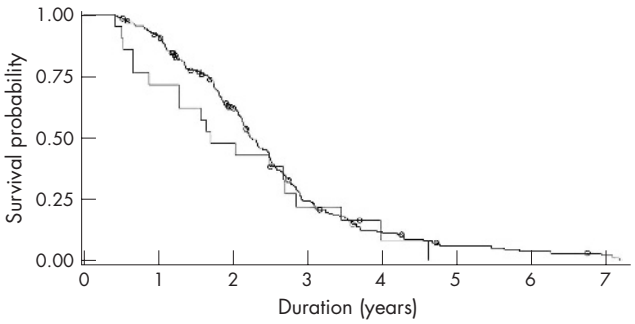

Figure 1 Kaplan–Meier survival curves of respiratory onset amyotrophic lateral sclerosis (ALS) (grey line) compared with bulbar onset ALS (black line). Censored individuals are indicated by a circle. The curves were not significantly different (p = 0.39, log rank).

headaches (n = 3), poor vocal projection (n = 5) and reduced cough efficacy (n = 5). Orthopnoea was so severe that four individuals slept upright in recliner chairs at the time of presentation to our clinic. Two individuals had isolated respiratory symptoms at presentation. Eight had bulbar symptoms or signs at the time of presentation and dysphagia eventually occurred in 15. Seven individuals had either neck flexion or extension weakness at the time of diagnosis. Ninety per cent of individuals had shoulder girdle weakness at presentation, reflecting the prominent involvement of motor neurones in the cervical segment. All patients were ambulatory at the time of presentation, although five had a foot drop.

Of the 14 charts that documented smoking status, 2 were of lifetime non-smokers and 4 were of current smokers. At the time of presentation, pulmonary function test evaluation showed a mean forced vital capacity (FVC) of 64% of that predicted, with a range of 33–111% of that predicted, and only a single individual had an FVC >90% of that predicted. Blood gas evaluation showed a mean partial pressure of carbon dioxide of 51.7 mm Hg (SD 9.4, normal 35–45 mm Hg) and mean bicarbonate value of 31.2 mmol/l (SD 4.4, normal 21–28 mmol/l).

Emergency intubation was required in three patients with hypercapnic respiratory failure without superimposed pneumonia. Only one of these three patients could be weaned off the ventilator, and only two patients of the entire 21-person cohort were maintained on long-term invasive ventilation.

Table 1 provides the survival characteristics. The mean survival time to death or permanent assisted ventilation in bulbar onset ALS was 31.2 months, which was not significantly different from that in respiratory onset ALS (p = 0.43, two tailed Student's t test). Also, the Kaplan–Meier survival curves for respiratory onset ALS versus bulbar onset ALS (fig 1) were not significantly different (log-rank statistic, p = 0.39).

NIPPV in the form of bilevel NIPPV was attempted in 13 patients and was tolerated in 9. Five of the 21 individuals were not offered NIPPV (all before 1996), and one individual who was offered NIPPV refused it. The mean survival time of respiratory onset ALS if NIPPV was tolerated was 36.4 (16) months and if NIPPV was not offered or tolerated was 21.5 (16) months. The difference in survival between those who used NIPPV and those who did not was significant (p = 0.02 for two-tailed Student's t test).

DISCUSSION

This is the largest reported case series of patients with respiratory onset ALS showing that these patients do not have a uniformly poor prognosis. Knowing that the literature suggests reduced FVC at diagnosis to be associated with a poor prognosis,[1] it was surprising to find that the survival time of patients with respiratory onset ALS was not significantly different from that in our patients with bulbar onset ALS, and was almost as long as general ALS survival rates reported in large case series. The mean survival time of patients with ALS in large case series is 30–37 months after the onset of symptoms,[13 14] which is similar to our findings of 30.6 months to death and 27 months to death or permanent assisted ventilation. The only other indication of prognosis in respiratory onset ALS comes from Louwerse,[9] who included four patients with respiratory onset ALS. Louwerse found that the mean survival time was only 2 months after diagnosis, which is much less than the 9.8 months we found. However, based on our larger cohort of 21 patients, we conclude that ALS with respiratory onset does not necessarily imply a rapidly progressive course.

The mean age of symptom onset in patients with respiratory onset ALS was slightly greater than the average age of ALS reported in the literature.[9 13 14] The male predominance in individuals with respiratory onset ALS (76%) is higher than reported in other ALS series where male percentage is approximately 59%. The de Carvalho study also noted an increased frequency of ALS with respiratory onset in males.[5]

Contrary to the literature,[3 5] patients with respiratory-onset ALS in our cohort infrequently required emergency intubation. In this series, only 14% of the individuals required emergency intubation. It is also important to note that PFTs and blood gases ranged from significantly abnormal to normal. One possible explanation for the discrepancy in results between PFT and respiratory symptoms is that diaphragmatic weakness may be missed on routine PFTs and may only be detected when PFTs are performed in both sitting and supine positions.[15] Our experience suggests that significant respiratory symptoms can occur in the setting of normal PFTs. Likewise, significantly abnormal PFTs can also occur in the absence of pulmonary symptoms. As a result, it is imperative that both symptoms and PFTs are assessed when evaluating the respiratory involvement in ALS.

NIPPV initiation, if tolerated, prolongs survival in patients with ALS.[10 11] In patients with respiratory onset ALS, NIPPV improves survival over patients who do not receive NIPPV by a mean difference of 14.9 months. It is also important to note that NIPPV is not tolerated by all patients.[10 11] It may be worthwhile to explain to patients offered NIPPV, that one-third of patients do not tolerate the intervention. Gruis *et al*[16] have used a multivariate approach to evaluate factors predictive of NIPPV tolerance and found that limb onset is an independent predictor of tolerance. However, they assessed only a small number of variables, and hence there is a need for other studies to evaluate other specific predictors of tolerance to NIPPV. For

example, severity of sialorrhoea and ability to remove one's own face mask may be factors associated with tolerance.

This study allows doctors to effectively counsel patients with respiratory onset ALS with regard to its prognosis and the benefits of NIPPV. Although these data are based on a tertiary care ALS clinic and probably represent almost complete case ascertainment within our region, a population-based study could accurately determine the true incidence of respiratory-onset ALS. However, a population-based study is unlikely to change the prognostic statistics that we have generated with our cohort.

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