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LETTER TO THE EDITOR

Early and rapidly progressing respiratory failure in a patient with amyotrophic lateral sclerosis: when FVC% is misleading

Grazia Crescimanno[1,2] · Marcello Romano[3] · Rossella Spataro[4] · Vincenzo La Bella[5] · Oreste Marrone[1]

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Introduction

Respiratory failure is the leading cause of death in amyotrophic lateral sclerosis (ALS) [1]. The involvement of respiratory function is a negative predictor of survival, which can be in part overcome by a prompt initiation of non-invasive mechanical ventilation (NIV).

Seated forced vital capacity (FVC%) is a widely used measure to monitor respiratory function, and it is often taken as a surrogate outcome measure in clinical trials. However, it may be within a normal range in ALS patients with respiratory dysfunction [2].

Here we report on a case of an ALS patient with a rapidly evolving respiratory insufficiency, despite a rather normal FVC%.

Case presentation

The patient, a 67-year-old man with non-significant past medical history, was referred to our Neurology Unit with 7-month history of progressive impairment of neck muscles that caused dropped head. Symptom onset was subtle, and it was followed by camptocormia. The neurological examination documented the camptocormic posture with a dropped head, and disclosed a mild tongue atrophy, slight hypophonia, and a mild dysphagia, with a moderate proximal and distal weakness and atrophy of the upper limbs; the lower limbs were clinically unaffected. Reflexes were present but not brisk in the four limbs.

A complete diagnostic work-up according to current guidelines, including determination of serum anti-ganglioside antibodies, was performed which allowed the diagnosis of ALS. Spirometry was performed to assess the respiratory function: FVC was 80% of predicted, a value within the normal range. Diaphragm compound muscle action potentials (CMAPs) were not measured.

The patient did not complain shortness of breath. Physical examination and X-ray showed no sign of diaphragmatic dysfunction. The revised ALS functional rating scale (ALSFRS-R) was 42/48 [3], with a predicted intermediate rate of progression ($\Delta FS = 0.86$). The respiratory subscores of the ALSFRS-R were 12/12. The dropped head was corrected with a collar. He started riluzole, and a 4-month follow-up visit was scheduled.

Some 30 days after diagnosis, he became increasingly lethargic over a few days and was admitted to the Emergency Unit. Altered arterial blood gases were found (PaO_2 26.4 mmHg, $PaCO_2$ 93.0 mmHg, pH 7.32). A CT scan of the lungs did not show radiological evidences of pneumonia or atelectasis. When inquired, relatives reported that the patient had his usual lifestyle, that he did not complain in the past days of significant respiratory problems, and that he did not take medications other than riluzole. The patient was intubated and placed on invasive mechanical ventilation, with a prompt improvement of the blood gases, i.e., PaO_2 74.3 mmHg, $PaCO_2$ 46.0 mmHg, pH 7.47, and a recovery of full consciousness. The assisted mechanical ventilation was continued.

One week later, the tracheal tube was removed and non-invasive ventilation (NIV) was started. In the following days,

✉ Grazia Crescimanno
grazia.crescimanno@ibim.cnr.it

1 Istituto di Biomedicina e Immunologia Molecolare, Consiglio Nazionale delle Ricerche, Via Ugo La Malfa, 153, 90146 Palermo, Italy

2 Centro regionale di riferimento perla prevenzione ed il trattamento delle malattie neuromuscolari genetiche rare, Ospedale Villa Sofia-Cervello, Palermo, Italy

3 Dipartimento di Neurologia, Ospedale Villa Sofia-Cervello, Palermo, Italy

4 IRCCS Centro Neurolesi Bonino Pulejo, Palermo, Italy

5 Centro di ricerca clinica sulla sclerosi laterale amiotrofica e Laboratorio di neurochimica, Università di Palermo, Palermo, Italy

he failed repeated spontaneous breathing trials. A tracheostomy procedure was programmed. However, he rapidly progressed to a severe shock and passed away.

Discussion

ALS is a phenotypically heterogeneous disease, with a wide spectrum of clinical presentations and rate of progression. Our patient presented with a dropped head, which is a rare manifestation of ALS (0.6% of cases), often associated with early respiratory failure [4]. These patients rapidly progress to weakness of axial muscles, and respiratory muscles might be impaired before FVC% could reveal it. The case of our patient is a strong support to this observation, as a rather normal seated FVC% and a clinically normal respiratory evaluation at diagnosis failed to predict the incoming respiratory failure that occurred in the next few weeks. This suggests that the common practice to plan periodic FVC% re-evaluations intervals at 3-4 months might not be recommended in some instances, as it happened in our patient.

Recently, Tilanus et al. queried whether FVC% may accurately reflect a respiratory muscular impairment [5]. The authors retrieved serial data of 110 ALS patients, and made evaluations with four different respiratory function tests in addition to FVC% [i.e., peak cough flow (PCF), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and sniff nasal inspiratory pressure (SNIP)]. They found that when a FVC < 70% was used as an alerting measure for an incipient respiratory failure, 35% of ALS patients were not timely referred for ventilation. Instead PCF best discriminated patients requiring NIV since the first time they were visited. Additionally, SNIP showed the greatest decline prior to NIV initiation. The authors' suggestion was therefore a regular PCF and SNIP utilization, in addition to FVC%, for the respiratory follow-up of ALS patients.

In line with this evidence, Polkey MI et al. performed respiratory muscle strength measurements in 78 patients with ALS. They included non-invasive (FVC%, MIP, MEP SNIP) and invasive tests, such as maximal sniff oesophageal (SnPes), trans-diaphragmatic pressure (SnPdi), un-potentiated twitch trans-diaphragmatic pressure, using cervical magnetic stimulation (Twitch Pdi), and maximal cough gastric pressure (Cough Pga). Although they found that SnPdi and Twitch Pdi were the best performing tests for prediction of ventilator-free survival, SNIP had excellence predictive power. Normal FVC% predicted a good prognosis only at 3 months [6].

In our patient, with a normal FVC% and with no clinical symptoms or signs of respiratory insufficiency at diagnosis, we did not perform additional evaluations before the first planned 4-months follow-up. It remains an open question whether other measures, as MIP, MEP, SNIP, and nocturnal oximetry, performed at diagnosis in addition to FVC%, might have added useful information about an early involvement of respiratory muscles and/or a dysfunction of the central drive in our case.

FVC% is still the most widely used measure for respiratory involvement in ALS, and it is extensively adopted as a surrogate marker in most clinical trials.

This case report and the revision of the current literature indicates that FVC% alone is most probably an insufficient measure for the identification of those patients at early high risk of early respiratory failure. In addition to FVC%, irrespective of its value, the respiratory follow-up of the ALS patients should routinely include several other tests, along with the now extensively used nocturnal oximetry, for a timely initiation of the non-invasive ventilation.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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