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COMMENTARY

Diagnosis of amyotrophic lateral sclerosis by respiratory function test

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ABSTRACT

The diagnostic criterion for amyotrophic lateral sclerosis (ALS) based on the findings of concomitant clinical and electrophysiological evidence of upper and lower motor neuron involvement may remain unsatisfied for months and in some patients, even for years in the early stage of the disease. Since respiratory involvement is an onset symptom of ALS in only 1-3% of patients, pulmonary assessment has never been considered useful in the early diagnosis of ALS. However, studies on pulmonary function are lacking, especially in those early stages where neurologic tests are also inconclusive. In contrast to the scarcity of data in the early stages, as the disease progresses, it is increasingly enriched by a rich set of symptoms and positive respiratory tests until respiratory failure occurs, which represents the main cause of death in ALS. Hereby we analyze the main pulmonary function tests (PFT) in the various stages of the disease, up to the recent evidence for the possibility of an early diagnosis.

Key words: amyotrophic lateral sclerosis; pulmonary function test; respiratory impairment.

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Introduction

Amyotrophic lateral sclerosis (ALS) is one main form of degenerative motor neuron diseases, clinically defined by the involvement of upper and/or lower motor neurons, inexorably progressive, that causes muscle weakness, disability and respiratory failure, usually progressive until the death. The disease is characterized by upper and lower motor neuron signs (muscle weakness, decreased muscle control, easy fatigability, altered muscle tone and exaggerated deep tendon reflexes, clonus, Babinski sign and muscle atrophy, weakness, fasciculations and hyporeflexia without sensory involvement) and atypical onset symptoms such as presentation of progressively painful muscle cramps may also occur. Two thirds of patients present with focal muscle weakness and wasting either distally or proximally in the upper and lower limbs. Gradually, spasticity may develop in one or more of the weakened atrophic limbs. Dysarthria and dysphagia may characterize the onset of bulbar ALS, and the involvement of the limbs can occur almost simultaneously or progressively in the 2 years following the appearance of bulbar symptoms, and in the vast majority of cases will occur within 1-2 years. Paralysis is progressive and leads to death due to respiratory failure within 3-5 years for limb onset ALS and 2-3 years for bulbar onset cases. The diagnosis of ALS is suspected in patients who meet diagnostic criteria assessed by history and physical examination, supported by electrodiagnostic studies, and not excluded by neuroimaging and laboratory studies [1]. At the moment, it is unknown either a ALS disease marker or a single diagnostic test that can confirm or rule out this diagnosis. The classification of a patient in one of the internationally recognized diagnostic categories (possible, probable, definite ALS) may require to assess over time the progression of signs and symptoms occurring in a body segment (cranial, cervical, thoracic, and lumbosacral) combined to the spread to other segments. Nevertheless, uncertainty can remain for a more or less long period of time that can even reach, in the most devious clinical presentations, a few years before diagnosis. Respiratory muscle weakness is the first manifestation of the disease in a very small percentage (1-3%) of patients and in most patients who meet the diagnostic criteria for ALS, respiratory muscle weakness is asymptomatic at rest but can be perceived during a physical activity or be evidenced instrumentally, thus suggesting that the onset of respiratory muscle involvement may be early [2].

Literature analysis

The respiratory impairment of the advanced stages of the disease is well known. The respiratory system involvement caused by ALS is due to inspiratory and expiratory muscle weakness, that can produce tachypnea, voice and speech modifications, use of accessory respiratory, abdominal paradox. As respiratory muscles become weaker, patients will often develop dyspnea and orthopnea, and successively develop a restrictive ventilatory pattern, which can lead to hypoventilation with hypoxic and hypercarbic respiratory failure. Respiratory complications are the most common causes of death in patients with ALS, so the early and periodic evaluation of respiratory function is mandatory. Once a diagnosis of ALS is established, signs and symptoms of respiratory failure in patients with ALS should be monitored closely [3] in order to consider initiating NIV [4] and to prevent death [5]. The problem arises in the very initial stages of the disease where neurological clinical and electrophysiological data do not yet meet the diagnostic criteria and the respiratory functional assessment is considered to be unhelpful. However, studies aimed at confirming or countering this assumption are lacking. The usefulness of targeted studies of respiratory function in the early stage of disease is suggested by the observation that in patients with early-stage ALS, despite they are respiratorily asymptomatic in the day time it is possible to measure hypoventilation during sleep [6]. Phenotypic presentation can be markedly varied in ALS, making early diagnosis more complicated. This is intricate by the fact that many phenotypic variants have been recognized [7]. While late stage disease is relatively easy to identify, early disease can be much more difficult to diagnose on clinical examination alone. In these situations, early in disease, abnormalities may be hidden from clinical appreciation, and electrodiagnostic evaluation with nerve conduction studies and electromyography (EMG) is mandatory. Sensory and motor nerve conduction studies and EMG are helpful when clinical evidence supporting the diagnosis of ALS is limited or conflicting. But in very early stage of the ALS also electrodiagnostic evaluation can be unsatisfactory.

In this paper we analyze studies about the usefulness of PFT in diagnosis of ALS, focusing our attention especially in early diagnosis, similarly to what has emerged in other diseases [8]. In fact, little or nothing is reported in the literature about respiratory function parameters that may be useful in a very early stage of disease, when yet neurological tests do not allow for a diagnosis of probability.

The most frequently used test to evaluate respiratory function in ALS is upright forced vital capacity (FVC) [9,10]. Chandrasoma *et al*., in a group of 32 consecutive patients with the diagnosis of definite ALS, found a mild restrictive pattern, defined by decrease of FEV_1 and FVC with preservation of the FEV_1/FVC ratio, without significant differences between types of disease onset (bulbar onset group versus the limb group) [11]. We know that there is no close relationship between lung volume and muscle strength [12] so the decrease in lung volume often becomes evident only late in the progression of the disease. Additionally, supine FVC has higher specificity for diagnosing diaphragmatic weakness than an upright FVC. A study showed that supine FVC correlates very well with diaphragm strength, as measured by transdiaphragmatic pressure [13].

Vitacca *et al*. performed a more complete respiratory analysis; they evaluated the time course of breathing pattern and respiratory mechanics in patients with ALS [14]. They studied 25 patients with definite diagnosis of ALS supported by standard laboratory radiograph, electromyography (EMG), multimodal evoked potentials and magnetic resonance imaging (MRI) of the brain and cervical spinal. In this group, in addition to the neurological status and common parameters of spirometry and blood gas analysis, they measured also breathing pattern, respiratory drive ($P_{0.1}$), respiratory muscle strength and respiratory mechanics. Beyond a mild restrictive pattern they found alteration of mechanics correlated with decreased survival and neurological impairment assessed by the Norris scale [15], but nothing is reported about the early stages of the disease.

In 73 patients with probable or definite ALS, Pirola *et al*. [16] evaluated forced vital capacity, both in seated and supine position (sFVC), peak expiratory flow (PEF) and peak expiratory cough flow (PCEF), together with ALS functional rating scale (ALSFRS) [17]. After 6 months all the respiratory parameters significantly correlated with disease progression rate , according to ALSFRS, and monthly declines of FVC% and sFVC%, significantly correlated with the survival. Also in this paper nothing is reported about the early stages of the disease.

In a recent paper, de Carvalho *et al*. aimed to assess the time-change of various respiratory tests in a group of 51 ALS patients to

assess the disease progression [18]. They found a strong correlation between some spirometric tests, in particular MVV (maximal voluntary ventilation) and phrenic nerve amplitude/area while respiratory muscle strength (MIP and MEP) did not change significantly at any time evaluation. In any case it is noteworthy that patients of this study were selected to include mildly affected ALS patients, who showed slow progression, and that at the time of entry into the study the patients were already classified as defined ALS. In a very recent research the possibility of carrying out an early diagnosis with new indices of respiratory function was evaluated [19].

Polverino *et al*. performed a retrospective analysis on the 5-yrs (2013-2017) database of pulmonary function test (PFT) of the Lung Division of "M. Scarlato" Hospital, Scafati (SA), Italy. The subjects corresponded to one of these three categories: A) patients with definite ALS, according "Gold Coast criteria" [1]; B) unexplained symptoms, defined "early ALS" (EA) in the paper; C) control group. All patients of groups A and B had a complete neurological diagnostic test, according to revised El Escorial World Federation of Neurology criteria (Airlie House criteria) [20-22] including a complete standard laboratory, electromyography (EMG), multimodal evoked potentials and magnetic resonance imaging (MRI) of the brain and cervical spinal cord to confirm or, alternatively, to exclude other diseases mimicking ALS.

Among the pulmonary function tests (PFT) were also evaluated the respiratory muscle strength inspiratory: MIP, and expiratory: MEP) and the respiratory drive ($P_{0.1}$).

The authors found that:

- group A had a restrictive profile (FVC and $FEV_{1.0}$ significantly lower than group B and C);
- in group B no difference was detected in FVC between sitting and supine position;
- all PFT values in group B of EA were close to 100% of the predicted without any significant difference with the mean value of controls;
- a slight lower value of PaO_2 was recorded in the group A in comparison with controls, even if no patient had overt hypoxemia.
- MIP and MEP were significantly different in the one-to-one comparison of the groups.
- The drive (p0.1) was significantly different between definite ALS (group A) and controls (group C) and between early ALS (group B) and controls (group C), while no statistical difference was found between definite ALS (group A) and early ALS (group B).

To enhance the muscular and respiratory center compromission, the authors calculated the ratio between respiratory drive and inspiratory muscle strength ($P_{0.1}$/MIP) in the 3 groups.

The ratio was significantly greater in definite ALS (group A) and in early ALS (group B) in comparison with controls (group C), while no statistical difference was found between definite ALS (group A) and early ALS (group B).

This study differs from the others for two reasons: i) the authors examined those patients with nuanced symptoms and still negative neurological tests, who subsequently had a definite diagnosis of ALS; ii) in addition to spirometry in the sitting and supine position, the authors also examined respiratory drive and muscle strength.

In this study the authors found that the 3 groups have statistically different respiratory strength values and that respiratory drive clearly differentiates the subjects of group B from the controls.

Respiratory drive ($P_{0.1}$) expresses the intensity with which the breath center receives mechanical and chemical afferents related to gas exchange and sends an impulse to to the respiratory muscles to adapt ventilation to the afferent chemical situation. During the normal breathing cycle, the respiratory system modulates its activity in order to keep the partial pressures of the alveolar gases (O_2 e CO_2) in the normality range, minimizing the mechanical workload of the respiratory muscles. This minimal consumption makes the cardiac output available for the muscles of the limbs, limits the energy consumption of the respiratory muscles, and reduces dyspnea and fatigue of the limbs during physical exercise.

Thanks to these mechanisms, healthy subjects keep the tidal volume, both at rest and during exercise, in normality ranges without airflow limitations. In fact, when a healthy subject undergoes a respiratory overload, several different compensatory mechanisms occur, that help the respiratory system adjusting to different conditions [23]. Some of these mechanisms depend upon specific features of the ribcage and the respiratory muscles. Others depend upon the nervous reflexes originating from the stimulation of the airway and ribcage receptors. Others arise from blood gas alterations, and other from the activation of memory pathways and learning mechanisms in the brain linked to past experiences. The force produced by the respiratory muscles depends, partially, on the neuromuscular drive that activates the muscles, but also on the intrinsic features of the muscles themselves. As feedback mechanism, as the force produced by a muscle decreases the drive increases in order to keep the muscular output. There are two main factors influencing the intensity of the respiratory drive in order to compensate the respiratory load and provide an adequate ventilation: the mechanical afferents, originating from the neuromuscular fuse and from the Golgi apparatus of the respiratory muscles and ribcage, and the chemical afferents of the chemoreceptors.

The authors hypothesized that the metabolic demand, coming from the central and peripheral chemosensors and muscular mechanoreceptors, sends a signal to the cortex in order to produce a grater stimulus to counterbalance the albeit minimal (and subclinical) muscular weakness of the very early stages of the disease, and the $P_{0.1}$ tends to be stronger. A similar mechanism has been described in osteoporosis [8]. To better highlight this alteration the authors normalized the drive to the inspiratory muscle strength ($P_{0.1}$/MIP): this ratio was significantly different between group A and controls and between group B and controls, while there was no statistical difference between group A and group B. That is, the behavior of this relationship in the group B of patients with nuanced symptoms and still negative neurological tests (early ALS) was similar to that of the group A with defined ALS. It is worth noting that 77% of patients in the group B (28 out of 35) had a ratio greater than 1.5 which is the maximum value found in the control group. This implied 80% sensibility, 100% specificity, 89% efficiency, 100% positive predicted value and 80% negative predicted value of the ratio $P_{0.1}$/MIP.

In the series of 415 individuals apart from the 35 ALS patients, 41 diagnosis of a neuromuscular disesase were made, which fell into one of the following categories, metabolic, inflammatory or mitochondrial myopathy, Myasthenia Gravis and myasthenic syndromes; SMA 3/4; chronic axonal motor neuropathy, paraneoplastic neuromyopathy. However, interindividual variability and low numerosity in each diagnostic category did not allow the authors to test statistically whether changes in respiratory function were specific to ALS or whether it was also shared by other neuromuscular diseases. This is a critical point in the study and comparisons between patients with suspected ALS and other neuromuscular diseases are needed in the future.

Conclusions

In conclusion, to date, there is no role for the usual PFT in the early diagnosis of ALS, since they are altered only in the more advanced stages of the disease when the diagnosis is already confirmed. Quite recently, however, the possibility of using other tests of respiratory function for an early diagnosis of ALS, at the first signs of the disease, when the symptoms have just faded and the neurological tests are still inconclusive, has been made. The decrease of inspiratory and expiratory strength, parallel to the increase in P0.1 (with the consequent increase of the ratio P0.1/MIP) are highly suggestive for an early diagnosis of ALS. The main finding of the Polverino *et al*'s. paper [19] is that the respiratory drive (P0.1), the MIP, and their ratio (MIP/ P0.1) are sensitive enough to discriminate patients with pre-clinical ALS from the controls way ahead of time. It should be assessed whether this behavior is specific to ALS or whether it is also shared by other neuromuscular diseases.

This work by Polverino *et al*. [19], therefore, represents a real perspective for an earlier diagnosis of ALS.

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