Title: DIPPER- Diaphragm Paralysis in Pompe investigation

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Introduction
The authors aim is to create a protocol for the diagnosis of adult-onset Pompe Disease in patients with diaphragmatic paralysis.

Study Objectives

- Primary objectives
Many patients who are follow-up in Pulmonology outpatient clinics with the diagnosis of diaphragm paralysis have no confirmed etiology. Our aim is to create a protocol for the diagnosis of adult-onset Pompe Disease in patients with diaphragmatic paralysis.

- Secondary objectives
Establish a diagnosis that has treatment in patient with neuromuscular disease.

Study Design
National multicentric epidemiological study, to be developed in 14 centers. All the investigators are Pulmonologists that have experience in treating patients with neuromuscular diseases, who will apply a protocol in all patients who suffer from diaphragm paralysis, followed in Pulmonology outpatient clinic, with the intention to identify Adult onset of Pompe´s Disease in a period of twelve months.

Study population

- Inclusion criteria:
  - Patients followed-up or referred to a pulmonologist for diaphragmatic paralysis (unilateral or bilateral) suspicion, with no history of surgery or trauma that may cause damage to the phrenic nerve.
- Patients followed-up by a pulmonologist for restrictive ventilatory syndrome (both FVC [forced vital capacity] and TLC [total lung capacity] < 80% of predicted and showing, at least, a 12% decrease in VC [vital capacity] in the supine position), decreased maximal inspiratory pressure (IPmax) and sniff nasal inspiratory pressure (SNIP) (at least -10 cm H2O of predicted) with no definitive diagnosis.

Note – Patients meeting the following criteria may also be subject to screening (always with confirmed diaphragmatic paralysis):

- Patients subject to neuromuscular diseases follow-up office visits for progressive chronic myopathy with respiratory involvement, particularly of the diaphragm, which muscle biopsy was not totally conclusive or lies in the “bag” of inclusion body myositis, or patients showing symptoms of Adult-onset Pompe Disease.

- Patients subject to Sleep-Related Respiratory Disorders follow-up office visits, showing central hypoventilations and/or central sleep apnoea during REM sleep, with no etiologic diagnosis.

- **Exclusion criteria:**
  - Neuromuscular junction diseases: Eaton-Lambert syndrome, miastenia gravis.
  - Myopathies: polymyositis and other mixed connective tissue diseases, dystrophy, mitochondrial myopathies, amyloidosis.
  - Myelopathy (spinal cord diseases): cervical spine injury, sarcoidosis, siringomiely, polyomyelitis, ALS (amyotrophic lateral sclerosis).
  - Peripheral neuropathies: cervical spine injury, mediastinal tumour, Guillain- Barré Syndrome, nutritional neuropathies (vitamin B12 deficiency) and lead neuropathy.
  - Active oncologic disease
  - Patients requiring invasive mechanical ventilation
  - Patients under 18 years old
  - Tracheostomized patients
  - Pregnancy

**Sample size**

100 patients

**Study duration**

12 months
Methods

A total of 100 patients diagnosed by the collaborative Portuguese centers will be included in the study. Information on clinical history, physical examination, and diagnostic parameters will be made according to a protocol based on the usual evaluation for patients with diaphragmatic paralysis.

All patients who match the inclusion criteria will be proposed for detection of Acid alpha-glucosidase activity (AAG) in dried blood spot (DBS), after providing written informed consent, and those who’s AAG is below the normal level will have the diagnosis confirmed by genotyping.

Statistical Analysis

Multivariable analysis to evaluate the association of diaphragmatic paralysis with the degree of loss in muscle straight that appears in Pompe’s disease. Because the loss of muscle straight characteristic of patients with Pompe’s disease cannot be distinguished by all the other causes of diaphragm paralysis, we created a protocol that will permit us to simplify the diagnosis algorithm.

The results will be analyzed by an independent statistical center.

REFERENCES