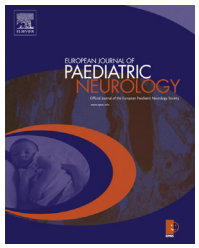
EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY XXX (2013) 1–9

Official Journal of the European Paediatric Neurology Society



Original article

Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3

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ARTICLE INFO

Article history:
Received 14 January 2013
Received in revised form
14 March 2013
Accepted 13 April 2013

Keywords:
Spinal muscular atrophy
Respiratory muscles
Lung function
Vital capacity
Sniff nasal inspiratory pressure
Diaphragm

ABSTRACT

Background: Spinal muscular atrophy (SMA) is a common genetic disorder that causes severe hypotonia and weakness, and often fatal restrictive lung disease. The aim of the study was to describe the natural history of the respiratory involvement in patients with SMA type 2 and 3 in order to assess the relevance of the clinical classification and identify the parameters associated with the earliest and most rapid decline over time.

Methods: Thirty-one patients aged 3–21 years were followed over a 10-year period. Lung function, blood gases, respiratory mechanics and muscle strength with recording of oesogastric pressures were measured during routine follow-up.

Results: At least two measurements were available in 16 patients (seven type 2 and nine type 3). Among all the volitional and non-volitional, invasive and non-invasive tests, forced vital capacity (FVC) and sniff nasal inspiratory pressure (SNIP) were shown to be the most informative parameters, showing lower values in SMA type 2, with however a similar rate of decline in patients with SMA type 2 and 3.

Conclusion: Our results confirm an earlier decline in lung and respiratory muscle function in patients classified as SMA type 2 as compared with patients classified as type 3. This decline can be assessed by two simple non-invasive tests, FVC and SNIP, with the last maneuver being feasible and reliable in the youngest children, underlying its interest for the monitoring of children with SMA.

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1090-3798/$ – see front matter © 2013 Published by Elsevier Ltd on behalf of European Paediatric Neurology Society.
http://dx.doi.org/10.1016/j.ejpn.2013.04.004

Please cite this article in press as: Khirani S, et al., Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3, European Journal of Paediatric Neurology (2013), http://dx.doi.org/10.1016/j.ejpn.2013.04.004

1. Introduction

Spinal muscular atrophy (SMA) is a common genetic neuromuscular disease involving the motor neurons. The incidence of SMA is estimated to be 1 in 6000 to 1 in 10,000 live births. SMA represents the second most common cause of mortality from a recessive genetic disorder and children with SMA are among the weakest patients with neuromuscular disorders. Due to the wide disease presentation, patients are classified in 3 types (type 1–3), based on the age onset, severity of disease and achieved motor milestones.[1,2] Indeed, the clinical presentation varies from a most severe infantile-onset form (type 1), associated with a high mortality rate, to a late-onset form with the majority of patients remaining independently ambulatory in adulthood (type 3). However the distinction between type 2 and 3 may be difficult, suggesting the potential interest for a reassessment of this clinical classification.[3–6]

SMA causes a predominantly bilateral proximal muscle atrophy and weakness.[1,7] The respiratory muscles are also involved with a weakness of the intercostal muscles and a relatively spared diaphragm.[8] This respiratory muscle weakness translates into an impairment of cough, resulting in poor clearance of airway secretions and recurrent pulmonary infections, restrictive lung disease due to a poor or insufficient chest wall and lung growth, nocturnal hypoventilation, and finally respiratory failure in the most severe patients.[7] Respiratory management consists of regular chest physiotherapy with the help of cough assist devices and non-invasive respiratory support in case of nocturnal hypoventilation and/or respiratory failure.[7,9]

Only a few studies have analyzed the natural history of the respiratory involvement in patients with SMA type 2 and 3.[9–17] However, these studies mainly focused on forced vital capacity (FVC) and maximal static pressures, which are volitional maneuvers which may be difficult to perform in young children and in patients with severe respiratory muscle weakness. As such, we previously developed other tests which are easier to perform by young children and which allow a precise quantification of the strength and endurance of both inspiratory and expiratory muscles.[8,18]

The objective of our study was therefore to describe the longitudinal course of the respiratory muscle involvement, expressed by a large number of parameters, in young children and adults with SMA type 2 and 3. We aimed to assess the relevance of the clinical classification as well as identify the parameters associated with the earliest and most rapid decline over time.

2. Material and methods

2.1. Patients

We retrospectively reviewed the charts of all the SMA patients followed in our multidisciplinary neuromuscular clinic between 2001 and 2011 (see Online supplement). For all the patients, the diagnosis of SMA was determined by clinical findings confirmed by mutation analysis of the *SMN*1 gene, located on chromosome 5q13, along with the presence of normal creatine kinase serum levels, and electromyographic and muscle biopsy patterns.[19] There has been controversy as to the exact criteria of classification of SMA.[6,20] In the present study, we adopted the criteria of the International SMA Consortium which adopted defined ages of onset and death as classification criteria.[21]

SMA type I (severe): onset from birth to 6 months; patients are never able to sit without support, and death occurs usually at 2 years; SMA type II (intermediate): onset before 18 months; patients are able to sit but are unable to stand or walk unaided, and death occurs usually at older than 2 years of age; SMA type III (mild): onset after 18 months of age; patients are able to stand and walk, and death occurs in adulthood.

Vertebral spine surgery was decided during a multidisciplinary discussion, based on the progression of spine deformity despite bracing and physical measures, cardiac function, and growth. Post-surgery lung and respiratory muscle tests were performed at least 6 months after spine surgery. Only data before the initiation of non-invasive positive pressure ventilation (NPPV) were taken in account. All the measurements were performed while the patients were clinically stable for at least one month.

The study was conducted in agreement with the French regulations and had received appropriate legal and ethical approval from the Institutional Review Board of the French Learned Society for Respiratory Medicine (Société de Pneumologie de Langue Française).

2.2. Lung function and respiratory muscle tests

Lung function and respiratory muscle tests, height or arm span and weight were recorded at each routine outpatient visit.[22,23] The frequency of visits varied according to the clinician's assessment of the patient, but was generally every 6–12 months. Only the data of the patients who attended at least two visits were considered.

2.3. Non-invasive non-volitional tests

Functional residual capacity was measured by the helium dilution technique (FRCHe %pr). Tidal volume (V_T) and minute ventilation (V_E) were measured and the rapid shallow breathing index (f_R/V_T) was calculated.[24,25] Capillary arterialized blood gases were determined.[26]

2.4. Non-invasive volitional tests

Thereafter, the patient performed at least three physician-accepted FVC curves and the curve with the highest FVC was registered. Afterwards, the best maximal sniff nasal inspiratory pressure (SNIP) from at least 10–20 short, sharp sniffs was noted.[27] When possible, maximal static inspiratory (MIP) and expiratory (MEP) pressures were measured from FRC and total lung capacity, respectively.[28]

2.5. Invasive non-volitional tests

Successively, an oesogastric catheter (Gaeltec, Dunvegan, Isle of Skye, UK) was inserted pernasally.[29] Transdiaphragmatic

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