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ORIGINAL RESEARCH

Peak cough flow in children and young people with spinal muscular atrophy types II and III

Pico de fluxo de tosse em crianças e jovens com atrofia muscular espinhal tipo II e tipo III

El pico flujo de tos en niños y jóvenes con atrofia muscular espinal tipo II y III

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ABSTRACT | Spinal muscular atrophy is a neurodegenerative disorder, which may be associated with progressive respiratory failure. Our aim is to describe the peak cough flow of children and young people with spinal muscular atrophy types II and III. This is a descriptive, cross-sectional study conducted at a neuropediatrics outpatient clinic between March 2011 and May 2012, with patients with spinal muscular atrophy types II and III, and aging more than 5 years. Out of the 53 eligible patients, 21 participated in the research. The measurement of peak cough flow was carried out through the peak flow meter, with patients sitting and lying down. After taking three measures, we selected the one with the highest value among them. Type-III individuals reached peak cough flow values higher than those of type-II individuals. Measures taken in the sitting position (SMA II 159.4 l/min; SMA III 287.9 l/min) were higher than those measured in the lying position (SMA II 146.9 l/min; SMA III 257.5 l/min), with significant difference (p-value=0.008 in sitting position, and p=0.033 in lying position). We concluded that individuals with SMA III manifest higher PCF, especially when sitting, in comparison with SMA II.

Descriptors | Spinal Muscular Atrophy; Peak Cough Flow; Cough.

RESUMO | A atrofia muscular espinhal é uma doença neurodegenerativa, que pode cursar com insuficiência respiratória progressiva. O objetivo deste trabalho é descrever o pico de fluxo de tosse de crianças e jovens com atrofia muscular espinhal dos tipos II e III. Trata-se de um estudo transversal descritivo realizado em ambulatório de neuropediatria entre março de 2011 e maio de 2012, com pacientes com atrofia muscular e espinhal dos tipos II e III com mais de 5 anos de idade. Dos 53 pacientes elegíveis, 21 participaram da pesquisa. A medição do pico de fluxo de tosse foi realizada através do *peak flow meter* com os pacientes sentados e deitados. Após registradas três medidas, foi selecionada a maior entre elas. Os indivíduos do tipo III alcançaram valores de pico de fluxo de tosse superiores aos dos indivíduos do tipo II. As medidas tomadas em posição sentada (AME tipo II 159,4 l/min; AME tipo III 287,9 l/min) foram superiores às medidas em posição deitada (AME tipo II 146,9 l/min; AME tipo III 257,5 l/min), com diferença significativa (p-valor=0,008 posição sentada e p=0,033 posição deitada). Concluiu-se que indivíduos com AME tipo III apresentam maior PFT, principalmente quando sentados, em comparação com o tipo II.

Descritores | Atrofia Muscular Espinhal; Pico do Fluxo Expiratório; Tosse.

RESUMEN | La atrofia muscular espinal es una enfermedad neurodegenerativa, que puede presentarse con insuficiencia respiratoria progresiva. Este trabajo pretende describir el pico flujo de tos de niños y jóvenes con atrofia muscular espinal tipo II y III. Se trata de un estudio descriptivo

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transversal realizado en la clínica ambulatoria de neuropediatría entre marzo de 2011 y mayo de 2012, con los pacientes con más de 5 años de edad con atrofia muscular espinal tipo II y III. De los 53 pacientes elegibles, 21 participaron del estudio. La medición del pico flujo de tos se llevó a cabo a través de *peak flow meter* en pacientes en la posición sentada y supina. Después del registro de las tres medidas, se seleccionó la mayor. Los individuos con tipo III tuvieron valores pico flujo de tos mayores que los con tipo II. Las medidas registradas en la posición sentada (AME tipo II 159,4 l/min; AME tipo III 287,9 l/min) fueron las más altas que la de posición supina (AME tipo II 146,9 l/min; AME tipo III 257,5 l/min), con diferencias significativas (p-valor=0,008 posición sentada y p=0,033 posición supina). Se concluyó que los individuos con AME tipo III presentan mayor PFT, especialmente en la posición sentada, comparados con los de tipo II.

Palabras clave | Atrofia Muscular Espinal; Pico Flujo Espiratorio; Tos.

INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular, autosomal recessive disorder, caused by homozygous deletion or mutation of the survival motor neuron (SMN1), located on chromosome 5q13[1], in the centromeric region, and the number of copies of SMN2 responsible for the transcription of the same SMN protein, which determines the clinical phenotype of SMA and the severity of the disease[2]. Degeneration of motor neurons in the anterior horn of the spinal cord results in weakness and progressive muscular atrophy[3], which is classified into three types according to functional ability: type I – patients present with symptoms until 6 months of age and do not sit alone; type II – muscle weakness starts after 6 months of age, patients sit, but they do not walk; type III – it starts after 18 months of age, patients are able to walk[4,5].

In SMA, the progressive muscle weakness affects respiratory muscles, resulting in dysfunction in cough, reduced expiratory flow rate, or peak cough flow (PCF), generating respiratory morbidity and mortality in neuromuscular patients when not treated. These disorders occur in SMA types I and II, and to a lower proportion in type III. The development of restrictive breathing pattern is the result of progressive respiratory muscle weakness, and it also involves decreased alveolar ventilation, causing hypoventilation during sleep, and inability to cough, resulting in inefficient clearance of the airways and underdevelopment of the lungs and rib cage, with recurrent respiratory infections[4,6].

The diameter of the trachea depends on the magnitude of the change in the pleural pressure[7], and cough is the main physiological mechanism to remove lung secretions. The rate of the airflow when coughing is the main factor responsible for airway clearance. High rates can be obtained with high flows or proper narrowing of the airway[8]. Rate of the airflow can be divided into four stages: nervous, inspiratory, compressive, and expulsive[9]. PCF is the maximum expiratory flow measured during a cough maneuver and allows us to measure the clearance of secretion in the airways[10-12]. During normal cough maneuver, we must achieve at least 60% of the predicted vital capacity (VC) in order to achieve 6-16 l/s of expiratory flow. In individuals with neuromuscular impairment, this measure is reduced at some point due to the worsening of cough efficiency, resulting from muscle respiratory weakness[13]. Respiratory care, such as assisted cough, noninvasive procedure or ventilatory support, invasive procedure and effective nutritional care, are directly related to increased survival among SMA I patients[14-16].

According to the Consensus Statement for Standard of Care in Spinal Muscular Atrophy, from 2007[4], respiratory assessment, including the PCF measurement, must be periodical, according to the condition and degree of SMA progression. Measures accounting for PCF>160 l/min are recommended to maintain effective cough and patent airway[17,18]. A PCF<270 l/min pose risk to patients to develop respiratory failure during episodes of lung infections[19]. Values >270 l/min allow us to detect patients who would benefit from the assisted cough technique[20]. PCF is also considered a marker of bulbar muscle weakness[21].

Ventilatory capacity in neuromuscular SMA patients is little studied, which generates ignorance regarding in which moment healthcare professionals should attend the patients. With our descriptive study on PCF, we aim to contribute to the improvement of respiratory care in SMA for children and young people.

METHODOLOGY

Descriptive, cross-sectional study with convenience sample of patients diagnosed with SMA selected at the

Outpatient Clinic of Neuropediatrics of the Martagão Gesteira Institute of Pediatrics (IPPMG), at the Federal University of Rio de Janeiro (UFRJ), from March 2011 to May 2012. We included patients aging more than 5 years, with SMA II and III confirmed by the clinical pattern and by at least one of the complementary examinations: electromyography, muscle biopsy, and molecular biology. We excluded patients with acute respiratory infection for about three weeks, or with tracheostomy, and those who did not agree, or whose legal guardians did not agree to participate and did not sign the informed consent form.

Evaluation methods

Patients with SMA types II and III were classified according to the *Consensus Statement for Standard of Care in Spinal Muscular Atrophy* [4].

We studied the following variables: age, sex, anthropometric measurements (height and weight), and PCF measurement by the peak flow meter (Mini-Wright AFS, EU Scale 30 to 400 L/min), with patients lying down and sitting.

For measuring height and weight, we used an electronic weighting scale (Welmy W110 H), with stadiometer for those who could reach the orthostatic posture. Weighing was carried out with the individual under study being sustained by the evaluator or legal guardian, disregarding their weight in order to achieve the actual weight of the patient. When we could not find the orthostatic posture, to estimate the patient's height we used the arm span, which is the length of the longest finger tip with the arm extended horizontally until the wishbone, measured with a measuring tape[22].

Before measuring PCF (in lying and sitting positions), patients received guidelines and demonstrations of how the maneuvers should be carried out. Two trained and qualified researchers applied the tests according to the guidelines of the European Respiratory Society[22-24].

To analyze the results and draw the graphs, we used the Excel software (Microsoft Office Home and Business 2013). Descriptive statistics, with frequency measures, percentages, minimum and maximum values, means, medians, standard deviations, and calculation of the p-value (level of significance <0.05), was carried out with the program SigmaStat® 3.1 (Systat Software Inc., Richmond, Califórnia, USA). The boxplot was created with the program SigmaPlot® 9.01 (Systat Software Inc., Richmond, Califórnia, USA).

RESULTS

Of a total of 53 patients, 32 were excluded due to no consent on the part of the parents, incomplete personal data in medical records, or no collaboration with the tests. One patient gave up on performing respiratory assessment tests, and only allowed researchers to take his anthropometric measurements. Hence, we evaluated 21 SMA patients, being: 9 type-II patients, and 12 type-III patients. General characteristics of the casuistry are presented in Table 1.

Table 1. Characterization of patients with spinal muscular atrophy types II and III

Variables	Spinal muscular atrophy (SMA)	
	Type II (n=9)	Type III (n=12)
Sex (M/F)	6/3	8/4
Age (years)		
Minimum-maximum	6-22	8-25
Median	9	13
Mean	11.6 (±5.8)	14(±14.1)
Weight (Kg)		
Minimum-maximum	13-58	23-60.2
Median	30	29.5
Mean	33.14(±15)	37.33(±14.3)
Height (cm)		
Minimum-maximum	102-162	117-174
Median	127	153.5
Mean	130.8(±19.1)	149.7(±17.6)

Values expressed as minimum, maximum, mean median, and standard deviation.

Mean age between the types was 13±4.9 years. Two individuals considered adults aged over 20 years (SMA II=22 years old, and SMA III=25 years old), representing 9% of the sample. The mean height was 141±20.2 cm; the mean weight of types II and II was of 35.5±14.4 kg.

PCF in sitting position accounted for a mean of 287.9 l/min for SMA III; and 159.4 l/min for SMA II (Table 2 and Figure 1).

Table 2. Mean values of peak cough flow in patients with spinal muscular atrophy types II and III, in sitting and lying positions

	SMA II	SMA III	p* value
	PCF (L/min)	PCF (L/min)	
Sitting	159.4(±98.1)	287.9(±100.3)	0.008
Lying down	146.9(±80.3)	257.5(±106.4)	0.033

SMA: spinal muscular atrophy Values expressed as mean, standard deviation, and p*∞0.05

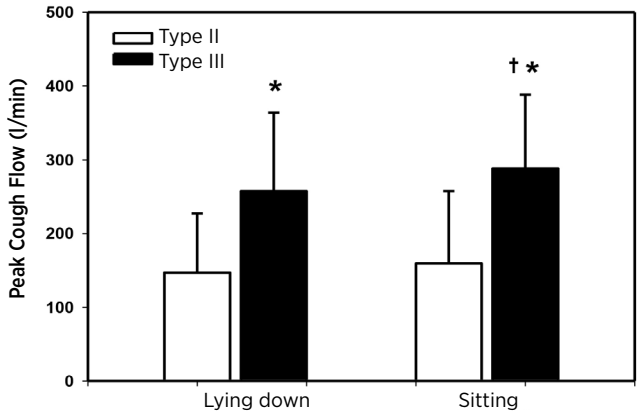

Figure 1. Peak cough flow in lying and sitting positions for SMA types II and III

Expressed values: l/min; SMA types: II and III. *: significant difference between SMA types in the same position, p-value=0.023 and p=0.011, respectively, in lying and sitting positions; †: significant difference, p-value=0.048 for type III in sitting position.

DISCUSSION

Our study showed higher PCF values in patients with SMA III than in SMA II patients. This suggests that cough is a mechanism more preserved in moderate manifestations of the disease. Factors, such as loss of orthostatism and ambulation, spinal deformities, and inspiratory and expiratory muscle weakness, can be associated with less effectiveness of cough[3].

Regarding the age of the participants, the greatest variation of PCF occurred for SMA III, in which symptoms are presented later and with slower progression, comprising different age groups[4]. Older participants, with SMA III, confirmed the classification of the disease, which impairs in a more smoothly way individuals from 18 months of age, and may persist until adulthood, unlike SMA II, which affects younger individuals and does not persist until adulthood. Individuals with SMA III showed better performance on tests of lung function, with higher values according to age, which can be justified by better physical condition and greater cooperation and attention during the tests.

The weight of the patients ranged from 13 to 60 kg between types II and III, with approximate weight means between the two types. Height was higher in type III, since overall, in this group, individuals are older.

In our study, type III featured the highest PCF for both evaluated positions, with higher standard deviation, because it is a heterogeneous group, composed of individuals who keep walking, wheelchair users, and people with and without spinal deformities[24,25].

Type III exceeded the limit of PCF 160 l/min, generating efficiency in the cough maneuver, and exceeded the 270 l/min measure, which generates minimal risk of respiratory failure during crises of the respiratory tract infection[10,18,26]. PCF measures have been related to the success or failure of extubation, and to the risk of acute respiratory failure in neuromuscular patients. The main therapeutic strategies aim at optimizing the cough through techniques that increase the PCF values[25]. PCF measure in the lying position was lower than in the sitting position. However, it is noteworthy that it can already be found in literature that there is a loss of 20% of the volume in the vital capacity measure when individuals are lying. That is because abdominal structures are displaced towards the cranial direction, hindering the movement of the diaphragm, which it is also a muscle associated with weakness[27,28].

According to the Consensus Statement for Standard of Care in Spinal Muscular Atrophy de 2007[4], respiratory care is recommended depending on the motor marker achieved by patients: those who cannot sit, those who sit, and those who walk. Periodic PCF evaluations are recommended (less frequently for those who walk), in addition to pulmonary function tests (including vital capacity and total lung capacity), enabling healthcare professionals to direct the choice of physiotherapeutic techniques[4]. Marques et al.[29] concluded, by observing patients with neuromuscular diseases, that the use of air stacking optimizes PCF, including for patients with SMA30. Jeong e Yoo30 corroborate this finding.

As limitations of our research, we highlight: since it is a cross-sectional study, we could not monitor the progressive PCF loss of the patients, according to the evolution of their disease. Some tests may have been harmed because the muscle weakness may cause air leak around the lips during the PCF measure, in addition to weakness for closing the mouth, with the need to interrupt and exclude the evaluation. Moreover, we excluded patients due to their difficulties in understanding the test, and there was quantitative loss of patients, considering that many could not walk to the outpatient clinic, and others had few financial resources to go to the location of the evaluations. Having no consent on the part of some patients' legal guardians, as well as the difficulty in establishing contact because of the outdating concerning data on the medical reports, was also an issue.

We perceived worst ventilatory parameters in accordance with the classification of the disease and the posture in functional assessment. Type-III SMA featured

lower harm to PCF measurement compared with type II, which would require greater monitoring of the respiratory pattern, mainly by restricting the PCF, which leads to cough inefficiency.

Therapeutic measures should be employed to optimize the expiratory flow, reaching airway secretion clearance and avoiding respiratory impairments. Such strategies are likely to be more efficient in the sitting position, since in the lying position the mechanical diaphragm disadvantage is evident.

The analysis of ventilatory parameters throughout the natural history of the patient with SMA can set marks for follow-up and therapeutic interventions. The effects on these respiratory aspects are of paramount importance for the multidisciplinary team that monitors SMA patients, aiming at improving their quality of life[31,32].

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