

Duchenne Muscular Dystrophy: a look at ventilatory disorders

Beatriz Sordi Chara¹, Tiago Neves Veras², Anna Paranhos Miranda Covaleski³, and Marcus Magno Gonçalves²

¹Universidade da Região de Joinville

²Universidade da Região de Joinville Departamento de Medicina

³Universidade Federal de Pernambuco

October 5, 2020

Abstract

Duchenne Muscular Dystrophy is an X-linked inherited disorder and the most common fatal degenerative muscle disease in pediatric patients. Its first symptoms usually manifest at an early age, with weakness, psychomotor developmental delay, evolving to cardiac and ventilatory muscle impairment. The involvement of the pulmonary musculature is demonstrated by the frequent episodes of obstruction and aspirations, sleep-disordered breathing, and by the development of a chronic restrictive breathing pattern. Failure of respiratory mechanics is a major cause of mortality in Duchenne Muscular Dystrophy, and the beginning of lung function deterioration is not always accompanied by symptoms, which reinforces the need for serial evaluations for early initiation of a ventilatory support. The present article is thought to provide a synthesized overview of the assessment and management of Duchenne Muscular Dystrophy ventilatory disturbances.

Duchenne Muscular Dystrophy: a look at ventilatory disorders

Beatriz Sordi Chara¹;Tiago Neves Veras²; Anna Paula Paranhos Miranda Covaleski³, Marcus Vinícius Magno Gonçalves⁴

1- Medical student - Department of Medicine, Universidade da Região de Joinville (UNIVILLE), Address: 10 Paulo Malschitzki St, Joinville, SC, 89219710, Brazil;

2 - Medical Doctor, MSc. and Professor of Pediatrics, Universidade da Região de Joinville (UNIVILLE), Address: 10 Paulo Malschitzki St, Joinville, SC, 89219710, Brazil;

3- Medical Doctor, MSc. and Professor of Neuropsychiatry, Universidade Federal de Pernambuco (UFPE), Address: 1235 Professor Moraes Rego Ave, Recife, PE, 5060901, Brazil;

4- Medical Doctor, Ph.D., and Professor of Neurology, Universidade da Região de Joinville (UNIVILLE), Address: 10 Paulo Malschitzki St, Joinville, SC, 89219710, Brazil.

Corresponding Author

Marcus Vinícius Magno Gonçalves

Department of Medicine - University of the Region of Joinville. Address: 10 Paulo Malschitzki St, Joinville, SC, 89219710, Brazil. Phone number: +55 47 9 9974-9668. E-mail: mvmpesquisa@gmail.com

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures. All authors and contributors agree to the conditions outlined in the Authorship and Contributorship section of the Information for Authors. The authors have read the Journal's position on issues involved in ethical publication. There was no sponsorship for the scientific article and there was no conflict of interest with all the authors.

Keywords

Duchenne Muscular Dystrophy, Dystrophin, Respiratory Failure, Ventilatory Depression

ABBREVIATIONS

DMD - Duchenne Muscular Dystrophy

FVC - Forced Vital Capacity

PSG - Polysomnography

PEF- Peak Expiratory Flow

ABSTRACT

Duchenne Muscular Dystrophy is an X-linked inherited disorder and the most common fatal degenerative muscle disease in pediatric patients. Its first symptoms usually manifest at an early age, with weakness, psychomotor developmental delay, evolving to cardiac and ventilatory muscle impairment. The involvement of the pulmonary musculature is demonstrated by the frequent episodes of obstruction and aspirations, sleep-disordered breathing, and by the development of a chronic restrictive breathing pattern. Failure of respiratory mechanics is a major cause of mortality in Duchenne Muscular Dystrophy, and the beginning of lung function deterioration is not always accompanied by symptoms, which reinforces the need for serial evaluations for early initiation of a ventilatory support. The present article is thought to provide a synthesized overview of the assessment and management of Duchenne Muscular Dystrophy ventilatory disturbances.

HIGHLIGHTS

- Loss of ventilatory function is one of the most severe complications of DMD;
- Frequent spirometries should be performed since the child is 5 years old
- A reduction in FVC and PEF can be detected before the first motor manifestations;
- One of the main life-threatening conditions related to DMD is sleep-disordered breathing
- Early initiation of patient monitoring, NIV and treatment with steroids are essential.

EDUCATIONAL AIMS

- Demonstrate the main ventilatory complications of Duchenne Muscular Dystrophy (DMD) and its mechanisms;
- Reinforce the importance of early-onset follow-up and serial assessments to monitor the evolution of DMD ventilatory manifestations;
- Point out the methods of diagnosis and monitoring of ventilatory syndromes associated with DMD;
- Expose available therapies to prevent disease progression.

FUTURE RESEARCH DIRECTIONS

Future studies may address the limitations that lead to the late diagnosis of DMD and consequently delay the beginning of ventilatory support and prophylactic therapies. It would also be relevant to analyze the effectiveness of the newest pharmacological treatments, in relation to its ability to contain the progression of ventilatory muscle deterioration.

INTRODUCTION:

Duchenne Muscular Dystrophy is an X-linked inherited disorder and the most common fatal muscle disease in pediatric patients, affecting one of 3,000 - 6,000 male births. It is caused by a mutated encoding gene that produces a dysfunctional dystrophin protein, resulting in progressive degeneration of cardiac and striated

muscles. DMD diagnosis is sustained by family history, typical clinical presentation, and altered laboratory findings, such as elevated transaminases and creatine kinase, however, is only confirmed through the absence of dystrophin in immunohistochemical tests of muscle biopsy or in genetic tests by detecting mutations in the DMD gene ^{1,2}. The first symptoms usually manifest at an early age, with weakness of lower limbs and shoulders, psychomotor developmental delay, calf hypertrophy, and, later, with signs of cardiac and ventilatory muscle impairment

2, 3, 4, 5.

Loss of respiratory function is one of the most severe complications of DMD. The involvement of chest wall and diaphragm muscles come out as muscle fatigue and thoracic deformities demonstrated by a decreasing Forced Vital Capacity (FVC) ^{1,6}. Spirometry is one of the leading tools for monitoring DMD, it is widely used and easily accessible. The progressive decline in its parameters, especially FVC and Peak Expiratory Flow (PEF), is an important indicator of clinical deterioration ⁷.

Early diagnosis is able to prevent unfavorable outcomes at very young ages. Unfortunately, delays in identifying DMD are common and can be devastating for patients and their families. A study by *Wong et al (2015)* found a time difference of 6 months to 4 years between the first concerns about the child's development and confirmation of DMD^{8,9}. Late diagnoses can impair access to corticosteroids, first-line drugs capable of altering the natural history of the disease ⁹.

The purpose of this non-systematic review is evaluate the main aspects of recognition, monitoring, and management of pulmonary changes in DMD.

METHODS

We performed searches for articles in multiple health-related databases, such as Pubmed, Scielo and Scholar Google, with a time restriction of 5 years, using the keywords "Duchenne Muscular Dystrophy", "ventilatory failure", "lung function", emphasizing in case series, cross-sectional studies, case-control, cohorts, clinical trials, systematic and non-systematic reviews.

DISCUSSION

Failure of ventilatory mechanics is a major cause of mortality in DMD. A study conducted by *McDonald and colleagues (2016)* with 114 children, detected important pulmonary complications in 34% of them. It is estimated that 55–90% of DMD's patients die from respiratory insufficiency between 16.2 and 19 years of age¹⁰. The spectrum of symptoms triggered by the involvement of the pulmonary musculature ranges from frequent obstructions, due to the weakening of upper airway muscles, to a chronic restrictive breathing pattern, as a result of chest-wall muscles degeneration. If spinal muscles are affected, orthopedic abnormalities may be present, such as scoliosis. These alterations, when associated with difficulty in expectorating and coughing, can lead to chronic aspirations, atelectasis, and fibrosis ^{11,12}.

One of the main life-threatening conditions related to DMD is sleep-disordered breathing, especially nocturnal hypoventilation, an independent predictor of severity, and a marker of ventilatory failure onset. It is more prevalent in the Rapid Eye Movement stage of sleep and can be identified by Polysomnography (PSG) with transcutaneous CO₂ capnography ³. In a 5-year retrospective analysis performed with 34 male patients with DMD, *Hoque et al (2016)* observed that 15 of them didn't present any abnormalities in PSG, 10 had obstructive sleep apnea, and 7 developed hypoventilation¹³. Beyond PSG studies, it is important to continuously monitor the pulmonary function of DMD patients, assessing forced vital capacity, ventilatory muscle strength, and oximetry, in order to recognize signs of clinical worsening like daytime hypoventilation ¹².

During the ambulatory stage, frequent spirometries should be performed since the child is 5 years old. Interestingly, the Forced Vital Capacity curve increases for a certain period, following the patient's growth, until it reaches a plateau and begins to decline. It is important to note that the beginning of lung function deterioration is not always accompanied by symptoms, for this reason, serial evaluations are essential ⁶.

A reduction in the values of FVC and PEF can be detected even before the first motor manifestations. According to *Mayer et al (2018)*, these parameters suffer an annual drop of 5%, from 5 to 24 years of age³. Advanced stages of Duchenne usually require hospital management. During this period, surgical correction for orthopedic abnormalities may be necessary. In the face of significant reductions in chest wall compliance, especially if FVC declines by more than 40%, the use of non-invasive ventilation (NIV), such as a manual self-inflating bag, is indicated, because of its capacity to contain the loss of FVC to only 0.5% per year^{6, 14}. In spite of this correlation, there is no high-level evidence to precisely associate the levels of FVC and PEF with the need for airway cleaning devices or mechanical ventilation³. Nocturnal ventilation is necessary when PSG studies identify a SpO₂ of 88% or less, an increase in petCO₂ of 10 mmHg above the daytime baseline or petCO₂ levels greater than 50 mmHg for more than 2% of sleep time⁶.

Manually assisted coughing may also be required. It is recommended for patients to have oximeters in their homes and increase the frequency of insufflations whenever O₂ saturation is less than 95%, in order to reduce the recurrence of pneumonia^{6, 15}. For the same reason, authors support the use of antibiotics in the presence of early pulmonary infection signs, like fever, hypoxemia, leukocytosis, high C-reactive protein levels, expectoration, or infiltrations on chest X-ray¹⁶. *Brazilian consensus on Duchenne muscular dystrophy (2018)* also emphasizes the need for an immunization regimen that includes 3 doses of Pneumococcal Conjugate Vaccine (Pn10 or Pn13), 1 dose of Pneumococcal Polysaccharide Vaccine (Pn23) and annual doses of Anti-Influenza Vaccine in children with DMD, particularly those using corticosteroids¹⁷.

Steroids, like Prednisone 0.75mg/Kg and Prednisolone 0.75mg/Kg, are first-line drugs used in DMD's therapy, as a second alternative, Deflazacort 0.9–1 mg/Kg can be prescribed. Meta-analyses showed its potential to increase the life expectancy of the patients by promoting sarcolemmal stabilization, improving motor function, preventing spine deformities, giving longer independent waking, and, mainly slowing down the progression of lung and cardiac injury^{2,18}. Glucocorticoids regimen should be started in boys after 2 years of age who begin to present motor deficits or over 5 years old, regardless of their degree of functionality. Frequently monitoring the possible adverse effects of the medication is crucial, as these patients often use continued corticosteroids throughout life. It is generally recommended that the interval between evaluations does not exceed 6 months, paying attention to cushingoid features and ophthalmological manifestations. Intolerable side effects are one of the few reasons for discontinuing these drugs in DMD².

Antioxidants, like Idebenone, despite not being approved by the Food and Drug Administration, have also proved valuable in maintaining the DMD pulmonary function². A research conducted by *McDonald et al (2016)* demonstrated a noticeable increase for FVC% and a reduction in the incidence of bronchopulmonary adverse events in favor of Idebenone when compared to placebo¹⁰. Other promising therapies described in the literature are read-through agents (Ataluren), exon skipping agents or even micro-dystrophin gene therapy, such as Drisapersen and Eteplirsen, which, through the deletion of defective exons, allow the production of functional dystrophin or even stem cell transplant, but like Idebenone, require further studies to be consolidated as a treatment for DMD^{2,19}.

CONCLUSION

Duchenne Muscular Dystrophy is an incurable disease with a poor prognosis. Its most severe complication is related to ventilatory muscle failure, for this reason, current disease control measures are focused on maintaining ventilation, preventing infections, and delaying the progression of muscle damage. Early initiation of patient monitoring, NIV and treatment with steroids are essential to maintain adequate lung function for a longer time and prolong life expectancy.

REFERENCES:

1. Birnkrant D, Bushby K, Bann C et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet Neurology*. 2018;17(3):251-267. doi:10.1016/s1474-4422(18)30024-3
2. Araujo A, Carvalho A, Cavalcanti E et al. Brazilian consensus on Duchenne muscular dystrophy. Part

- 1: diagnosis, steroid therapy and perspectives. *Arq Neuropsiquiatr* . 2017;75(8):104-113. doi:10.1590/0004-282x20170112
3. Mayer O. Pulmonary function and clinical correlation in DMD. *Paediatr Respir Rev* . 2018;30:13-15. doi:10.1016/j.prrv.2018.08.003
4. Aliverti A, LoMauro A, D'Angelo M. Assessment and management of respiratory function in patients with Duchenne muscular dystrophy: current and emerging options. *Ther Clin Risk Manag* . 2015:1475. doi:10.2147/term.s55889
5. Finder J, Mayer O, Sheehan D et al. Pulmonary Endpoints in Duchenne Muscular Dystrophy. A Workshop Summary. *Am J Respir Crit Care Med* . 2017;196(4):512-519. doi:10.1164/rccm.201703-0507ws
6. Birnkrant D, Bushby K, Bann C et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *The Lancet Neurology* . 2018;17(4):347-361. doi:10.1016/s1474-4422(18)30025-5
7. Mayer O, Finkel R, Rummey C et al. Characterization of pulmonary function in Duchenne Muscular Dystrophy. *Pediatr Pulmonol* . 2015;50(5):487-494. doi:10.1002/ppul.23172
8. Fox H, Millington L, Mahabeer I, van Ruiten H. Duchenne muscular dystrophy. *BMJ* . 2020:17012. doi:10.1136/bmj.l7012
9. Wong S, McClaren B, Archibald A et al. A mixed methods study of age at diagnosis and diagnostic odyssey for Duchenne muscular dystrophy. *European Journal of Human Genetics* . 2015;23(10):1294-1300. doi:10.1038/ejhg.2014.301
10. McDonald C, Meier T, Voit T et al. Idebenone reduces respiratory complications in patients with Duchenne muscular dystrophy. *Neuromuscular Disorders* . 2016;26(8):473-480. doi:10.1016/j.nmd.2016.05.008
11. Lo Mauro A, Aliverti A. Physiology of respiratory disturbances in muscular dystrophies. *Breathe* . 2016;12(4):318-327. doi:10.1183/20734735.012716
12. Buu M. Respiratory complications, management and treatments for neuromuscular disease in children. *Curr Opin Pediatr* . 2017;29(3):326-333. doi:10.1097/mop.0000000000000498
13. Hoque R. Sleep-Disordered Breathing in Duchenne Muscular Dystrophy: An Assessment of the Literature. *Journal of Clinical Sleep Medicine* . 2016;12(06):905-911. doi:10.5664/jcsm.5898
14. Katz S, Barrowman N, Monsour A, Su S, Hoey L, McKim D. Long-Term Effects of Lung Volume Recruitment on Maximal Inspiratory Capacity and Vital Capacity in Duchenne Muscular Dystrophy. *Ann Am Thorac Soc* . 2015. doi:10.1513/annalsats.201507-475bc
15. Toussaint M, Pernet K, Steens M, Haan J, Sheers N. Cough Augmentation in Subjects With Duchenne Muscular Dystrophy: Comparison of Air Stacking via a Resuscitator Bag Versus Mechanical Ventilation. *Respir Care* . 2015;61(1):61-67. doi:10.4187/respcare.04033
16. Sheehan D, Birnkrant D, Benditt J et al. Respiratory Management of the Patient With Duchenne Muscular Dystrophy. *Pediatrics* . 2018;142(Supplement 2):S62-S71. doi:10.1542/peds.2018-0333h
17. Araujo A, Nardes F, Fortes C et al. Brazilian consensus on Duchenne muscular dystrophy. Part 2: rehabilitation and systemic care. *Arq Neuropsiquiatr* . 2018;76(7):481-489. doi:10.1590/0004-282x20180062
18. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur A. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database of Systematic Reviews* . 2016. doi:10.1002/14651858.cd003725.pub4
19. Gogou M, Pavlou E, Haidopoulou K. Therapies that are available and under development for Duchenne muscular dystrophy: What about lung function?. *Pediatr Pulmonol* . 2019;55(2):300-315. doi:10.1002/ppul.24605