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Original article

Identification of sleep hypoventilation in young individuals with Becker muscular dystrophy: A pilot study

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Abstract

Aim: To report on sleep hypercapnia in Becker muscular dystrophy (BMD) at earlier stages than ever recognized.

Subjects and methods: This retrospective study examined nocturnal hypercapnia in six young Becker muscular dystrophy (BMD) patients with deletions of one or more exons of *DMD* gene. Clinical information, consecutive data on forced vital capacity (FVC%), forced expiratory volume in one second (FEV1%), peak expiratory flow (PEF%), peak cough flow (PCF), average PCO_2 in all-night monitoring, and left ventricular ejection fraction (LVEF) were reviewed.

Results: In five BMD patients, including three who were still ambulant, nocturnal average PCO_2 was elevated to >45 mmHg at 12–31 years of age. Noninvasive positive pressure ventilation was initiated in four patients. Gradual declines in FVC% and PEF% were evident in one BMD patient with exon 3–7 deletion, whereas these functions did not change in the remaining BMD patients. PCF, FEV1%, and LVEF were less informative for the assessment of respiratory function in this patient series.

Conclusion: Sleep hypercapnia was present in certain BMD patients, which was unexpected from the routine pulmonary function tests. Individualized assessment of nocturnal PCO_2, partly based on the deletion types, should be further explored in the clinical practice of BMD patients.

Keywords: Becker muscular dystrophy; Noninvasive positive pressure ventilation; Respiratory function; Sleep disordered breathing; Hypercapnia

1. Introduction

X-linked Duchenne and Becker muscular dystrophies (DMD and BMD, respectively) are allelic disorders

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caused by mutations in the Duchenne muscular dystrophy (*DMD*) gene, which consists of 79 exons and encodes the dystrophin protein. Motor decline in DMD emerges before ten years of age and results in loss of ambulance before 13 years of age. The initial symptoms of BMD, which was first recognized as a benign variant of DMD, are recognized usually in patients in their teens, and it exhibits a slower progression with loss of ambulance after the age of 16 years (26.4 years on average) [1–6]. The difference in severity between the two presentations could be explained by the reading frame theory [3,7,8], and the most frequent exception to this rule includes deletions of exons 3–7 at the N-terminal domain, which can result in either the DMD or BMD phenotype [3,9].

Clinical severity in BMD patients varies from loss of ambulance during adolescence and death in their early 20s to preserved walking ability in their 60s and survival to their 80s, depending on the site and the range of deleted exons [1,7,8]. Similar trend was observed in the onset age of dilated cardiomyopathy (DCM) [10], and the severity of DCM has been regarded as the main factor in shortened life expectancy in BMD patients [11]. In terms of the decline in respiratory function in BMD, a study reported that only one patient used night-time noninvasive mechanical ventilation starting at the age of 48 years among 48 BMD patients [12], whereas other studies reported that ventilotherapy was not needed in 21 BMD patients that were older than 35 years [13]. In contrast to these reports, our experience involved some BMD patients who exhibited hypercapnia during sleep and required nocturnal noninvasive positive pressure ventilation (NIV) at 10–30 years of age. Given the variability in BMD phenotype, we herein describe the respiratory assessment of patients with relatively common deletions, and discuss on the genotype-oriented assessment of respiratory function in BMD.

2. Subjects and methods

Clinical and laboratory data of BMD patients who met the criteria of (1) clinical diagnosis of BMD, (2) deletions of one or more exons of *DMD*, and (3) average PCO_2 above 45 mmHg on overnight monitoring and/or initiation of NIV due to accompanying desaturation between 2010 and 2017 were collected from the medical records of the Department of Pediatrics, Matsue Medical Center and the Division of Child Neurology at Tottori University Hospital. Clinical information of these patients was retrospectively collected from their medical charts, including onset age and symptoms, initial age of wheelchair dependency, cognition levels, degree of scoliosis, findings on electrocardiography (ECG), complications in cardiorespiratory and other systems, and regular prescription of cardiac medications and steroids. Consecutive data on respiratory function such as forced vital capacity (FVC) and peak expiratory flow (PEF) presented as their proportion to the value expected by the age, height and weight; peak cough flow (PCF); forced expiratory volume in one second (FEV1); and overnight PCO_2 monitoring as well as serum levels of creatine kinase (CK) and left ventricular ejection fraction on cardiac ultrasonography were plotted to find age-dependent changes. FVC, PEF, and FEV1 were measured with a CHESTAC-8800 spirometer (CHEST Medical Instruments, Tokyo, Japan), and PCF was assessed by an ASSESS peak flow meter (Royal Phillips, Amsterdam, The Netherlands). Overnight SpO_2 and PCO_2 monitoring was conducted by end-tidal CO_2 ($EtCO_2$)/SpO_2 monitors, Capnostream (Medtronic Japan, Tokyo, Japan) or COSMO capnograph, and pulse oximeter monitor (Novametrics, Bethesda, MD) before 2008 and by transcutaneous CO_2 ($TcCO_2$)/SpO_2 monitor or TCM TOSCA (Radiometer, Crawley, England) after 2009. For each patient, age at NIV initiation and/or the average PCO_2 was first elevated above 45 mmHg during sleep, functional disability stage [14], symptoms related to nocturnal hypoventilation, and blood gas levels at the time of NIV initiation were identified. The study design was approved by the ethical committees of Matsue Medical Center and Tottori University.

3. Results

3.1. Characteristics of the patients with BMD (Table 1)

We identified five male patients with BMD, aged 13–34 (mean: 27) years at last follow-up. The follow-up periods ranged from 13 to 23 years (mean, 20). In addition, data from a 13-year-old patient with deletion of exons 45–55, which is well recognized as the cause of most benign BMD phenotypes [9,15], was also collected for comparison (Table 1). NIV was initiated in two further patients with BMD; however, these patients were not included our analyses due to the fact they lacked a genetic diagnosis. The five BMD patients (patients 1–5) with elevated PCO_2 during sleep had deletions of exons 45–53, 45–49 ($n = 2$), and 3–7 ($n = 2$), whereas the remaining asymptomatic BMD patient (patient 6) had a deletion of exons 45–55, as described above. The onset of skeletal muscular symptoms was 6–26 (mean, 12) years of age in the five BMD patients. Four patients showed abnormal ECG findings during the course of the disease. Cardiac medication with angiotensin-converting-enzyme inhibitors and β-blockers were initiated in four patients when their LVEF were $\leq$55%. Prednisolone was prescribed in patient 5 during his

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