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COVID-19 in advanced Duchenne/Becker muscular dystrophy patients

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Abstract

Duchenne muscular dystrophy (DMD) is the most common childhood muscular dystrophy. As a result of progressive muscle weakness, pulmonary function decreases during the second decade of life and lung disease contributes significantly to morbidity and mortality in these patients. Corticosteroids are the current standard of care for patients with DMD, despite known adverse effects such as obesity and immunosuppression. Over the past year (2020), the novel coronavirus (COVID-19/SARS-CoV2) outbreak has caused a global pandemic. Restrictive lung disease due to low lung volumes, chronic immunosuppressive treatment with corticosteroids, and obesity are potential risk factors that may contribute to a more severe course of the disease. Out of 116 Duchenne/Becker muscular dystrophy patients treated in our tertiary neuromuscular center, six patients with DMD and one with advanced Becker muscular dystrophy were found to be positive for COVID-19 infection. Two of the DMD patients were admitted for hospitalization, of whom one was dependent on daily nocturnal non-invasive ventilation. All patients recovered without complications despite obesity, steroid treatment and severe restrictive lung disease.

Keywords: Duchenne muscular dystrophy; Becker muscular dystrophy; Restrictive lung disease; Non-invasive ventilation; COVID-19.

1. Introduction

Duchenne muscular dystrophy (DMD) is one of the most common neuromuscular disorders of childhood. This progressive genetic disease globally affects approximately 1 in 5000 newborn males. Becker muscular dystrophy (BMD) is a milder form of this dystrophinopathy [1]. The clinical course of DMD includes progressive weakness, loss of ambulation and motor skills, and, ultimately, pulmonary and cardiac failure [2–4]. Severe weakness of respiratory muscles causes restrictive respiratory disease and weak cough [5,6]. Lung infections increase mucus production, and may lead to atelectasis due to inadequate ventilation and stagnation of secretions [5-8].

Corticosteroids have become the standard of care for patients with DMD [9–11]. The benefits of corticosteroids are attributed to their anti-inflammatory effects, which can help preserve ambulation pulmonary function by delaying the loss of muscle strength [12,13]. However, prolonged glucocorticoid steroid treatment is associated with adverse effects, such as linear growth failure and excessive weight gain [12]. Additionally, long-term corticosteroids can cause an immunosuppressive effect, making long-term users more vulnerable to infections.

The global incidence of coronavirus disease 2019 (COVID-19) has continued to rise since December 2019. The disease is caused by severe acute respiratory virus coronavirus 2 (SARS-CoV2). Obesity, immunosuppression, cardiovascular disease and respiratory failure are known risk factors for increased severity of complications during and after COVID-19 infection [14,15].

In the recent global COVID-19 pandemic, DMD patients are classified as a high-risk group [14,16]. Currently, there

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is no data regarding how COVID-19 infection affects these patients. The aim of this study is to describe the clinical presentations and outcomes of patients with advanced dystrophinopathies infected with COVID-19 during the global outbreak.

2. Methods

All DMD/BMD patients followed in Schneider Children's Medical Center (SCMC) in Israel who were tested and found to be infected with SARS-CoV2 from March through December of 2020 were included in the study. Our hospital is a tertiary university affiliated hospital. DMD/BMD patients have routine visits, typically carried out every 6–12 months. During the study period, all patients were followed by either routine follow-up visits or by phone/virtual encounters. Patients were asked about infection with COVID-19 during regular visits or whenever hospitalized. Infected patients came for a regular visit to the neuromuscular clinic after recovery. During these visits, physical examination, lung function tests and chest X-Ray were done and compared to those obtained at the last visit prior to the COVID-19 infection. Data retrieved from patients' charts included demographics, past medical history, clinical presentation, laboratory findings, imaging studies, treatment and outcome.

Fisher exact test and chi-square tests were used for comparison between groups. The study was approved by the local Institutional Review Board (IRB).

3. Results

Among 116 DMD/BMD patients followed at SCMC during the study period, 7 (6%) were positive for COVID-19. Patients' characteristics are summarized in Table 1. The median age of infected DMD/BMD patients was 14 years (range 8–17), compared to median age of 11 years (range 4–27) for all DMD/BMD patients followed at SCMC not infected with COVID-19 ($p = 0.26$). Five of the COVID-19 positive patients were non-ambulatory, two were ambulatory. The clinical neurological status of the BMD patient was similar to that of the DMD patients, as he lost ambulation at a young age. All patients were infected by a first degree family member according to family report.

Of the 7 patients, two non-ambulatory DMD patients were symptomatic and required hospitalization. Indications for admission were dyspnea and chest pain for one patient and headache with fever for the other.

The first symptomatic patient's chest x-ray showed low lung volumes and bi-basilar hyper-density (small patch infiltrates). This patient was suspected to have pseudomonal co-infection due to previous cultures and respiratory exacerbations in prior years, and was consequently treated with both ceftazidime and azithromycin. He was also treated with dexamethasone (6 mg x 2/day) for 2 days and afterwards returned to the regular prednisone treatment. This patient was dependent on daily nocturnal non-invasive ventilation before admission. While hospitalized, he increased the daily amount of time during which he utilized ventilation until one day before discharge.

The other admitted patient's chest x-ray showed low lung volumes with no infiltrates, and he did not require antibiotics or a change in corticosteroid dose.

Both patients were admitted in designated negative-pressure air-conditioning rooms, in order to lower the transmission to the medical team since one was ventilated with NIV and both used cough-assist machines.

Both patients were discharged after 5 days.

All patients recovered without any overt sequelae; they felt well and were asymptomatic when assessed following the infection. The 5 asymptomatic patients were tested for SARS-CoV2 due to other infected family member.

All patients had been treated with corticosteroids since early childhood. Three patients were treated with angiotensin-converting enzyme (ACE) inhibitors, all of whom were asymptomatic.

Five of the seven DMD patients with COVID-19 suffered from obesity, the 2 symptomatic patients with severe obesity - BMI of 33 kg/m^2 (>99% for age). Mean and median BMI for all DMD/BMD COVID patients were 26.7 (SD±8.19) and 31.2 (range 15.2–33.4) kg/m^2, respectively.

On a follow-up pulmonary hospital visit, physical examination was similar to the most recent examination prior to COVID-19 infection. A follow-up lung function test was done in 4 patients (0.5–4 months after the COVID infection, median 1 month), in order to compare lung functions to their last regular clinic visit (ranged 1–24 months prior to the COVID infection, median 12 months). An improvement in lung function was observed in 2 patients at regular visits following the infection. In the other two patients, there was a mild deterioration from the most recent lung function values, obtained one year before COVID19 infection. Three patients declined to undergo lung function tests following the infection.

When comparing FVC (% predicted for age) among DMD patients positive for COVID-19 before vs. after COVID-19, there was a small increase in the median FVC% from 76 (range 10–112%) before COVID-19 infection to 79.5 (range 12–101%) afterwards, but the increase was not statistically significant ($p = 1$).

No changes were needed in the parameters of supportive ventilation and cough assist machines for patients supported by these machines.

4. Discussion

In the present study we describe the clinical presentations and outcomes of patients with DMD/BMD who were found positive to COVID-19. Most were asymptomatic. All symptomatic patients recovered without any significant sequelae. As opposed to adult patients with chronic lung disease and obesity, we did not observe a severe course of disease in our patients. Similarly, we did not observe significant residual lung disease following the infection.

Table 1
Demographics and clinical characteristics of DMD/BMD COVID-19 patients.

No. Patient	1	2	3	4	5	6	7
Age (years)	17	12	8	17	14	17	12
Genetics	exons 4–19 deletion	exon 45 deletion	exons 48–52 deletion	exons 45–46 deletion	exons 46–47 deletion	exons 56–63 deletion	exon 45 deletion
DMD/BMD	DMD	DMD	DMD	BMD	DMD	DMD	DMD
Ambulation	No	No	Yes	No	No	No	Yes
BMI kg/m^2 (Percentile for age) (SDS)	33.3 (>99%) (+2.49)	31.2 (>99%) (+2.88)	15.3 (30%) (−0.52)	15.2 (5%) (−3.47)	32.3 (>99%) (2.27)	33.4 (>99%) (2.24)	26.2 (>99%) (1.822)
Comorbidity	Cognitive developmental delay	Glaucoma; Suspected fat emboli a month prior to COVID infection	–	–	–	Cardiomyopathy	–
Corticosteroid chronic treatment	Prednisone 20mg	Prednisolone 15mg	Prednisolone 15mg	Prednisone 20mg	Prednisolone 15mg	Prednisolone 10mg	Prednisone 15mg
ACE inhibitors	–	Enalapril	–	Enalapril	–	Enalapril	–
Source of COVID19 infection							
Suspected source of infection	Family member (mother)	Family member (first degree)	Family member (first degree)	Family member (first degree)	Family member (first degree)	Family member (mother)	Family member (first degree)
Clinical findings at admission							
Duration of symptoms (days)	10	none	none	none	none	5	none
Chest x-ray findings	Low lung volumes and hyper density in the bases bilaterally	–	–	–	–	Low lung volumes without infiltrates	–
Lung functions before /after COVID19 infection							
No. Patient	1	2	3	4	5	6	7
FVC (L) (%predicted for age) before COVID19	0.33 (10%) (1 year before)	1.96 (67%) (1 year before)	1.24 (85%) (1 year before)	2.37 (56%) (6 months before)	2.32 (96%) (2 years before)		1.39 (112%) (1 year before)
FVC (L) (%predicted for age) after COVID19	0.38 (12%) (1 month after)	2.33 (79%) (1 month after)			2.53 (80%) (2 weeks after)		1.32 (101%) (4 months after)
TLC (L) (%predicted) before COVID19		3.41 (91%) (1 year before)		4.23 (92%) (6 months before)	3.27 (106%) (2 years before)		2.12 (134%) (1 year before)
TLC (L) (%predicted) after COVID19		3.73 (99%) (1 month after)			3.4 (85%) (2 weeks after)		1.97)119%) (4 months after)
PCF (L/min) before COVID19			106.8 (1 year before)	251.4 (6 months before)	234.6 (2 years before)	256.2 (2 years before)	142 (1 year before)
PCF (L/min) after COVID19	149.4 (1 month after)	283.8 (1 month after)			194.4 (2 weeks after)		131.4 (4 months after)

DMD – Duchenne Muscular Dystrophy; BMD - Becker Muscular Dystrophy; ACE - angiotensin-converting enzyme; NIV – Non Invasive Ventilation; BiPAP - Bilevel Positive Airway Pressure; FVC – Forced Vital Capacity; TLC – Total Lung Capacity; PCF – Peak Cough Flow.

The incidence of COVID-19 infection amongst DMD/BMD patients (6%) in our cohort was slightly lower than the incidence of COVID-19 amongst all children in Israel)8% according to PCR test and 7% according to serology screening) as of October 2020 [17]. However, since most of the patients were asymptomatic, additional patients in our DMD clinics might have been infected without notice.

The absolute low number of DMD/BMD infected patients prevents us from establishing conclusions about their vulnerability relative to other children, but we hypothesize that their muscular illness might have caused more social distancing due to fear from the disease. As far as we know, there is no data concerning the vulnerability of DMD patients to other specific viral infections, although infections are thought to be the most common cause of respiratory exacerbation by increasing mucus production and, consequently, worsening airway clearance [7].

One of the known risk factors for severe disease in COVID-19 infected patients in the general population is

obesity [18,19]. This may also be a risk factor for symptomatic (though not severe) infection in DMD/BMD patients, as the symptomatic DMD COVID-19 patients were severely obese, although a correlation was not established due to the small number of patients.

Other risk factors in correlation to severe disease, such as hypertension, renal disease, COPD, diabetes and malignancy [19–21], were not observed in our cohort. One of the symptomatic patients suffered from cardiomyopathy, but his illness was mild.

Since there has been no data regarding the influence of COVID-19 infection on DMD patients, there were no clear guidelines for treatment. Recently, an expert panel consensus statement suggested to continue the patient's regular therapy [16].

Our small cohort data supports this recommendation [16], since the COVID-19 course in these individuals did not seem to differ from healthy children. Most of our DMD patients who developed COVID-19 exhibited mild disease symptoms [16]. All were treated with corticosteroids chronically prior to the infection. Altering or stopping corticosteroid therapy abruptly carries the potential for a progressive decrease in muscular and respiratory function [16]. In some DMD cases, the dose of corticosteroids should be increased in order to meet standard infection/stress steroid protocols [16] when febrile illness begins. Recent studies support the benefit of corticosteroid usage in the treatment of COVID-19 patients [22], as an early course of corticosteroids may attenuate progression to the hyper-inflammation phase of COVID-19 that requires an escalation of care [23]. It is not known whether chronic corticosteroid treatment may protect from severe COVID-19 disease.

NIV usage may be of assistance in the treatment of COVID-19, even at home. Increased time of ventilation may be efficient in preventing hospital admission or shortening the time of hospitalization stay. Continuation of NIV is necessary and should be promoted, while taking suitable precautions due to the risk of COVID-19 spread. Since NIV in a COVID-positive patient may increase the risk of viral transmission [24], it is recommended to isolate the patient in a designated negative air-pressure room or in a designated corona ward in order to reduce the risk of infection for the medical team. Caregivers should carefully balance the patient's need for ventilation support with the commitment to reduce environmental viral spread as much as possible.

Supportive inhalations with bronchodilators and inhaled corticosteroids (ICS) should be considered as supportive care in order to reduce sputum and mucus plaques and prevent atelectasis. Although their place in the specific treatment of COVID-19 infection has not yet been proven, it seems that ICS might have a protective role in preventing severe disease in COVID-19 infected patients [25]. Chest physiotherapy should be continued with the suitable precautions, preferably performed by a family member qualified to perform the treatment.

Although the small cohort is a main limitation of the present study, to the best of our knowledge, this is the first report of COVID-19 in patients with DMD/BMD. Due to the small number of patients, the favorable outcome of the patients should be interpreted with caution. However, our data suggests a tendency toward a favorable course. The well-known good prognosis for COVID-19 amongst young people compared to the adult population may help explain this trend. Again, due to small numbers, the propensity for lung function to improve after the COVID-19 infection cannot be implied, but surely no deterioration was seen.

Despite the favorable outcome, even for the patient with the strongest risk factors and NIV use, these seven cases cannot support a definitive conclusion as to whether patients with DMD/BMD should be considered a high or low-risk group for COVID-19, however, they may encourage an optimistic view.

Declaration of Competing Interest

We have no conflicts of interest to disclose.

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