New Survival Target for Duchenne Muscular Dystrophy

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Abstract: We report a patient with a typical phenotype and clinical history of Duchenne muscular dystrophy who is currently 53 years old. Because of improvements in cardiopulmonary care, there has been a great improvement in survival and preservation of quality of life for many of these patients. Whereas it is no longer rare to find patients with Duchenne muscular dystrophy living into their fifth decade, this is the first report of a patient in his sixth decade of life. We believe that besides use of continuous noninvasive respiratory support, the fortuitous absence of dilated cardiomyopathy associated with the particular point mutation of his dystrophin gene has permitted prolonged survival.

Key Words: Duchenne Muscular Dystrophy, Neuromuscular Disease, Survival, Noninvasive Mechanical Ventilation

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Duchenne muscular dystrophy (DMD) is a genetic disorder with X-linked recessive inheritance, characterized by progressive muscle degeneration and weakness. Duchenne muscular dystrophy is caused by absence of the cell membrane dystrophin. Duchenne muscular dystrophy mainly affects males with symptom onset usually between ages 3 and 5. In 1986, the gene defect was identified as a mutation on the X chromosome[1]; and in 1987, dystrophin was described.[2] Without ventilatory support, DMD survival did not extend much beyond the teen years. However, with advances in cardiorespiratory care, life expectancy has increased into the late 20s for patients using continuous tracheostomy ventilatory support and is approximately 40 years for patients using continuous noninvasive ventilatory support (NVS),[3] with occasional reports of survival into the late 40s.[4] Now, however, we report a well-documented patient in his sixth decade with a rare genotype by which he appears to have been spared dystrophinopathy-associated cardiomyopathy.

CASE STUDY

The patient was born in September 1962. Early motor milestones including head control, rolling, sitting, and standing, were essentially normal. He walked at 15 months of age, but Gower sign was noted by age 4. He had progressive muscle weakness and was wheelchair dependent by age 11. He never used orthoses or received glucocorticoids and developed severe musculoskeletal deformities (Fig. 1) including severe kyphoscoliosis. He has not undergone any spinal surgery.

At age 18, he complained of chronic headaches; at age 20, he complained of hypersomnolence for which he was hospitalized and severe hypercapnia was noted. Initial treatment with supplemental oxygen exacerbated the hypercapnia. Tracheostomy was recommended but was refused. He was then placed in an iron lung for 1 month, and then this was switched to using a Poncho negative pressure ventilator (DIMA, Italy) which he continues to use for sleep (Fig. 2) at −22-cm H_2O pressure, rate 14, along with pressure preset noninvasive positive pressure ventilation mainly to maintain airway patency, at 13-cm H_2O with 4-cm H_2O of positive end-expiratory pressure on assist control mode (Puritan Bennett, Covidien). By age 22, he had become continuously dependent on noninvasive mechanical ventilation without being hospitalized. However, using the Poncho obliged him to remain recumbent until age 34 when he was introduced to full ventilator setting pressure preset NVS. He used daytime NVS via nasal interface (Fig. 3) at 23-cm H_2O, rate 12, in assist control mode (Puritan Bennett, Covidien). His lips were too weak for transition from nasal to mouthpiece NVS. He continues to prefer and feels safer using Poncho ventilation for sleep. His vital capacity at age 38 was 200 mL, and it is currently unmeasurable. He has never been hospitalized for acute respiratory failure or intubated because he and his caregivers have been trained in and equipped to use mechanical insufflation-exsufflation (MIE) during intercurrent respiratory tract infections to maintain his oxyhemoglobin saturation at greater than or equal to 95% as described.[4,5] On his last arterial blood gas samplings in October 2015 while using NVS, his $PaCO_2$ was 44 mm Hg. Several 2-dimensional echocardiograms and 2 radio scintigraphy scans at ages 42 and 52 indicated left ventricular ejection fractions greater than 55%. He is currently taking perindopril, 4 mg once a day, as cardioprotection therapy.

With absence of muscle tissue to perform biopsy, in 2004, a skin biopsy was negative for dystrophin immunostaining for the striated arrector pili muscles. In 2007, a hemizygous genotype for the pathological W1586X (Trp1586Stop—exon 34) mutation was documented.

DISCUSSION

The survival of patients with DMD is increasing owing to mechanical ventilation, MIE,[4–6] and possibly, cardioprotective medications.[7] It has now become more common for people with DMD to live into their 30s and even 40s. In 2011, Bach and DeCicco[8] reported one patient who died from cardiomyopathy

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FIGURE 1. Nine years old (on the left), with typical Duchenne phenotype.

at age 48; this, however, is the first report of a patient surviving into the sixth decade. This is remarkable because Tamura et al.[9] reported that Muga scans demonstrated cardiomyopathies for 96% of patients with DMD and their patients were much younger than ours, implying that all patients with DMD have cardiomyopathies. Indeed, the reason why this patient with typical phenotypic DMD has preserved cardiac function is unclear. It may be partly because dystrophin has different functions in skeletal and cardiac muscle, or quite possibly, because of his particular point mutation in the dystrophin gene that we have been unable to find reported elsewhere. Whereas cases have been reported of subjects with Xp21 mutations having severe cardiac disease without marked involvement of skeletal muscle[10] and severe dilated cardiomyopathy has been reported in patients as young as 9 years of age, this case is unique because of his advanced age and absence of dilated cardiomyopathy. Thus, we believe his survival is due to well-preserved cardiac function along with continuous NVS.

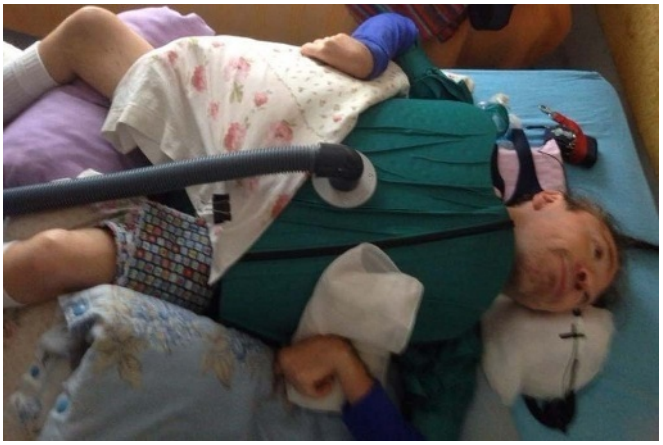

FIGURE 2. Fifty-three years old, using NVS for sleep.

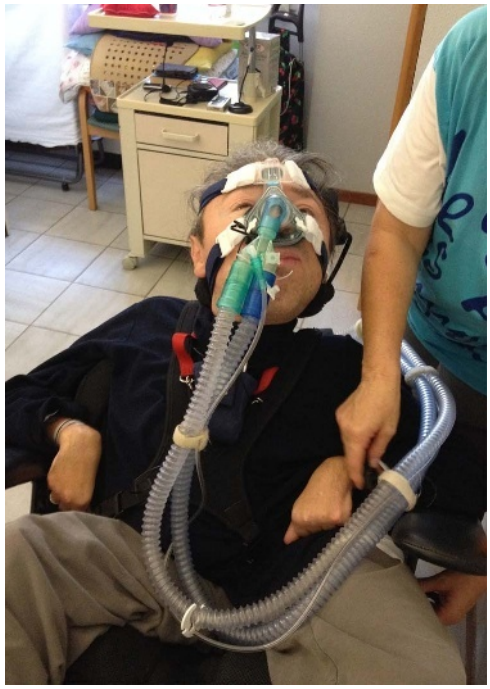

FIGURE 3. Fifty-three years old, using nasal interface for daytime noninvasive ventilatory support.

It might be noted that negative pressure ventilation causes obstructive sleep apneas that can be avoided by administering concomitant continuous positive airway pressure[11] and that an ATS consensus statement[12] pointed out that noninvasive positive pressure ventilation need not be used along with negative pressure body ventilators. In our case, however, the −22-cm H_2O pressure settings of the Poncho were relatively minimal so inspiration was augmented by the inspiratory positive airway pressure, expiratory positive airway pressure difference of 9-cm H_2O to provide for normal assisted ventilation. In addition, this patient began negative pressure ventilation and became accustomed to it long before NVS was available in Italy.

In a controlled study,[3] DMD survival was 10 years longer by NVS than by tracheostomy mechanical ventilation. Considering that some patients may still be using negative pressure ventilation without adequate control for obstructive apneas and the relatively poor prognosis of resorting to tracheotomy, full ventilator setting NVS should be the first choice for all symptomatic hypercapnic patients with DMD and extended through daytime hours as needed. This can be especially beneficial for survival for patients with preserved cardiac function.

SUPPLEMENTARY CHECKLIST

CARE Checklist: http://links.lww.com/PHM/A299

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