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Case Report

Non-ambulatory Duchenne muscular dystrophy: observations, interventions, and outcomes of a single case

Sevria Yetty Anggraina Noer, Sunartini, Purnomo Suryantoro

Duchenne muscular dystrophy (DMD) is an X-linked recessive gene defect manifesting as a fatal, progressive neuromuscular disease. Treatment goals aim to inhibit disease progression, increase patients' quality of life, and lengthen life expectancy. We report here a single case of non-ambulatory DMD. **[Paediatr Indones. 2022;62:208-16 DOI: 10.14238/pi62.1.2022.208-16**].

Keywords: *Duchenne Muscular Dystrophy; non-ambulatory; gene deletion; outcome*

Duchenne muscular dystrophy (DMD) is an X-linked disorder affecting 1 in 3,600-6,000 liveborn males.[1] Patients with DMD typically lose their walking ability by 13 years of age. The prevalence of DMD is threefold higher than that of Becker muscular dystrophy (BMD), a milder phenotype. In 2010, approximately 1.4 per 10,000 male individuals aged 5-24 years, were affected in the United States.[2] To date, no national DMD prevalence data is available in Indonesia. From 2014 to 2019, the patient registry at Dr. Sardjito Hospital, Yogyakarta, reported 47 new cases of DMD confirmed by genetic testing and/or muscle biopsy.

Absence of appropriate interventions for the respiratory, orthopedic, and cardiac complications of DMD can precipitate death. The median age of death due to respiratory problems is 17.7 (range 11.6-27.5) years in non-mechanically ventilated patients, but intervention with a home ventilator increases survival to a mean age of 27.9 (range 23-38.6) years. The median age of death due to cardiac problems is 19.6 (range 11.6-27.5) years.[3]

Specific therapy is unavailable for the vast majority of DMD cases, but the natural course of the disease can be altered by interventions targeting the clinical manifestations and complications. The life expectancy of DMD patients has increased since the widespread recommendation of corticosteroids; there is evidence that they have a protective effect on respiratory and cardiac function.[4] Patients with DMD require a multidisciplinary clinical team to anticipate and manage complications.[5] Challenges faced by the family include financial problems, lack of knowledge, and difficulty accessing healthcare facilities due to geographical conditions. There are no national guidelines for the diagnosis and management of DMD in Indonesia.[6] This disorder can have a substantial economic impact on patients' families. Hence, health policy evaluation, financial support planning, and economic study design are needed.[7] Here we report a case of a non-ambulatory adolescent with DMD and the treatment outcomes during 2.5 years of observation.

From the Department of Child Health, Universitas Gadjah Mada Medical School/Dr. Sardjito Hospital, Yogyakarta, Central Java, Indonesia.

Corresponding author: Sevria Yetty Anggraina Noer. Department of Child Health, Universitas Gadjah Mada Medical School/Dr. Sardjito Hospital, Jl. Kesehatan no 1 Sekip Yogyakarta 55284. 08125934999. Email: dr.sevria24@gmail.com.

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The case

A boy aged 12 years and 6 months was brought to our hospital with a chief complaint of weakness of the extremities since the age of five years. Prior to symptom onset, he had a history of mild gross motor delay, having been able to walk independently at 20 months of age, and later was able to ride a tricycle. Other pre- and postnatal development history were unremarkable.

At five years of age, weakness of the limbs started; he could not run as fast as his peers and sometimes fell when running. At six years old, he required crutches and held on to supports when walking. At seven years old, he lost his ability to stand independently. He had been brought to our hospital at the time, but diagnostic investigations and physical therapy was discontinued due to financial constraints. His condition progressed further and at eight years old he could not get up to an upright position or rise from the bed by himself. He was hospitalized due to pneumonia episode at 11 years of age. By the next year he became easily tired when sitting and was then referred back to our hospital for further investigation and intervention.

His laboratory results showed a creatine phosphokinase (CPK) level of 2020 U/L (normal range 39-308 U/L), creatine kinase myocardial band (CKMB) level of 162 U/L (normal range 7-25 U/L), aspartate aminotransferase (AST) of 72 U/L, and alanine aminotransferase (ALT) of 68 U/L. Electroneuromyography (ENMG) showed signs of myopathy, while a nerve conduction study (NCS) revealed a mild axonal neuropathy. Muscle biopsy was performed, and the histology and immunohistochemistry results were consistent with DMD (**Figure 1**). Genetic

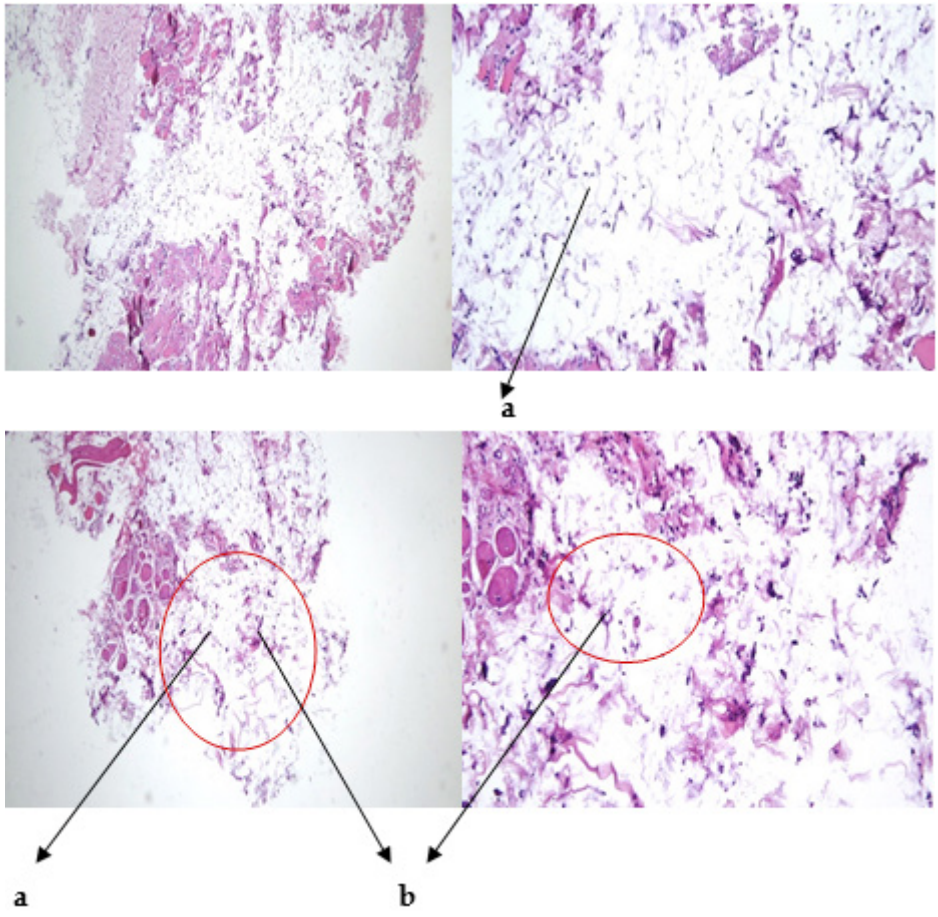

Figure 1. Cross-section of gastrocnemius muscle histopathology from a muscle biopsy specimen showed extensive replacement of disappearing striated muscle tissue (a) by fat tissue (b). Absent dystrophin staining in the muscle bundle membrane supported the DMD diagnosis. The image of cross-sectional gastrocnemius muscle showed extensive replacement of muscle tissue by fat tissue.

testing showed an exon 17-43 deletion on the dystrophin gene. Genetic carrier testing of his mother indicated she was not a carrier.

The patient was the second of four male children. He was the only affected male in the family. There was no history of any family member with the same symptoms. Based on genetic carrier testing, mother was not a carrier. His family genogram can be seen in **Figure 2**.

The patient was diagnosed with DMD and given glucocorticoid therapy with prednisone 0.75 mg/kg/day, alternating 10 days on and 10 days off. He was also given influenza and pneumococcus vaccines to help prevent pneumonia episodes.

During our observation he underwent serial spirometry. In his first spirometry, his FVC was low at 0.47 (20% of predicted value) and FEV1 was also low at 0.38 (19% of predicted value). These results indicated severe restrictive lung function. In the following 6-month evaluation after the first spirometry, FVC and FEV1 had declined further to 0.50 (16% of predicted value) and 0.48 (18% of predicted value), respectively, indicating worsening lung function. Peak cough flowmeter measurement yielded 125 L/min (normal value >160 L/min). After manually assisted exsufflation it was 135 L/min and after assisted air stacking it was 120 L/min. After both air stacking and manually assistive maneuvers were performed, his peak cough flow improved to 140 L/min. He was then advised to do breathing exercises and air stacking maneuvers with a bag resuscitator twice a day. The third spirometry a year later showed improving lung function, with FVC 0.75 (30% of predicted value) and FEV1 0.68 (30% of predicted value).

His blood gas analysis results showed pH 7.421, PCO_2 33.7, HCO_3 22.4, base excess -2.4, and no hypercarbia. Overnight sleep study monitoring with oximetry and capnography revealed episodes of desaturation to 83%.

Pulse, blood pressure, and cardiac examinations were within normal limits. Electrocardiography and echocardiography showed no cardiomyopathy with a left ventricular ejection fraction (LVEF) of 66.9%. After 1 year, re-evaluation of his cardiac function also revealed a normal LVEF (64.9%), with no signs of cardiomyopathy.

When the patient first came to our hospital, he had already developed scoliosis with a Cobb angle of 45º. Initially, conservative intervention was planned with back bracing and a neck collar. By the age of 13 years, scoliosis had worsened to 73.8º; and at 15 years of age the Cobb angle was 80º (**Figure 3**).

Bone densitometry was conducted after 18 months of prednisone treatment. His bone mineral density Z-score was -4.4 (normal reference value >-2.0), indicating osteoporosis. He also had vitamin D deficiency as his 25-OH vitamin D was 11.5 ng/mL (normal ≥30 ng/mL). He was given high-dose

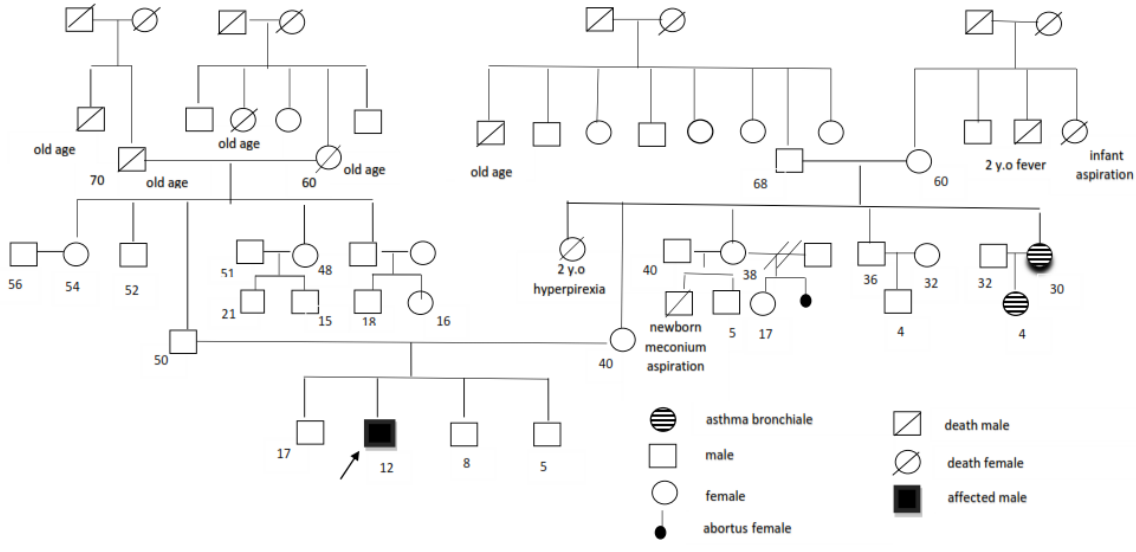

Figure 2. Family genogram of the patient

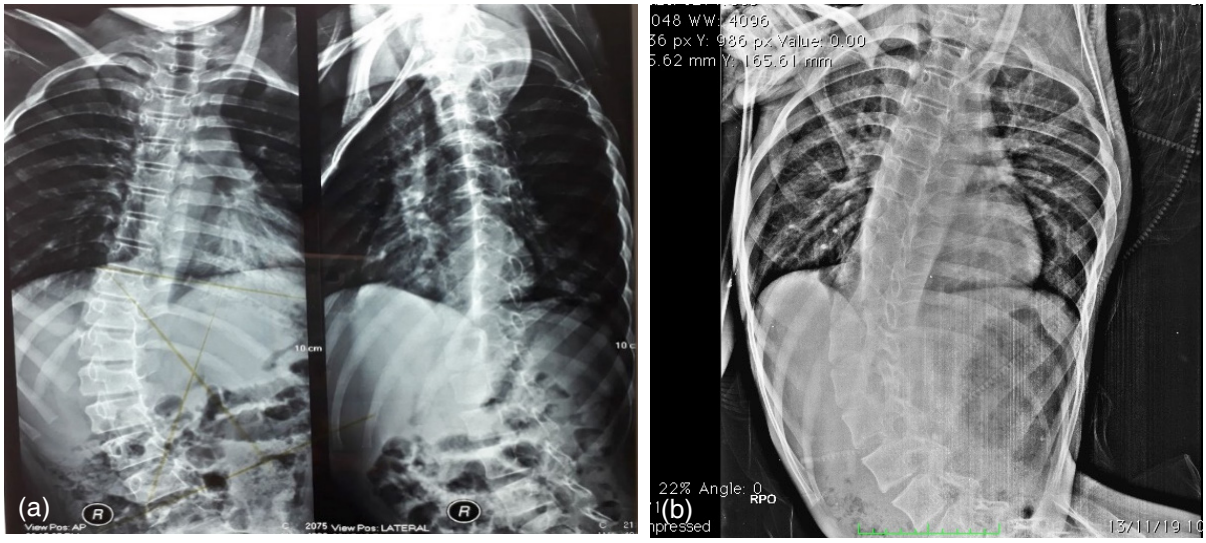

Figure 3. Scoliosis Cobb angle: (a) 45º at 15 years of age and (b) 80º at 12.5 years of age.

vitamin D of 2000 IU daily for 6 weeks, followed by a maintenance dose of 400 IU/day. He was also advised to get adequate sun exposure.

Growth assessment was performed every 3 months. His initial body weight at 12.5 years of age was 24.5 kg. With a predicted height of 144 cm, his BMI was 11.8 (BMI-for-age Z-score <-3 and height-for-age Z-score -2<z<-1 based on the WHO Child Growth Standards), consistent with severe malnutrition and normal predicted height. At 15 years of age, his body weight had decreased to 22 kg despite having been provided with nutritional management, with a normal predicted height of 154.5 cm and BMI 9.38 (BMI-for-age Z-score <-3 and height-for-age Z-score -2<z<-1, revealing deteriorating nutritional status. He had no difficulty eating, but he tended to take a long time to eat. He ate 3 meals a day and was given high-calorie milk twice a day. When using the DMD body weight curve, he also fell under the tenth percentile (**Figure 4**).[8]

Physiotherapy was initially done routinely every week at the hospital, but due to various problems, it was continued at home. The physiotherapy program included muscle strengthening of the neck, shoulder, back, and limbs, as well as stretching and breathing exercises. The patient was also referred to a psychologist, who found that the patient had an IQ of 91 (average), as well as emotional problems due to his physical condition. He received counseling and was encouraged to engage in self-empowerment exercises as well as keep an optimistic outlook.

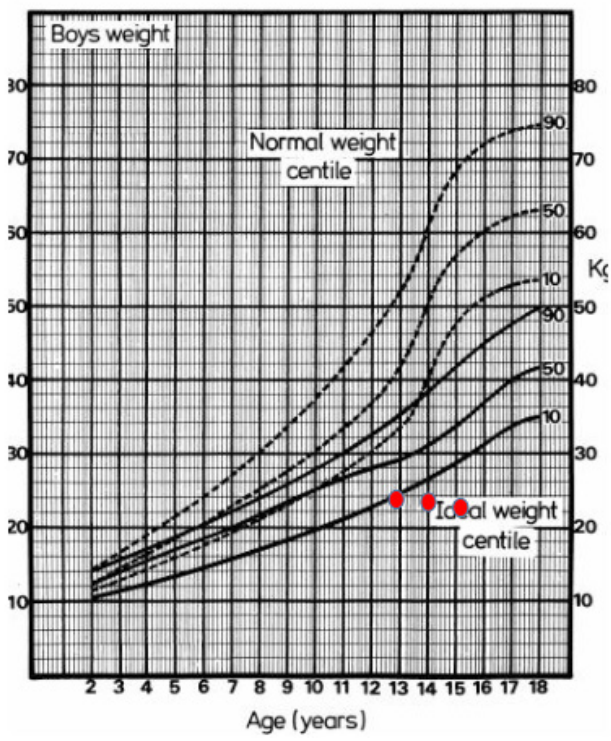

Figure 4. Patient's weight on the DMD ideal body weight chart,[8] patient was always under p10 while the nutritional intervention was done. Significant muscle wasting resulted in further weight loss. This also was accentuated by eating difficulties leading to a reduced food intake.[9]

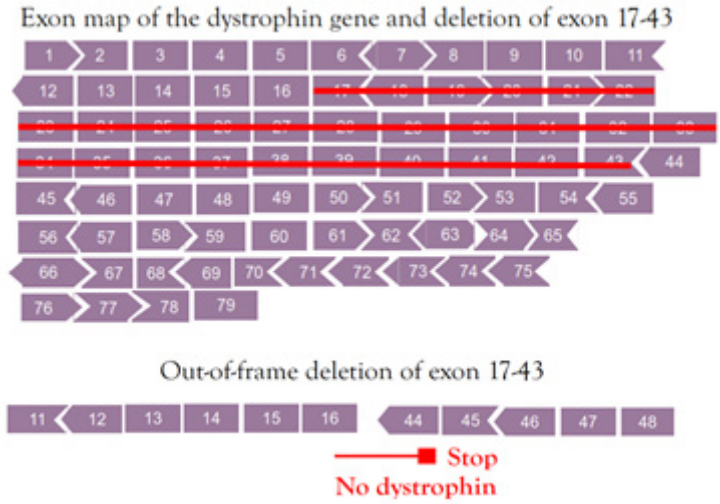

Figure 5. Deletion of exon 17-43

Genetic testing pointed to a deletion of exon 17 to 43 **(Figure 5)**, causing a premature stop codon. Exons 16 and 44 could not form a reading frame after the deletion, which was evidence of an out-of frame or frameshift mutation. As a result of this mutation, no dystrophin was formed, manifesting as Duchenne muscular dystrophy.

Discussion

Duchenne muscular dystrophy is a chronic disease with unavoidable progression towards severe physical dependency. The main goals of DMD management are to optimize good health and quality of life. Patients with DMD will experience significant deterioration of quality of life due to limitations in daily physical activity, which may hamper their functioning in school. Our patient sometimes complained of pain or discomfort, which affected his emotional state.[10] He also had severe problems in school, such that after graduating from elementary school, he did not continue his studies nor did he attend a school for the disabled, due to financial, geographical, and transportation problems.

Several studies have reported the mean age of loss of ambulation in children with DMD as ranging between 9.5 to 14 years. The mean age of death has been reported to be 18.1 to 20 years. With mechanical ventilation, life expectancy can extend to 27.3 to 30.4 years; 26 years when cardiomyopathy is present.[11] We hoped that our interventions could extend the natural course of the disease in our patient to 18-20 years or even to to the late 20s if supported with a mechanical ventilator. However, due to our hospital's lack of resources and the family's limitations, we were unable to provide a non-invasive assisted ventilator at home; thus, our interventions were not optimal.

On genetic testing, there was a frameshift or out-of-frame mutation, giving rise to the patient's severe DMD clinical phenotype. If this wide mutation had formed a reading frame, the patient's clinical condition might have been milder or manifested as BMD. Family members of DMD or BMD patients need to be genetically tested in order to identify carriers and to receive appropriate genetic counseling. However, one-third of mothers of DMD patients have no mutation, indicating that they are not carriers and that a de novo mutation is responsible for the disorder.[12]

A study mentioned that maternal DMD carrier frequencies were 53.5% for deletion, 66.7% for duplication, and 67.9% for point mutation. The maternal carrier frequency of deletion-type DMD is lower, which may be associated with a natural mutation, in which a deletion occurs due to unequal crossover in oogenesis. It was also suggested that de novo mutations are more prevalent for deletions than other mutations.[13] In our patient, genetic testing of the family revealed that the mother was not a carrier and the three brothers of the patient were not affected, indicated that a de novo mutation was likely the case.

During observation, our patient had no episodes of pneumonia episodes. The family had been educated to limit his chances of infection by wearing masks if anyone in the home had an upper respiratory tract infection; our patient had also received pneumococcus and influenza vaccinations. Respiratory failure in DMD patients may occur because of impaired secretion clearance, mucus blockage, and inadequate cough during respiratory tract infections. Coughing is ineffective if the peak cough flowmeter reading is <160 L/min; our patient had a peak cough flow of 125 L/min. After practicing air stacking using a manual ventilation bag, his results improved. A combination of manual exsufflation with a manual ventilation bag and air stacking maneuvers improve cough performance and are recommended as the first step in respiratory management in DMD patients.[6] Toussaint et al. showed the cough effectiveness in DMD patients was similar between patients practicing air stacking by ventilator or by bag resuscitator. Manual resuscitator use is able to effectively improve cough capacity, is affordable, and easy to use in non-ambulatory DMD patients.[14]

Another study comparing lung function test results in patients with and without steroid treatment found that mean FVC decreased 6.89% per year, but only 0.47% in patients taking steroids.[15] In our last evaluation, we found significant improvement in our patient's FVC and FEV1. Chest deformity is also a serious problem, because it restricts the air flow in the compressed area. Halfway through the course of the disease, the maximal inspiratory and expiratory pressure gradually deteriorates. Along with stage progression, total lung capacity decreases and residual volume increases. The PCO_2 increment in patients without respiratory tract infection indicates a poor prognosis.[16] Fortunately, we did not find hypercarbia in our patient.

Our patient had normal ejection fraction and no cardiomyopathy, this might be the effect of corticosteroids. The loss of the dystrophin gene causes progressive myopathy and cardiomyopathy. There is evidence that corticosteroids can improve muscle strength, including heart muscle strength.[17] Cardiomyopathy is the main cause of death in these patients , as lesions in myocardial tissue decrease left ventricular systolic function.[18]

The long-term effects of glucocorticoid use in non-ambulatory patients are preserved upper limb strength, delayed scoliosis progression, and prevention of lung and heart involvement.[5,19] Steroid use in a non-ambulatory patient is controversial, as the effectiveness is unclear.[19,20] A meta-analysis on a 6-month steroid treatment coursea in DMD patients showed that corticosteroid dose of 0.75 mg/kg/day with prednisone or prednisolone improved muscle strength and function compared to placebo. There is some evidence from randomized controlled trials on more sustained effects of corticosteroids.[21] The timing of steroid discontinuation also remains controversial.[22] Generally, corticosteroid therapy is continued as long as the patient feels its benefit for their quality of life. Most cases involve older patients, who can decide whether they wish the therapy to be continued.[23] Other studies found that steroids reduced the risk of death and might be beneficial if continued for the patient's lifetime.[24,25] Corticosteroid side effects must be monitored at regular intervals. We did not find any significant side effects in our patient.

The patient was advised to do upper and lower limb strengthening, stretching, and breathing exercises prescribed by physical medicine and rehabilitation specialists. He was also given a back brace and neck collar based on the orthopedic surgeon's suggestions for the scoliosis. A study in Taiwan noted that the mean age of scoliosis onset was 13.29 years, and the progression was 11.48° per year. The study mentioned that the Cobb angle in non-steroid-taking DMD patients increased by 13.75° but only 4.93° in patients undergoing steroid treatment , but this result was not statistically significant (P=0.05).[15] The mechanism of the development of scoliois has not been completely eludcidated, but it is thought that poor mobility and muscle weakening alters the spine and leads to severe scoliosis. The angle accretion is between 16-24° per year, and increases quickly in the adolescent growth spurt period. Scoliosis prevention is important in DMD, but once it has developed, surgical correction is the only solution. In fact, the use of bracing or corsets to prevent scoliosis progression has been shown to be ineffective.[26] Posterior spinal instrumentation is recommended for prepubertal patients with >20° curvature who are not taking glucocorticoid therapy. When a patient on glucocorticoids did develop scoliosis, it is reasonable to wait until the scoliosis worsens before performing surgical correction.[27] For

this reason, our patient was not advised to undergo surgical intervention, even with a 45° scoliosis curvature, since he was entering the adolescent growth spurt period and he was on glucocorticoid therapy. When our patient showed worsening of his scoliosis over the disease course, the spine subspecialist advised that he undergo surgical correction. However, after the patient and his parents reviewed the risks and benefits of the procedure along with considerations from the respirologist and cardiologist, it was decided that the patient would forego the surgical procedure.

The patient had osteoporosis with vitamin D deficiency. Physical inactivity might have been the main cause of the osteoporosis, since the strain of muscles against the bone caused by activity and weightbearing directly influences bone growth and geometry. Non-ambulatory DMD patients frequently show vitamin D deficiency due to lack of sun exposure, which reduces calcium absorption efficiency. Glucocorticoid therapy might also harm bone health.[28] Accordingly, it was necessary to ensure adequate calcium intake, and ensure vitamin D supplementation if indicated, and get enough sun exposure to maintain sufficient vitamin D levesl.[29]

Severe malnutrition. Muscle weakness is the main cause of hypoalimentation. Dysphagia, gastrointestinal problems (constipation or delayed gastric emptying), longer mealtimes, and dependence on others for eating are all consequences of muscle weakness. Hypoalimentation and increased energy needs cause a negative energy balance and weight loss. As the disease progresses, DMD patients tend to have significant muscle wasting, resulting in weight loss. This condition is worsened by eating difficulties which interfere with intake volume. Other explanations are the reduction of neck range of motion, inadequate care, and low cognitive function. These patients also have difficulty opening their mouth and chewing, causing them to have longer mealtimes and frequent aspiration.[30] Such was the case in our patient. In patients who have difficulties with eating leading to undernutrition, gastrostomy tube placement may be indicated.[9,31] Once again, many aspects of the case should be considered. Since our patient was in advanced stage and had respiratory insufficiency with a high risk of major complications during anesthesia or sedation, he did not undergo gastrostomy tube placement.[9]

Our patient's condition had significant progression that fit the natural course of the disease. Our interventions were not optimal since we could not administer nocturnal assisted ventilation device to increase his quality of life and survival. Economic constraints are often the major challenges for medical personnel and family. The high cost of a ventilator that was not covered by the new Indonesian Universal Health Insurance plan was the main obstacle interfering with our patient's care. Further observation and intervention were necessary, particularly concerning his lung and heart function. It was also necessary to monitor our patient's quality of life, nutritional intervention, varicella vaccination, and annual influenza immunization.

Our patient was bedridden, dependent on others for his care, and unable sit in his wheelchair for longer periods of time. His wheelchair was modified such that it could be set in a reclining position to keep him comfortable. At last follow-up, he was in a late stage in the disease course for a non-ambulatory patient, and he might soon need palliative care . As Indonesia is a low-to-middle income country, only corticosteroid treatments and palliative care are affordable for the patient.[32] Our patient and his family need support to prepare them for his eventual terminal stage. Respiratory failure in DMD patients can occur gradually, but it can also happen suddenly when precipitated by a respiratory infection. The patient and family must be informed about ventilator and palliative care options in a timely way. The family's views about patient quality of life, their financial situation, as well as their cultural, legal and religious aspects require consideration.[33] We hope that, in addition to medical care, the family, and environment, social workers, or community members can provide support and aid. Multidisciplinary and comprehensive management is constantly needed to manage pediatric DMD patients.

Conflict of interest

None declared.

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