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Case Report

Motor clinical progression in a series of pediatric Duchenne and Becker muscular dystrophy cases

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Muscular dystrophy is a neuromuscular disorder that begins with muscle weakness and impaired motor function. Duchenne muscular dystrophy (DMD) is more severe and destructive than Becker muscular dystrophy (BMD), and both are progressive in nature. These 2 types of muscular dystrophy are caused by mutations in related to X-chromosome genes.[1] The mutations that occur in DMD are nonsense mutations. Deletion is present in 60% of DMD cases, while duplication occurs in 10% of DMD cases, resulting in loss of dystrophin protein. Mutations in BMD are missense mutations, so dystrophin is still formed, but in decreased amounts and quality.[2,3]

The prevalence of DMD was reported to be three times greater than that of BMD, with a prevalence of 1.02 per 10,000 male births *vs.* 0.36 per 10,000 male infants, respectiveley.[4] Anatomical pathology examination revealed loss of dystrophin in the examination of muscle biopsy without the presence of evidence leading to other neuromuscular diseases. Clinical DMD symptoms begin to appear at the age of 2-4 years. The child is observed to fall often and has difficulty climbing stairs. Muscle weakness worsens, especially in the upper limbs, continuing with heart and respiratory problems. The main causes of death in DMD are respiratory failure and heart failure.[5] The BMD has varied clinical symptoms, beginning with the appearance of myalgia, muscle cramps, and arm weakness progressing towards myopathy. Some patients are asymptomatic until the age of 15, but 50% of patients show symptoms at age 10, and almost all by age 20.[6] **[Paediatr Indones. 2019;59:104-12; doi: http://dx.doi.org/10.14238/pi59.1.2019.104-12].**

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The DMD diagnosis is based on clinical history, physical examination, muscle biopsy examination, and genetic testing. Muscle biopsy reveals the progression of muscle degeneration and regeneration. Histopathological examination of the muscle biopsy with immunohistochemical staining can show diminished or missing dystrophin.[7] However, one study that examined progression in DMD using MRI to observe muscle cross-sectional area (CSA) at various ages, showed differential fatty-tissue infiltration across

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the lower extremity muscles. The CSA were lower in boys who suffer from older DMD when compared to younger patients.[8]

Clinical motor progression in muscular dystrophy may worsen to the point that patients lose the ability to climb the stairs and have difficulty standing on their own. The progression leads to disability and eventual death. A previous study has shown that motor degeneration in DMD and BMD patients correlated with age.[9] Decreased gross motor function can be used to predict motor stages in DMD patients, but fine motor function does not show a decline.[10] Malnutrition is found in 50% of DMD patients, and if not properly managed, may aggravate the patient's muscular dystrophy condition. Multidisciplinary management is expected to slow the deterioration of this disease and optimize patient quality of life. Here we present six cases of DMD and BMD who were diagnosed with gastrocnemius muscle biopsy, hematoxylin eosin (HE), and immunohistochemical (IHC) staining using dystrophin antibody, followed by a reading of histopathologic preparations. We followed up motor clinical progression in patients who had been diagnosed for more than one year.

The Cases

We used medical record data from six patients who had been diagnosed with DMD or BMD for more than one year, from January 2012 to December 2016 at Dr Sardjito General Hospital, Yogyakarta. Pediatric neurologists evaluated the patients' motor clinical progression, gross motor skill (by motor function measure score/MFM), fine motor skill (by MACS score), nutritional status, steroid therapy use, and physiotherapy undertaken.

The motor clinical stages of DMD was divided into 5 stages, namely (I) Presymptomatic: the diagnosis at this stage is made from an increase in creatine kinase levels or if there is a family history. Children may experience developmental delays but have not had a walking disorder; (II) Early ambulatory: marked by a gower sign, waddling gait, walking with heels, the child can climb up the stairs; (III) Late ambulatory: marked loss of ability to climb stairs and get up from the floor; (IV) Early non ambulatory: children can still maintain body position, limited self movement and begin to experience scoliosis; (V) Late non ambulatory: the function of the upper limb and the ability to maintain posture are very limited.[11] Gross motor function in muscular dystrophy is measured by MFM score that includes 3 motor functions: standing and moving in sub-section (D1), upper limb motor function (D2), and lower limb motor function (D3).[10] The decrease in walking capacity (D1) within a year is 40%, the total decrease in motor function in one year from all aspects is 70%.[12]

The manual ability classification system (MACS) was designed to classify how children with cerebral palsy use their hands when handling objects in daily activities that require upperlimbs. Fine motor function in muscular dystrophy was examined by MACS score that divided into 5 categories: (1) handles objects easily and succesfully; (2) handles most objects but with somewhat reduced quality and/or speed of achievement; (3) handles object with difficulty, needs help to prepare and/or modify activities; (4) handles a limited selection of easily managed objects in adapted situations, requires continuous support and assistance for even partial achievement of the activity; (5) does not handles objects and has severely limited ability to perform even simple actions.[13]

Children's nutritional status was measured by WHO chart 2006. The cut off points used were according to z-score. Children aged less than 5 years were declared severely malnourished (severely wasted) if weight for length/height is below -3. Children aged ≥ 5 years old were declared severely malnourished if body mass index (BMI) is below -3. Mild malnourished (wasted) if weight for length/height or BMI between -3 < z score < -2. Normal nutrition if weight for length/height or BMI between -2 < z score < +1.[14]
Patients was categorized as steroid therapy group if they received prednisone in a dose of 0.5-0.75 mg/kgBW/day with good adherence to the therapy.[15] Physiotherapy was defined as routine if was done 3 times a week with standardized physiotherapy from rehabilitation centre.[16]

The six patients' characteristics are shown in **Table 1.**

Case 1

A boy aged 9 years and 9 months was admitted to our hospital with a complaint of often falling when walking, as observed by his parents. The child also

Table 1. Clinical findings in 6 DMD and BMD patients

Muscular dystrophy	Diagnosis			Follow up						
	Sex	Age	Motor clinical stage	Age	Motor clinical stage	Gross motor function score	Fine motor function score	Nutritional status	Steroid use	Physiotherapy
Case 1	M	9 yr 9 mo	DMD	11 yr 7 mo	IV	29.2%	3	Good	No	No
Case 2	M	9 yr 2 mo	II	12 yr 7 mo	IV	31.3%	3	Severe malnutrition	No	Yes
Case 3	M	7 yr	III	9 yr	III	57.3%	2	Good	Yes	Yes
Case 4	M	8 yr 10 mo	II	13 yr	IV	38.5%	3	Good	No	No
Case 5	M	6 yr 6 mo	II	7 yr 10 mo	II	80.2%	1	Good	Yes	Yes
Case 6	F	16 yr	BMC II III	17 yr	III	41.7%	2	Good	No	Yes

had difficulty climbing stairs and walking on tiptoes. Physical examination showed decreased strength of the lower extremities. His motor clinical stage was II (early ambulatory stage). His enzymes were as follows: serum creatinine kinase (CK) was increased to 9,159 U/L, creatine kinase M-B (CKMB) was 287 U/L, and lactate dehydrogenase (LDH) was 1,936 g/dL. Electroneuromyography (ENMG) showed polymyositis. Hematoxylin eosin staining of a muscle biopsy showed variable muscle fiber size, with fibrosis and infiltration of adipocytes. The IHC staining revealed no evidence of dystrophin protein in the cellular membranes (**Figure 1** and **Figure 2**). Hence, the patient was diagnosed with DMD. At the age of 11 years and 7 months, the patient was reevaluated. Steroid therapy and physiotherapy had not been undertaken. His motor clinical stage had deteriorated to an early non-ambulatory stage (stage IV). The boy's MFM score was 29.2% and MACS score was 3. Upon evaluation, the patient had both impaired gross motor function and fine motor function, but his nutritional status was good.

Case 2

A boy aged 9 years and 2 months was hospitalized with a chief complaint of weakness in the lower extremities for the past year. Gower's sign and Duck sign were observed. From physical examination, he was in late ambulatory motor clinical stage III. Complete blood count was normal. His CK was 10,499 U/L, CKMB 257 U/L, and electrolytes within normal limits. Electroneuromyography (ENMG) revealed myopathy. The HE staining of a muscle biopsy showed adipocyte infiltration in muscle fiber and fibrous tissue replacement. The IHC staining showed no evidence

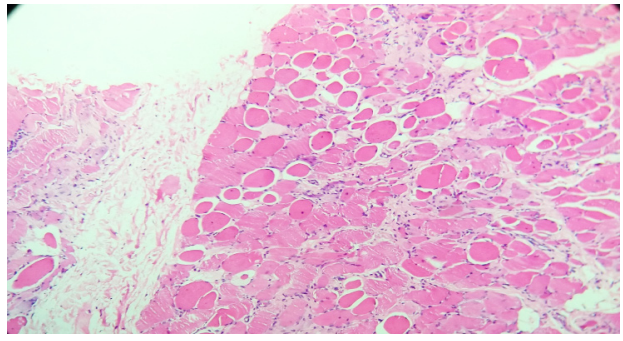

Figure 1. Case 1 HE staining: infiltration of adipocytes in muscle fiber and fibrous tissue replacement

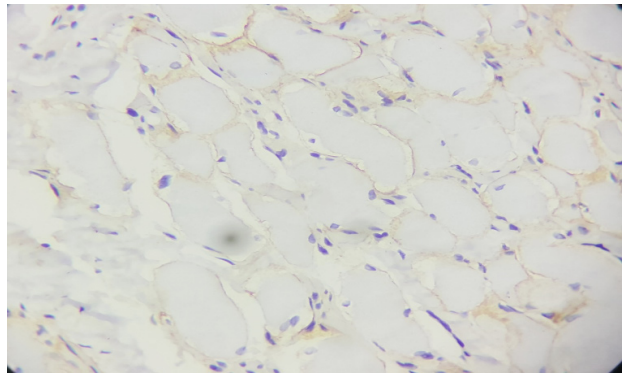

Figure 2. Case 1 IHC staining: no evidence of dystrophin in the cellular membranes

of dystrophin in the cellular membranes (**Figure 3** and **Figure 4**). The patient was diagnosed with DMD. He had never received steroid therapy, but had undergone routine physiotherapy. The patient was reevaluated at the age of 12 years and 7 months. His motor clinical stage was IV and he had impaired gross motor function (MFM score 31.3%) as well as fine motor function (MACS score 3). This patient also suffered from severe malnutrition and scoliosis.

Case 3

A 7-year-old boy was admitted with the chief complaint of frequent falling while walking during the two months prior to admission. He developed weakness in his lower extremities without any history of trauma. He also had difficulty standing from a squatting position and the complaints worsened over time. He had early ambulatory motor clinical stage II. His CK was 10,443 U/L and CKMB was 314 U/L. ENMG revealed myopathy. The HE staining of a muscle biopsy showed adipocyte infiltration in muscle fiber and fibrous tissue replacement. The IHC staining showed dystrophin-negative staining (**Figure 5** and **Figure 6**). He was diagnosed with DMD and entered a longitudinal study for two years. He received both steroid therapy and routine physiotherapy. The patient was reevaluated at 9 years of age. His motor clinical stage had progressed to III and his gross motor function was impaired (MFM score 57.3%). However, his fine motor function was not impaired (MACS score 2). The boy's nutritional status remained good and he was able to attend school using a wheelchair.

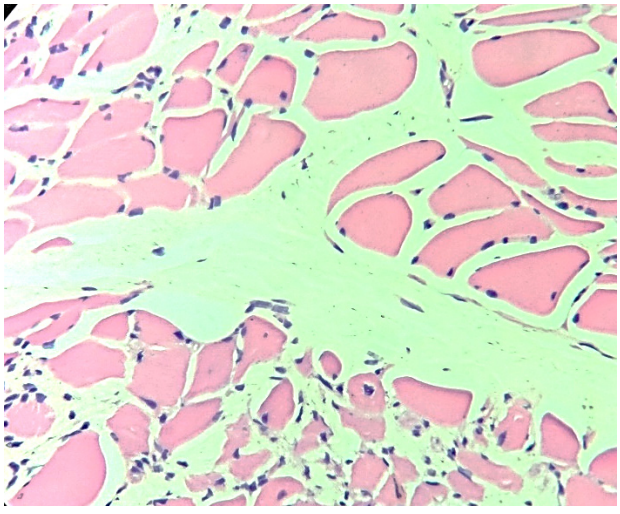

Figure 3. Case 2 HE staining: infiltration of adipocytes in muscle fiber and fibrous tissue replacement

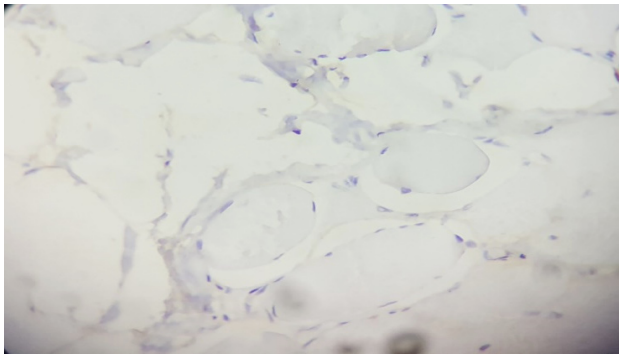

Figure 4. Case 2 IHC staining: no evidence of dystrophin in the cellular membranes

Case 4

A boy aged 8 years and 10 months with a history of difficulty walking for several months was admitted to the hospital for a muscle biopsy. His brother had died after similar complaints. Physical examination showed Gower's sign. This patient was in stage II at diagnosis, but he was able to attend school. His CK was 285 U/L, CKMB 91 U/L, and ENMG revealed

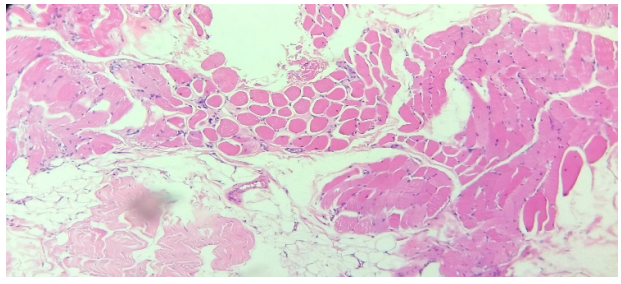

Figure 5. Case 3 HE staining: infiltration of adipocytes in muscle fiber and fibrous tissue replacement

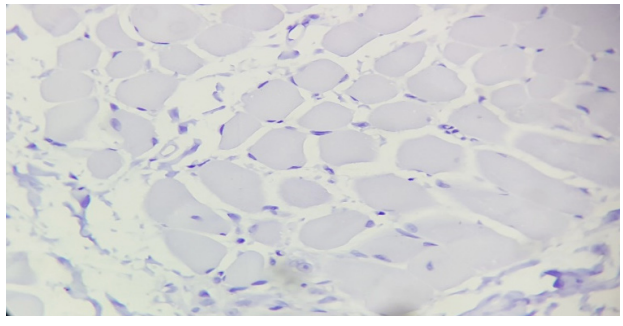

Figure 6. Case 3 IHC staining: no evidence of dystrophin in the cellular membranes

myopathy. The HE and IHC staining led to a diagnosis of DMD due to fibrous replacement in muscle fiber and dystrophin-negative staining (**Figure 7** and **Figure 8**). The patient was evaluated at 13 years of age, at which time his motor clinical stage had progressed to IV and scoliosis was discovered. From history-taking, we found that the family had refused medication and physiotherapy. The boy had impaired gross motor function (MFM score 38.5%) and fine motor function (MACS score 3). The nutritional status of this patient was good at evaluation.

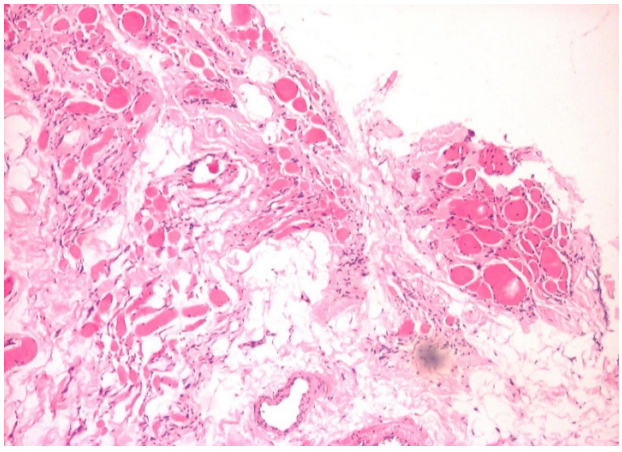

Figure 7. Case 4 HE staining: infiltration of adipocytes in muscle fiber and fibrous tissue replacement

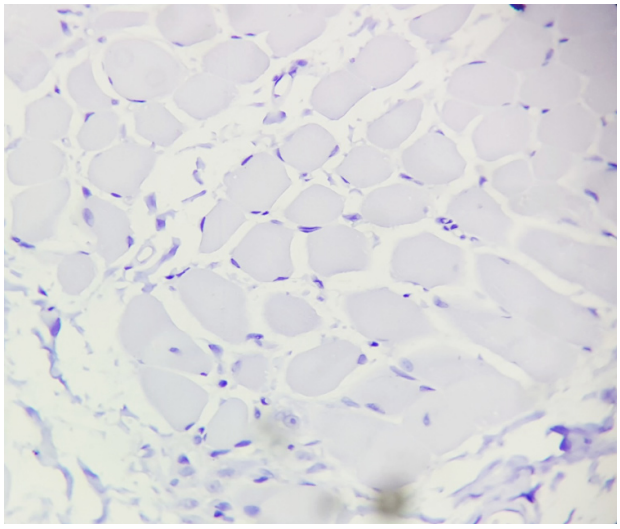

Figure 8. Case 4 IHC staining: no evidence of dystrophin in the cellular membranes

Case 5

A boy aged six years and six months was admitted to our hospital due to frequent falling while walking since six months prior, without a history of trauma. His grandfather's brother reportedly had similar signs. Physical examination revealed stage II motor clinical muscular dystrophy. He had CK 16,550 U/L, CKMB 831 U/L, and his ENMG showed myopathy. The HE staining showed muscle fibers of variable sizes with infiltration adipocytes and fibrosis. The IHC staining showed partial staining of dystrophin in the cellular membranes (**Figure 9** and **Figure 10**). This patient was diagnosed with BMD and was enrolled in a longitudinal study. After one year, the reevaluation showed motor clinical stage II, and no impairment in gross or fine motor function (MFM score 80.2% and MACS score 1). This patient received steroid therapy and routine physiotherapy. His nutritional status was good.

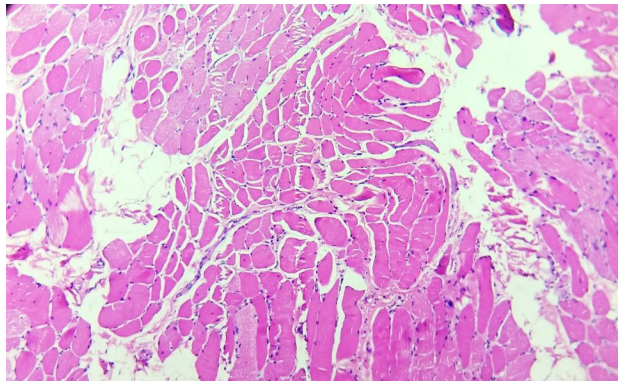

Figure 9. Case 5 HE staining: muscle fibers of variable sizes with infiltration of adipocytes and fibrosis

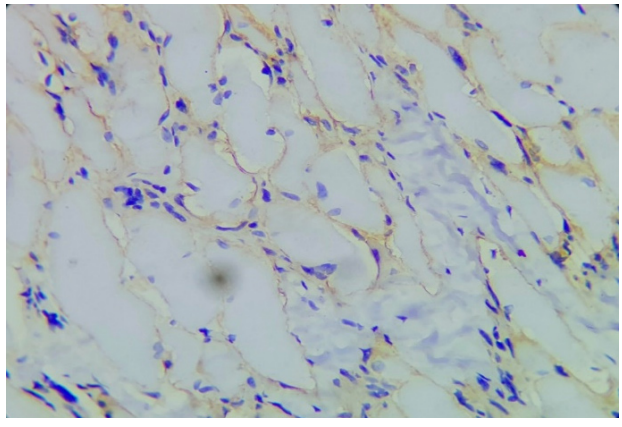

Figure 10. Case 5 IHC staining: evidence of dystrophin in the cellular membranes

Case 6

A girl aged 16 years was admitted because of weakness in her lower extremities and difficulty walking. She had both duck and Gower's signs. Her brother had died at 17 years of age with similar signs that worsened. Her serum CK was 2,412 U/L. The patient had previously undergone ENMG examination, which revealed polyneuropathy. The HE staining of the muscle biopsy showed muscle fibers of variable sizes with infiltration of adipocytes and fibrosis. The IHC staining showed that dystrophin was partially stained, indicating decreased amounts in the cellular membranes (**Figure 11** and **Figure 12**). She was diagnosed with BMD and motor clinical stage of III. She did not receive steroid therapy, but had routine physiotherapy. At the one-year evaluation, her motor clinical stage had not deteriorated. Her gross motor function was impaired (MFM score 41.7%), but her fine motor function was good (MACS score 2). The girl's nutritional status was good and at 17 years of age she was still able to attend school using a wheelchair.

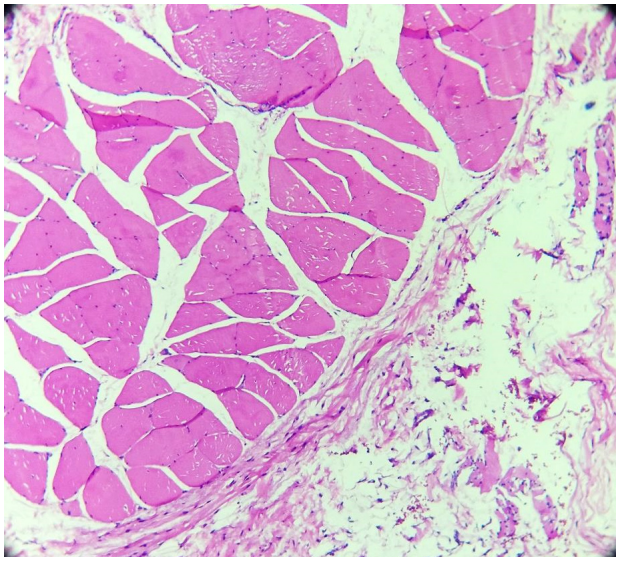

Figure 11. Case 6 HE staining: muscle fibers of variable sizes with infiltration of adipocytes and fibrosis

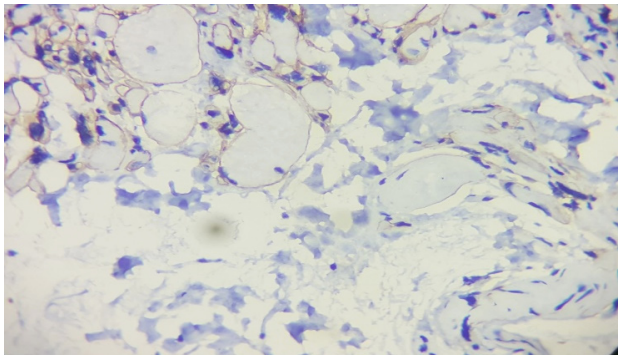

Figure 12. Case 6 IHC staining: evidence of dystrophin in the cellular membranes

Discussion

A Centers for Disease Control and Prevention Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet) team followed the birth of baby boys from 1982-2011 in the United States. The most common muscular dystrophy was DMD, with a prevalence of 2.83 times more than BMD (1.02/10,000: 0.36/10,000).[4] Currently at Dr. Sardjito General Hospital, Yogyakarta, diagnosis of muscular dystrophy is done by patient history, onset of symptoms, family history of similar disease, serum creatine kinase, and muscle biopsy.

All 6 cases walked had abnormal gait. Scoliosis was found in one patient with motor clinical stage IV. Clinical progression of DMD can be assessed by periodic examinations, including changes in walking, clinical motor weakness, motor capacity examination with a 6-meter walking test, and respiratory function checks. Systematic search results suggest that motor clinical progression in DMD begins at age 8 and becomes more severe by the age of 16-18 years. On average, symptoms start at the age of 10 years. Average motor clinical deterioration occurs at the age of 19.9 years. Scoliosis was found in 3.9% of DMD cases in Japan and 52.1% of cases in France. Loss of motor abilities in 1 year was estimated at about 3%, and 29% in 3 years after the onset of symptoms. One study mentioned a loss of motor skills up to 43% within 1 year of observation.[17]

Muscular dystrophy diagnoses in this case series were obtained through gastrocnemius muscle biopsy HE staining and IHC staining using anti-dystrophin antibody. Histopathologic preparations can be used to determine the degree of infiltration of adipocytes and fibrosis, which indicate the degree of muscle damage. The DMD patients have dystrophin-negative staining in muscle fiber membranes, whereas BMD patients have partial staining of dystrophin proteins.[7] A previous study at Dr. Sardjito General Hospital

reported that a diagnostic test of stage III muscle biopsy with HE staining had 50% sensitivity (95%CI 1 to 99), and 40% specificity (95%CI 15 to 65). The accuracy of histopathologic diagnoses of grade 4 muscle biopsy with HE staining was 50% sensitivity (95%CI 1 to 99) and 60% specificity (95%CI 35 to 85). The IHC examination is considered reliable for DMD diagnosis, but not for BMD diagnosis.[18] A study showed that myofiber examination in muscular dystrophy patients, the anti-dystrophin antibody were lower compared to controls. They also reported that a comparison of various anti-dystrophin antibodies for quantifying purposes revealed degradation of 83% of dystrophin in pediatric DMD patients using ab15277 antibodies, with a dystrophin mean of 4000 intensity values (i.v.). If using MANDYS106 anti-dystrophin antibodies, there was a 70% decrease in dystrophin, with a mean dystrophin yield of 4700 i.v. In contrast, BMD patients had more dystrophin protein, with mean of 13,600 i.v by examination of either ab15277 antibody or MANDYS106.[19]

In mothers with children who have DMD, the risk of her being a carrier was 33%.[20] Another study reported that 51% of DMD patients had a carrier mother and 38% of BMD patients had a carrier mother.[21] A case report on a 14-year-old girl with muscle weakness, was diagnosed with BMD based on chromosome analysis 46, XX, and a deletion in exon 45-55. The BMD is rare in women.[22] The DMD patients aged 9-17 years are often obese due to the effects of steroid therapy. By the age of 17 years, the patient may become malnourished.[23] Malnutrition in such cases has been correlated to muscle function. Increased infiltration of fat tissue in skeletal muscle causes increased fat mass in muscle. Weight loss due to muscle wasting affects physical ability and daily activities of muscular dystrophy patients. Weight loss also occurs due to feeding difficulties, such as swallowing disorders leading to insufficient intake of energy, protein, and micronutrients. The recommended diet for muscular dystrophy patients is 80% of the recommended daily allowance (RDA) in patients who can still walk, and 70% of the total RDA in patients who use wheelchairs.[24]

A study of DMD patients aged 10 to 16 years who underwent prednisone therapy (0.75 mg/kg/day) from diagnosis to an average observation of 8.5 years noted that 40% of patients were still able to stand from a sitting position and 50% were capable of completing a 30-foot running test. Their pulmonary function capacity was also normal. In patients aged 10-13 years, 13% had ventricular systolic dysfunction; in patients > 13 years, 21% had ventricular systolic dysfunction. Only 6% of 16-year-old DMD patients had scoliosis.[25] Our results differed because in Dr Sardjito Hospital the patients did not receive adequate steroid therapy due to poor medication adherence, and delayed diagnosis, as our patients often presented at a later stage of disease.

Physiotherapy can prevent contractures. Recommendations include low intensity exercise and passive stretching. Two contraction mechanisms, concentric and eccentric, are targets for physiotherapy. Concentric contractions occur when the sarcoma is shortened and the muscle cells also shorten because of pressure. Eccentric contractions include elongation of cells and sarcomas under the same emphasis conditions. Eccentric contractions damage the sarcoma and cells, as well as increase inflammation. The target of physiotherapy and activity in muscular dystrophy patients is an increase in muscle cell function.[26] Other studies have shown that physiotherapy significantly prolonged life and decreased disability in muscular dystrophy patients.[27]

Here we show motor clinical progression in six DMD and BMD patients diagnosed from muscle biopsies. The results of a muscle biopsy may be used as a predictive factor of motor clinical progression in muscular dystrophy. Muscular dystrophy should be monitored on an ongoing basis to improve the patient's quality of life.

Conflict of Interest

None declared.

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