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Case Series

Duchenne muscular dystrophy: case series of rare inherited muscular disorder

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a rare muscular disorder caused by mutation of gene encoding dystrophin protein which required for maintaining muscle stability during contraction. DMD occurs in 1 in 5000 male live births and characterized by progressive muscular weakness associated with motor development delay, loss of independent ambulation, respiratory failure, and cardiomyopathy. We present a case series of 3 DMD patients who were diagnosed at Prof. dr. I.G.N.G. Ngoerah general hospital, Denpasar over a period of four years (2019-2022). Clinical manifestation of patients includes progressive weakness of lower extremities and difficulty to stand up from sitting position. Physical examination revealed pseudohypertrophy of calf, winged scapula, positive Gower's sign, and waddling gait in all three cases. Supporting examination showed an increase of alanine transaminase and aspartate transaminase 5.6 times and 6.1 times the upper limit of normal, respectively. Definitive diagnosis of all patient was made based on immunohistochemistry staining which revealed an absent of dystrophin protein around muscle membrane.

Keywords: DMD, Dystrophinopathies, Inherited disorder

INTRODUCTION

Duchenne muscular dystrophy (DMD) is the most common type of dystrophinopathies**,** a spectrum of X-linked muscle disease that characterized by progressive muscular weakness. The incidence of DMD is approximately 1 in 5000 male live births with initial symptoms mostly reported before age of 6 years.[1,2] Affected patient typically present with progressive muscle weakness which led to motor development delay. Mainly, patient become wheelchair-bearing by the age of 12 and die in their twenties due to respiratory failure or cardiomyopathy.[3]

Creatinine kinase (CK) is a widely used biomarker of DMD. CK level are generally increase since birth, before the development of clinical sign and symptoms. In the absence of creatinine kinase examinations, other level of enzyme such as ALT and AST may provide an important clue of possible muscle damage. Absent of dystrophin protein on immunohistochemistry staining remains the gold standard for diagnosing DMD.[4,5]

There is no curative treatment for DMD. To date, the only treatment modality of DMD is corticosteroid which has been shown to delay the progressivity of the disease. In addition to corticosteroid therapy, physiotherapy also plays an important role to preserve muscle function, optimize support to organ system failure, and improve patient quality of life. Hence, a multidisciplinary approach is needed.[6] We report three patients diagnosed with DMD at Prof. dr. I.G.N.G. Ngoerah general hospital, a tertiary hospital in Bali from 2019 to 2022.

CASE SERIES

We present three patients diagnosed with DMD based on immunohistochemistry staining at Prof. dr. I.G.N.G. Ngoerah general hospital in a three-year period, from 2019 to 2022. All patients were boys with age ranged from 7 to 9 years old. All patient presented with progressive weakness of lower extremities and difficulty to stand up from sitting position. Out of three patients, one patient reported mild delayed on motor development and abnormal gait as the initial noticed symptoms, while the others reported frequent fall starting at 3 and 4 years of age as the earliest symptom. Family history of similar symptoms in second-degree uncle was found in one case. On physical examination, reduced power of the lower limbs, pseudohypertrophy of calf, winged scapula, positive Gower's sign, and waddling gait were observed in all cases.

According to clinical manifestation, laboratory examinations, electromyography (EMG), and muscle biopsy of gastrocnemius muscle was performed. Laboratory findings showed an elevated level of alanine transaminase (ALT) and aspartate transaminase (AST). Mean increasement of ALT was found to be 5.6 times the upper limit of normal (range 73-421.2 U/L) and mean increasement of AST was found to be 6.1 times above upper limit of normal (range 112.3-345.1 U/L). Serum creatinine kinase examination was not performed on all reported cases. EMG examination revealed myopathy in all three cases.

Haematoxylin and Eosin (H&E) staining showed a variable size of muscle fibers, some of nuclei were located at the centre, endomysial fibrosis, and fatty replacement of muscle fibers (Figure 1). Immunohistochemistry staining of all cases revealed a complete absent of dystrophin protein, confirmed DMD (Figure 2).

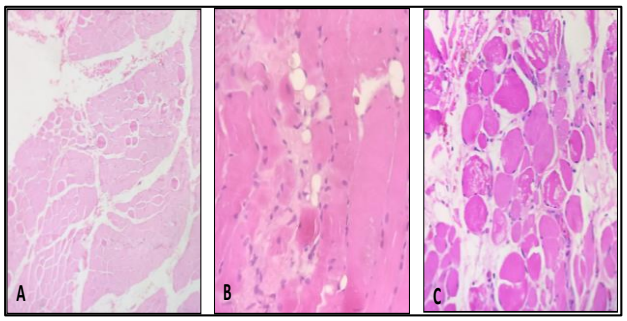

Figure 1 (A-C): Histological findings showed a variable size of muscle fibers, endomysial fibrosis, fatty replacement of muscle fibers, and some of nuclei were located at the centre (H and E, 100x-400x).

Based on clinical presentation, laboratory examination, and histopathological findings, the patients were diagnosed with DMD. All cases received prednisolone 0.75 mg/kg/day, consulted to physiotherapy, and advised to undergo annual assessment of cardiac and respiratory function.

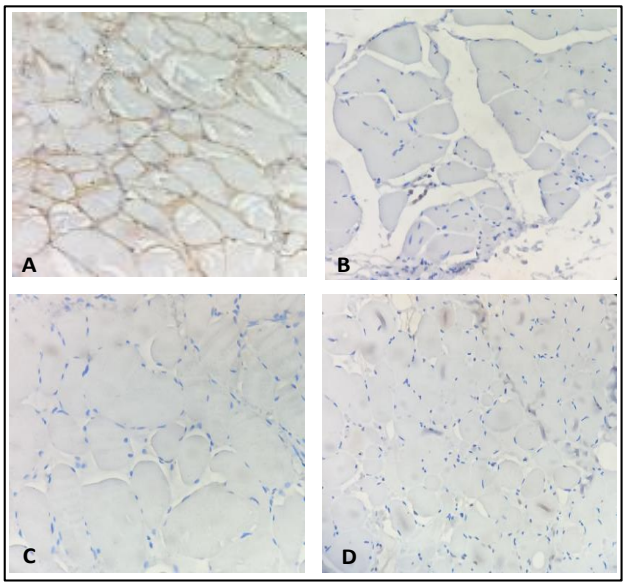

Figure 2 (A-D): Immunohistochemistry stain; control of normal skeletal muscles revealed dystrophin that completely surround the muscle fibers (A) complete loss of dystrophin in the entire membrane of muscle fibers in all cases (B-D).

DISCUSSION

DMD is a rare muscular disorder caused by mutation of DMD gene that located on the short arm of X chromosome. DMD gene is one of the largest gene in human body that consist of 79 exons, making it is more susceptible for mutation. Dystrophin gen encode a protein called dystrophin, part of dystrophin-associated glycoprotein complex that link between cytoskeletal actin and extracellular matrix around muscle cells. This link play role in stabilizing the muscle membrane (sarcolemma) during muscle contraction. Therefore, absent of dystrophin protein will lead to contraction-induced muscle damage.[3] The most common type of DMD gene mutation is deletion (69.3%), followed by point mutation (16%), and duplications (14.8%).[2] Two third of DMD cases is inherited from asymptomatic female carrier, while the rest of it caused by de novo mutation, which means that the patient has no familial history of muscular dystrophy.[1] In this case series, two cases have negative family history.

Since DMD is inherited in an X-linked recessive pattern, DMD will predominantly affects male children, while female likely to be asymptomatic healthy carriers.[1] DMD occur in 19.8 per 100,000 live male births and initially present with progressive muscle weakness starting from proximal lower limb leading to frequent falls, difficulty in standing, walking, and climbing stairs.[7] Weakness predominantly affects lower limb more than the upper limb and commonly present around 2-5 years of age.[3,8] Multiple organ dysfunction including scoliosis, joint contracture,

restrictive lung disease, cardiomyopathy, and respiratory failure may develop as the disease progress.[8] In this case series, patient presented with typical DMD symptoms with no cardiac and respiratory involvement.

Physical examination of DMD patient will reveal a calf pseudohypertrophy due to loss of muscle regeneration ability and replacement of damaged muscle cells with fat and fibrotic tissue. Moreover, in order to getting up from laying position, patient need arm supports off the floor, known as Gower's Sign. Waddling gait and walking on tip-toe, another classical sign of DMD may also be observed.[8] These signs are in line with the presentation of our patients.

Patients suspected of having DMD based on clinical presentation, family history, and physical examination needs to undergo further diagnostic test to confirm the clinical diagnosis. An elevation of serum CK level more than 50 times normal is suggestive for DMD. These elevations peak by age two and progressively decrease as muscle cell replaced by fatty and fibrous tissue.[8] These abnormal elevations caused by muscle membrane instability that led to progressive leakages of intracellular components into plasma.[4,9]

In addition to elevated CK level, high level of ALT and AST can also be used as a biomarker of DMD. ALT and AST are enzyme that commonly used as a biochemical indicator for hepatocellular disease because of its concentrated mostly in hepatocyte. However, ALT and AST can also be found in cardiac and muscle cell. Thereby, an elevation of transaminase may also cause by other origin besides liver disease such as muscle cell damage.[9]

Previous study stated that up to 97% of DMD patient had elevated transaminase level. ALT and AST value may elevate up to 22.6 and 8 times the upper limit, respectively.[10] Exact mechanism of this condition is still unknown. Some study assumed that under abnormal conditions such as DMD, there is a leakage of transaminases that occurs along with creatinine kinase leakage and lead to elevation of serum transaminase.[9] In this case series, creatinine kinase examination was not performed. However, ALT and AST value was found to be elevated without any sign of liver disease, indicates the possibility of muscle damage.

On EMG examination, signs of myopathy including positive sharp wave, fibrillation, and presence of polyphasic, short duration, and low-amplitude Motor Unit Action Potentials (MUAPs) will be found. Since the EMG finding is not specific to DMD, patient with a high suspicion of DMD may proceed to muscle biopsy.[11] Sign of myopathy were found in all three cases reported.

The diagnosis of DMD in our case series was made by histopathologic findings. In DMD, haematoxylin and eosin staining of muscle biopsy will show a wide variation of muscle fiber size, endomysial connective tissue proliferation, myofiber necrosis, and replacement of muscle with adipose tissue and fat.[4,8] Immunohistochemistry staining, the gold standard for diagnosing DMD will demonstrate an absence of dystrophin expression at the muscle membrane.[8] Both H and E and immunohistochemistry staining features of DMD were coherent with microscopic findings in our case series.

Treatment with corticosteroid remains the therapeutic option for DMD. Corticosteroid with recommendation dose of 0.75 mg/kg/day are known to prolong independent ambulation by stimulating insulin-like growth factors, decreasing cytokine production, decreasing apoptosis of myotubes and myofibers necrosis, and enhancing myoblast proliferations. Previous study also found that corticosteroid may delay the onset of cardiomyopathy, preserve pulmonary function, and reduce risk of scoliosis.[5,8] However, long-term use of corticosteroid is associated with many side effects, including obesity, osteoporosis, short stature, behavioral changes, and cataracts.[6]

In addition of corticosteroid therapy, physiotherapy also plays an important role in maintaining skeletal muscle function. Regular passive stretching of ankle, knee, and hip is recommended to prevent muscle contracture and deformity.[8] Optimal positioning of wheelchair-bound patient may also help to prevent scoliosis and other later complication due to scoliosis such as restrictive lung disease.[6]

CONCLUSION

DMD is a rare muscular disorder caused by mutations of dystrophin gene. DMD typically present in early childhood with rapidly progressing muscle weakness as the primary manifestation. As this condition is associated with high morbidity and mortality, achieving a timely diagnosis of DMD is a crucial aspect of care to improve patient's quality of life.

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