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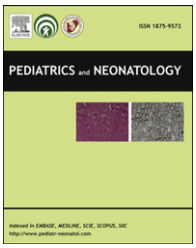

CASE REPORT

Manifesting Pediatric Carrier of Isolated Dystrophinopathy with Initial Presentation of Myalgia and Persistent HyperCKemia

Chien-Hua Wang [a,b,*], Wen-Chen Liang [b], Yi-Ning Su [c,d], Wen-Chieh Lee [a], Ching-Chyuan Su [e], Yuh-Jyh Jong [b,f]

[a] *Department of Pediatrics, Antai Medical Care Cooperation Antai Tian-Sheng Memorial Hospital, Ping-Tung, Taiwan*
[b] *Department of Pediatrics, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan*
[c] *Department of Medical Genetics, National Taiwan University Hospital, Taipei, Taiwan*
[d] *Graduate Institute of Clinical Genomics, College of Medicine, National Taiwan University, Taipei, Taiwan*
[e] *Department of Thoracic Cardiovascular Surgery, Antai Medical Care Cooperation, Antai Tian-Sheng Memorial Hospital, Ping-Tung, Taiwan*
[f] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*

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Dystrophinopathy is caused by mutations in the dystrophin gene at Xp21. Although manifesting carriers of dystrophinopathy have been documented in adults, symptomatic dystrophinopathy in female children is rare. We report on a 13-year-old girl with initial presentation of myalgia at age 7 years and an incidental finding of increased transaminases and creatine kinase at regular health check at age 12 years. At age 13 years, manual muscle testing revealed asymmetric bilateral proximal weakness of extremities. Slight calf hypertrophy and winged scapulae were found. Muscle biopsy revealed a mosaic pattern in dystrophin immunostaining. Mutation analysis of the dystrophin gene revealed a novel *de novo* c.1150-2delA mutation. Accordingly, the patient was found to be an isolated dystrophinopathy carrier, manifesting limb-girdle pattern of muscle weakness in her childhood. This report suggests that dystrophinopathy should always be considered in female patients with sporadic myopathy. Dystrophin immunostaining and mutation analysis for the dystrophin gene are necessary for final diagnosis, subsequent genetic counseling, and long-term care.

* Corresponding author. No.100, Shih-Chuan 1st Road, Kaohsiung 807, Taiwan.
E-mail address: s920268ch@yahoo.com.tw (C.-H. Wang).

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1. Introduction

Mutations in the dystrophin gene at Xp21 lead to a spectrum of phenotypes termed the dystrophinopathies, comprising Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD), and dilated cardiomyopathy (DCM). DMD is the most severe phenotype, with onset of weakness in early childhood, wheelchair dependence by the early teen years, and death usually in the third decade due to cardiac and respiratory failure. BMD is less common and is a milder form of the disease, in which patients are usually ambulatory until adult years and may have a normal life span. Due to the X-linked inheritance of this disorder, female carriers are not supposed to display disease phenotypes. However, approximately 2.5-10% of female carriers have been shown to be symptomatic, and 2% of them had no family history of muscular dystrophy.[1–3] A cohort study reported that the mean age of onset was 33 years, and symptoms were usually not evident before age 16 years among manifesting female adult carriers.[4] Muscle weakness was the most common presenting symptom to variable extent. Elevated serum creatine kinase (CK) has been observed in half of DMD carriers.[4] The most common mechanisms accounting for manifesting female carriers have been associated with a skewed X-inactivation and X-autosome translocation.[5,6] Herein, we report on a 13-year-old girl with early onset of myalgia and incidental finding of hypercreatine kinasemia (hyperCKemia), leading to the discovery of isolated dystrophinopathy with a novel *de novo* microdeletion mutation (c.1150-2delA).

2. Case Report

This 13-year-old girl had no family history of neuromuscular disease. She was a full-term baby born via normal spontaneous delivery. Her developmental milestones were normal during infancy. However, she was able to walk independently at the age of 18 months and claimed to be a slow runner since early childhood. At the age of 7 years, she easily felt fatigue and myalgia while dancing or running. The condition was stationary and nonprogressive thereafter. At the age of 12 years, the patient was incidentally found to have hypertransaminemia (glutamic-oxalacetic transaminase: 89 IU/L, glutamic-pyruvic-transaminase: 59 IU/L, normal range: 10-42) at a regular health check and subsequently elevated serum CK level (4,268 IU/L; normal range $<$150 IU/L). In the meantime, she also frequently complained of muscle cramps. It took 22 seconds for her to run 100 m. Due to these findings, she was referred to us for further investigation. On physical examination, the girl had slight calf hypertrophy and mild contracture in the right knee joint. Mild winged scapula was also noted, along with symmetric facial expression and completely buried eyelashes. Opthalmoplegia was negative. Toe and heel gait were normal. Gowers' sign was negative. The Achilles and patellar tendon reflexes were both decreased. Grip and percussion myotonia were both negative. Manual muscle test (MMT) identified asymmetric muscle weakness, predominantly in the right shoulder and pelvic girdle (MMT score: 3 of 5 in the right extremities and 4 of 5 in the left extremities).[7] The patient had an MMT score of 5 in the distal joints, including wrist and ankle joints.

Laboratory tests including lactate, complete blood count, autoantibodies, thyroid function, and electrolytes all revealed normal values. A routine urine test showed no myoglobinuria. Electrocardiogram, echocardiogram, and cognitive function also revealed no abnormalities. However, electromyogram demonstrated myopathic change, showing abnormal spontaneous activity with positive wave and fibrillation, and small amplitude motor unit potential (Figure 1). A computed tomography scan of muscle showed no significant atrophic change. Thus, a muscle biopsy specimen was obtained over the left biceps brachii for further evaluation. On hematoxylin-eosin staining, dystrophic changes including myofiber size variation, increased number of internal nuclei, and scattered necrotic and regenerating fibers were seen. Dystrophin immunostaining demonstrated a mosaic pattern, compatible with the findings for carriers of dystrophinopathy[8] (Figure 2). Immunohistochemical studies for α-, β-, γ-, and δ-sarcoglycan revealed faint stainings at the sarcolemma of dystrophin-deficient myofibers. Other immunohistochemical stainings including α-dystroglycan, merosin, dysferlin, vaceolin-3, and collagen VI all showed no abnormalities. Meanwhile, a multiplex polymerase chain reaction test combined with multiplex ligation-dependent probe amplification was performed, and no deletion or duplication of the dystrophin gene was detected. High-resolution melting analysis with direct sequencing of the dystrophin gene identified c.1150-2delA mutation, which presented as a splicing site mutation. The same mutation was not found in either of the patient's parents (Figure 3). The patient was not on any specific treatment but followed up regularly for skeletal muscle and cardiac functions.[9]

3. Discussion

The initial presentation of disease in our patient was myalgia when she was 7 years old. The disease became noticeable because of elevation of liver aminotransferases at the age of 12 years, which then led to the finding of hyperCKemia and ultimately the diagnosis of muscular dystrophy, although muscle weakness was still not prominent. Our report suggests that dystrophinopathy should be considered for female patients with persistent

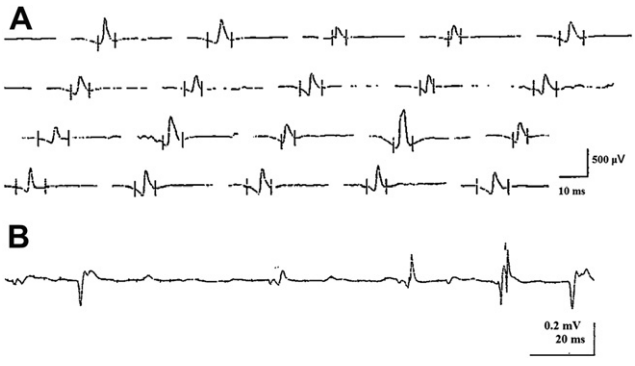

Figure 1 (A) Motor unit potential (MUP) from the deltoid posterior muscle showed myopathic pattern. Mean duration of MUPs was 7 ms, and mean amplitude of MUPs was 389 μV. (B) Spontaneous fibrillation potentials and positive wave were observed.

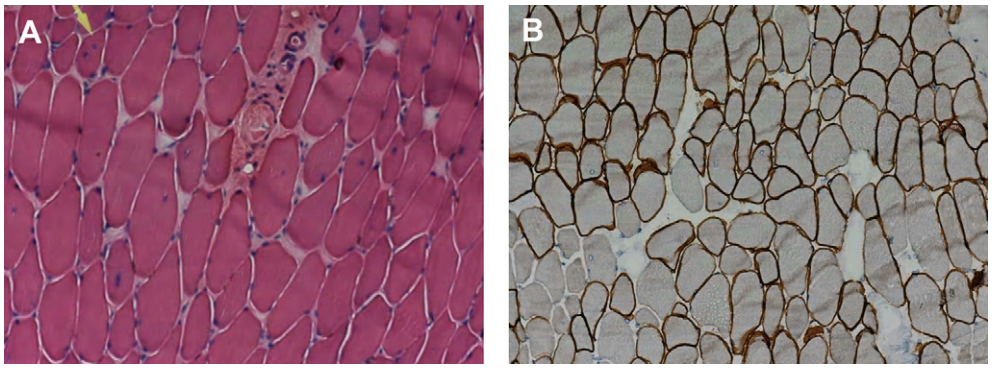

Figure 2 (A) Hematoxylin-eosin staining of the muscle biopsy from the biceps brachii showed variations in myofiber size, an increase in central nuclei, and scattered regenerating fibers and necrotic fibers. (B) An immunohistochemical study with anti-C-terminus (DYS3) antibodies showed some muscle fibers with complete membrane staining and others with either reduced or variable staining (mosaic pattern).

hyperCKemia even in the absence of a family history of dystrophinopathy.[10]

The spectrum of clinical presentations in manifesting carriers is quite wide, ranging from a rapidly disabling DMD-like phenotype to a very mild late-onset presentation.[11] However, the most common symptom has been shown to be muscular weakness. In 22 carriers with muscle weakness, 18 (82%) carriers were predominately asymmetric involved. Nine carriers (41%) had weakness limited to shoulder girdles or upper arms.[4] The clinical manifestation somehow resembles limb girdle muscular dystrophy, a heterogenous group of muscle disorders characterized by predominant weakness and wasting of muscles of the pelvic and shoulder girdle. Our report thus shows that muscle biopsy remains a commonly useful and sometimes irreplaceable method to differentiate dystrophinopathy from other muscular dystrophies.[11]

Approximately 70% of DMD carriers have preclinically or clinically evident myocardial involvement, and the incidence increases significantly with age. More than 90% of carriers with cardiac involvement become symptomatic after the age of 16 years.[12] In a prospective study among 99 DMD/BMD carriers with a median follow-up of 9 years, 11 carriers (approximately 10%) with DCM were identified. Nine of them eventually developed DCM during the follow-up period. Cardiac abnormalities in DMD/BMD carriers are progressive, as in patients with DMD/BMD.[13] Therefore, we should inform the patient of the risk of developing DCM and the importance of regular cardiac assessments.[14]

Previous studies found no correlation between phenotype and genotype in manifesting carriers.[5,11] However, behavior problems have been reported to be associated with deletion or duplication of the dystrophin gene.[5] In our patient, mutation analysis revealed a splicing site mutation (c.1150-2delA) that was supposed to cause deletion or insertion. Our patient showed normal mental and cognitive functions. Future studies with larger numbers of participants would be necessary to further verify whether a genotype-phenotype

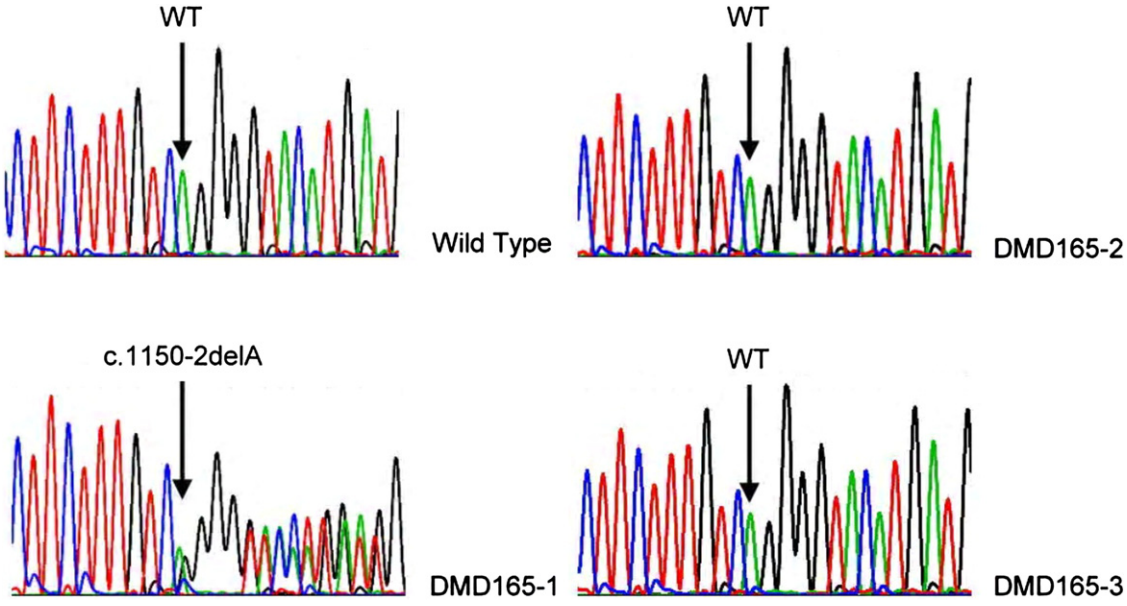

Figure 3 The index patient carried dystrophin gene microdeletion (c.1150-2 del A). Her father and mother did not carry the deletion.

correlation actually exists. Beyond the direct effect of the dystrophin gene mutation, skewed X-inactivation is potentially relevant to the phenotypic presentation in females.[5,11] However, X-inactivation was not tested in our patient.

In conclusion, careful pattern recognition in dystrophin immunostaining and dystrophin gene analysis is necessary to make a correct diagnosis because prompt diagnosis of dystrophinopathy carriers is important for further genetic counseling, and prognostic information to patients and families is essential for prophylactic monitoring cardiac disease. In addition, because of subtle onset symptoms that may be more likely to be misinterpreted in such girls, it is important for clinicians to keep this disease in mind for early identification of dystrophinopathy carriers.

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