γ-Sarcoglycan Deficiency Muscular Dystrophy in Two Adults

Kuang-Lin Lin, Huei-Shyong Wang, Sien-Tsong Chen,¹ and Long-Sun Ro¹

Abstract: All dystrophin-associated proteins contain sarcoglycan complex. Different forms of muscular dystrophy are caused by defective expression of different proteins of this structure. γ-Sarcoglycan deficiency muscular dystrophy, so-called severe childhood autosomal recessive muscular dystrophy (SCARMD), is a rare disease that has not been previously reported in Taiwan. This paper describes two Taiwanese adults with this disease: a 26-year-old man with calf pseudohypertrophy who had weakness in both legs for 1 year; and a 43-year-old woman who had progressive weakness in all four limbs, with the initial symptom of gait disturbance at the age of 32 years. Analysis of muscle biopsy specimens, which showed total deficiency of γ-sarcoglycan protein on immunostaining, confirmed the diagnosis of SCARMD in both cases. However, the clinical manifestations in these two patients, including lower proximal limb weakness initially developing in adulthood with a slow progressive course, are different from previously reported cases of SCARMD. The literature on this disease is reviewed and possible mechanisms of these distinct clinical presentations are discussed.

Dystrophin, the defective protein in Duchenne and Becker muscular dystrophy, is associated with a complex of sarcopenal glycoproteins linking the cytoskeleton of muscle fibers to laminin, a major component of the extracellular matrix [1, 2]. Deficiencies in any component of the transmembrane connection may disrupt the link between the cytoskeleton and the extracellular matrix and lead to muscle necrosis [1, 3].

The large dystrophin-associated oligomeric complex is composed of three sub-complexes: dystroglycan complex, sarcoglycan complex, and syntrophin complex [1, 4]. Unlike the dystroglycan complex, which is ubiquitously distributed, the four components of the sarcoglycan complex are muscle-specific [5, 6]. Many forms of muscular dystrophy are induced by defective expression of the sarcoglycan complex and a differential diagnosis may be achieved by labeling muscle biopsy specimens with antibodies to these proteins.

Limb-girdle muscular dystrophy (LGMD) is a genetically and clinically heterogeneous group of neuromuscular disorders. It is now known that mutations in the genes coding for four dystrophin-associated glycoproteins, α-β-, γ- and δ-sarcoglycan, are responsible for four forms of recessive LGMD. One of these, LGMD 2C, is caused by γ-sarcoglycan deficiency in muscle. This subtype was first described in Tunisia by Ben Hamida et al in 1977 and 1980, and was previously called severe childhood autosomal recessive muscular dystrophy (SCARMD), because of its Duchenne-like phenotype [7, 8]. It may be very difficult to distinguish Duchenne-like muscular dystrophy from Duchenne muscular dystrophy on clinical grounds. SCARMD has not previously been reported in Taiwan. Here we describe two adult Taiwanese patients with SCARMD and discuss their clinical, laboratory, and histopathologic findings.

Case Reports

Case 1

A male patient with no family history of muscular disease was first examined at 26 years of age because of a 1-year history of weakness in both legs. He had been unable to walk in the past...
2 months. He presented with calf pseudohypertrophy and thigh atrophy. On examination, he had proximal limb weakness with positive Gower’s sign and normal deep tendon reflexes. Sensory nerve conductive velocity (SNCV) and motor nerve conductive velocity (MNCV) were normal. Electromyography (EMG) showed a myopathic pattern. The serum creatine phosphokinase (CPK) concentration was 827 IU/L (normal, 15–130 IU/L). Antinuclear antibody was negative. Muscle biopsy findings showed a marked increase in endomysial connective tissue, muscle fiber splitting, central nucleation, and variability of fiber diameters, which were consistent with muscular dystrophy.

Case 2

A 43-year-old woman with no family history of muscular disease visited our hospital because of progressive weakness of all four limbs for 11 years. She had the initial symptom of gait disturbance at the age of 32 years. Her symptoms had become aggravated in the past year, with the development of dyspnea. SNCV and MNCV were normal. EMG showed denervation and reinnervation in the proximal muscles of the extremities. The serum CPK concentration was 142 IU/L. Muscle biopsy findings showed evidence of dystrophic change, such as increased central nucleation, endomysial connective tissue, fiber splitting and variability of fiber diameter, and some fibers undergoing necrosis and regeneration.

Dystrophin and sarcoglycan immunohistochemical staining

Frozen sections (8 µm) were placed on Superfrost Plus slides (Dako, Kyoto, Japan) and allowed to air-dry for 2 hours. Dystrophin immunocytochemistry was performed using mouse monoclonal antihuman sarcoglycan antibodies: α, 1:200; β, 1:200; γ, 1:100; δ, 1:50 (Novocastra). We also used mouse monoclonal antibodies (Novocastra; merosin, 1:100; emerin, 1:40; dystroglycan, 1:20) to identify merosin, emerin, and dystroglycans.

Dystrophin immunostaining occurred in a normal pattern in these two patients. γ-Sarcoglycan immunostaining showed total absence of γ-sarcoglycan; α-, β-, and δ-sarcoglycans, and emerin, merosin, and β-dystroglycan all showed normal expression (Figure).

Discussion

Sarcoglycans α, β, γ, and δ are transmembrane, dystrophin-associated glycoproteins expressed in skeletal and cardiac muscle [9]. The primary sarcoglycanopathies have been estimated to account for about 5% of muscular dystrophy in patients with normal dystrophin findings [10]. LGMD 2C has been shown to be associated with mutations in the gene encoding the dystrophin-associated protein γ-sarcoglycan [10, 11]. Sarcoglycans act as a complex, so that a defect in one component usually results in secondary deficiencies in the other three [4, 9]. Sewry et al concluded that none of the patients in their series had a defect in only one component of the sarcoglycan complex [9]. Molecular analysis confirmed that a total absence of one sarcoglycan is usually associated with reduced expression of other sarcoglycans [9]. Our patients had a total absence of γ-sarcoglycan with a normal pattern of α-, β-, and δ-sarcoglycan staining, indicating primary γ-sarcoglycan deficiency. This condition is markedly different from that of the patients in Sewry et al’s study, who had deficiencies in other sarcoglycans.

Most patients with γ-sarcoglycan deficiency muscular dystrophy have severe Duchenne-like phenotype and develop symptoms in childhood [8, 12]. In general, the first clinical

![Figure](https://example.com/figure.png)
manifestations appear between the ages of 3 and 12 years [13]. Muscle weakness is symmetric, predominantly affecting the girdle muscles, and there is consistent and early hypertrophy of the calves. In most cases, inability to walk occurs between 10 and 20 years. Laboratory examinations usually show a high CPK value, and normal dystrophin pattern in muscle biopsy specimens. Our patients had their initial complaints of muscle weakness at the age of 25 and 32, respectively. The late onset of muscle weakness in our patients with \( \gamma \)-sarcoglycan deficiency was different from previously reported cases of SCARMD [7–13]. Patient 2 developed dyspnea at 41 years of age, with a low CPK value, a characteristic indicative of the end-stage of muscular dystrophy.

McNally et al studied four families with Brazilian muscular dystrophy for mutations in the \( \gamma \)-sarcoglycan gene, and found that three affected siblings in one family had a milder clinical course, two were more than 20 years old, and one was 14 years old [11]. In these late-onset patients, a complete absence of \( \gamma \)-sarcoglycan in muscle was found, with a variable pattern for the other three sarcoglycans. In the Dutch family reported by Kooi et al, all five patients with LGMD had an onset of symptoms in childhood with slow progression and preserved ability to walk until about 40 years of age [14]. One explanation for the milder phenotype might be the higher amount of remaining sarcoglycans [15]. Alternatively, modifier genes might be present [11].

In this report, we have described two patients with a mild form of \( \gamma \)-sarcoglycan deficiency with adult onset. Our findings suggest that the higher amount of remaining sarcoglycans in these patients, or other genes, may modify the severity of the clinical course of SCARMD.

ACKNOWLEDGMENTS: The authors are grateful to Ms. Lin-Lu Wang and Ms. Lilly Lee for their technical assistance.

References