Different Phenotypes in Dysferlinopathy

Key words: dysferlin, limb-girdle muscular dystrophy, Miyoshi myopathy

Limb-girdle muscular dystrophy (LGMD) is a heterogeneous group of disorders and consists of 9 autosomal recessive types (1–9), and 5 autosomal dominant types (10, 11).

Recently two different clinical forms of muscular dystrophy, LGMD2B and Miyoshi myopathy have been shown to have a dysferlin defect (12–14), which is a protein of approximately 230 kDa, and is located in the muscle plasma membrane. The clinical features of LGMD 2B are characterized by difficulty with running and climbing stairs at the onset of this disorder because of early involvement of the posterior muscle compartment of the thighs and legs, and the shoulder and upper limb muscles become involved later. Miyoshi myopathy was first described by Miyoshi et al (15) in Japanese families in 1986. Miyoshi myopathy is an autosomal recessive distal muscular dystrophy characterized by difficulty with standing on the toes due to weakness of the soleus and gastrocnemius muscles in the posterior compartment of the legs initially and characterized by very high serum CK. In the early phase if you take the skeletal muscle CT scan, the paraspinal muscles are also involved which may explain the high serum CK up to 5,000 IU/l in many cases. Though the above 2 disorders are quite different in clinical phenotypes, they are found to lack dysferlin, and the term dysferlinopathy was made.

Ueyama et al (16) studied 74 dysferlinopathy patients with known dysferlin gene mutations and divided them into four subtypes according to the initial distribution of muscle involvement; 1) limb-girdle muscular dystrophy 2B (56.8%), 2) Miyoshi myopathy (32.4%), 3) distal anterior compartment type (6.8%), and 4) scapuloperoneal type (1.4%).

See also p 532.

However, they were not able to detect any specific genotype-phenotype correlation. They concluded that there may be an unknown factor other than the dysferlin gene causing clinical heterogeneity in dysferlinopathy. Other investigators subdivide dysferlinopathy into 3 groups: LGMD 2B, Miyoshi myopathy, and hyper-CKemia. At present, the different clinical presentations in dysferlinopathy cannot be explained. Dysferlin is located in the muscle plasma membrane; dysferlin is likely necessary to maintain the structural integrity of the muscle fiber plasma membrane, and lack of dysferlin may cause plasma membrane injury as an early event which eventually causes

muscle damage (17). The problem remaining to be solved is that the lack of dysferlin causes proximal muscle weakness in some cases, while it causes distal muscle weakness in others.

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