Dysferlinopathy and Very-Long-Chain Acyl Coenzyme A Dehydrogenase Deficiency Segregating in the Same Family

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Limb girdle muscular dystrophy is the collective name for a diverse group of disorders characterized by progressive weakness of the shoulder and pelvic girdle. It is caused by mutations in multiple genes encoding proteins involved in all aspects of muscle cell biology. To date, 21 cases of LGMD, classified by mode of inheritance, have been identified.

Very-long-chain acyl coenzyme A dehydrogenase deficiency is a disorder of fatty acid oxidation and ketogenesis. It is one of eight inherited defects within the mitochondrial beta-oxidation pathway. When fatty acid oxidation is impaired, fatty acid-dependent organs such as cardiac and skeletal muscle, liver and brain undergo decompensation. Milder variants of the disease may manifest as chronic weakness, pain or recurrent rhabdomyolysis in adolescence or early adulthood.

In the present report we describe a patient with a family history and manifestations compatible with VLCAD deficiency who was, however, ultimately diagnosed with limb girdle muscular dystrophy type 2B (LGMD2B). These findings emphasize the clinical and genetic distinction between these two disorders and the importance of the correct diagnosis.

PATIENT DESCRIPTION

An 18 year old man presented with persistent exercise-induced muscle cramps of 6 months duration. He reported no change in the color of his urine. The patient was the third of four children born to consanguineous parents (first-degree cousins) of Jewish Iraqi origin. His early development was entirely normal. Family history revealed that three siblings who were first cousins to the patient and whose parents were also blood related had had similar complaints of paroxysmal exercise intolerance and were diagnosed with VLCAD deficiency. They were found to be homozygous for a novel mutation, G637A, in which alanine 173 is replaced by threonine [1,2]. The family pedigree is shown in the Figure.

Physical and neurological examination on admission revealed no abnormalities. Laboratory tests showed a creatine phosphokinase level of 30,000 IU/L. Given
the family history of consanguinity and VLCAD deficiency, we tested for blood level of acylcarnitine, which participates in the oxidation of very-long-chain fatty acids. Surprisingly, the result was within normal range. Genetic testing for the specific VLCAD mutation found in the cousins was negative. These findings prompted a muscle biopsy study which disclosed an inflammatory and degenerative process. On immunohistochemical investigation, staining was negative for dysferlin and normal for dystrophin, merosin, and sarcoglycan alpha and gamma. On Western blot analysis, complete absence of the dysferlin signal was noted. These results were consistent with dysferlin-deficient muscular dystrophy. Molecular genetic testing was performed for the most common mutation in Jewish patients with dysferlinopathy originating from Libya [3] and the Caucasus region [4]. The results were negative.

On follow-up 3 years later, the patient had difficulty walking, climbing stairs and standing on his toes. When he stood with his knees slightly bent, we observed the “diamond on quadriceps” sign.

**COMMENT**

Dysferlin is a 237 kDa protein expressed predominantly in skeletal muscle fibers. It includes C2 domains thought to be important for calcium-mediated membrane fusion and membrane repair of skeletal muscle fibers. Mutations in the dysferlin gene on chromosome 2p13 cause four distinct phenotypes of muscular dystrophy. Characterized by a lack of VLCAD, an enzyme responsible for breaking down medium chain triglycerides is recommended. In the present case, the initial manifestations were muscle cramps and elevation of muscle CK. On repeated evaluation of the case history, we found that the patient’s cousins – who had a known VLCAD deficiency – also presented with exercise intolerance and paroxysmal myoglobinuria, with CK levels up to 100,000 IU/L. However, in contrast to the cousins in whom the CK levels normalized after 3 weeks (once they were started on a low fat diet supplemented with carnitine), in our patient the CK levels remained persistently high. This finding, together with the patient’s muscle biopsy results, negative laboratory results for acylcarnitine, and negative genetic tests for the specific mutation found in the cousins, suggested a different diagnosis and prompted further immunohistochemical evaluation. We assume that the patient has LGMD2B, which might be associated with a Jewish Iraqi founder mutation.

It is of interest that two diseases of different etiologies and a distinct chromosome linkage appeared in a single double-consanguineous family. The prevalence of a mutation in the DYSF gene among Jews from Libya and the Caucasus region is probably high [4]. Likewise, VLCAD deficiency is relatively frequent in Jews of Iraqi origin. Given that the two myopa-

| CK | creatine kinase |
thies are caused by mutations in different genes located on different chromosomes, we believe their occurrence in the same family of Iraqi origin was coincidental. This report highlights the importance of careful family history taking and proper laboratory and genetic testing in preventing erroneous diagnostic assumptions. Establishing an unequivocal diagnosis in patients with suspected genetic myopathy is essential to ensure successful therapy.

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References

Capsule

Antibiotic resistance is escalating, driven mostly by human activities, but whether low amounts of antibiotic pollution also contribute to antibiotic resistance is unclear. For several well-defined mutants of Escherichia coli and Salmonella enterica, Gullberg and co-researchers tested how little antibiotic is needed to enrich for resistant bacteria. Using tetracycline, fluoroquinolone and aminoglycoside antibiotics in competition experiments between susceptible and resistant bacteria, they found selection for resistance occurring at picogram to nanogram concentrations. They specify this threshold as the minimal selective concentration, which is the concentration at which the fitness cost of resistance is balanced by the selective advantage of the mutation. Twenty susceptible lineages of S. typhimurium grown in the presence of low concentrations of streptomycin contained subpopulations tolerating eightfold greater concentrations of streptomycin by 400 generations. Thus, the surprisingly high frequencies of antibiotic-resistant bacteria found in animals from relatively pristine environments may be explained by this low concentration enrichment effect.

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Capsule

Synthetic biology aims to systematically design and construct novel biological systems that address energy, environment, and health issues. Saeidi et al. describe the development of a synthetic genetic system, which comprises quorum sensing, killing, and lysing devices, enabling Escherichia coli to sense and kill a pathogenic Pseudomonas aeruginosa strain through the production and release of pyocin. The sensing, killing, and lysing devices were characterized to elucidate their detection, antimicrobial and pyocin release functionalities, which subsequently aided in the construction of the final system and the verification of its designed behavior. The authors demonstrated that this engineered E. coli sensed and killed planktonic P. aeruginosa, evidenced by 99% reduction in the viable cells. Moreover, they showed that the engineered E. coli inhibited the formation of P. aeruginosa biofilm by close to 90%, leading to much sparser and thinner biofilm matrices. These results suggest that E. coli carrying our synthetic genetic system may provide a novel synthetic biology-driven antimicrobial strategy that could potentially be applied to fighting P. aeruginosa and other infectious pathogens.

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“it’s always the right time to do the right thing”
Martin Luther King Jr (1929-1968), American clergyman, activist and prominent leader in the African-American Civil Rights Movement. Using non-violent methods and following the teachings of Mahatma Gandhi, King is considered a heroic leader in the history of modern American liberalism

“It is curious that physical courage should be so common in the world and moral courage so rare”
Mark Twain (1835-1910), American author and humorist