

MYOTONIA CONGENITA AND MYOADENYLATE DEAMINASE DEFICIENCY

Case report

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ABSTRACT - Approximately 1-2% of the population has a deficiency of the enzyme myoadenylate deaminase. Early reports suggested that patients with myoadenylate deaminase deficiency had various forms of myalgia, and exercise intolerance. However, a deficiency of the enzyme has been described in many conditions, including myopathies, neuropathies, and motor neuron disease. We report a patient with clinical diagnosis of myotonia congenita and absent myoadenylate deaminase reaction on the muscle biopsy. This is the first description of myoadenylate deaminase deficiency with myotonia congenita. Myoadenylate deaminase deficiency is the most common enzymatic deficit of muscle, and the association with other neuromuscular diseases is coincidental.

KEY WORDS: myotonia congenita, myoadenylate deaminase, muscle biopsy.

Miotonia congênita e deficiência de mioadenilato deaminase: relato de caso

RESUMO - Aproximadamente 1-2% da população apresenta deficiência de mioadenilato deaminase (MAD). Estudos iniciais sugeriam que pacientes com deficiência de MAD apresentavam várias formas de mialgias e intolerância ao exercício. Contudo, a deficiência de MAD já foi descrita em várias situações, incluindo miopatias, neuropatias e doenças do neurônio motor. Relatamos um paciente com o diagnóstico clínico de miotonia congênita e deficiência de MAD na biópsia muscular. Essa é a primeira descrição de deficiência de MAD associada a miotonia congênita. A deficiência de MAD é o déficit enzimático mais comum nos músculos esqueléticos e sua associação com diversas doenças neuromusculares é apenas coincidência.

PALAVRAS-CHAVE: miotonia congênita, mioadenilato deaminase, biópsia muscular.

Approximately 1-2% of the population has a deficiency of the enzyme myoadenylate deaminase (MAD)¹. This condition is inherited as an autosomal recessive trait. Early reports suggested that patients with MAD deficiency had a syndrome of myalgia, and exercise intolerance². However, deficiency of the MAD has been described in many conditions, including myopathies, neuropathies, and motor neuron disease³. We report a patient with clinical diagnosis of myotonia congenita and absent myoadenylate deaminase reaction on the muscle biopsy.

CASE

A 12-year-old boy presented since the age of 4 years episodes of myotonia, mild muscular weakness, and learn-

ing disability. He had normal achievement of motor milestones. His parents were healthy, and unrelated. His younger sister has diagnosed myotonia congenita, and atypical Rett syndrome. General physical examination was normal. On neurological examination, he presented normal cranial nerves, normal muscle bulk and tonus, muscular strength grade IV+ (Medical Research Council), symmetrical +/IV deep tendon reflexes, myotonia on hands, brachial biceps and deltoids (triggered by percussion), and difficulty in starting gait due to myotonia. Coordination, and sensation were normal. Complete blood count, serum muscle enzymes, and lactic acid were normal. Needle electromyography showed myopathic features and myotonic discharges in all tested muscles. The muscle biopsy disclosed decreased type 2B fibers, and absent histochemical reaction for myoadenylate deaminase (Figure). Phenytoin was started with moderate symptom improvement.

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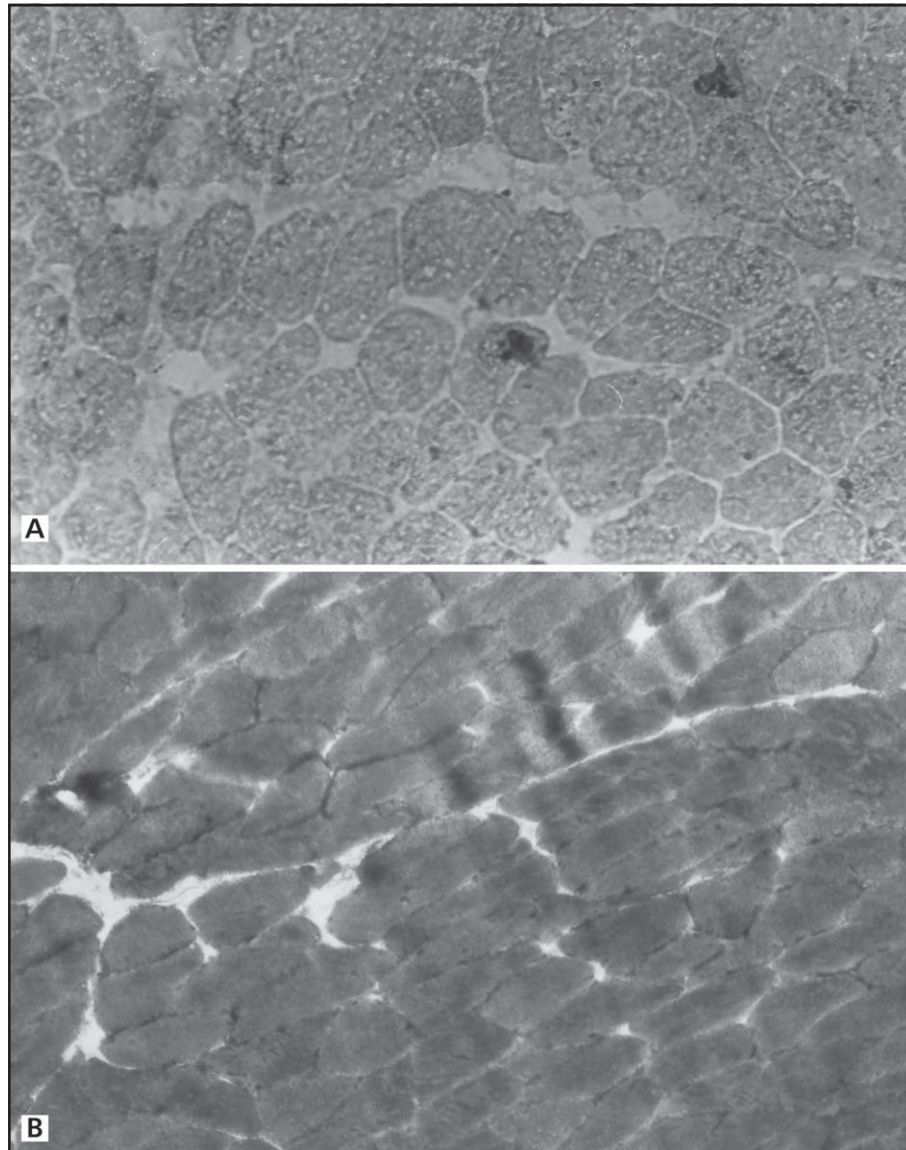


Fig. (A) Muscle biopsy showing absence of reaction for myoadenylate deaminase x174 (MAD). (B) Muscle biopsy showing normal reaction for MAD x174.

DISCUSSION

In 1978, Fishbein et al. described MAD deficiency in skeletal muscle of 5 patients with exercise-related muscle cramps, and myalgias². In skeletal muscle MAD catalyzes the deamination of adenosine monophosphate (AMP) to inosine monophosphate (IMP) and ammonia. One proposed role of MAD is to prevent a large increase in AMP, thereby attenuating accumulation of adenosine diphosphate (ADP) and inhibitory influence of low ATP/ADP ratio on muscle function. In accordance with the proposed function of MAD, the absence of the enzyme would be expected to be associated with exercise intolerance¹. MAD deficiency is generally caused by a homozygous point mutation, a C → T transition at nucleotide 34 in the second exon of the MAD gene in the chromosome 1,

which results in a premature termination codon in exon 2, and thus in a severely truncated enzyme⁴.

The classical clinical findings associated with MAD deficiency correspond to those of a metabolic myopathy with exercise-related symptoms such as early fatigue, muscle pain, and muscle cramps. In typical cases, the symptoms are either induced or aggravated by exercise. However, there is a wide variation in the severity of symptoms and age at onset, and asymptomatic cases have been described⁵.

MAD deficiency is the most common among known enzymatic deficits of muscle, and may occur in association with other neuromuscular diseases. Absence of MAD occurs in approximately 2% of muscle biopsy submitted to pathologic examination for

suspected neuromuscular disease⁶. MAD deficiency have been described in muscle biopsy of patients with polyneuropathy, infantile spinal muscular atrophy, congenita myopathy with type-2 fiber atrophy, facioscapulohumeral myopathy, polymyositis, dermatomyositis, myotonic dystrophy, limb-girdle muscular dystrophy, dystrophinopathies, systemic sclerosis, McArdle's disease, phosphofructokinase deficiency, and hyperornithinaemia with gyrate atrophy of the retina^{3,7-9}.

MAD deficiency associated with other neuromuscular disorders was previously thought to be the result of a limitation in MAD transcript availability, secondary to the pathological abnormalities in a variety of neuromuscular or rheumatological disorders. Verzijl et al.⁷ found that isolated MAD deficiency and MAD deficiency associated with other neuromuscular disorders had the same underlying molecular DNA defect. In the latter cases, MAD deficiency is merely a chance association, due, a concurrence of the frequently occurring mutant MAD allele with another neuromuscular disorder.

Currently, considering the high frequency of the mutant allele in the general population, even the association of MAD deficiency with exercise intolerance is controversial and could be coincidental. Norman's study demonstrated that the prevalence of MAD deficiency in the healthy population was 2%¹. Moreover, healthy individuals with MAD deficiency had normal exercise tolerance.

Our patient has clinical and histopathological features of myotonia congenita. Patients with myotonia congenita present myotonias, which usually occur when initiating a rapid motion, such as starting to run. The myotonia often decreases as the motion is continued. Myotonia congenita occurs in two forms: autosomal dominant (Thomsen's disease) and autosomal recessive (Becker's disease)¹⁰. Clinical classification as either Thomsen's or Becker's disease is entirely based on inheritance patterns, but transient weakness is more common in Becker's myotonia. Both disorders are chloride channelopathies, and many mutations in the chloride channel gene (CLCN1) have been described in Thomsen's disease^{11,12}.

Analyzing the molecular basis of the three diseases, there are no clear-cut similarities among them that clearly justify their occurrence in our patient and his family. Myoadenylate deaminase deficiency is the most common metabolic disorder of skeletal muscle in the Caucasian population, affecting approximately 2% of all individuals has been attributed to a single mutant allele characterized by double C to T tran-

sitions at nucleotides +34 and +143 in mRNA encoded by the AMPD1 gene¹³. Mutations in the muscle chloride channel gene CLCN1, cause myotonia congenita, an inherited disorder of skeletal muscle excitability leading to a delayed relaxation after muscle contraction¹². In some 80% of girls with Rett Syndrome, there are mutations in the methyl-CpG-binding protein-2 (MECP2) gene on Xq28¹⁴.

Determining the mode of inheritance is not easy and requires the carefully investigation of family members because dominant mutations show variable penetrance and may present with very mild symptoms¹⁰⁻¹³.

This is the first description of MAD deficiency with myotonia congenita. Since this enzyme defect is very common, patients with other neuromuscular disorders can present a coincidental MAD deficiency. The clinical significance of MAD deficiency associated with other neuromuscular disorders remains unknown. Whether patients with neuromuscular disorders and MAD deficiency have different clinical features or course from those without MAD deficiency was not evaluated. However, the similar frequencies of MAD deficiency in patients with exercise intolerance, in patients with other neuromuscular complaints, and in healthy volunteers suggest that MAD deficiency cannot be considered a disease in itself.

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