Adenosine monophosphate deaminase deficiency

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Abstract
There are two types of adenosine monophosphate deaminase deficiency. Myoadenylate deaminase deficiency is an inherited disorder of muscular energy metabolism with lack of AMP (adenosine monophosphate) deaminase activity in skeletal muscle. Lack of activity of the erythrocyte isoform of AMP deaminase has been described in subjects with low plasma uric acid levels without obvious clinical relevance. Therefore, this chapter focusses only on myoadenylate deaminase deficiency. About 1% of the Caucasian population carries the genetic defect causing myoadenylate deaminase deficiency, but only a minority develops symptoms. The typical symptoms are exercised-induced muscle pain, cramps and/or early fatigue. The vast majority of patients with this disease is homozygous for the C34-T *mutation in the AMPD1 gene. The symptoms can be ameliorated by intake of D-ribose. However, this sugar only works while it is taken, and has no beneficial effect on subsequent days.*

Keywords
AMP deaminase, myoadenylate, myopathy, ammonia.

Disease name and synonyms

Adenosine monophosphate deaminase deficiency
Adenylate deaminase deficiency
AMP deaminase deficiency
Myoadenylate deaminase deficiency
MAD deficiency (MAD: myoadenylate deaminase)

AMP deaminase

AMP deaminase catalyzes the deamination of adenosine monophosphate (AMP) into inosine monophosphate (IMP). Together with adenylosuccinate synthetase and adenylosuccinate lyase, it forms the purine nucleotide cycle which produces fumarate, an intermediate of the Krebs cycle, and therefore yields energy. Several AMP deaminase isozymes have been identified [4], which are encoded by different genes [1, 6, 9, 11].

AMP deaminase deficiency

AMP deaminase deficiency was initially identified by Fishbein and co-workers [3]. Since then,

more than 200 patients with the disorder have been reported. The deficiency disrupts the purine nucleotide cycle [14], and thus muscle energy production. Surprisingly however, asymptomatic AMP deaminase-deficient subjects are found.

Diagnosis criteria - definition
There are no specific diagnostic criteria, and no clinical or biochemical definition for this disorder [5]. AMP deaminase deficiency should be considered as a possible explanation in all patients with exercise-related muscular symptoms of any kind, specifically rapid fatigue, pain and/or cramps. The diagnosis is based on the biochemical detection of a deficient activity of adenylate deaminase in a muscle biopsy, or on the genetic detection of the disease-causing mutation.

Differential diagnosis
All kinds of metabolic myopathies have to be excluded in the differential diagnosis of myoadenylate deaminase deficiency.

Prevalence
About 2-3 % of all diagnostic muscle biopsies in Caucasian patients show myoadenylate deaminase deficiency [2, 5]. Genetic studies in Caucasian populations have shown that about 1% of the population is homozygous for the disease-causing mutation [10].

Clinical description
Men and women are equally affected. The vast majority of patients suffer from post-exercise symptoms: rapid fatigue, cramps or myalgias. About equal proportions of the patients first develop symptoms as children, as teenagers, as young, or as older adults. After progression of the symptoms over the first few years, there is usually no further worsening. There is no evidence of muscular dystrophy or muscular wasting. The disorder exclusively affects skeletal muscle. Smooth muscle or other organs are not affected since the disorder is a specific lack of the skeletal muscular type of adenylate deaminase activity.

Management
Unfortunately, there is no medical cure for this disorder. The only possibility to treat patients is the administration of D-ribose [7, 17]. This pentose is easily absorbed in the gut and rapidly cleared by metabolic pathways. It presumably serves as an additional source of energy for muscle, and is only efficient as long as it is present in blood. Due to its short half-life, it has to be taken constantly to be beneficial. Per hour, about 0.1 - 0.15 mg/kg body weight has to be taken. A lower dose is usually without effect, a higher dose causes diarrhoea.
These limitations are major disadvantages of this treatment. Therefore, it is usually only reasonable to take ribose during the time of increased workloads. In addition, ribose is not approved by any organisation for the treatment of patients. It has to be bought from the chemical industry.

Etiology
The genetic basis of myoadenylate deaminase deficiency is a nonsense mutation in the AMPD1 gene (*C34T*) [10]. The vast majority of patients is homozygous for this mutation. In addition, there seem to be secondary types of myoadenylate deaminase deficiency: in various inflammatory or degenerative muscular disorders, reduced activity of the enzyme is found [2, 13]. Most likely, the majority of the patients with this secondary type of myoadenylate deaminase deficiency are heterozygous for the *C34T* mutation.

Diagnostic methods
In patients with exercise-induced muscular symptoms the ischemic forearm test can be used to screen for myoadenylate deaminase deficiency. This test has been described in detail [15, 16]. In summary, blood flow to the forearm arm is interrupted by a cuff. When exercising under this condition, skeletal muscle does not produce ammonia in patients with myoadenylate deaminase deficiency, whereas large amounts of ammonia are produced by healthy muscle.
The diagnosis is based on histochemical staining or biochemical analysis of a muscle biopsy showing lack of adenylate deaminase activity [2,3].
Since the vast majority of patients is homozygous for the *C34T* mutation in the AMPD1 gene, genetic techniques can be used to diagnose these patients as well.

Unresolved questions
So far, there is no answer to the question why the vast majority of *C34T* homozygous patients do not develop clinical symptoms. Presumably, there are alternative pathways for energy production in asymptomatic homozygous patients but this has not yet been clarified. In addition the therapy of symptomatic patients with D-ribose has major disadvantages as described before. There is need for better understanding of how ribose works in order to develop better therapeutic alternatives. The observation that *C34T* heterozygocity could improve clinical outcome in heart failure [8], possibly via an

increase in cardiac adenosine production, also deserves further study.

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