

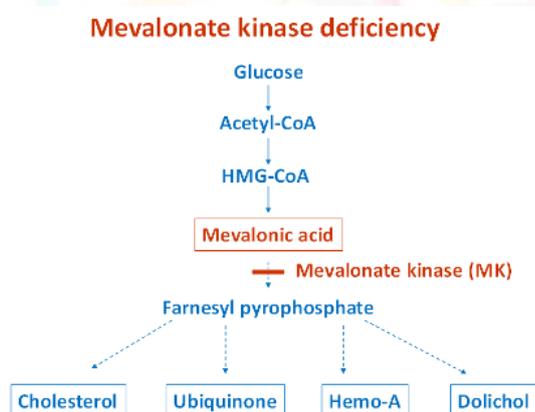
MEVALONIC ACIDURIA

WHAT IS MEVALONIC ACIDURIA?

Mevalonic aciduria is **an inborn error in one of the first steps of cholesterol metabolism**, caused by deficiency of the enzyme mevalonate kinase.

Because of this defect, mevalonic acid accumulates in body tissues and fluids.

WHAT IS THE MEVALONATE KINASE (MK)?



Mevalonate kinase is the enzyme which converts mevalonic acid into phosphomevalonic acid.

Mevalonic acid is the **precursor** of various **compounds** which have great **biological importance** such as cholesterol, ubiquinone, heme A and dolichol.

Cholesterol modulates cell membrane fluidity, is involved in embryonic development and is a precursor of steroid hormones.

Ubiquinone is a powerful antioxidant and, together with **heme A**, is a vital component of the mitochondrial respiratory chain.

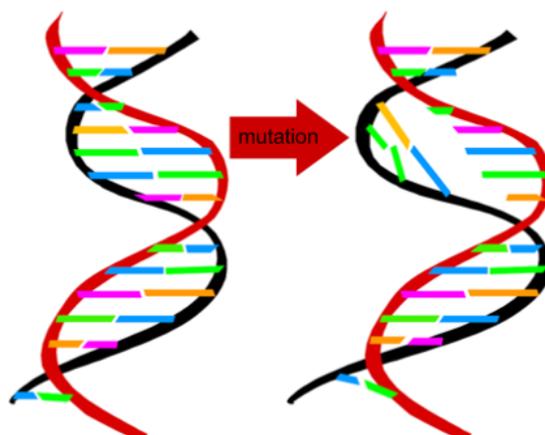
Dolichol is involved in the synthesis of glycosylated proteins.

WHAT CAUSES A DEFECT IN THE ENZYME MEVALONATE KINASE?

When a mutation (stable, inherited change) occurs in the gene which encodes mevalonate kinase, it can

cause alterations in the enzyme's structure or concentration which may alter its function. Not all MK gene mutations have the same effect on the enzyme leading to a **broad spectrum of clinical forms** of mevalonic aciduria.

Mevalonic aciduria is inherited as an autosomal recessive genetic disorder.



WHAT ARE THE CONSEQUENCES OF A DEFECT IN MK ACTIVITY?

If MK activity is deficient, toxic levels of mevalonic acid will accumulate within body tissues and fluids. The synthesis of cholesterol, ubiquinone, dolichol and heme A, will also be affected. This can cause serious consequences due to the biological importance of these compounds. These changes can cause clinical manifestations of varying severity.

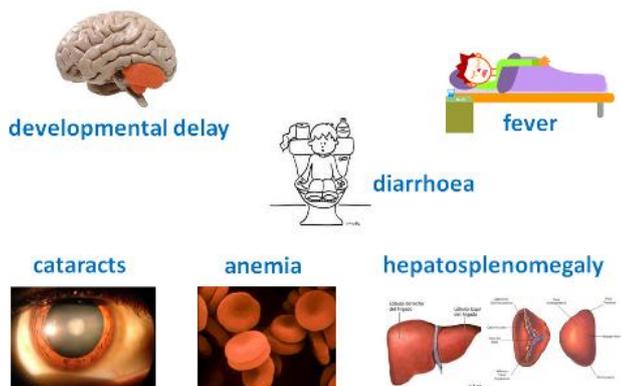
WHAT ARE THE CLINICAL MANIFESTATIONS OF MK DEFICIENCY?

In severe forms of mevalonic aciduria, clinical manifestations begin in infancy with **severe and progressive multi-systemic symptoms** which exhibit considerable heterogeneity.

The most seriously affected patients, who generally present symptoms at an early age, show **severe developmental delay, dysmorphic features, cataracts, hepatosplenomegaly, lymphadenopathy and anemia**, as well as **diarrhea and malabsorption**.

Patients with **milder forms** show delayed psychomotor development, hypotonia, muscle weakness and ataxia.

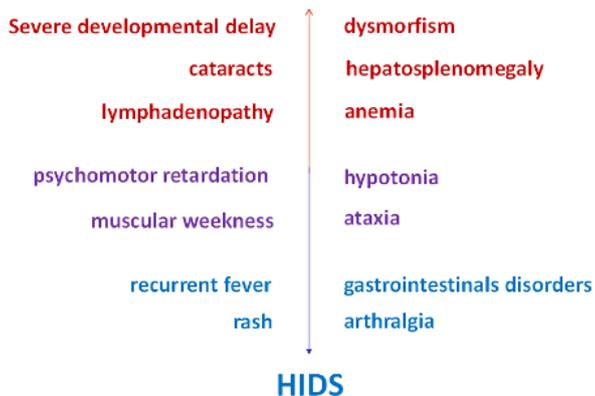
Clinical features of mevalonic aciduria



Many patients exhibit **recurrent attacks of fever**, lymphadenopathy, hepatosplenomegaly, arthralgia, edema and skin rash.

Others patients present with failure to thrive, susceptibility to infections, hepatosplenomegaly, cataracts and psychomotor retardation. The dysmorphic features exhibited can include dolichocephaly, microcephaly, triangular face, sloping forehead, anteverted nostrils, low-set and rotated ears, and slanted eyes with long eyelashes.

Mevalonate kinase deficiency



One mild form of mevalonic aciduria is associated **hyperimmunoglobulinemia D and periodic fever syndrome (HIDS)**. This condition is characterized by recurrent episodes of fever associated with lymphadenopathy, arthralgia, gastrointestinal disorders and skin rash.

The level of mevalonic acid excretion is much lower than in classic mevalonic aciduria and occurs only during episodes of fever.

The relationship between MK deficiency and inflammatory periodic fever is not clearly understood. However, elevation in body temperature inhibits MK activity which adversely affects the synthesis of cholesterol and other derivatives causing inflammation and fever.

The clinical presentations of MK deficiency encompass a continuous **phenotypic spectrum** from the most severe form, **classic mevalonic aciduria**, to the milder **HIDS** rather than constituting two distinct clinical entities.

HOW IS MEVALONIC ACIDURIA DIAGNOSED?

In classic mevalonic aciduria, very high concentrations of **mevalonic acid** are detected in the body fluids of all patients, as demonstrated by the study of organic acids.

The concentration of mevalonic acid excreted in urine correlates with the severity of the clinical presentation.

Deficiency in mevalonate kinase activity is demonstrated using the patient's fibroblasts and lymphocytes. There appears to be no correlation between residual MK enzyme activity, which is almost undetectable, and the level of excretion of mevalonic acid or the clinical severity.

Serum IgD values vary depending on clinical symptoms.

Diagnosis of mevalonic aciduria



Clinical suspicion?

Biochemical study



Anemia?
↑ IgD



↑ mevalonate



↓ MK

Genetic study



MK Mutations

In general, patients with severe mevalonic aciduria present the full array of neurologic symptoms plus acute relapsing fever, and exhibit elevated IgD which increases during crises.

Identification of **MK gene mutations** enables genetic counseling and prenatal diagnosis.

CAN MEVALONIC ACIDURIA BE TREATED?

Treatment of mevalonic aciduria has traditionally been based on **avoiding deficiency of the metabolic products of MK activity** (cholesterol and its derivatives) and **preventing accumulation of an excessive concentration of mevalonic acid**. However, a variety of therapies have proved unsuccessful.

Oral supplementation with cholesterol aggravated the diarrhea and general malaise. Administration of a combination of **cholesterol, ursodesoxycholic acid, ubiquinone-10 and vitamin E**, was without obvious clinical results.

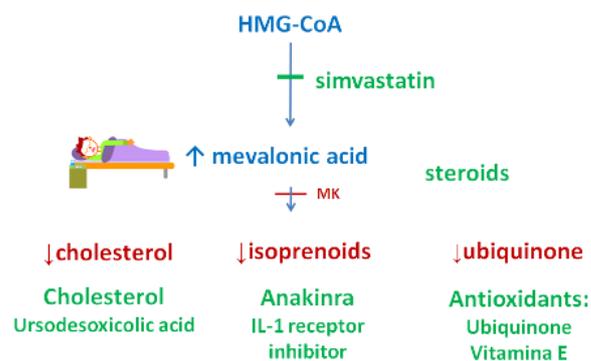
Attempts have been made to prevent the formation of excessive amounts of mevalonic acid by blocking its synthesis with **inhibitors of the enzyme 3-hydroxymethylglutaryl-CoA reductase**, such as **statins**, but the treatment triggered severe descompensaciones with episodes of high fever and increased creatine kinase, and had to be abandoned.

However, the use of **steroids** during severe attacks clearly improved symptoms and also appear to improve psychomotor development in some patients.

Recently, it has been described that some **isoprenoid compounds**, such as farnesyl pyrophosphate, can reverse cellular inflammation. The positive clinical response observed in some patients to **anakinra**, and other interleukin receptor antagonist (IL-1) suggests that blocking IL-1 is the most effective treatment option for many patients with mevalonic aciduria. Anakinra prevents the fever attacks caused by vaccines, without inhibiting the induction of antibodies and without significant side effects. Treatment with anakinra reduces the duration and severity of fever attacks in HIDS crises.

Moreover, some patients with the severe form of mevalonic aciduria have successfully been treated by **bone marrow transplantation**.

Treatment of mevalonic aciduria



Mevalonic aciduria may have severe consequences for patients. The early diagnosis and treatment, and good control of nutritional status can help these patients.

Translation

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