Hyperimmunoglobulinemia D (hyperIgD) and periodic fever

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Abstract

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Abstract

The syndrome associating fever and hyperimmunoglobulinemia D (hyperIgD) is characterized by periodic febrile attacks occurring every 4-8 weeks with an intense inflammatory reaction accompanied by lymphadenopathies, abdominal pain, diarrhea, joint pain, hepatosplenomegaly and cutaneous signs. The first attack usually takes place during infancy. It is difficult to treat. Unlike familial Mediterranean fever, colchicine has no preventive effect against febrile episodes. Mutations in the gene encoding the enzyme mevalonate kinase (MVK) are responsible for this syndrome. The gene is located at chromosome 12q24 and is subjected to autosomal recessive inheritance. MVK deficit is known and causes the developmental disease called mevalonic aciduria. The diagnosis is based on a group of clinical signs associated with an elevated serum concentration of IgD (albeit inconstant and poorly specific), it can currently be confirmed by pathologic low activity of mevalonate kinase. Simvastatin treatment and TNF inhibitors have been recently tested with some success, for inflammatory attacks of the hyperimmunoglobulinemia D and periodic fever syndrome.

Key-words
Periodic fever, inflammatory reaction, mevalonate kinase (MVK) gene, lymphadenopathies, joint pain, diarrhea, onset in the infancy

Name of the disease and its synonyms

Hyperimmunoglobulinemia D and periodic fever
Fever and hyperIgD syndrome
Hyper IgD syndrome (HIDS)
Dutch-type periodic fever

Excluded diseases
Familial Mediterranean fever
Recurrent autosomal dominant fever

Grateau G. Hyperimmunoglobulinemia D (hyperIgD) and periodic fever. Orphanet encyclopedia, February 2005.
http://www.orpha.net/data/patho/GB/uk-hyperIgD.pdf
**Definition/Diagnostic criteria**
The diagnosis is based on a group of clinical signs associated with a biochemical marker: elevated serum concentration of IgD. This elevation is due to mevalonate kinase (MV) deficiency, MV is a key enzyme involved in cholesterol and nonsterol isoprene biosynthesis.

**Differential diagnosis**
It includes a wide range of diseases that can be considered depending on the predominant clinical symptoms observed.

**Incidence**
It is unknown.

**Clinical description**
The hyperIgD and periodic fever syndrome is characterized by febrile attacks every 4–8 weeks associated with an intense inflammatory reaction, accompanied by adenopathies, abdominal pain, diarrhea, joint pain, hepatosplenomegaly and cutaneous signs. The first attack usually occurs during infancy.

**Management and treatments**
This disease is difficult to treat. Unlike familial Mediterranean fever, colchicine does not prevent attacks. To control the symptoms of fever and pain many patients benefit from the use of non-specific drugs like paracetamol. In limited clinical trial, to test the hypothesis that inhibition of HMG-CoA reductase would ameliorate the inflammatory attacks, simvastatin has been tested with some success in patients with hyper-IgD syndrome. TNF inhibitors seems also to be efficient against inflammatory features.

**Etiology**
Mutations in the gene coding for mevalonate kinase (MVK) are responsible for the disease. It is located at chromosome 12q24 and is subjected to autosomal recessive inheritance. Mevalonate kinase deficiency is known and gives rise in children to a developmental disease called mevalonic aciduria.

**Biological methods of diagnosis**
The diagnosis is based on clearly elevated serum IgD concentrations, > 100 U/mL or 141 mg/L, during and between attacks. Increased IgD concentration is not specific and can be observed in other inflammatory diseases: Familial Mediterranean fever, TRAPS, etc. The diagnosis can currently be confirmed by pathologic low activity of mevalonate kinase.

It can be established by the detection of elevated excretions of mevalonic acid in urine during fever episodes or by dosage of level of mevalonate kinase in lymphocytes.

**Unresolved questions and comments**
The inflammatory mechanism of this metabolic disease remains to be discovered.

**References**


