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# Increased urinary leukotriene E<sub>4</sub> during febrile attacks in the hyperimmunoglobulinaemia D and periodic fever syndrome

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## Abstract

**Background**—The hyperimmunoglobulinaemia D and periodic fever syndrome is a hereditary periodic fever, caused by deficiency of the enzyme mevalonate kinase. It is unclear how this defect leads to recurrent fever episodes.

**Aim**—To assess the involvement of cysteinyl leukotrienes in the pathogenesis of fever attacks as reflected by urinary leukotriene E<sub>4</sub> (LTE<sub>4</sub>) excretion.

**Methods**—Urinary LTE<sub>4</sub> was measured in seven patients while febrile and afebrile.

**Results**—LTE<sub>4</sub> was raised during fever in all subjects (46–199 nmol/mol creatinine, mean 92; normal <40). Urinary LTE<sub>4</sub> was normal between attacks, as well as in normal children with fever as a result of miscellaneous causes.

**Conclusion**—Our results suggest that cysteinyl leukotrienes play a role in the pathophysiology of this disorder. As no effective treatment is yet available, leukotriene receptor antagonists might offer a new therapeutic approach for patients with the hyperimmunoglobulinaemia D and periodic fever syndrome.

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Keywords: cysteinyl leukotrienes; leukotriene E<sub>4</sub>; mevalonate kinase; periodic fever; immunoglobulin D

the biosynthesis of cholesterol and other isoprenoid compounds.

Another disorder, mevalonic aciduria<sup>7</sup> (MA, MIM# 251170), has been described in which mutations in the *MVK* gene virtually abolish all enzyme activity of mevalonate kinase. This disease is characterised by failure to thrive, developmental delay, hypotonia, seizures, cerebellar ataxia, hepatosplenomegaly, anaemia, and a dysmorphic facies. Patients with MA suffer from recurrent attacks of generalised inflammation, similar to those observed in HIDS, but often more severe.<sup>8</sup>

The cysteinyl leukotrienes (LTC<sub>4</sub>, LTD<sub>4</sub>, and LTE<sub>4</sub>) are endogenous lipid molecules derived from arachidonic acid through the 5-lipoxygenase pathway.<sup>9</sup> These compounds are very potent proinflammatory mediators, acting at subnanomolar concentrations. Several cell types are capable of producing cysteinyl leukotrienes, including macrophages, eosinophils, and mast cells. Endogenous urinary LTE<sub>4</sub> excretion is a reliable index of the systemic production of cysteinyl leukotrienes in vivo.<sup>10</sup>

The pathogenesis of inflammation in both MA and HIDS remains unknown. However, in patients with mevalonic aciduria urinary excretion of LTE<sub>4</sub> was found to be highly increased,<sup>11</sup> suggesting a pathogenic role for cysteinyl leukotrienes in MA. In the present study, we tested the hypothesis that cysteinyl leukotrienes are similarly involved in HIDS.

## Patients and methods

After obtaining informed consent, urine samples were collected from seven children (aged 7–13 years), whose diagnosis of HIDS had been confirmed by demonstration of mutations in both copies of the *MVK* gene. From each case samples were obtained twice, once during a fever episode and once between attacks. Clinically, the fever could be attributed to an attack of HIDS (and not to an intercurrent infectious disease). Samples were collected in polypropylene containers and either immediately frozen and stored at –80°C (cases 1–3) or frozen at –20°C, thawed, transferred to smaller containers, and then stored at –80°C (cases 4–7) until analysis. The presence of pathological constituents was excluded. Mevalonate concentrations were determined with a stable isotope dilution assay and gas chromatography–mass spectroscopy.<sup>5</sup> Urinary LTE<sub>4</sub> was measured as described previously.<sup>10,12</sup> Briefly, <sup>3</sup>H-LTE<sub>4</sub> (Du Pont–New England Nuclear, Boston, Massachusetts) was added as an internal standard. All urine samples were then acidified to pH 4.5 by addition of 0.1 mol/l HCl. Extraction of LTE<sub>4</sub> was performed on Sep-Pak C<sub>18</sub> cartridges (Waters Associates,

Dutch type periodic fever (MIM#260920), also known as the hyperimmunoglobulinaemia D syndrome (HIDS), is an autosomal recessive disorder, characterised by febrile attacks recurring at more or less regular intervals and the presence of an increased serum IgD concentration.<sup>1</sup> Temperature typically rises abruptly, remaining continuously increased for three to six days. Febrile episodes recur every two to eight weeks from infancy. During these attacks patients often complain of malaise, chills, headache, arthralgias, nausea, vomiting, diarrhoea, and abdominal pain. The affected children often have striking cervical lymphadenopathy and may have splenomegaly, hepatomegaly, arthritis, and a variety of skin rashes.<sup>2</sup> In the patient's blood, markers of inflammation such as white cell counts, erythrocyte sedimentation rate, and serum concentrations of several proinflammatory cytokines, are raised during febrile episodes,<sup>3</sup> and the urine concentration of neopterin is acutely raised.<sup>4</sup> Mutations in the *MVK* gene, which encodes mevalonate kinase, have been identified as the underlying genetic defect.<sup>5,6</sup> These mutations lead to a substantially reduced activity of mevalonate kinase, a key enzyme in

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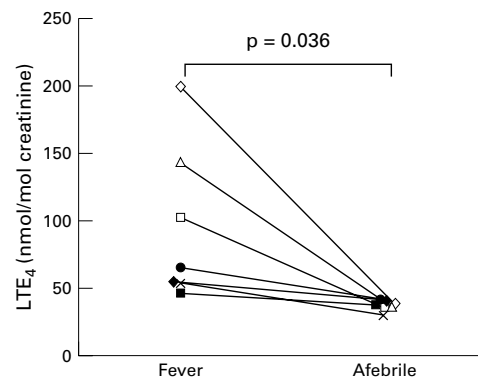


Figure 1 LTE<sub>4</sub> concentrations during and between fever episodes.

Milford, Massachusetts); separation of LTE<sub>4</sub> from other leukotrienes was carried out by reversed phase high pressure liquid chromatography. Quantification of LTE<sub>4</sub> was performed by enzyme immunoassays with specific antibodies (Cayman, Ann Arbor, Michigan). The corresponding specificity for the LTE<sub>4</sub> antibody was 100% for LTE<sub>4</sub>, 10% for LTC<sub>4</sub>, 9% for LTD<sub>4</sub>, and <0.01% for LTB<sub>4</sub>.

Statistical analysis was performed using a paired samples *t* test (SPSS 8.0).

## Results

Between fever episodes the mean urinary LTE<sub>4</sub> excretion in HIDS patients was 36 (range 30–40) nmol/mol creatinine, well within the normal limit (<40 nmol/mol creatinine). During fever episodes, urinary excretion of LTE<sub>4</sub> increased in all patients (mean 92, range 46–199 nmol/mol creatinine; fig 1). This was significantly higher than the values recorded when patients were afebrile (*p* = 0.036). As expected in HIDS, the concentrations of mevalonic acid in urine were increased during fever periods. However, there was no correlation between urinary concentration of mevalonic acid (4.2–41.5 mmol/mol creatinine; normal <0.1 mmol/mol creatinine) and that of LTE<sub>4</sub> (data not shown). In addition, urinary LTE<sub>4</sub> was found to be within normal limits (30.8 (6.5) nmol/mol creatinine) in 20 infants and children with fever caused by viral or bacterial infections as well as fever of unknown origin, recruited from outpatients and inpatients at the University Children's Hospital, Heidelberg, Germany. Urinary LTE<sub>4</sub> remained unchanged in the same group of otherwise normal children when afebrile (31.4 (6.3) nmol/mol creatinine).

## Discussion

Cysteinyl leukotrienes have a pathophysiological role as mediators of inflammation in disease states like bronchial asthma, juvenile rheumatoid arthritis, or inflammatory bowel disease.<sup>13 14</sup> In addition, LTE<sub>4</sub> excretion was found to be enhanced in the most severe form of mevalonate kinase deficiency, MA.<sup>15</sup> In this disorder and in contrast to HIDS, urinary LTE<sub>4</sub> is constantly raised, even though the highest values are found during febrile episodes.

In this study, we showed increased excretion of LTE<sub>4</sub> in seven patients with the mild form of mevalonate kinase deficiency, HIDS, during

fever, but not between attacks. The concentrations of LTE<sub>4</sub> during the attacks of cases 4–7 (open symbols in fig 1) were lower than those in the clinically equally severe cases 1–3 (closed symbols in fig 1), which in part might reflect the temporary thawing of urine samples in combination with the instability of LTE<sub>4</sub>. However, independently from the storage procedure, all urine samples from the patients with HIDS showed significantly raised LTE<sub>4</sub> concentrations during fever episodes.

Although the number of patients is small, our data point to a role of cysteinyl leukotrienes in the pathogenesis of the episodic inflammation in HIDS. While increased LTE<sub>4</sub> excretion is not specific for MA or HIDS, it is not merely a consequence of fever, as urinary LTE<sub>4</sub> is not raised in children with fever caused by viral or bacterial infections. The introduction of cysteinyl leukotriene receptor antagonists should help to elucidate the role of these mediators in HIDS. It is speculative whether such agents could reduce the severity of fever attacks in HIDS. As these have thus far been resistant to all current anti-inflammatory treatment,<sup>2</sup> a future new therapeutic approach would be most welcome.

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