Increased generation of cysteinyl leukotrienes in Kawasaki disease

E Mayatepek, W D Lehmann

Abstract

Endogenous cysteinyl leukotriene synthesis was assessed in 10 patients with Kawasaki disease and 10 healthy controls by measuring excretion of leukotriene E4 (LTE4) in urine. LTE4 was increased more than fivefold in patients with Kawasaki disease compared with controls (median (range) 55.3 (31.8-120.6) v 10.2 (7.1-14.9) nmol/mol creatinine); this suggests that cysteinyl leukotrienes are involved in the pathophysiology of Kawasaki disease. Leukotriene synthetase inhibition or receptor antagonism may therefore offer a new potential therapeutic approach in children with this disease.

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Kawasaki disease is an acute multisystem vasculitis of infancy and early childhood.1 About 25% of patients develop coronary vasculitis severe enough to cause aneurysm formation, stenosis, and thrombosis of coronary arteries.2 During the acute phase of the disease a number of immunoregulatory abnormalities have been demonstrated including pathologically endothelial cell damage.3 It has been suggested that the arachidonic acid pathway is activated in Kawasaki disease. An enhanced in vitro biosynthesis of thromboxane A2 by platelets4 and increased in vitro production of leukotriene (LT) B4, a powerful chemooattractant, by stimulated polymorphonuclear cells has been reported in patients with Kawasaki disease.4

The cysteinyl leukotrienes LTC4, LTD4, and LTE4 are potent endogenous proinflammatory 5-lipoxygenase products also derived from arachidonic acid acting at nanomolar concentrations.5 Because they induce increased vascular permeability by endothelial cell interaction, affect microvascular tone, and are released during episodes of myocardial ischaemia,6 a role of these lipid mediators in the pathophysiology of Kawasaki disease seems possible.

Tracer experiments have demonstrated that urinary LTE4 can be used as an index metabolite to assess cysteinyl leukotriene synthesis in vivo.5 In this study, we measured urinary LTE4 excretion in 10 patients with Kawasaki disease and 10 healthy children to elucidate the potential role of cysteinyl leukotrienes in the pathogenesis of Kawasaki disease.
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Previous studies have shown an increased in vitro biosynthesis of thromboxane A_2 and LTB_4 by isolated blood cells suggesting an involvement of the arachidonic acid cascade in Kawasaki disease. However, in vitro data from isolated cells must be interpreted cautiously, as characteristically cells must be incubated with labelled arachidonic acid or appropriately stimulated to synthesise eicosanoids such as thromboxane or leukotrienes.

Urinary LTE_4 excretion, however, is a reliable index metabolite to assess whole body synthesis of cysteinyl leukotrienes in vivo. The present findings therefore strongly suggest that cysteinyl leukotriene synthesis and generation is enhanced in Kawasaki disease.

It must be pointed out, however, that urinary LTE_4 is not a specific marker for Kawasaki disease. In other diseases, such as asthma, cystic fibrosis, and juvenile rheumatoid arthritis, an enhanced urinary excretion of LTE_4 has been demonstrated. This implies that LTE_4 is not specific for a single disease but might provide a sensitive index of inflammation. In Kawasaki disease increased synthesis of cysteinyl leukotrienes might mediate certain symptoms associated with the disease. For example, it has been pointed out that cysteinyl leukotrienes are released during episodes of myocardial ischaemia providing evidence for their involvement during and after acute myocardial infarction and unstable angina attacks. Therefore and because of their potent vasoconstrictive capacity, cysteinyl leukotrienes might be involved in the origin of vasculitis and stenosis of coronary arteries in Kawasaki disease.

The definitive role of cysteinyl leukotrienes in Kawasaki disease has to be evaluated in further studies by the use of specific 5-lipoxygenase inhibitors or receptor antagonists. Measurement of urinary LTE_4 provides a non-invasive and specific method useful to monitor the effect of these drugs on leukotriene synthesis in Kawasaki disease. Our results imply that leukotriene synthetase inhibition or receptor antagonism may offer a new potential therapeutic approach in children with Kawasaki disease.

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