

FEVER AND HIGH C-REACTIVE PROTEIN LEVEL AS THE SOLE MANIFESTATION OF ALLERGY TO COW MILK

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The definition of a fever of unknown origin is the presence of a temperature greater than 38.3°C taken during numerous measurements over a period exceeding three weeks, and failure to reach a diagnosis despite one week of inpatient investigation or at least three days in the hospital.¹ In differentiation diagnostics, infections, trauma, malignancies and autoimmune conditions are considered first, as well as miscellaneous causes, such as drug-induced fever.¹⁻³ Failure to reach a diagnosis of the cause of fever for several months constitutes a source of justified patient (and parent/guardian) frustration and anxiety.

We present a girl, born weighing 3200 g, the first child of young, healthy parents. She was breast-fed for 18 months. Ultra-high-temperature treated cow milk was introduced to the diet only after ending breast-feeding. During the period between 21 and 30 months of age, she was examined by 16 doctors (family, pediatricians, otolaryngologists, allergist, cardiologist, and gastroenterologist) due to a fever of unknown origin. She was hospitalized for seven days at a university pediatric clinic. Episodes of fever of up to 40°C to 41°C, poorly reacting to treatment including paracetamol and/or ibuprofen, lasted from a few days up to three weeks. During most bouts of fever, no infectious focus was found that was a source of worry for either the parents or the consulting doctors. Neutropenia and deficiencies of immunoglobulins were excluded. The following chronic viral infections were ruled out: Cytomegalovirus, Epstein-Barr virus, human immunodeficiency virus, hepatitis B virus, and hepatitis C virus. The high temperature was always accompanied by an increase in C-reactive protein (CRP) levels to values ranging from 100 to 200 mg/L ($N < 5$ mg/L). A slight increase in leukocyte concentration (a maximum of 16,000 μ L) was noted in only some of the episodes, as well as a high erythrocyte sedimentation rate (a maximum of 40 mm). Tests for the presence of the following systemic disease markers were negative: antinuclear antibodies and antineutrophilic cytoplasmic antibodies. Antibiotic therapy did not have a significant impact on the duration or the recurrence of fever. C-reactive protein levels normalized quickly after the reduction of fever despite the lack of antibacterial and anti-inflammatory therapy administration. Physical and psychological development anomalies were excluded.

Allergy diagnostics showed a slight increase in total IgE concentration (65 kU/L, $N < 60$ kU/L); no specific IgE antibodies for basic food and inhalatory allergens were found; skin tests were negative. Parasitic diseases, including toxocariasis, were excluded.

At the age of 30 months, the child was consulted at our hospital. The medical interview revealed that she had a high daily intake of milk (approximately 500-750 mL) and her mother presented her personal observation of the recurrence of fever whenever the child would drink milk after a few days of abstinence from dairy products. The mother was instructed to have the child follow a strict milk-free diet for four weeks, during which period there was no recurrence of fever. The patient was treated with a dairy elimination diet for seven consecutive months. During this time, neither the child's temperature nor markers of infection were shown to rise. Due to the suspicion of an IgE-independent cow milk protein allergy, the proliferative responses of peripheral blood mononuclear cells to milk proteins were tested before and after milk provocation. While on the diet, no increase in the proliferation of lymphocyte cultures with added cow milk proteins was observed. In further tests, after two months of following a milk-inclusive diet, lymphocyte transformation—in response to cow milk protein provocation—rose considerably. Once again, bouts of fever of unknown origin lasting a few days at a time were observed with CRP > 150 mg/L. After returning to a strict milk-free diet, the patient's CRP normalized within one week and fever recurrence was not observed.

Dhar et al⁴ previously described a young adult female in whom the source of fever of unknown origin turned out to be an allergy to cow milk proteins, but in contrast to our presented patient, the woman displayed characteristic symptoms of malabsorption syndrome. The case of our patient shows how important it is not to underestimate suggestions from the patient herself or her guardians regarding suspected causes of ailments. Presumably, the exposure of our allergic patient to cow milk proteins initiated immunological disorders linked with the development of inflammation. Despite a lack of typical allergy symptoms, the absence of alimentary tract disorders and negative results for the presence of specific IgE for food allergens, observations of the patient's mother persuaded us to administer a milk-free diet as trial therapy as well as milk provocation testing to confirm the diagnosis. The food challenge is currently the most effective means to determine whether an individual truly reacts to the food under consideration.^{5,6} Non-IgE-mediated allergic reactions are regarded as an important pathomechanism of the development of allergic diseases, though the possibilities of their laboratory diagnosis are limited.⁷ Some authors regard proliferative tests of lymphocyte cultures as a valuable method of diagnosis of non-IgE-mediated food allergies.^{8,9} Our case shows that this test can be helpful in establishing an individual food allergy diagnosis and is not limited simply to comparative scientific case studies of groups of patients with allergic illnesses, as was inferred by Hoffman et al.¹⁰ The specificity of positive results of lymphocyte proliferation tests with protein milk antigens only for non-IgE-mediated cow milk allergies has recently

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been called into question due to obtaining similar results in patients suffering from an IgE-mediated allergy.⁷

According to the authors, the two-year clinical observation of the patient as well as allergy test results justify the conclusion that the direct cause of fever and raised CRP levels in the presented patient was a non-IgE-mediated allergy to cow milk proteins.

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