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## Diagnosis of cow milk allergy in the gut, never an easy task

Jon A. Vanderhoof\*

The paper by Lins et al.<sup>1</sup> is an important study because it highlights several key features of cow milk protein allergy. The investigators identified 66 patients who had adverse reactions to cow's milk protein by history. These included a variety of cutaneous, gastrointestinal, and systemic complaints. Total and allergen specific serum immunoglobulin IgE levels were measured including casein, beta lactoglobulin and alpha lactalbumin. Patients were instructed to follow a cow's milk free diet for at least 2 weeks using a soy protein based formula. After symptoms remitted, an in-hospital cow's milk protein challenge was performed and weekly follow-up visits were continued for 4 consecutive weeks following the in-hospital challenge, during which time patients continued to consume cow milk. About half of the patients did not have a positive reaction to cow's milk protein. In those who did, a delayed reaction was common, occurring in 77% of those testing positive. Patients relapsed as late as the third week on cow milk protein. Specific IgE levels of two subfractions of cow's milk protein were elevated in only a very small percentage of patients testing positive by challenge.

The obvious conclusion of the paper is that many children in whom symptoms are thought to be related to cow's milk protein allergy probably have another cause for their symptoms. Other not so obvious but equally important conclusions to be remembered from the study include the observation that most cow's milk protein allergy in infancy and early childhood is not IgE mediated. This form of allergy is characterized by delayed hypersensitivity as is nicely illustrated by the relapse in symptoms rather late in the course of challenge, up to 3 weeks. Therefore,

one cannot reliably diagnose or exclude cow's milk allergy based on prick skin testing or measurement of specific IgE antibodies in infants and small children. Likewise, when an oral challenge is performed, it must be conducted with a prolonged period of observation, up to 4 weeks as the authors have demonstrated.

Cow milk allergy in infants is known to resolve relatively early in life in many cases, often during the first year.<sup>2</sup> It is therefore possible that the investigators might have underestimated the percentage of infants that were actually cow's milk allergic, as a few might have outgrown their allergy prior to the challenge. We have no way of knowing but the number of such cases is likely small.

The significance of these observations will likely increase in coming years as the spectrum of cow's milk protein allergy appears to be increasing. The observation that eosinophilic esophagitis is an allergic disease and the response to dietary treatment even outside of infancy and early childhood will increase the need for better diagnostic criteria and diagnostic methodology for food allergy.<sup>3</sup> Presently, we are limited to repetitive biopsy to assess both food sensitivities and therapeutic responses. It now appears that cow's milk allergy can cause constipation outside of infancy, as well as rectal bleeding in toddlers much the same as it does in infants.<sup>4</sup> Again, measuring response to dietary intervention can be difficult and histological features while present are nonspecific. For disorders such as these, traditional challenges to validate the diagnosis will be even more difficult.

Cow milk allergy has proven to be a relatively common cause of a variety of gastrointestinal and cutaneous

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manifestations in infants and small children. The diagnosis of this condition remains difficult, so, confirmation with a milk challenge is ideal in order to avoid expensive and difficult overtreatment. When cow milk challenge is performed, it must be done so with the understanding that one is likely dealing with a non-IgE allergy and a prolonged observation interval with careful observation for a variety of symptoms is required.

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