



Treatment Rather Than Avoidance May Be Within Reach for Children With Food Allergies

Anita Slomski

THE PEANUT BUTTER SANDWICH THAT most American adults view nostalgically as a mainstay of their childhood has become a food to be feared by an increasing number of parents today. Although data on the epidemiology of food allergies are scant, studies suggest that peanut allergies have tripled in the last 15 years, with 3 million Americans now claiming to be allergic to peanuts or tree nuts. Allergies to cow's milk, egg, wheat, and soy have also spiked.

"We believe there are just as many milk and egg allergies as there are for peanut, but those studies haven't been done," said Robert Wood, MD, professor of pediatrics and chief of the Division of Allergy and Immunology at Johns Hopkins Children's Center. The National Center for Health Statistics reported in 2007 that 3.9% of children had a food allergy in the past 12 months—an 18% increase from 1997 to 2007.

"There is more allergic and autoimmune disease today than there was previously, but food allergies seem to outpace that," said Wesley Burks, MD, chair of pediatrics, University of North Carolina, Chapel Hill.

A number of hypotheses attempt to explain the rise in food allergies in the United States and other developed countries. One is that parents may have unwittingly made their children more prone to food allergies by delaying the introduction of potentially allergenic foods in their babies' diets and following World Health Organization guidelines to exclusively breastfeed for the first 6 months.

"Years ago, babies started solid foods much earlier," said Gideon Lack, MD, professor of pediatric allergy at Kings

College, London, who is leading 2 allergy-prevention trials to determine whether introducing peanut, milk, egg, fish, wheat, and sesame in the first year of life may protect against the development of food allergies. The LEAP (Learning Early About Peanut Allergy) trial is following up 640 babies for 7 years with results expected in 2014, and the EAT (Enquiring About Tolerance) trial will have results in 2015.

In a 2008 study, Lack and colleagues showed that Jewish children in Israel, who are typically weaned at 6 months with a peanut food called Bamba, were one-tenth as likely to develop peanut allergy compared with Jewish children in the United Kingdom, who typically are not given peanuts when they are infants (Du Toit G et al. *J Allergy Clin Immunol.* 2008;122[5]:984-991).

"If indeed oral tolerance works, there may be a relatively narrow window of immunological opportunity to expose children to allergenic foods and induce (natural) tolerance," said Lack. "We suspect with peanuts it's in the first

10 months of life. For egg, based on an Australian study, it's probably in the first 6 months, and for cow's milk, it could be even earlier."

Cleaner living environments have also shielded children from exposure to infectious agents, thereby altering the gastrointestinal microbiome. Bacteria in the gastrointestinal tract aren't regulating allergic immune responses as effectively as they did in the past, so children are reacting to more potential allergens, said Hugh Sampson, MD, chief of the Division of Allergy and Immunology in the Department of Pediatrics and director of the Jaffe Food Allergy Institute at Mount Sinai Medical Center in New York City. Hyper hygiene may also be behind the rise in eczema, which is a portal for allergens to enter the body.

"About 90% of babies who develop food allergies have eczema in the first year of life," said Lack. "Eczema is also a strong predictor of asthma and allergic respiratory disease, as are egg and peanut allergies."



Scientists studying allergies to foods such as as peanuts, tree nuts, milk, eggs, wheat, shellfish, and fish are investigating ways to induce tolerance to food allergens in affected individuals.



Food processing may also be contributing to food allergies. For example, said Sampson, “the Chinese eat as much peanut per capita as we do in the United States, but there is virtually no peanut allergy in China.” The Chinese, he explained, eat peanuts in a boiled or fried form; the dry-roasted form preferred in the United States alters peanuts’ protein structure, possibly making the food more allergenic.

IMMUNOTHERAPY OFFERS PROMISE

Avoiding food allergens during pregnancy and breastfeeding also does not appear to be effective in preventing food allergies in children, researchers have found. And once a food allergy has emerged, subcutaneous immunotherapy, long used to treat allergic rhinitis and asthma, is not an option for food allergies because subcutaneous introduction of allergen frequently induces anaphylaxis. Currently, people with food allergies must simply try to avoid exposure to the foods, but accidental ingestion is common, causing 30 000 cases of anaphylaxis and 100 to 200 deaths each year in the United States, according to a 2006 National Institutes of Health report (<http://tinyurl.com/6nmfhba>).

Eighty percent to 85% of children who are allergic to milk, egg, wheat, or soy will outgrow those allergies before adulthood, but only 20% of those allergic to peanuts, tree nuts, shellfish, or fish will develop permanent tolerance to the foods. Peanut, tree nut, and shellfish allergies are associated with the highest risk of anaphylaxis, but all allergenic foods can cause life-threatening respiratory and cardiovascular reactions, as well as hives, vomiting, stomach pain, and diarrhea.

Researchers are optimistic, however, that oral immunotherapy (OIT) will become an effective treatment for food allergies within 7 to 10 years. Although OIT is more than a century old, only in the past decade has it captured the serious interest of food allergy researchers in the United States.

“Oral immunotherapy had been tried for inhalant allergens with very modest results and hadn’t been used very much because of that,” said Marshall

Plaut, MD, chief of the food allergy, atopic dermatitis, and allergic mechanisms section at the National Institute of Allergy and Infectious Diseases. But he added that fundamental differences between food allergens and inhalant allergens may account for the “rather impressive, albeit preliminary data” that OIT can desensitize people with food allergies.

“Oral immunotherapy has also been associated with fairly high adverse reaction rates, which may be one reason it disappeared” for many years, said Sampson. Between 10% and 20% of children with food allergies drop out of OIT studies because of intolerable adverse effects—chronic gastrointestinal symptoms, a flare-up of eczema, or anaphylaxis. Children will experience some symptoms during the therapy, he noted, such as itchy mouth or throat, dry cough, stomach pain, or swelling of the lips and tongue. But symptoms abate as children respond to therapy.

Sublingual immunotherapy (SLIT) greatly minimizes the risk of adverse reactions because the doses of allergen given to increase tolerance are quite small. Only micrograms to milligrams of allergen extract are held under the tongue, vs the milligrams or grams of the allergen that are consumed with OIT. That’s the difference between receiving 1/100th of a peanut every day with SLIT vs 10 peanuts a day with OIT, said Burks. But SLIT also doesn’t result in allergen tolerance levels as high as OIT. In Wood’s recent study that involved 28 children with severe allergy to cow’s milk, those receiving SLIT “got very little protection,” Wood said. They tolerated only 1000 mg of milk protein after therapy—equivalent to 1 ounce of milk—whereas those in the OIT group tolerated an average of 8000 mg (Keet CA et al. *J Allergy Clin Immunol*. doi:10.1016/j.jaci.2011.10.023 [published online December 1, 2011]).

Wood speculates that SLIT may have utility as a first phase in therapy to reduce allergic responses before switching children to the more potent OIT. Putting children on SLIT for a longer

period—perhaps 4 or 5 years—may also be more effective, said Sampson, who is leading a trial to answer that question.

PERMANENT TOLERANCE IS ELUSIVE

Oral immunotherapy and SLIT, however, are no cure for food allergies—at least not yet.

“The OIT studies suggest that 70% to 80% of children will become desensitized to the food within the first year or two of therapy,” but no study has demonstrated that they will permanently lose the allergy, said Sampson. In Wood’s trial involving children allergic to cow’s milk, after 60 weeks of therapy, children on SLIT followed by OIT were able to consume from 4 to 8 ounces of milk without a reaction—much more than the teaspoon or less they could tolerate at the start of the trial. However, most lost their desensitization to milk when the food was withdrawn, some as soon as a week after they stopped therapy.

“What we don’t know is whether continuing the treatment for 3 or 4 years will make the allergy go away permanently,” said Burks. For now, children have to keep taking the food daily or every few days to protect themselves from having an allergic reaction to it. That’s not difficult to do in the case of egg or milk allergies since milk and egg are contained in many baked foods, but “patients who have peanut allergy often detest the taste and smell of peanuts and may not be able to keep them in their diets on a regular basis,” said Wood. “A month or two after stopping (therapy), they can be back to where they were at the beginning and have a life-threatening allergy.”

Because of the risks involved with OIT, some researchers advocate not treating children with transient food allergies. “If children have a chance of outgrowing their food allergies within 3 to 5 years, there is no way I would put them through a year or two of this kind of treatment just to free them of the allergy quicker,” said Wood. “We’re focusing on children who we think will never have a chance of outgrowing their food allergy.” As an alternative to OIT



and SLIT, Sampson is conducting a study to determine whether children with egg and milk allergies will quickly develop a tolerance for these foods if the foods are baked at a high temperature for a prolonged period. Overall, 75% to 80% of children with transient allergies to milk and egg can eat cakes, muffins, and pizza with no allergic reaction. By having them eat such foods daily, “about two-thirds will develop tolerance to all egg and milk over 2 to 3 years with virtually no adverse reactions,” said Sampson.

There is still much work to be done before OIT and SLIT are ready for the clinic. “We need to do studies with 300 to 400 people, not the ones we’re doing now with 20 to 40 people,” said Wood. “We think we have the scientific knowledge to do them, but we don’t have the funding.” The nonprofit Food Allergy Initiative is attempting to raise money for a trial that would enroll hundreds of patients with peanut allergies, said Sampson.

And there are still many unanswered questions about the therapy,

such as duration of treatment and optimum dosing for safety and efficacy. The unknowns are especially worrisome for researchers who say that some allergists, encouraged by the studies’ promising results, are already treating children with OIT or SLIT.

“All the investigators who conduct controlled trials are concerned because we see a lot of adverse reactions” with the therapy, said Sampson. “If a bad accident happened because of oral immunotherapy, it could make it pretty difficult for us to continue research.” □

Breast Cancer Symposium Highlights Risk, Recurrence, and Research Trials

Tracy Hampton, PhD

SAN ANTONIO, TEX—Some of the biggest challenges in breast cancer research are determining what factors put an individual at risk for developing the disease or for experiencing recurrences and finding the best treatment combinations for different tumor types. Investigators who are tackling these challenges presented their latest findings at the 2011 CTRC-AACR (Cancer Therapy and Research Center–American Association for Cancer Research) San Antonio Breast Cancer Symposium held here in December.

ROOTING THROUGH RISKS

Although known factors such as inherited gene variations play an important role in risk for breast cancer, other less-defined factors are also important. Evidence indicates that obesity and diabetes are among these factors, reported Swedish researchers who examined health records of 2724 women for up to 10 years before these women developed breast cancer and 20 542 individuals who never developed the disease.

Obesity in women older than 60 years was associated with a 55% increase in breast cancer risk, from an approximate 8% risk in nonobese women

to an approximate 12% risk in obese women. In addition, in adult women, who have about a 10% lifetime risk of developing breast cancer, having diabetes that had been diagnosed up to 4 years before cancer was diagnosed was associated with a 37% increase in risk for developing the disease.

Having abnormally low levels of cholesterol and other blood lipids also was associated with an increased risk for breast cancer, while having high levels of blood lipids was associated with a lower risk for breast cancer. While

surprising, similar findings have been reported in previous studies.

“We’d like to extend the follow-up time, but this is useful information for women who want to know their risk and who can take steps to lower it,” said lead author Håkan Olsson, MD, professor in the departments of oncology and cancer epidemiology at Lund University.

An Institute of Medicine report presented during the conference looks closely at potentially avoidable environmental risks that are associated with breast cancer (<http://www.nap.edu>)



Certain factors, such as having certain gene variants, as well as smoking, alcohol consumption, and obesity, are associated with an increased risk of breast cancer.