Peanut Hypersensitivity is Transferred Through Blood Donations

Alerting Blood Transfusion Recipients of Peanut Sensitivity

Tag Words: Peanuts, Peanut Allergy, Blood Transfusions, FDA, Food Allergy

Authors: Kevin Moy and Julie M. Fagan, Ph.D.

Summary: The prevalence of food allergy among children in the United States is roughly 8%, with peanut allergies alone affecting over 1% of all children. It has recently been found that peanut (and maybe other) allergies are temporarily transferred through blood transfusions. Recipients of blood transfusions are unaware of their new allergy which, if exposed to the allergen, could trigger a life threatening anaphylactic event. We communicated with the FDA’s Center for Biologics Evaluation Research, to request that donors provide their allergy history and then recipients be alerted of their possible temporary food allergy.

Video Link: https://www.youtube.com/watch?v=wJdZmKASf5c

The Prevalence of Food Allergies in the US

Individuals with food allergies have learned, from a lifetime of experience, how to avoid contact with trigger foods. From sneezing, to breaking out in hives, to being unable to breath, they know exactly what symptoms to expect, and what to do when they happen. However, there is still much to be learned about allergies. What is happening to our bodies when we are having an allergic reaction? Is it genetic? Will our children have allergies? Currently, food allergies affect about 4% of the adult population and around 8% of the adolescent population in the United States (1).

Among food allergies, the most prevalent is the allergy to peanuts. Perhaps even more alarming is the growing incidence in peanut allergies in children over the past 17 years. In 1997, 0.4% of children were estimated to have peanut allergies in the US, in 2002 the number was 0.8%, and in 2008 it was as high as 1.4% (2). While many food allergies, such as to milk or eggs, are often outgrown, allergies to peanuts tend to be lifelong and often severe. Often times, people who do not have allergies do not realize how severe food allergies can be.

Allergy Biology

Allergies manifest with a wide variety of signs and symptoms. How can one allergen result in a runny nose, while another irritates your stomach lining? Quite a few different mechanisms have been discovered, but the most prevalent source is related to IgE, an antibody mostly found in the lungs, skin and mucous membranes. Covering our outer layers, antibodies assist as our first line of defense against harmful pathogens. In the case of an allergy, this response is inappropriately initiated against a harmless substance. When an IgE antibody comes in contact with a trigger antigen, it grabs on to it, and then communicates to specialized cells in our body to initiate an
immune response. These cells, known as basophils and mast cells, release chemical signals to the rest of the body to trigger inflammation, white blood cell aggregation, and the release of enzymes that assist in the breakdown and elimination of foreign material (1,3,4).

Mast cells release a wide variety of factors including histamine, prostaglandins, proteolytic enzymes and platelet activation factor among others. The most notorious of these is histamine. Histamine binds various receptors in the body. Depending on the type of tissue that it interacts with, it can cause a myriad of different symptoms (3,4). In the mouth and airway, histamine causes vasodilation, which is when your arteries and veins become wider and more permeable to fluid. It also causes the smooth muscles of the airway to constrict. This combination results in the puffy face appearance, along with wheezing or whistling sound produced when breathing. In the mucous membranes, histamine increases secretion of fluids, including saliva, mucous and stomach acid. Histamine also increases muscle contractions in the stomach. The combination of increased acid, contractions, and inflammation, are the cause of the severe stomach pain that is then experienced. Once the allergen is absorbed through the digestive system, it enters the portal vein, where it is then sent to the liver and then the rest of the circulatory system. In our circulatory system, dilation occurs. The blood vessels enlarge, and blood pressure drops. The drop in blood pressure results in decrease blood supply to the brain. This is why antihistamines are so widely used to combat allergies.

Antihistamines are the main medication used to combat allergic reaction. However, antihistamines do not remove the histamine that was released, nor do they reverse the effects that have already occurred. This is where the EpiPen comes in. Epinephrine has the opposite effect of histamine on most of the cells in the body. It will reduce the swelling of the airway, constrict blood vessels to increase blood pressure, increase blood supply to the lungs, and decrease secretions in the mucous membranes. Unfortunately, epinephrine can only be used for acute alleviation, as the heart cannot tolerate prolonged exposure to high concentrations of epinephrine. In situations where greater intervention is required, hospitals can administer corticosteroids. Corticosteroids are controlled drugs which are not available to the public without a prescription from a physician. For these reasons, severe allergic reactions can be very difficult to manage.

**Peanut Allergens**

Antibodies bind proteins sort of like puzzle pieces. While the socket may be designed for a specific piece, sometimes a wrong piece fits the socket as well. The International Union of Immunological Societies recognizes 13 different peanut proteins that may cause allergic reaction. The scientific name of the peanut is Arachis hypogaea, and thus many of its proteins are named Ara h, followed by a number representing the order of discovery. These proteins are further divided into groups and families based on their structure and function. The categories are Cupins, Conglutins, Profilins, Pathogenesis-Related Proteins, Nonspecific Lipid Transfer Proteins, Oleosins, and most recently Defensins (5,6).

Ara h 1, 3, and 4 are part of the Cupin family. In peanuts, these proteins function as seed storage proteins, and are found mostly within the shell of the peanut. Ara h 1 has been studied extensively and constitutes 12-20% of the total protein content in peanuts (5). It is also one of
two peanut proteins that have been studied and found to be airborne after the consumption of peanuts (6). It is estimated that Ara h 1 alone is a trigger protein in 63-90% of individuals with peanut allergies. Ara h 3 and 4 are triggers in little over 50% of such individuals, and thus have been less studied.

Ara h 2, 6 and 7 are part of the Conglutin family. These proteins are related to albumin. The human variant of albumin functions primarily to transport hormones, fats, and other molecular entities within our blood. In peanuts it functions as a storage protein and can be found throughout the peanut. With this group, Ara h 2 is the biggest culprit. Ara h 2 is also estimated to be a trigger in 90% of individuals with peanut allergies (5, 6). Comparatively, scientists consider Ara h 2 a more predictive allergen when compared to Ara h 1 due to conflicting studies estimating a lower prevalence of Ara h 1. Due to this, Ara h 2 is currently the most widely used representative of peanuts in allergy tests. Ara h 2 accounts for 5.9-9.3% of the total protein content, and is the second of the two allergens found to be airborne post peanut consumption in the study performed by Johnson and Barnes (6). Ara h 6 is a trigger in 38% and so it is much less studied. Ara h 7 is a trigger in 43% of peanut allergies, however it only accounts for 0.5% of the total protein content, which makes extraction and study difficult (5). The Conglutin family in particular is known to be very stable and compact proteins, and become more difficult to metabolize when heated (5, 7). Ara h 2 in particular presents a bigger problem in that when it is roasted (as peanuts sometime are), it becomes a trypsin inhibitor, further delaying digestion of the peanut proteins and prolonging their allergen effect (7).

Ara h 5 is a profilin and is found in the pollen of the peanut flower. Only 13% of people with peanut allergies exhibit hypersensitivity to this protein, and thus few studies have been performed (5).

Ara h 8 is a pathogenesis-related protein. This class of proteins function in response to stressors on the peanut plant, such as viral, bacterial, fungal, or even parasitic infections. The nature of this protein makes extraction and study difficult, although it is found to cause reaction in 70% of individuals with peanut allergies (5).

Ara h 9 is a nonspecific lipid transfer protein, and is part of the prolamin family. It can be found within the peanut fruit and in pollen. Ara h 9 is allergenic in 43.2% of individuals with peanut allergies (5).

Ara h 10 and 11 are oleosins. As their name may suggest, these proteins cover the oil bodies in the peanut. They provide stability, and increase the surface area to volume ratio (5, 7). These proteins are highly amphipathic, meaning they cling very tightly to both oil and water, making separation very difficult. These are the proteins responsible for allergies to the highly popular, peanut oil.

Ara h 12 and 13 are newly implicated proteins. They are part of the defensins family. These proteins are much smaller than the other proteins, and are specifically involved in immune response. Ara h 12 and 13 were recently added to the list provided by the International Union of Immunological Societies in August of 2012 and so, little has been published in their regard (7).
Of these 12 proteins, homology has been found in legumes, tree nuts, seeds, fruits and pollen. This means that a person with an allergy to peanuts is very likely to have minor allergic reactions to a greater range of foods (5, 8). Ara h 1 and 3 share homology with other legumes and tree nuts. Ara h 2 shares homology with the almonds and brazil nuts. Ara h 9 shares reactivity with peaches and hazelnut. Ara h 8 shares homology with soy and lentil. Ara h 5 shares reactivity with birch and grass pollen. Ara h 10 and 11, the oleosins, share homology with other oleosins from buckwheat and soy. Ara h 6, 7, 12 and 13 have no currently known cross-reactivity. Cross-reactivity is not guaranteed, but it provides a list of foods to approach with caution when you are aware of your current food allergies.

**Delayed Exposure to Allergen**

One proposed theory to reduce peanut allergy incidence was to delay the timing of exposure to peanuts. The general mechanism of immune response starts with an allergen being captured by a dendritic cell. The dendritic cell then digests and breaks down the allergen into pieces and labels it with ubiquitin. Then a cascade of events is initiated that perpetuates the allergen as “harmful” through formation of memory B cells, the cells responsible for antibody synthesis. It was hypothesized that the early digestive tract was not developed enough to digest whole peanut proteins, thus the immune system was activated. To test this theory, in the UK in 1998 it was recommended that pregnant and breast feeding mothers avoid consuming peanut butter, and avoid giving peanut butter to their children. However, in an investigation performed by Hourihane et al. in 2003-2005, the families that had taken this advice had a similar frequency of peanut allergy as the general population (9). 1.8% of children were shown to have peanut allergy. It was concluded that delaying peanut consumption was not significantly related to acquired peanut allergies.

**Genetic Involvement**

With current advances in genetics and genomic sequencing, scientists are able to rapidly and affordably compare genetic sequences. In a study published in 2013, Madore et al. sought to find a genetic link between peanut allergies and a gene responsible for dendritic cell binding of allergens (10). The study included 590 children with peanut allergies from the Uk, US, and Canada. DNA samples were extracted from saliva and compared with DNA samples of children who were allergy-free. The results of the study found that there exists a great deal of variation in human genes. The HLA-DQB1*02 allele was found to be significantly preventative of peanut allergies, while HLA-DQB1*06:03P was found to increase probability of developing peanut allergies. However, the vast majority of individuals had neither of these alleles. The authors admit that a much greater population needs to be examined to make any sort of conclusions regarding the effects of other alleles.

**Immunotherapy**

Immunotherapy is a method that has been gaining popularity in combating allergies. The process seems counterintuitive, but has shown some promise. In phase II of the “STOP” trial, individuals with a known peanut allergy were given increasing doses of peanut protein (11). Participants started with doses of 2 mg/day and increased gradually every two weeks until a final
maintenance dose of 800mg/day. By the end of the trial, 62% of the participants were completely
desensitized to the peanut allergy, able to tolerate a challenge of 1,400 mg of peanuts (roughly
equivalent to 10 peanuts). However, at an average of 9 months after the trial, individuals that had
not continued regular consumption of peanuts began to show a loss of desensitization.

Allergies Can be Transferred by Blood Transfusions

Historically, transfer of allergies through transfusion has been rare. One of the earliest
documented cases was in 1919, when an anemic patient received blood from an individual who
was allergic to horse dander (12, 13). The allergy was discovered when the patient went back to
his horse carriage and developed asthma. In 1921, inspired by the previous mentioned incident, a
man by the name of Prausnitz injected himself with his friend Kustner’s blood (12, 14). Kustner
was known to be allergic to cooked fish. To confirm the findings recorded in 1919, Prausnitz
injected a small amount of boiled fish extract into his skin, and witnessed a positive reaction.
Prausnitz would then go to confirm this result be performing the same test on several other
healthy individuals, and was met with the same result. Prausnitz, however, found he could not
transfer his own mild allergy to grass pollen to his friend Kustner. He speculated that perhaps a
stronger allergic response was needed in order to transfer allergy.

In a more recent study in 2007, Arnold DM et al. took a step forward and analyzed serological
results (15). The case was with an 80 year old woman who received a blood transfusion to adjust
her blood clotting factor before a surgical procedure. She received two pints of fresh frozen
blood plasma. Two days later, she ate a muffin with peanut butter, and within minutes developed
throat tightness, difficulty breathing and swallowing, and developed hives. She was rescued with
the use of epinephrine along with intravenous injections of corticosteroids to relieve her
symptoms. The 80 yr old woman reported never having a peanut allergy before. This led Arnold
et al. to trace the source of the fresh frozen plasma. It turned out it had been donated by a young
woman who had a known peanut allergy. They obtained a second sample of her donated blood,
and ran serological tests. They separated the blood into its components by standard filtration
procedures, and found that IgE levels were as high as 56 kU/L in fresh frozen plasma, 21 kU/L in
platelets, and 16 kU/L of red blood cells. All that was needed to trigger a reaction was 3 kU/l in
patient’s blood (15). Fortunately, it was found that the foreign IgE lasted no longer than 2
months in the recipient’s blood stream. However, it is important that in the two months after a
blood transfusion, the patient be made aware of their newly acquired allergy, as to avoid further
life threatening incidents. People may differ significantly in the amount of allergy-related IgE
they have circulating in their blood. From the study by Arnold DM et al., 2007, we gain some
insight to the specific values that may trigger such reactions.

Community Action: Alerting Blood Transfusion Recipients of Peanut Sensitivity

The government body charged with regulating blood transfusions is the Food and Drug
Administration (FDA). Within this vast organization, there is a sub group known as the Center
for Biologics and Research (CBER), which is an agency appointed by the US government’s
Department of Health and Human Services (HHS). CBER works with many other agencies under
the Public Health Service (PHS). Within the CBER, the Office of Compliance and Biologics
Quality (OCBQ) has the responsibility of inspection, surveillance, and compliance. Among their
many other responsibilities, the OCBQ directs the CBER’s program for Biological Product Deviations Reports (BPDRs), and monitors blood transfusions and collection.

The FDA currently supports donor history questionnaire documents created by the AABB Center for Cellular Therapies and the Protein Plasma Therapeutics Association (PPTA). The most recent questionnaires provided by both of these organizations do not list allergies as a topic of concern. It is my hope that by sending letters to each of these organizations emphasizing the risks associated with not knowing the allergy history of a donor, that they will at the very least include a line requesting such information. That way, after a recipient receives a transfusion, a simple 30 second counseling on foods to temporarily avoid, is all that will be needed to prevent a life-threatening reaction.

The letter below was sent to:

AABB
8101 Glenbrook Road
Bethesda, MD 20814-2749
Phone: +1.301.907.6977
Fax: +1.301.907.6895
e-mail: aabb@aabb.org

and

PPTA Headquarters in America
147 Old Solomons Island Road, Suite 100
Annapolis, MD 21401 USA
Phone: +1.202.789.3100
Fax: +1.410.263.2298

Dear Representative of the Plasma Protein Therapeutics Association,

As early as the year 1919, there has been evidence that recipients of blood transfusions may also receive the allergies of the donor. It is already widely accepted that immunoglobulins remain in the blood during donations. Several such events have been catalogued in a paper written by D. Atkins and J. Malka-Rais (2010). Many of the screening procedures currently performed on blood rely on presence of specific antibodies for markers. So it should come as no surprise that primary mediator of allergic reaction, IgE, would also remain in the blood. Currently, the allergy history of donors is not recorded, putting recipients at unnecessary risk. Individuals requiring transfusion are typically very ill, thus an anaphylactic reaction can be a highly detrimental event.

A simple solution would be to simply have the donors give their allergy history upon donation. People are usually aware of most of their own allergies, and such information alone is not necessarily an identifier that would violate HIPAA. There is no need for the costly screening of blood for its ability to trigger food allergens, nor is it necessary to discard the blood for its IgE content. In a serological analysis performed by Arnold DM et al (2007), IgE levels were
investigated. It was found that donated IgE are diluted in the host and, over a period of about two months, will diminish to levels no longer capable of eliciting an immune response.

We simply request that you add a section on your PPTA Donor History Questionnaire that lists allergy history as a survey field. This would allow physicians, or other healthcare professionals to briefly counsel recipients on which allergens to avoid. Even though onset of an unsuspected allergic reaction due to blood transfusion is a relatively rare outcome, it is a highly preventable event. Given the rising incidence of allergy prevalence in the population, we believe this is a matter that will become increasingly important in new generations.

Thank you for your time and consideration. We are interested in your comments and your thoughts about putting our suggestion into practice.

Sincerely,
Kevin Moy
Julie M. Fagan Ph.D.

investigated. It was found that donated IgE are diluted in the host and, over a period of about two months, will diminish to levels no longer capable of eliciting an immune response.

As the governing body in charge of monitoring the safety of blood and blood components for transfusion, your organization is in a particularly instrumental position to requesting or requiring donors to provide allergy history information. This could be accomplished by simply requesting the donor to be asked about their allergy history as a survey field on the PPTA Donor History Questionnaire. This would allow physicians, or other healthcare professionals, to briefly counsel recipients on which allergens to avoid. Even though onset of an unsuspected allergic reaction due to blood transfusion is a relatively rare outcome, it is a highly preventable event. Given the rising incidence of allergy prevalence in the population, I believe this is a matter that will become increasingly important in new generations.

Thank you for your time and consideration. We are interested in your comments and your thoughts about putting our suggestion into practice.

Sincerely,
Kevin Moy
Julie M. Fagan Ph.D.


References


Letter to the Editor
Dear Editor of the Star Ledger,

Recently it has been found that when a person donates blood, they also donate their immunoglobulins, meaning that the person receiving the blood may also receive the allergies the donor has. Below I have written a short article briefly covering the importance of blood donations, followed by a summation of an event where an elderly woman had received blood and developed a new allergy similar to that of the donor.

Most of the epidemiology information can be found on the NHLBI section of the National Institute of Health website. The cited case in the article is from "Passive transfer of peanut hypersensitivity by fresh frozen plasma" by Arnold DM et al. originally published in the Archives of Internal Medicine, Apr 23, 2007, volume 167

Please consider my post for publication in your online newsletter. If you would like to contact me, please email me at kevinmoy@scarletmail.rutgers.edu. If you decide to publish it, please send me a reference so that I can look it up. Thank you for your time, Sincerely, Kevin Moy

NEW CONCERNS FOR PEOPLE RECEIVING BLOOD TRANSFUSIONS
When it comes to blood donations, we have all seen the cardboard signs that almost seem to shout, “Blood drive today!” Donating blood is a very noble act, and is directly related to saving lives. Whether you are donating whole blood, red blood cells, platelets, or plasma, contributions are always appreciated. It is estimated that, in the US alone, nearly five million people will require a blood transfusion in the course of a year. There are a variety of conditions where a blood transfusion is necessary for a patient’s survival. Some conditions that require blood transfusion are:

1. Severe trauma, such as from a motor vehicle collision, or a natural disaster
2. Liver disease, where the body is unable to create essential components of the blood
3. Severe anemia as a result of sickle cell, iron deficiency, or any other cause
4. Bleeding disorders such as hemophilia, the decreased ability of the blood to clot, or thrombocytopenia, the excessive clotting of the blood
5. Leukemia where patients may completely lack, or have dysfunctional blood cells.
6. Surgical procedures where excessive blood loss is expected

Recently, it has been reported that people receiving blood transfusions may also receive the allergies of the donor for an extended period of time. In this specific case, an 80 year old woman had received a blood transfusion prior to a surgical procedure. Two days later, she ate a muffin with some peanut butter and quickly developed symptoms of a severe allergic reaction, including throat tightness, difficulty breathing and swallowing, and the formation of an itchy rash. The patient reported never having a peanut allergy in her previous 80 years of life. The health care professionals performed a skin prick test to peanut proteins and measured her serum IgE, to which she had positive results for both. However, nearly two months later, repeat tests were performed, to which both came back negative. An additional month later, a supervised oral peanut challenge was performed, and no adverse reaction was observed.

The donated blood was traced back to an 19 year old female who had donated the blood used in the transfusion a year prior. A second sample of the individual’s blood was requested and obtained to perform serological tests of IgE concentrations when separated into commonly donated components. It was found that the IgE antibody was found in all components, with the greatest concentration in fresh frozen plasma, followed by platelets, then red blood cells.

These findings show that blood donors should be screened for allergies in addition to all the usual screening criteria. People who receive blood transfusions are typically ill, and cannot afford an unexpected anaphylactic event. Therefore it is important that we begin screening for allergies at blood drives, and continue to stay up to date with current medical information.

Kevin Moy