

CASE REPORT

Allergy-induced preterm labor after the ingestion of shellfish

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Abstract

Preterm parturition is a syndrome caused by several mechanisms of disease, including intrauterine infection/inflammation, uteroplacental ischemia, uterine overdistension, cervical disease, maternal/fetal stress, abnormal allogeneic responses, allergic reactions, and unknown insults. An allergic-like mechanism was proposed as a potential etiology for the preterm parturition syndrome, based on the observation that eosinophils were present in the amniotic fluid in a fraction of women with preterm labor and a history of allergy, coupled with the observation that conditioned media from degranulated mast cells (the effector cells of type 1 hypersensitivity) induced contractility of human myometrial strips. This communication describes a case of a pregnant woman who had an allergic reaction and regular uterine contractions after the ingestion of lobster meat, to which she was known to be allergic. Preterm labor subsided after the treatment of antihistamines and steroids. The patient subsequently delivered at term. At follow-up, the child was diagnosed with atopy and asthma, and required frequent use of inhaled corticosteroids and β -2 adrenergic agents. The immunological basis for preterm labor induced by an allergic-like reaction (hypersensitivity) is reviewed.

Keywords: Allergy, preterm delivery, preterm birth, eosinophils, uterine allergy, pregnancy, preterm parturition, seafood, hypersensitivity, atopy, gestation, parturition, labor, allergic reaction

Case report

A 28-year-old Hispanic woman was admitted at 31 weeks of gestation with an episode of spontaneous preterm labor and a generalized pruritic maculopapular rash (Figure 1), both of which developed shortly before admission following ingestion of lobster meat. Her medical and surgical histories, as well as her prenatal care, had been unremarkable. On admission, she had regular uterine contractions every 3 min which were subjectively strong as assessed by the obstetrician and patient. An antihistamine (clorphenamine) and betamethasone were administered orally, after which both the rash and

uterine contractions subsided. The pregnancy progressed satisfactorily and at 40 weeks gestation, the woman was admitted in spontaneous labor. The patient underwent a cesarean section because of failure to progress in labor (arrest of dilation). A viable male infant weighing 3780 g, with Apgar scores of 9 and 9 was delivered. Her postoperative course was uneventful and the mother and baby were discharged home on the 4th postoperative day. Follow-up of the child revealed the development of atopic disorders which included repeated rashes as well as asthma, requiring frequent administration of inhaled corticosteroids and β -2 adrenergic agents.



Figure 1. Extensive exanthemous lesions in the lower extremities in a pregnant woman at 31 weeks of gestation, which developed shortly after eating lobster meat.

Discussion

We report this observation to call attention to clinicians of the association between an allergic reaction to a food allergen and the onset of preterm labor, as well as the response of the clinical manifestations of allergy (skin rash) and uterine contractions to an antihistamine and betamethasone.

Hypersensitivity, allergy and atopy

The general view of the immune system is that it evolved to protect the host against invading microorganisms. Therefore, after the primary invasion, re-exposure to the insult should lead to a lesser injury because of protective immunity (largely due to adaptive immunity which has memory).

The notion that the immune system could cause damage to the host (e.g. autoimmune disease, allergy, etc.) developed in 1894 after a simple set of observations in which guinea pigs immunized with diphtheria toxin became ill or even died after re-exposure to a second dose of the toxin, even if the doses of the toxin were so low that it would not have an effect in non-immunized animals. Emil von Behring called this phenomenon “hypersensitivity” and proposed that it was caused by the toxin [1]. A similar observation was reported in 1898 by Charles Richet and Jules Hericourt [2] after re-exposure of animals to eel toxin. However, the effect was also attributed to the toxin in the animals.

The seminal breakthrough occurred in experiments conducted by Portier and Richet in 1902 [3,4]. When attempting to immunize dogs against marine toxins, a laboratory assistant at the Sorbonne, France noticed that if the toxin was injected into surviving dogs, even the smallest dose of the toxin caused a systemic reaction and clinical shock. This time, Richet concluded that the phenomenon was due to a hypersensitive state caused by an immune

system primed to the toxin. Richet named the phenomenon “anaphylaxis,” which means “against protection” (from the Greek “ana: opposite” and “phylaxis: protection”). This discovery was recognized with a Nobel Prize in Physiology and Medicine in 1913 (for a detailed account of the history of anaphylaxis and Charles Richet, the reader is referred to excellent reviews by Kroker [5] and Löwy [6]).

The origins of the concept of “allergy” has an equally fascinating history. In 1903, Arthus [7] at the Institute Pasteur demonstrated that repeated injections of horse serum into the dermis of rabbits resulted in a local reaction at the injection site characterized by neutrophil infiltration, hemorrhage, and tissue death. He called this phenomenon “the Arthus reaction.” Two years later, two pediatricians in Vienna, Austria, Von Pirquet and Schick [8], revisited earlier reports that some patients receiving anti-diphtheria and anti-tetanus serum (as part of passive immunization) became ill with local and systemic symptoms. They termed this phenomenon “serum sickness.” The debate at the time was centered on the controversy of why the immune system would protect the host in some cases, and harm it in others (e.g. hypersensitivity). Von Pirquet coined the term “allergy” (allergy from “allos: other” and “ergon: work”) to refer to any immunological response, regardless of its clinical outcome. The purpose of von Pirquet intended to emphasize the change in reactivity that occurred in response to a wide variety of biological stimuli. His view was that immunity and hypersensitivity were closely related manifestations of allergy. Some objected at the time to the term “allergy” [9]. Importantly, Von Pirquet believed that an antibody–antigen reaction was the basis for allergy. However, the antibody was not demonstrated until Prausnitz and Küstner described this in Germany in 1921 [10]. The key observations were that an antibody was shown to be present in the serum of allergic individuals and capable of transferring immediate hypersensitivity to the skin of normal recipients. This test became known as the “Prausnitz-Küstner” reaction. The precise nature of the antibody responsible for the allergic reaction is not known.

The concept of atopy was coined in 1923 by Coca and Cooke [11] to describe the clinical manifestations of hypersensitivity in humans. The word “atopy”, which means “out of place”, was adapted from the Greek. It appears that Coca and Cooke were not aware of the work of Prausnitz and Küstner. Soon after, Coca and Grove [12] introduced the term “atopic reagins” as the specific substances present in the serum of atopic individuals responsible for the clinical manifestations of atopy, such as hay fever and bronchial asthma.

The next development was the discovery of immunoglobulin E (IgE) in 1968 [13]. Johansson and Bennich [14] at Uppsala University discovered that the serum of a patient with multiple myeloma had high concentrations of a para-protein, which lacked antigenic determinants for the four then known immunoglobulin heavy chains (γ , μ , α , and δ), which were IgG, IgM, IgA, and IgD. Subsequently, Stanworth et al. [15] asked the question of whether this new protein was capable of blocking the sensitization of a normal person's skin induced by serum in a Prausnitz-Küstner reaction. The experiment was completed within 5 days (Humphrey volunteered for the experiment), and a positive result laid the ground for the definition of the molecular basis of allergy. Ishizaka et al. [16] had previously demonstrated that a normal human β 2A globulin was capable of blocking the Prausnitz-Küstner reaction [17]. At a meeting in Lausanne, Switzerland, three groups working in the field agreed on naming this new immunoglobulin "IgE" [18].

What is the difference between atopy and allergy?

It has been proposed that these widely used terms should be used in the context of IgE-mediated allergy. "Atopy" refers to an exaggerated tendency to mount an IgE response to several common environmental allergens, and implies a predisposition to allergic diseases. "Allergy", in contrast, refers to the clinical expression of atopic IgE-mediated disease [19]. Atopic individuals may or may not have clinical symptoms. Allergic diseases are expressed as hyper-responsiveness of a particular organ (often called "target organ"), which includes the skin (urticaria), nose (rhinitis), eye (conjunctivitis), tracheobronchial tree (asthma), gastrointestinal tract (food allergies), and the uterus (uterine contractions, preterm labor, and possibly fetal distress). When atopy is expressed as a systemic response, it is called anaphylaxis, and involves the entire body. It is worth noting that not all hyper-responsiveness is mediated by IgE. For example, some patients have atopic asthma, which is airway inflammation mediated by IgE, but not all cases of asthma are the result of atopy. The former is often referred to as "intrinsic asthma", and the latter as "extrinsic asthma"[2].

Classification of hypersensitivity reactions

In 1963, Gell and Coombs [20] classified hypersensitivity into four types:

1. Type I, IgE-mediated hypersensitivity (e.g. allergic rhinitis, asthma, systemic anaphylaxis).
2. Type II, direct antibody-mediated cytolytic hypersensitivity (e.g. drug allergies such as penicillin or chronic urticaria).
3. Type III, Immune complex-mediated hypersensitivity (e.g. serum sickness or Arthus reaction).
4. Type IV, delayed type cell-mediated hypersensitivity (e.g. contact dermatitis or chronic asthma).

These hypersensitivities develop in two stages: the sensitization stage, and the effector or elicitation stage. The sensitization stage is basically a primary immune response, whereas the effector stage is a secondary immune response that has an early and late component. In this context, hypersensitivity is defined as any excessive or abnormal secondary immune response to a sensitizing agent. The precise reasons why one individual may be sensitized to an antigen (and thus will experience a hypersensitivity reaction upon a secondary exposure), and another primed only by the antigen (will mount a normal secondary immune response) remain obscure [2].

Type I hypersensitivity

This reaction is mediated by IgE directed against common environmental allergens. It is also known as immediate hypersensitivity, because the response is rapid and occurs within 30 min of exposure to the allergen. Most individuals generate IgG, IgM, or IgA antibodies against common environmental antigens. These antibodies help in clearing the allergens, and the antigen-antibody reaction produces no adverse events to the host. However, among individuals producing IgE antibodies, type I hypersensitivity reactions have a broad clinical spectrum, ranging from itching and swelling to breathing difficulties, and even shock or death. It is unknown why some individuals produce IgE after exposure to the same allergen, and others do not. Similarly, it is not known why some allergens induce a localized reaction (e.g. allergic rhinitis) and others induce a systemic reaction (anaphylaxis) [2].

Sensitization is initiated when antigens penetrate the skin or a mucosal barrier, and is identified by immature dendritic cells or other antigen-presenting cells located in the area of penetration. The allergen is then presented to the draining lymph nodes, where the now mature dendritic cells present the processed allergen to a naive Th-cell. The question of why allergens induce dendritic cells to mature and activate Th-cells is a puzzling one, if one assumes that allergens are innocuous, and therefore, should not supply a "danger signal". Some have argued that allergens induce either cellular stress or damage in every subject. However, in non-atopic individuals,

the response is mediated by IgG antibodies, and would be asymptomatic [2].

Allergen-activated B-cells and Th-2 cells in the lymph nodes draining from the point of entry express tissue-specific homing receptors. This allows them to mobilize back to the target tissue, in which the allergens enter. Presumably, the cooperation of allergen-specific B- and Th-2 cells is designed to eliminate the allergen. Free IgE antibodies bind to high-affinity FcεR1 on mast cells in tissues and basophils in blood. Such cells are now considered to be armed or sensitized. An important step in the development of a Type I hypersensitivity reaction is the differentiation of naive allergen-specific T-cells into Th-2 cells. This is favored by cytokines such as interleukin (IL)-4 and IL-13. These Th-2 cells producing IL-4 and IL-13 stimulate allergen-specific plasma cells to produce IgE [2].

After sensitization is accomplished (arming of mast cells and basophils), the re-exposition to an allergen elicits the effector stage of Type I hypersensitivity. The early phase is mediated primarily by the degranulation of mast cells and basophils. The primary mediators of allergic symptoms are histamine, serotonin, and other preformed molecules. The high speed of Type I hypersensitivity is attributed to the release of preformed mediators. After the initial release of mediators, mast cells start to break down and generate arachidonic acid from membrane phospholipids, which leads to the production of prostaglandins and lipooxygenase products such as leukotrienes. These mediators have been implicated in sustaining the allergic response for several hours. Histamine is a key mediator and induces vasodilatation, increased vessel permeability, bronchial smooth muscle contraction, mucous production, and sensory nerve stimulation. An interesting feature of mast cells is that they contain stored large intracellular pools of tumor necrosis factor (TNF)-α, which is released during the course of a type I hypersensitivity reaction [2,21].

Four to six hours after the initiation of the type I reaction, chemotactic factors locally released at the site of allergen exposure bring other immune cells including neutrophils, eosinophils, Th-2 lymphocytes, mast cells, macrophages, and basophils. The chemokines involved include IL-8 (which attracts neutrophils), IL-5, IL-3, and GM-CSF. The latter three chemokines induce activation and differentiation of eosinophils. Eosinophils are the key cells implicated in the tissue damage occurring in the late phase of a Type I hypersensitivity reaction. Eosinophils can degranulate and release leukotrienes, platelet activating factor, IL-4, IL-10, major basic protein, eosinophilic cationic protein, and eosinophilic derived neurotoxin. In addition, eosinophils can release and/or activate proteases including

collagenases and peroxidases, setting the stage for more tissue damage. Natural killer T-cells appear to have a role in the late phase of a type I hypersensitivity reaction. Mice lacking NKT-cells have reduced allergen-induced airway inflammation, and the administration of NKT-cells from wild mice allows the development of airway damage. Of interest is that this deleterious effect is not observed with the transfer of NKT-cells from IL-4 and IL-3 knockout mice. This suggests that NKT-cells supply part of the IL-4 required to support the Th-2 differentiation of allergen-specific memory T-cells [2].

The reasons for the appearance of IgE in mammals are unclear. Although some believe that IgE is involved in the protection against helminthes [22,23], others have argued that the primary function of IgE is defense against environmental toxins and venoms [24]. It is unknown why type I hypersensitivity reactions occur in response to environmental inert antigens and not to microbial pathogens. Thus, humans can be allergic to pollen and dust mites but not allergic to group B streptococcus. The IgE class of antibodies is thought to have evolved in vertebrates within the last 300 million years [25], before the evolution of modern mammals, and there is evidence that an allergic-like response exists in some known mammalian species [24].

Clinical manifestations of type I hypersensitivity reactions

The clinical manifestations of allergy occur at the site at which mast cell degranulation occurs. If the allergen enters the bloodstream or is absorbed from the gut, systemic anaphylaxis can occur. If the port of entry is the respiratory tract, this can result in allergic rhinitis or allergic asthma, depending upon whether mast cell degranulation occurs in the nose or in the tracheobronchial tree. The skin is also a place for immediate and delayed reactions. Examples are atopic dermatitis or eczema, and urticaria (hives) [21]. The uterus is a rich source of mast cells that can be found in the myometrium and endometrium. Thus, degranulation of mast cells can lead to increased uterine contractility and labor [26].

Evidence that allergy is a mechanism of disease for premature labor

The term "Great Obstetrical Syndromes" [27] was coined to propose that obstetrical disorders responsible for maternal death and perinatal morbidity and mortality are conditions characterized by: (1) multiple etiologies; (2) a long preclinical stage; (3) frequent fetal involvement; (4) clinical manifestations that are often adaptive in nature; and (5) predisposition to a particular syndrome influenced by gene-environment interactions. Several mechanisms of

disease have been proposed for premature labor [28,29], such as intra-amniotic infection/inflammation [30–49], cervical disease [50,51], uterine overdistension [52], endocrine disorders [51,53–55], vascular insults [56–59], abnormal allograft reaction [56–60], and allergy [61]. Indeed, we have suggested that a type I hypersensitivity reaction may be associated with preterm labor [61]. The evidence in support of this proposal is the following: (1) the uterus is a rich source of mast cells – the effector cells of allergic-like immunologic reactions [62]; (2) several products of mast cell degranulation can induce myometrial contractility (i.e., histamine and prostaglandins) [63,64]; (3) pharmacologic degranulation of mast cells with a compound called “48/80” induces myometrial and cervical contractility [65–67]; (4) incubation of myometrial strips from sensitized and non-sensitized animals with an anti-IgE antibody increases myometrial contractility [65]; (5) human myometrial strips obtained from women known to be allergic to ragweed demonstrate increased myometrial contractility when challenged *in vitro* by the allergen in comparison to that of women not allergic to ragweed [26]. Moreover, sensitivity of the myometrial strips of non-allergic women can be transferred passively by preincubation of the strips with human serum [26]; (6) non-pregnant guinea pigs sensitized with ovalbumin and then challenged with this antigen demonstrate increased uterine tone [65,68]; (7) traditional descriptions of animals dying of anaphylactic shock demonstrate enhanced uterine contractility when autopsy was performed immediately after death [69,70]; (8) we have identified a sub-group of patients with preterm labor who have eosinophils in the amniotic fluid as the predominant white blood cell [61]. Under normal circumstances, white blood cells are not present in amniotic fluid. The presence of eosinophils, therefore, suggests an abnormal immune response and may represent a marker for an allergic-like response in preterm labor; (9) we have been able to induce preterm labor and delivery in a guinea pig model of type I hypersensitivity. Animals sensitized with ovalbumin who were challenged during pregnancy with the same protein were more likely to deliver a preterm neonate than those challenged with saline.

Moreover, preterm labor and delivery were prevented with treatment with antihistamines. Sensitization with ovalbumin by itself without a challenge during pregnancy did not change the duration of gestation [71]; (10) preterm labor and delivery induced by a type I hypersensitivity reaction could be prevented by pretreatment with a histamine H1 receptor antagonist (ketotifen) [71]; (11) patients with asthma are at increased risk for preterm delivery [72,73]; and (12) case reports have documented that

exposure to allergens can induce uterine contractions [74–76]. Collectively, this evidence is persuasive that type I hypersensitivity reaction can induce preterm labor and delivery.

Questions that require further research are what is the nature of the allergens that induce this reaction, and why uterine mast cells should be preferentially degranulated. It is known that the human fetus is exposed to common allergens (i.e. house or dust mites), as this has been detected in amniotic fluid in the midtrimester of pregnancy and in fetal blood. Moreover, the concentrations of the allergen are higher in fetal than maternal blood [77]. However, it is not clear yet whether the fetus is participating in the type I hypersensitivity reaction. It is noteworthy that allergen-specific reactivity has been demonstrated in umbilical cord blood at birth and as early as 22 weeks of gestation, indicating that the human fetus can recognize allergens in early pregnancy [78].

Pregnancy is considered a state in which there is preponderance of a Th-2 cytokine response which favors the differentiation of naïve CD4⁺ T cells to the Th-2 phenotype with increased capacity for cytokine secretion in the IL-4 gene cluster and predisposes to a switch to IgE production by B cells. Human decidua contains immune cells capable of identifying local foreign antigens, including macrophages and dendritic cells, as well as B and T cells [79–81].

Food allergy

Food allergies affect approximately 3.7% of the population [82], and are more frequent in children than in adults [83], and in women than in men [84]. It may be expected that the clinical manifestation of food allergies would be largely restricted to the gastrointestinal tract, but this is not the case: acute asthma, laryngeal angioedema, and cardiovascular collapse have all been reported [85,86]. It is noteworthy that food allergy is the most common cause of life-threatening anaphylaxis [87] and carries a fatality risk of 1% [88,89]. Hence, the clinical spectrum of food allergy ranges from a skin reaction to life-threatening anaphylaxis. In the current case report, the skin and the uterus were the target organs.

It is estimated that IgE-mediated food allergy affects nearly 4% of the US population [82], with fish and shellfish being the two most common causes of food allergic reactions. Many allergens have been identified in fish and shellfish, with cross-reactivity between shellfish, arachnids, and insects. Shellfish is a non-taxonomic term that includes crustaceans (shrimp, crab, crawfish, lobster) and mollusks which, unlike fish, are invertebrates. The major antigen

responsible for cross-reactivity among distinct species of fish and amphibians are parvalbumins, a group of proteins resistant to thermal and enzymatic degradation which controls calcium flow in the sarcoplasm of white meat [90]. The major shellfish antigen is tropomyosin, a protein which is essential for muscle contraction in both vertebrates and invertebrates. Tropomyosins are the pan-allergens responsible for cross-reactivity between crustaceans, arachnids, and mollusks [91]. Cross-reactivity is the recognition of distinct antigens by the same IgE antibody which results in a clinical manifestation caused by antigens which are homologous to different species. Although 50% of individuals allergic to some type of fish are at risk of reacting to a second species, those allergic to some types of crustaceans carry a 75% risk of cross-reactivity because of the greater similarity among tropomyosin compared to parvalbumins [92].

Tropomyosin is the major antigen responsible for cross-reaction between shrimp and crab [93], lobster [94], insects such as cockroaches [95], arachnids such as house dust mites [96], and mollusks such as squid [97], oyster [98], snail [99], mussels, clams, and scallops [100]. More than 80% of individuals with shrimp allergy are positive on skin prick tests to crab, crawfish, and lobster [101], and those with an immediate reaction to shrimp ingestion have reaction rates of 50–100% to lobster, crab, and crawfish [102]. This degree of cross-reactivity can cause risk and embarrassment for fish and shellfish individuals, as many of the antigens may be hidden (e.g. Worcestershire sauce contains anchovies). A population of shrimp-naïve orthodox Jews, who obeyed strict Kosher dietary laws prohibiting the ingestion of shellfish and who suffered perennial allergic rhinitis and house dust mite/cockroach hypersensitivity, were found to be prick skin test positive for shrimp antigen [103]. A comprehensive list of allergens and the species from which they derive their name is shown in an excellent review by Wild and Lehrer [90].

Type I hypersensitivity reactions and uterine contractions in humans

We have identified three reports demonstrating that an allergic reaction can lead to increased uterine contractility. In one report, a woman who, following ingestion of shellfish during pregnancy, a woman developed erythema of the palms and urticarial areas of the face and abdomen, uterine contractions every 3–4 min, and hypotension (90/60). The patient was treated with ephedrine (5 mg intravenously). A second dose of ephedrine was administered, because there was no improvement in the maternal blood pressure. After 10 mg of ephedrine, the fetal heart

rate increased to 180–185 bpm, and the fetus subsequently developed late decelerations. Two hours later, the patient recovered, and the fetal heart rate abnormalities gradually disappeared. The patient eventually delivered a term newborn appropriate for gestational age, after a cesarean section [74]. The second case is a report of anaphylactic shock in response to a wasp sting during pregnancy [75]. The third case is a patient with a history of atopic dermatitis who developed a severe anaphylactic reaction after a vaginal examination with a latex glove. Within 2 h, the clinical condition improved, but the patient developed regular uterine contractions [76].

Conclusion

We present a case in which ingestion of shellfish led to hives and the onset of regular preterm uterine contractions. Both abated after treatment with antihistamines and steroids. We propose that this case, along with others previously reported and a body of experimental literature, supports the view that type I hypersensitivity reaction with degranulation of uterine mast cells during pregnancy may lead to premature labor.

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