

IMMUNOLOGY

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#15

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By ~~Moammar~~ **Moammar** ~~Nash~~ **Nash**

HYPERSENSITIVITY/ TYPE I

So far we've talked about the immune response and the things that happen in it, we also started talking about the pathologies that occur. The pathologies if you remember are:

- 1- Auto-immunity pathologies (we have talked about them)
- 2- Immunodeficiency pathologies (we will know more about them in the future)
- 3- Impaired/abnormal pathologies that occur even though the immune system is conserved (our topic today)

Hypersensitivity

It's a "normal" immune response but it's inappropriate, not in the right place and tends to go on and on for reasons that we don't really understand.

It's characterized by continuous activation that is not necessary and is usually directed against something that's not very serious (it can even be a self-antigen). Eventually, because of this continuous inflammatory process, the associated tissues get damaged.

The immune reaction is against an antigen and not necessarily a bacteria or parasite, and sometimes it's even against self antigen.

There are four types of hypersensitivity; type I, type II, type III and type IV. The first three of these are actually antibody mediated and the fourth one is cell-mediated. Today, we are going to talk about **Type I hypersensitivity**.

Type I hypersensitivity

This type is mediated mainly by an antibody which is **IgE**. IgE is a normal antibody used to combat parasitic infections. When the body experiences any parasitic infection, it produces IgE that has actions which help get rid of the parasite (we will talk about them later).

Unfortunately, some people produce IgE instead of other antibodies (like IgG). They end up inappropriately producing IgE for antigens that don't deserve to be combated by it. One such example is pollen. It's not a very serious antigen and it doesn't cause any problems. If a normal body is encountered by it, it usually produces IgG to get rid of it. However, some people will produce IgE instead of other immunoglobulin classes and are labeled as **atopic**.

An **ATOPIC** patient is one who tends to produce IgE against these antigens rather than other types of immunoglobulins, and this condition is known as atopy. Of course not everybody is atopic, only a certain percentage of people is and this depends on geographical distribution. In some places it might be 10% like in USA, while in other areas of the incidence is less than 10%.

Atopy, by definition, is allergy which is mediated through IgE (type I hypersensitivity)

There are other allergies, for example someone is allergic toward something like rubber, and this allergy is mediated by cells and is not considered as atopy.

Why these people produce IgE instead of other Immunoglobulin classes is not really well understood. There's probably some genetic background and that is evident in a person who has an allergy like hay fever; there will be some people in his family who are also allergic to something (either to the same antigen or other). So there's definitely some genetic element to the production of this condition.

There's also a suggestion that it's related to the absence of parasitic diseases. It's been found that people who live in communities where there are no parasitic diseases tend to be more atopic than those who live in the developing world where there is still a high tendency of parasitic diseases.

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قلة
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To explain this, some people said that when the cells that function to produce IgE don't find parasites to deal with, they will produce IgE against some proteins and antigens that are innocuous. It's actually very well documented that when you have increased clearance of parasitic diseases, the incidence of atopy is higher than in countries with high percentage of parasitic diseases.

Usually these antigens which cause the allergy are not very serious. They are soluble and tend to enter the body through the mucous membranes, either through the gastrointestinal tract or the respiratory tract.

Antigens that produce such allergic reactions don't come through the skin.

What is the sequence of defense in type I hypersensitivity?

The first step is exposure to the antigen which could be rose pollen (which cause hay fever) or anything else. The antigen goes inside through the mucous membrane of the respiratory tract and somehow it induces the production of IgE. This is known as **sensitization** which is during the first ever exposure to the antigen.

Symptoms will not appear but the body will produce IgE. The produced IgE will not circulate in the serum at all or very little of it will circulate. (In normal conditions, the IgE serum concentration is probably the lowest of all the immunoglobulin classes because most of these IgEs are on the surface of mast cells and basophiles).

Remember that macrophages and neutrophils have Fc receptors for IgG whereas mast cells have Fc receptor for IgE.

So far, the mast cells in your body have IgE on their surface which is specific for a particular antigen and the body is sensitized. If the body is exposed again to the same antigen, what will happen?

The antigen will come and crosslink a couple of IgE's on the surface and by this cross-linking it will induce degranulation of these mast cells and the release of their contents outside the cell. The main contents of mast cell granules are histamine and eosinophil chemotactic factor. These chemicals are already formed and stored in granules since the first exposure and are called **pre-formed mediators**.

- **Histamine** is a mediator of inflammation, it has several actions:

- 1- It produces vasodilatation
- 2- It produces increased permeability
- 3- It produces contraction of the smooth muscle
- 4- It irritate nerve endings

If the patient has parasitic infection, these actions will be helpful:

The contraction of smooth muscle will increase peristalsis in GIT and the increased secretion and permeability will increase the production of fluid in the GIT >> this will help flush the parasite (the worm) outside the GIT if the body can't kill it via the kinetic-flush action.

- **Eosinophilic chemotactic factor:**

As mentioned, **Eosinophils** are important for killing parasites because they have basic proteins. One of the pre-formed mediators is the eosinophilic chemotactic factor which acts as chemotactic factor for eosinophils to come to the site of activation and help in killing the parasite. This is the normal picture for getting rid of the parasite.

In normal set of events, parasite is the antigen that should trigger the degranulation of mast cells. But in hypersensitivity, other antigens will do that

Type I hypersensitivity is known as **Immediate hypersensitivity**, which means that symptoms will appear within minutes (at the most 15-30 minute) from the exposure to the antigen for the second time (patient should be sensitized). Immediate means release of the pre-formed mediators from the mast cells causing the acute phase of symptoms. This effect will not last long (about half an hour) and then it will stop acting. In some atopic cases, manifestations can go a little bit longer than that and there is what's called a **late phase**. The late phase is produced by mediators that are synthesized **de novo** in the mast cell. These mediators are the metabolites of **arachidonic acid** (prostaglandins and leukotriens) and platelets activated factors, and they have cell action like histamine but are much more prolonged.

Arachidonic acid (Cholesterol) which is present in the membrane of cells can be metabolized by two pathways. One is known as the **cyclooxygenase pathway** and the other is known as the **lipooxygenase pathway**.

The product of these pathways:

Cyclooxygenase >>> prostaglandins

Lipooxygenase >>> leukotriens

Example: Asthma

The patient has the immediate effect after exposure to the antigen >> the symptoms appear >> then they may get little bit better >> but after few hours (6-8 hours) the patient gets the late phase.

The late phase is a manifestation of symptoms due to the production of de novo mediators like prostaglandins and leukotriens.

What are the symptoms that occur when atopic one become exposed to antigen?

The patient may have symptoms or disease/pathology which is localized to one area of the body, or on the other extreme the patient may have generalized reaction to the allergic antigen and this is known as anaphylaxis. Let's talk about them one by one.

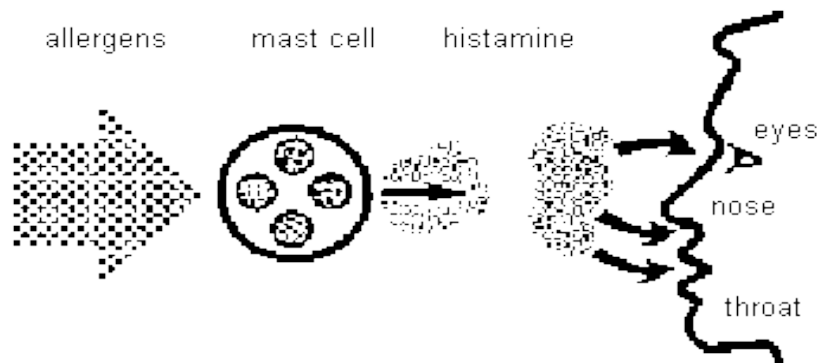
1) Hay fever حمى القش

Some of you may have suffered from it and it's due to the pollen in the trees and grass. The antigen will be taken through the nose, so mainly the symptoms are going to be confined to the upper respiratory tract.



Symptoms :

Let's think about the action of histamine:



- Increase permeability >> increase secretions in the nose (Rhinorrhia)
- Dilatation and swelling of the mucous membrane >> will lead to blockage of the nose
- Irritation to the nerve endings >> Sneezing
- The eyes may be affected >> will be red because of dilatation of blood vessels and there will be itching in the eyes with increase tear secretion

So these are the symptoms of hay fever. Every time spring comes around people who are atopic and have hay fever will suffer from these symptoms as long as they are exposed to pollen.

2) Asthma

Asthma affects the respiratory tract and involves the airway passage to the lungs. The offending antigen in this case is believed to be the **feces of the house dust mites**. In the dust you will find bulks that actually grow and they are known as mites (you can see them with naked eye or under the microscope). They are microscopic creatures that live with you and feed on the skin that you shed every time you change your clothes at home.

Unfortunately, atopic people become allergic to the feces. The feces go through the dust and people inhale them:

In normal people >>> no problems, they produce IgG against them.

Atopic people >>> produce IgE against feces antigen of these house dust mites and they will suffer with asthma.

The problem with these antigens that they always present in the home and cannot be controlled, unfortunately, atopic people will suffer from asthma every time they inhale them.

Main symptoms of asthma due to antigens found in home dust mites:

The main symptom of asthma is wheezing because of obstruction of air flow

1) Constriction of the smooth muscle in bronchi leads to obstruction of the airway passages and they will have wheezing.

2) Increase secretion: they bring up phlegm (may be white and infected) and also will have a cough due to the phlegm which is being produced along with the irritation of the nerve endings.

People with asthma suffer with the late phase manifestations. At first they will experience the mentioned symptoms, but later on they will suffer with late phase effects mediated by prostaglandin and leukotriens. These mediators will prolong the symptoms and usually people with asthma have asthma attacks that last for 1-3 days, so you have to be careful of that.

For these people as well, the accumulation of the cells that have been recruited to the site of the activation with IgE will damage cells and tissues. This damage of tissues will give rise to the constriction of bronchi which becomes more chronic.

In theory, when there's histamine and constriction of bronchi, if you give alloferin during acute stage >> it dilates the bronchi and in this case the constriction is reversible.

But for people with asthma, because of this late phase (if it reoccurs again and again)>> they go into a chronic stage of obstruction and have superimposed infection.

Asthmatic bronchitis

Some people have something known as asthmatic bronchitis rather than asthma as allergy. This means that the patient gets viral (probably) or bacterial bronchitis which is accompanied by constriction and narrowing of the airway passage which results in wheezing.

If someone has asthma bronchitis during childhood, as he grows up older he will not have it anymore. (Dr will leave that to chest physician to talk about next year)☺

3) Food allergy

Some people can be allergic to the Kiwi (:P), peanuts ... etc.



The most food that are associated with atopic reactions are: milk, egg, strawberries, peanuts, nuts(in general), fish and shellfish. When someone eats these foods, the main symptoms are going to be associated with GIT. Again, he going to have IgE>> degranulation of mast cells>> diarrhea (watery) and may have abdominal pains with crabs, theses are really the main manifestations.

Unfortunately, food allergies can precipitate anaphylaxis as well. People with asthma or hay fever don't experience anaphylaxis, but in food allergy sometimes the patient might get anaphylaxis which can be fatal.

4) Urticaria or hives

Sometimes also, the skin can be the site of the manifestation of the allergic reaction, and this manifests as urticaria or hives.

Urticaria is a swelling of the skin which appears as redness and swelling. The redness is not deep; it's likely to appear as pink color. The patient gets big blotches or patches that appear on the skin and they actually branch if you burst them and become white. They disappear within 12 hours or at the most 24 hours. They are itchy because of irritation of nerve endings. This can happen because of fruits like strawberry.



What is urticaria?

(This is explanation about some unclear points mentioned by the Dr, please read it carefully)

Commonly referred to as hives, is a kind of skin rash notable for pale red, raised, itchy bumps. Hives may cause a burning or stinging sensation. They are frequently caused by allergic reactions; however, there are many nonallergic causes. Most cases of hives lasting less than six weeks (acute urticaria) are the result of an allergic trigger. Chronic urticaria (hives lasting longer than six weeks) is rarely due to an allergy.

Wheal-and-flare reaction

a skin eruption that may follow injury or injection of an antigen. It is characterized by swelling and redness caused by a release of histamine. The reaction usually occurs in three stages, beginning with the appearance of an erythematous area at the site of injury, followed by development of a flare surrounding the site; finally a wheal forms at the site as fluid leaks under the skin from surrounding capillaries.

In this type of hypersensitivity, the manifestation can be either in the respiratory tract, the gastrointestinal tract or in the skin. These are main sites where we can get localized manifestation of allergy.

Anaphylaxis (Generalized hypersensitivity) :

On the other hand, the reaction can be extensive and this is called **anaphylaxis**. Anaphylaxis can be immunologic or non-immunologic. Not only atopic people suffer from anaphylaxis, anybody can have anaphylaxis which is mediated by other mediators rather than IgE.

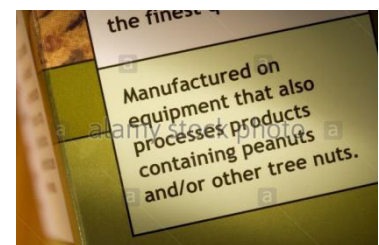
- Anaphylactic reactions mediated by IgE is referred to as **Anaphylaxis or anaphylactic reaction**
- Other anaphylactic manifestations that are not mediated by IgE are known as **Anaphylactoid reactions or non-immunological anaphylaxis**.

Examples:

- sometimes people have radiography or IVP (intravenous pyelogram), a coloured scan for the kidneys in which a patient is injected with **radioiodine** containing contrast to take X-rays. Some people can be very allergic to iodine contrast and they have anaphylaxis mediated by an unknown mechanism but not mediated by IgE.
- If you have **excessive activation of the complement system** for some reason or another, the body produces a lot of C5a and C3a, known as **anaphylatoxins** that cause release of histamine and cause an anaphylactic reaction which is not necessarily mediated by IgE.
- If you got **stung by a bee or a wasp**, you may have anaphylaxis by the sting itself. (not necessary to be mediated by IgE)
- Some people are allergic to **penicillin**, when he gets intravenous injections he will get problems.

Anaphylaxis involves all the body. It is serious and can be fatal. All mast cells are going to be involved.

With anaphylaxis, the antigen usually enters the body through the blood. This could be through intravenous injection because it has to enter the body in a big amount and be distributed all over to produce generalized reaction. Sometimes eating the antigens can be enough like in the case of peanuts, it's very common and there are people who died because of peanut. So if you buy sweets, it may be written on the packet that it contains traces of nuts or peanuts. Even traces of peanuts can be dangerous so people with peanut allergy should be very careful not to eat anything containing or contaminated with peanuts even in very small amounts.



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What happens to the body in cases of extensive amounts of histamine??

The patient will have vasodilatations everywhere which will cause **hypotension**. The extensive contraction of smooth muscle in the bronchi will manifest in an **asthmatic attack**; there will be blocking in normal breathing because of obstruction of airways. These patients will pass out because of drop in pressure, have **breathing problems, tightness of the chest, abdominal pain** (because of GIT infection) and **rashes**. All of these are the symptoms of anaphylaxis. The patient may die unless they are given adrenaline, the treatment of choice for anaphylactic shock. Injecting adrenaline should reverse the symptoms of anaphylaxis.

The generalized complication of type I hypersensitivity is anaphylaxis which is very serious

People who had suffered anaphylaxis or atopy and are more likely to get such reactions are provided with **self injected syringe that contains adrenaline**. They're supposed to take it everywhere (like a mobile :P) so that whenever they need it, they can use it (self administration of adrenaline).



If you want to read more about anaphylaxis, this website is really helpful:
<http://www.aaaai.org/conditions-and-treatments/library/at-a-glance/anaphylaxis.aspx>

"Inspiration is one thing and you can't control it, but hard work is what keeps the ship moving. Good luck means, work hard. Keep up the good work. "

Sorry for any mistake

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shout out to Saja Bataineh