Tolerance & Immunodeficiency

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Tolerance

is a state of unresponsiveness of normal immune system (capable to react to variety of microbes ,but does not react against each individual's antigen).

The most important form of tolerance is non-reactivity to self antigens , but it is possible to induce tolerance to non-self antigens. When an antigen induces tolerance, it is termed **Tolerogen**.

Mechanisms of immunological tolerance

- Central tolerance
- Peripheral tolerance

❑ Central tolerance

Is the mechanism of tolerance only for the self antigens that are presented in the generative lymphoid organs : bone marrow & thymus . Immature lymphocytes have specificity to self antigens undergo :-

1- Deletion (apoptosis) :- (if **T cells** have peptide bind to self MHC; these cells will receive signals trigger apoptosis & die before complete their maturation ,this process called (negative selection)

2- Some T cells will develop into **Regulatory T cells (CD4 T cells only)**

In case of (B-cells) when immature B lymphocytes interact strongly with self antigen in the bone marrow ,B cells either they are **killed** (negative selection) or they **change in receptors** (**Receptor editing B cells**)new different light chain is produce that changes the specificity of the receptor so it no longer recognize a self proteins.

About 50 % of self reactive B cells under go receptors editing

❑ Peripheral tolerance

T-cell tolerance

Some of self reactive lymphocytes may not complete their maturation & enter to the peripheral tissue and they undergo :-

1- Clonal anergy :-T cells become functional inactivation and that occur when these cells recognize antigens without adequate level of the costimulators (second signals)that are need for full T cell activation

2-Clonal ignorance :- self reactive T cells will ignore self antigen either by physical separation from that target Ag (blood – brain barrier)or ignorance self Ag because they are present in such small amounts

3- Suppression by regulatory T cells :- This process take place by development of T regulatory cells in the thymus or in peripheral tissue on recognition of self antigens (by a process that is depend on transcription factor Foxp3,IL-2 and TGF-β)and that occur by blocking the :-

- Activation of harmful lymphocytes
- Macrophages & other APCs

All these will produce T-Lymphocytes tolerance

But

Self polysaccharides ,lipids, and nucleic acids are T-independent antigens that are nor recognized by T cells ,so these antigen must induce tolerance in B lymphocytes to prevent autoantibody production

Peripheral B cells tolerance :-

Mature B lymphocytes that activated to self antigen in peripheral lymphoid tissue without T cells help is functionally inactivated and become incapable of responding to that antigen so it becomes (Anergic).

It will become excluded from lymphoid follicles and may be die by apoptosis

AUTOIMMUNITY

Autoimmunity can be defined **as breakdown of mechanisms responsible for self tolerance and induction of an immune response against self antigen.**

The term *autoimmune disorder* is used when immunoglobulins (autoantibodies) or cytotoxic T cells display specificity for self antigens, or autoantigens, and contribute to the pathogenesis of the disorder .

The principal factors in the development of autoimmunity are :-

1- Genetic factors :-present of suitable genes

2- Environmental factors triggers autoimmune disease such as infections

Factors influencing autoimmune disease

1- Genetic Factors

2- Patient Age

3- Exogenous Factors

GENERAL CLASSIFICATION

Autoimmune diseases are generally classified on the basis of the organ or tissue involved. These diseases may fall:-

- **Organ-specific** in which the immune response is directed against antigen(s) associated with the target organ being damaged ex:-type I diabetes mellitus (most of causes it due to cellular immunity)

- **Non-organ-specific (systemic)** in which the antibody is directed against an antigen not associated with the target organ. ex:- Systemic Lupus Erythematsus (SLE)

CAUSES OF AUTOIMMUNITY DISEASE

The exact cause of autoimmune diseases is not known. However, various theories have been offered:-

1- Sequestered antigen

Lymphoid cells may not be exposed to some self antigens during their differentiation, because their is may be late-developing antigens or may be confined to specialized organs (*e.g.*, testes, brain, eye, *etc*.). A release of antigens from these organs resulting from accidental traumatic injury or surgery can result in the stimulation of an immune response and initiation of an autoimmune disease.

2- Escape of auto-reactive clones

The negative selection in the thymus may not be fully functional to eliminate self reactive cells. So that lead to develop of self reactive T lymphocytes against self antigens.

3- Lack of regulatory T cells

There are fewer regulatory T-cells in many autoimmune diseases.

4- Cross reactive antigens

Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to effector cell or antibodies against tissue antigens. Post streptococcal nephritis and carditis and anticardiolipin antibodies during syphilis

DIAGNOSIS

Diagnosis of autoimmune diseases is based on symptoms and detection of autoantibodies (and/or T cells) reactive against antigens of tissues and cells involved .

Autontibodies against cell/tissue associated antigens are detected by either by ELISA , radioimmunoassay or by immunofluorescence.

Treatments for autoimmune disease by using of immunosuppressive & anti-inflammatory drugs

Immunodeficiency

Immunodeficiency is the failure of the immune system to protect against disease or malignancy.

Primary Immunodeficiency is caused by genetic or developmental defects in the immune system. These defects are present at birth but may show up later on in life.

Secondary or acquired immunodeficiency is the loss of immune function as a result of exposure to disease agents, environmental factors, immunosuppression, or aging.

Individuals with immunodeficiencies are susceptible to a variety of infections and the type of infection depends on the nature of immunodeficiency

Primary immunodeficiency

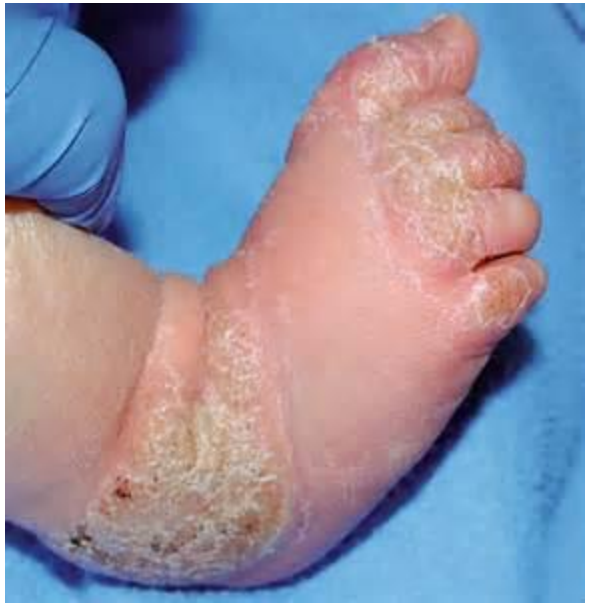
Primary immunodeficiency is inherited defects of the immune system .

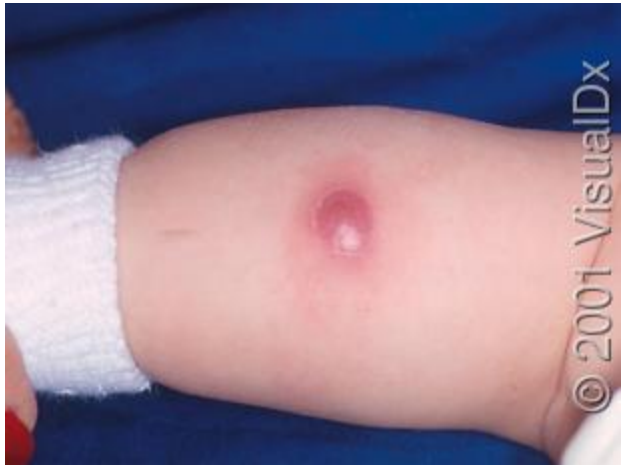
A. Deficiencies of innate immune mechanisms

- **Chronic granulomatous disease (CGD)**

is a rare inherited primary immune deficiency disorder that affects certain white blood cells (neutrophils, monocytes, macrophages & eosinophils). It caused by ***inherited defects in an important enzyme in white blood cells that manufactures oxidants for microbial killing***

The disorder is characterized by an inability to resist repeated pyogenic infection and a tendency to develop chronic inflammation. Life-threatening recurrent fungal and bacterial infection affecting the skin ,lungs and bones may occur along with swollen areas of inflamed tissues known as granulomas that can be widely distributed. Symptoms usually begin in infancy or childhood. Individuals with mild forms of the disorder may not develop symptoms until the teens or adulthood.

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➢ Complement system deficiencies

The complement system is part of the innate immune system. The complement system plays an important part in defense against pyogenic organisms.

- ➢ It promotes the inflammatory response
- ➢ Eliminates pathogens
- ➢ Enhances the immune response.
- ➢ Act as mediator in both the pathogenesis and prevention of immune complex diseases

Deficiencies in the complement cascade can lead to over wheeling infection and sepsis.

Complement deficiencies are comprise about (1 - 10%) of all primary immunodeficiencies. The genetic deficiency of early components of the classical pathway (C1q, C1r/s, C2, C4) tend to be linked with autoimmune diseases , whereas C5 - C9 may have enhanced susceptibility to infections.

• B- Disorders of B lymphocytes

There are a number of diseases in which T cell numbers and functions are normal, but B cell numbers may be low or normal but immunoglobulin levels are low.

1-Hypogammaglobulinemia

a- Agammaglobulinemia (X- linked hypogammaglobulinemia), also referred to as Bruton's hypoglobulinemia is the most severe hypogammaglobulinemia in which B cell numbers and all immunoglobulin levels are very low.

Causes :-The patients have failure of B-cell maturation associated with a defective B cell tyrosine kinase (*btk*) gene(Btk enzyme which is require to develop of B-cells in bone marrow) . Thus, B cells exist as pre-B cells . It is more common in male rather than female The children are subject to repeated infection by pyogenic bacteria *S aureus, S. pyogenes* and *S. pneumoniae, Neisseria meningitidis, Haemophilus influenzae*

Diagnosis is based on enumeration of B cells and immunoglobulin measurement. Patients have no immunoglobulins and suffer from recurrent bacterial infections.

Treatment :-administration of human gamma-globulin to maintain adequate concentrations of circulating immunoglobulin.

b-Transient hypogammaglobulinemia

Children, at birth, have IgG levels comparable to that of the mother. Because the half life of IgG is about 30 days, its level gradually declines, but by three months of age normal infants begin to synthesis their own IgG. In some infants, however, IgG synthesis may not begin until they are 2 to 3 years old. This delay has been attributed to poor T cell help. This results in a transient deficiency of IgG which can be treated with gamma-globulin.

Diagnosis:- measurement the level of Ig

Treatment :-administration of human gamma-globulin to maintain adequate concentrations of circulating immunoglobulin.

2- IgA deficiency

IgA deficiency is result from a defect in class switching. About 20% of individuals with IgA deficiency also may have low IgG.

IgA-deficient patients are very susceptible to gastrointestinal, eye and nasopharyngeal infections and suffering from recurrent bacterial infection. why???

Diagnosis:- Depend on the measurement the level of IgA in the serum

Treatment :- There is no specific treatment for these cases except by using of antibiotic .

3- Selective IgG deficiency

Deficiencies of different IgG subclasses have been found. These patients are susceptible to pyogenic infections(any infection that results in pus production).

4- X-linked Hyper-IgM immunodeficiency

Individuals with this type of immunodeficiency have low IgA ,IgG and IgE concentrations with abnormally high levels of IgM. **These patients cannot make a switch from IgM to other classes and that is attributed to a defect in CD40L (CD154) on their CD4 cells.**

They are very susceptible to infection with a wide variety of bacteria, viruses, fungi, and parasites. In addition, they are at increased risk for developing autoimmune disorders and malignancies.

The infection should be treated with intravenous gamma-globulins.

- **C- Disorders of T cells**

Patients with no T-cells or poor T-cell function are vulnerable to opportunistic infections since B-cell function is to a large T-dependent, T-cell deficiency also has negatively effect on humoral immunity.

Dysfunctional T-cells often permit the emergence of allergies, lymphoid malignancies and autoimmune syndromes.

Most cases of T-cell immunodeficiency are congenital which result either

1- Reduces in T cells numbers
2- Or present of normal T cell numbers with reduced functions
3- Or some time there is **MHC deficiency**

D- Lymphoid lineage immunodeficiency

If the lymphoid progenitor cells are defective, then all of the T , B and NK cells are affected and result in the **severe combined immunodeficiency (SCID)**. It affecting one child in approximately every 80 000 live births. These infants exhibit defects in cellular and humoral immunity, with death occurring within the first year of life due to severe and recurrent opportunistic infections. Prolonged diarrhea resulting from gastrointestinal infections and pneumonia due to *Pneumocystis carinii* are common; *Candida albicans* grows vigorously in the mouth or on the skin. If vaccinated with attenuated organisms these infants usually die of progressive infection.

SCID is the most severe form of primary immuunodeficiencies and there are now at least 9 different known genes in which mutations lead to a form of SCID. Both are characterized by an absence of T cell and B cell (or very low numbers)

Diagnosis is based on enumeration of T and B cells and immunoglobulin measurement. SCID can be treated with a bone marrow transplant (Hematopoietic stem cell transplantation).

SECONDARY (ACQUIRED) IMMUNODEFICIENCIES

•Immunodeficiencies associated with infections

Bacterial, viral, protozoan, helminthic and fungal infections may lead to B cell, T cell, PMN and macrophage deficiencies. Most prominent among these is acquired immunodeficiency syndrome (AIDS).

•Immunodeficiencies associated with aging

These include a progressive decrease in thymic cortex and reduction in the size of thymus, a decrease in suppressor cell function and increase in auto-reactivity, a decrease in CD4 cells functions. By contrast B cells functions may be somewhat elevated

•Immunodeficiencies associated with malignancies and other disease

B cell deficiencies have been noted in multiple myeloma and chronic lymphocytic leukemia. In the Hodgkin's disease and advanced solid tumors are associated with impaired T-cell functions. Most chemotherapeutic agents used for treatment of malignancies are also immunosuppressive.

Other conditions in which secondary immunodeficiencies occur are sickle cell anemia, diabetes mellitus, protein calorie malnutrition, burns, rheumatoid arthritis, renal malfunction, *etc*.