Autoimmune Diseases

Definition: Autoimmune disease is a pathologic condition caused by an acquired or adaptive autoimmune response. An autoimmune disease is caused by a breakdown of immunologic homeostasis; the body responds to its own self –antigens to a degree in which promote tissue damage

Cellular: The autoimmune response can be innate or acquired. B and T lymphocytes are comprised of distinct subsets, as B cells are responsible for antibody production and T cells are responsible for cellular mediation. Innate immune cells are monocytes/macrophages, granulocytes, NK cells, and dendritic cells. Adaptive immune cells are B and T cells that produce BRC and TCRs respectively. The control of the immune system is to identify the antagonist and destroy it without harming the body.

Innate immunity: Innate immune response is developed centrally during embryonic period. Innate immunity is present from birth and does not change permanently during an individual's lifetime.

Components of innate immunity are •Physical barriers-tighly associated epithelial cells including those of the skin and the membranous sheets lining the gastrointestinal, genitourinary, and respiratory tracts. •Biochemical barriers from epithelial surfaces such as sweat, saliva, tears, and earwax. •Enzymes in epithelial and phagocytic cells such as lysozyme. •Inflammation-related serum proteins including complement, C-reactive protein, lectins (carbohydrate-binding proteins) such as mannose-binding lectin and ficolins). •Antimicrobial peptides (defensins, cathelicidins, and many more) on the surfaces of cells and within phagocyte granules. •Cell receptors that sense microorganisms and signal a defensive response these are called Toll-like receptors. •Cells that release cytokines and inflammatory mediators such as macrophages, mast cells, natural-killer cells.

The innate immune system's primary response is detection of microorganisms and providing a first-line defense against invasion and infection. Innate immunity provides protective reaction to identify sources inflammatory processes through signs such as swelling, redness, heat, and pain. Thus once the antagonist is destroyed it is important for the body to return to a normal state.

Acquired/adaptive Immunity: The immune system becomes further tolerant to self-antigens through the two main stages of adaptive immunity, central and peripheral tolerance Generation of clonal diversity is a process in the acquired immunity in which antigenic determinants are produced. Proliferation and progressive development of incompetent T and B-cells takes place in the primary lymph organs (thymus and bone marrow). Various dysfunctions in this innate immune development stage can occur with both B and T-cells at the central or peripheral tolerance stage.

Central Tolerance: Central Tolerance is one stage at which tolerance for self-antigens is maintained through the deletion of autoreactive B or T cells in the thymus by either clonal deletion or negative selection.

T lymphocytes: The precursor cells (lymphoid stem cells) developed in the embryonic period deposit in the thymus whereby they undergo proliferation and progressive development of characteristic to become immunocompetent T cells by interaction with various thymic cells and thymic hormones. There is a complex developmental limitation to the body producing T cells in the thymus when a mutation exists in the genes that develop the thymus in utero by a partial deletion of chromosome 22. This is known as DiGeorge Syndrome. •DiGeorge syndrome is characterized by defects in the thymus resulting in T cell deficiency •Negative selection: It is essential for the T cell to interact with thymic stromal cells to develop T-cell receptors (TCR). Normally in this phase if a T-cell's TCR bind strongly with self-antigens, they are deleted. Intrathymic presentation of autologous antigens is regulated by autoimmune regulator (AIRE) gene and mutation of this gene will improperly present the self-antigens in the thymus therefore the TCR's don't bind strongly with self-antigens and cell deletion is not achieved or is incomplete. This can cause several combinations of autoimmune endocrine diseases •Clonal deletion: the thymic cells express Self-antigens, and many of those cells express MHC (major histocompatibility complexes) class I or MHC class II molecules. If the T cell's TCR strongly react to MHC class I or II the T cell will undergo apoptosis Although auto-reactive T cells escape depletion this does not result automatically in autoimmune disease, as there are other means of control in the peripheral tolerance.

B lymphocyte: Lymphoid stem cells enter the bone marrow then interact with stromal cells with guide further proliferation and differentiation process through direct cell-to-cell contact and the production of cytokines and hormones by the stromal cells. •Negative selection: Many of these B cells interact with stromal cells that express self-antigens and thus undergo negative selection.

Peripheral tolerance: Peripheral tolerance is a form of acquired immunity that is maintained in secondary lymphoid organs by regulatory T lymphocytes or antigen-presenting dendritic cells. The peripheral tolerance is a means to inactivate or kill lymphocytes that are specific for pervasive self-antigens that escaped central tolerance. Failure to control T cell responses or regulatory control by B cell leads to failure of self-tolerance and development of autoimmune disease.

The two principal mechanisms of peripheral tolerance are activation-induced cell death (AICD) and anergy. The single-gene defects that result in autoimmunity are all defects in lymphocyte regulation, indicating that tolerance is often maintained by the control of lymphocyte responses to self-antigen. The existences of distinct pathways of T cell tolerance suggest that different types of antigens induce tolerance by distinct mechanisms.

In CD4+ T lymphocytes, AICD is induced by repeated stimulation, with high levels of interleukin (IL)-2 production. Under these conditions, the T cells co-express Fas (CD95) and Fas ligand (FasL), and engagement of Fas triggers apoptotic death of the T cells (Van Paris, Perez, Abbas, 1998). This is seen in humans with mutations in the Fas such as in systemic lupus erythematosus. Anergy forms when there is an absence of B7, which is an important costimulator in the presence of an antigen, causing an arrest state of the T cell. T-regulatory cells are T cells that develop for regulator purposes of immune response to avoid inadvertently attacking self-antigens or to avoid over activation of the immune response to protect the host's own tissues against autoimmune reactions. Failure of B cells regulatory control is related to two factors. First mature B cells can bind T-dep self-antigens in periphery then anergized because of lack of helper T cells. Another mechanism is when T-ind self-antigens in periphery are present in insufficient density to activate B cells.

Tissue: Protection of the tissues in systemic immune system begins with the secretory mucosal immune system. This is where the antibodies or B cells present in bodily fluids to protect against antigens that haven't penetrated tissues. All tissues contain phagocytic cells. During inflammation cytokines are released by T cells, which activate macrophages, which are phagocytic cells. The macrophages increase phagocytic actions of ingestion and kill microbes, and dead host cells. This stimulates leukocytes from the blood.

Organ: Autoimmunity is either organ-specific or systemic. In organ-specific diseases, such as thyroiditis, type 1 diabetes, inflammatory bowel disease, or multiple sclerosis, a normal immune response is misdirected against a self-antigen or organ, and inflammation and production of autoantibodies are usually confined to antigens specific to the target organ.

System Level: Multiple organs are targets in systemic autoimmune diseases, such as systemic lupus, Sjögren's syndrome, or systemic sclerosis. These autoimmune diseases are usually chronic in manifestation of activation in the innate and adaptive immune cells where they present with an array of clinical manifestations. Autoimmune disorders can have organ-specific immune process but are involved systemically because of their autoantibody to autoantigen outside of a specific organ. For example, rheumatoid arthritis is primarily a joint-selective disease, but other autoantibodies can cause extra-articular manifestations.

Genetics: Genetic factors that contribute to autoimmunity are easier to identify than the original insult that initiates the disease. Currently, at least 68 genetic risk variants have been associated with various autoimmune diseases, and several loci have been identified as being associated with more than one autoimmune disease. Studies with monozygotic twins have been done to determine the genetic basis for many autoimmune diseases. The concordance rate does not reach 100% for any autoimmune disease, which means that factors other than genetics must have a role in the pathogenesis. AIRE is an autosomal recessive gene that is responsible for intrathymic presentation of the number of autologous antigens. Mutations in AIRE gene cause several combinations of autoimmune endocrine diseases, such as autoimmune polyendocrinopathy Candidiasis ectodermal dystrophy (APECED), because the appropriate self-antigens are not properly presented in the thymus.

Epidemiology: Over 50 million people are diagnosed with some form of autoimmune disease in the United States, and studies show prevalence is rising. Autoimmune disease encompasses a variety of clinical conditions. Autoimmune disease can be caused by the exposure of a previously sequestered antigen, the development of a neoantigen, the complications of infectious disease, the emergence of forbidden clone of lymphocytes, or consequence of ineffective peripheral tolerance. They vary according to the body system/ organs that they affect and their associated morbidity. More than 80 autoimmune diseases have been identified in humans. Many autoimmune diseases follow a progressive course, even with appropriate management, and serious or life-threatening complications may develop. Functional limitations, disability, and poor quality of life are substantial concerns. There are standard criteria established to identify a clinical diagnosis of autoimmune disease. These are classified in three categories direct evidence, indirect evidence, and circumstantial evidence.

1.Direct evidence: the ability to transfer autoimmune disease 2.Indirect evidence: the ability to reproduce the autoimmune disease in animal models 3.Circumstantial evidence: the association of autoantibodies with disease in appropriate clinical settings

Environmental factors effecting autoimmune diseases: 1.Infectious agents 2.Stress 3.Sex hormones (estrogens and androgens) 4.Cigarette smoking

Disease described: Each autoimmune disease has its own classifying agents. However there are multiple manifestations that are shared among several autoimmune diseases.

Common Characteristics: 1.Majority are female 2.Similar symptom profiles 3.Difficult to diagnosis 4.Importance of history and physical examination 5.Disease management is similar

Sign and Symptoms: 1.Extreme fatigue 2.Low-grade fever 3.Dizziness 4.General malaise

Vague, nonspecific symptoms tend to wax and wane over the long-term, causing periods of remission with intermittent disease flare-ups.

Diagnosis Antibody testing may be specific to autoimmune disorders however because naturally occurring autoantibodies are common in nonspecific disease or injury. Testing for autoantibodies may only give the result of the disease process not the cause and effect relationship to their presence. Autoimmune diseases are difficult to diagnose secondary to overlapping symptoms, and the high rate of co-occurring autoimmune diseases. Evidence-based guidelines for diagnosis, management, and/or follow-up are available for some autoimmune diseases, but diagnosis frequently remains a challenge, because symptoms are often overlapping and definitive diagnostic testing is lacking for most diseases.

Treatment The specific treatment of autoimmune diseases depends on the particular systems or organs affected, but the overall goals of treatment are similar. Treatment goals: 1.Relieve symptoms (primary goal) 2.Preserve organ function 3.Control the autoimmune process, (often with immunomodulatory/immunosuppressant drugs)

Treatment challenges: 1.Complexity of symptoms 2.The need to manage long-term medications for preserving organ function 3.The long-term adverse effects of immunosuppressant drugs

Patient challenges: 1.Coping: denial, frustration, overwhelmed 2.Different perceptions of health and disease

As with diagnostic criteria, practice guidelines for the treatment of autoimmune diseases are available but limited. The long-term management of individuals with autoimmune diseases requires a multidisciplinary approach, with potential referral to specialists, such as rheumatologists, endocrinologists, gastroenterologists, neurologists, nutritionists, physical/occupational therapists, and counselors. The primary care provider, with clear articulation of specific roles, best coordinates this multidisciplinary care. Because of the influence of stress on the immune system-coupled with the stress of a chronic disease-the management of autoimmune diseases should include stress reduction interventions. (Alexander, L. 2011)

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