INTRODUCTION

Selective immunoglobulin A deficiency (IgAD) is the most common primary immunodeficiency. The current definition, established by the Pan-American Group for Immunodeficiency and the European Society for Immunodeficiencies, defines this disorder as serum IgA levels <0.7 mg/dL with normal IgM and IgG levels in individuals ≥4 years of age(***Notarangelo et al., 2009***).

Most individuals with IgAD are clinically asymptomatic, but the defect may be associated with recurrent respiratory and gastrointestinal tract infections/disorders, autoimmunity and allergies***(Latiff and Kerr., 2007)***.

IgAD is strongly associated with the major histocompatibility complex (MHC) region, in particular with the human leukocyte antigen (HLA)-B8, DR3, DQ2 (8.1) haplotype(***Cunningham et al., 1991***), and up to 45% of IgAD patients have at least one copy of this haplotype compared to 16% in the general population. Homozygosity for the ancestral 8.1 haplotype increases the risk of development of the disease even further(***Mohammadi et al; 2010***).

Interestingly, the ancestral 8.1 haplotype is also reported to be associated with Graves' disease (GD), systemic lupus erythematosus (SLE), type 1 diabetes (T1D) and celiac disease (CeD. In addition, telomeric portions of this haplotype have also been shown to contain a risk factor for myasthenia gravis (MG) and rheumatoid arthritis (RA) (***Jawaheer et al., 2002, Ramanujam et al., 2011***).

There is also a considerable overlap in concomitant diseases; for example, T1D is prevalent in patients with GD,

SLE, CeD and RA. Furthermore, CeD is overrepresented in patients with GD(***Zhernakova, van Diemen and Wijmenga***., ***2009***), and patients with SLE also show a higher prevalence of thyroid disorders(***Appenzeller; 2009, Antonelli et al., 2010***).

IgAD is thought to be present from birth in most cases. Theoretically, the increased frequency of infections associated with IgAD could therefore precipitate autoimmune disorders such as GD and SLE. However, in CeD, IgAD has occasionally been reported to occur after the onset of the gastrointestinal symptoms. Thus, the common genetic background is likely to be the main contributor to the different autoimmune disorders where environmental factors determine if, and when, the primary and subsequent diseases will appear***(Yel.2010)***.

Similarities in the genetic susceptibility suggest involvement of common pathophysiological pathways, implicating that IgAD, as suggested by ***Ferreira et al. (2010)***, may in fact be an autoimmune disease. However, additional dense sequencing of the implicated genes may be required to fully understand the mechanisms involved.

The mechanism underlying the induction of IgAD still remains elusive. It is however likely that the pathophysiological process involves a break of tolerance against IgA itself (since 30% of IgAD patients have demonstrable titers of IgG antibodies against IgA) ***(Wang et al; 2011)***.

AIM OF THE WORK

The aim of this work is to investigate the prevelance of Selective immunoglobulin A deficiency in patients with autoimmune diseases and highlighting its possible pathophysiological mechanisms.

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1AUTOIMMUNE DISEASES

AUtoimmune+ diseases occur when there is interruption of the usual control process, thereby allowing the immune system to malfunction and attack healthy cells and tissues in which the adaptive immune response is directed to a self-antigen. It usually involves both T-cell and B-cell responses. A common example of autoimmune disease is Type I Diabetes. Some other common autoimmune disorders include rheumatoid arthritis, systemic lupus erythematosus and vasculitis ***(Davidson and Diamond, 2001).***

Autoimmune disorders typically fall into two categories: systematic and local. Systemic autoimmune diseases are associated with autoantibodies, which are not tissue specific, and the spectrum of damage may affect a wide range of tissues, organs, and cells of the body. Localized autoimmune diseases are associated with organ-specific conditions that affect a single organ or tissue. This may be restricted to certain organs as in autoimmune thyroiditis or involve a particular tissue in different places as in Good pasture's disease which may affect the basement membrane in both the lung and the kidney. However, the boundary between systematic and nonsystematic disorders becomes blurred during the course of the disease as the effect and scope of localized autoimmune disorders frequently extend beyond the initially targeted areas ***(Wang L, Wang, F. S and Gershwin. M. E., 2015).***

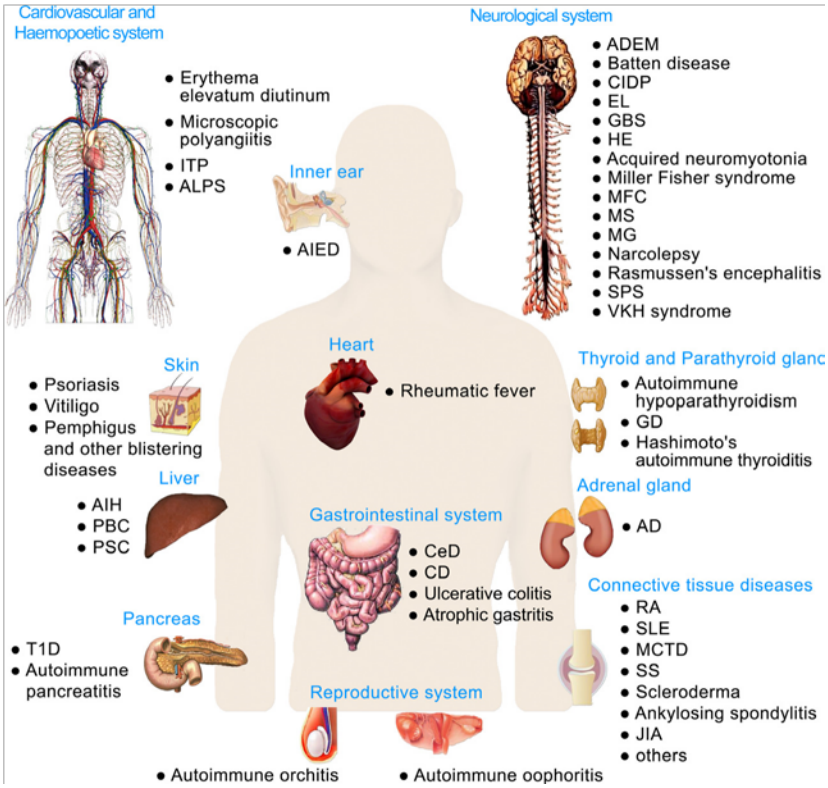

Figure (1): Representative organ specific and systemic autoimmune diseases ***(Wang L, Wang, F. S and Gershwin. M. E., 2015).***

The onset of autoimmune disease is associated with a trigger, which can be pulled in numerous ways. Certain substance in the body that is normally confined to a specific area may be released into another area due to internal trauma; the translocation may stimulate the immune system to recognize a natural body component as foreign and trigger an autoimmune response ***(Wang , Wang f.s. and Gershwin., 2015).***

In another scenario, a normal component of the body may be altered via virus, a drug, sunlight or radiation; the altered substance may then appear foreign to the immune system. Very rarely, a foreign substance resembling a natural body component may enter the body, thereby inducing the immune system to target both the similar body substance and the foreign substance ***(Fruman and Walsh, 2007).***

A major understanding of the underlying pathophysiology of autoimmune diseases has been the application of genome wide association scans that have identified a striking degree of genetic sharing among the autoimmune diseases ***(Cotsapas and Hafler, 2013).***

Just as the triggers for autoimmune disorders are wide and varied, so are their effects. The debilitating effects of various autoimmune disorders include the destruction of a specific type of cell or tissue, stimulation into excessive growth, or interference in function. Organs and tissues affected by more common autoimmune disorders include components of the endocrine system, such as thyroid, pancreas, and adrenal glands; components of the blood, such as red blood cells; and the connective tissues, skin, muscles, and joints ***(Wang , Wang f.s. and Gershwin., 2015).***

Epidemiology:

Autoimmune diseases are generally thought of as being relatively uncommon, but their effects on mortality and morbidity are significant. The overall prevalence of autoimmunity is approximately 3-5% in the general population. Yet, despite enormous advances in the diagnosis and the treatment of autoimmune diseases, there is still a paucity of data on the etiological events that lead to clinical pathology ***(Eaton et al., 2007)***.

Incidence and prevalence vary amongst the autoimmune diseases. The geoepidemiology becomes more complex when variations in age, gender, ethnicity and other demographic features are considered. Autoimmune diseases can occur at any age, but different diseases have their own characteristic age of onset. In almost all patients, the prevalence is increased in first-degree bias of relatives and is even higher in monozygotic twins. There is an increased frequency of autoimmune diseases in women, with a female-to-male ratio ranging from 10: 1 to 1: 1 [an exception is Crohn's disease, with a ratio of 1: 1.2]. The sex autoimmunity has attracted enormous attention, but remains unresolved ***(Wahren-Herlenius and Dörner., 2013)***.

The incidence and prevalence of autoimmune diseases differ between geographical regions. For example, multiple sclerosis (MS) is unevenly distributed throughout the world; its prevalence varies between <5 cases per 100 000 persons in tropical areas and also in Asia and >200 cases per 100 000 persons in temperate areas. The incidence of MS has been reported to be 0.8-8.7 per 100

000 person-years in Europe, 2.7-7.5 per 100 000 person-years in North America and 0.7-3.6 per 100 000 person-years in Asia and the Middle East ***(Milo and Kahana., 2010)***.

The incidence of type 1 diabetes mellitus (T1D) is 5-10, 10-20 and <1 per 100 000 person-years in populations from Europe, the USA and China, respectively. Between 1990 and 2011, the incidence of coeliac disease (CeD) increased from 5.2 to 19.1 per 100 000 person-years in the UK ***(West et al., 2014)***.

However, an annual 1.8% decline in incidence of systemic lupus erythrematosus (SLE) in the UK between 1999 and 2012 was reported, whilst the prevalence increased from 64.99 to 97.04 per 100 000 persons per year during the same period ***(Cross et al., 2014)***. For rheumatoid arthritis (RA), the global prevalence was estimated to be 0.24% in 2010, which was essentially no different from the prevalence of 0.25% in 1990 ***(Rees et al., 2014)***. Traditional analytical epidemiological studies have shown that genetic susceptibility and environmental factors are the key risk factors that lead to loss of tolerance ***(Leung et al., 2013)***.

The Immune System and Autoimmunity:

An immune system is a highly regulated biological mechanism that identifies and reacts to antigens from various foreign substances found in an organism's body and reacts to these possible pathological threats by producing certain types of lymphocytes such as white blood cells and antibodies that

have the ability to destroy or neutralize various germs, poisons and other foreign agents ***(Pauley, Cha and Chan, 2009)***.

Typically, the immune system is able to distinguish the foreign agents from the organism's own healthy cells and tissues. Autoimmunity, on the other hand, describes a diseased condition in which an organism fails to recognize its own cells and tissues, thereby enabling the immune system to trigger a response against its own components ***(fiore et al., 2010)***.

A low degree of autoimmunity is an integral part of an effective immune system. For example, low-level autoimmunity has been demonstrated to be a possible factor in reducing incidence of cancer through versatile CD8+ T cells, which kill target self-cells by releasing cytokines capable of increasing the susceptibility of target cells to cytotoxicity, or by secreting chemokines that attract other immune cells to the site of autoimmunity ***(Dai and Ahmed, 2011)***.

Autoimmune disease is a pathologic condition caused by the adaptive autoimmune response. However, these definitions can be unclear since it is frequently difficult to assign causality when dealing with a human disease. It useful, therefore, to consider the evidence of an autoimmune etiology of a human disease with three degrees of stringency ***(Davidson and Diamond, 2001).***

Direct evidence: Direct evidence implies that an autoimmune response causes disease. This usually involves reproducing the disease, totally or in part, by transfer of

autoantibody from a patient to a healthy recipient, either another human or an animal.

- One striking example of antibody transfer is the reproduction of pemphigus by injection of patient serum into a neonatal mouse**.** This procedure reproduces the essential pathologic features of the disease ***(Anhalt et al., 1982)***.
- Human-to-human transfer of autoantibody may result from transplacental transmission of the disease. Examples of maternal-fetal transmission have been well-documented in cases of Graves' disease, myasthenia gravis ***(Drachman, 1990)***, the complete heart block and other cardiac abnormalities in neonatal lupus associated with maternal lupus and Sjögren's syndrome ***(Reichlin et al., 1994)***.

Most of the clinical manifestations in the offspring are temporary, because the autoantibody in these cases is provided through passive transfer of serum from the mother. An exception is the congenital heart block and other cardiac abnormalities of neonatal lupus, which are persistent and potentially life-threatening ***(Hornberger and Al Rajaa, 2010).***

There are situations in which the pathologic effects of antibody can be reproduced in vitro. Examples are diseases of the blood, such as hemolytic anemia, leukopenia, or thrombocytopenia. Antiphospholipid antibodies, another example, are autoantibodies that may affect blood clotting in laboratory tests ***(Hornberger and Al Rajaa, 2010).***

Indirect evidence: A second level of proof of causality relies upon indirect evidence. In human autoimmune disease, this requires the availability of an appropriate animal model in which the necessary transfer studies can be carried out to prove a cause and effect relationship:

- Reproduction of disease in animals via immunization with the appropriate antigen
- Naturally occurring disease in animals that resembles its human counterpart
- Disease resulting from manipulation of the immune system

A good example of an experimental model is autoimmune thyroiditis in the mouse ***(Vali, Rose and Caturegli, 2000)***. Here, the experimental antigen, thyroglobulin, is a major target of autoantibody production in patients. In genetically susceptible strains of mice, immunization with thyroglobulin produces a pathological picture of chronic thyroiditis that closely resembles the human disease. Another useful example is myocarditis, which can be reproduced by immunization of susceptible mice with murine myosin ***(Rose and Hill, 1996)***.

The most widely-studied model of autoimmune disease is experimental allergic encephalomyelitis (EAE) ***(Swanborg, 1995).*** The demyelinating changes in the experimental disease bear many similarities to multiple sclerosis in humans. Three antigens can induce this disease in rodents: myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte

glycoprotein (MOG). The last produces axonal loss as well as demyelination and has a relapsing and remitting course similar to multiple sclerosis in humans ***(Weissert et al., 2002).***

Manipulation of components of the immune system, such as the introduction of a T cell receptor for a disease-producing antigen into an otherwise disease resistant strain, has suggested that activation of antigen presenting dendritic cells is a first step in inducing autoimmunity. These animal models are valuable for studying pathogenesis but may not be useful indicators of etiology ***(Waldner, Collins and Kuchroo, 2004).***

Circumstantial evidence: The lowest level of proof, circumstantial evidence, attributes an enigmatic human disease to autoimmunity. The first piece of suggestive evidence is the presence of autoantibodies. The hazards of using this kind of evidence as the basis for concluding that a disease is caused by autoimmunity is that natural autoantibodies are very common and may even rise nonspecifically during the course of a disease process ***(Frustaci et al., 2002).***

A second kind of circumstantial evidence comes from the finding that autoimmune diseases tend to cluster, probably because they share some genetic susceptibility traits. As examples, a single individual will have more than one autoimmune disease, and members of the family share the same or even other autoimmune diseases. The association of one disease of unclear etiology with another of authentic

autoimmune etiology strengthens the possibility that the former is also an autoimmune disorder ***(Eaton et al., 2007).***

The best-studied autoimmune diseases show a particular bias to certain human leukocyte antigen (HLA) haplotypes, usually the Class II category. Since the class II major histocompatibility complex (MHC) genes are critical in antigen presentation and disease induction, they are usually most critical in initiating a particular autoimmune response. Next, a large number of regulatory genes contribute to normal immunologic homeostasis. Allelic differences in these genes may contribute to greater or lesser susceptibility to various autoimmune diseases. They include such regulatory genes as Cytotoxic T lymphocyte− associated antigen 4 *(CTLA4)* and Protein tyrosine phosphatase gene (PTPN22) ***(Effraimidis and Wiersinga, 2014; Sanford and Bottini, 2014).***

Yet, in the aggregate, all of these heritable traits, MHC class II and regulatory genes, contribute less than half of the susceptibility to autoimmune diseases, even in genetically identical twins. Therefore, the majority of patients with an autoimmune disease present without a clear family history. In part, this paradox underlines the role of environmental factors ***(Cotsapas and Hafler, 2013).***

In addition, post-genomic epigenetic effects are responsible for incomplete concordance of monozygotic twins. Epigenetic changes in gene expression occur by mechanisms other than alterations in the DNA sequence. They include such

mechanisms as methylation of DNA nucleotides and histone post-translational modifications affecting chromatin structure. These and many other epigenetic markers account for the fact that even monozygotic twins do not have identical immune responses ***(Stanford and Bottini, 2014)***.

Furthermore, most but not all autoimmune diseases are more common in women than men. A sex bias, therefore, provides increased circumstantial evidence of an autoimmune etiology. The sex-based differences in autoimmune diseases have provided new information on the important role of sex hormones in the pathogenesis of autoimmune disease. Therefore, the response of a disease to immunosuppressive treatment is often an initial clinical indicator of a possible autoimmune etiology ***(Rubtsova et al., 2015).***

Mechanisms involved in autoimmune diseases

1-Inductive mechanisms:

The presence of autoimmunity is the defining characteristic of an autoimmune disease. An autoimmune response can be initiated by autologous or foreign antigens. Like all immune responses, autoimmunity is under strict genetic control of antigen recognition, cellular interactions, and eventual outcomes. In addition, non-genetic environmental agents may promote autoimmune responses ***(King,Tangye andMackay ., 2008)***.

The microorganisms that generally inhabit body surfaces including the skin and mucus membranes also influence both the initiation and progression of an autoimmune response. In individuals, populations of commensal microorganisms ("microbiota") can profoundly affect the induction of such diseases as inflammatory bowel diseases ***(Elson and Alexander, 2015).***

In addition, infection can provide the inflammatory context that favors immune responses, activating through the innate immune responses ***(Fairweather, Frisancho-Kiss and Rose ., 2005)***. Thus, renewed attention has focused on Epstein-Barr virus as an instigating agent in systemic lupus erythematosus (SLE) and other autoimmune conditions . ***(Toussirot and Roudier.,2008).***

2-Pathogenetic mechanisms:

Despite their diverse etiology, certain pathogenetic mechanisms are common to all autoimmune diseases. With few exceptions, they require the presence of self-reactive CD4-positive T lymphocytes. Diseases in which there is a chronic inflammatory response but no evidence of adaptive immunity in the form of self-reactive T cells are referred to as autoinflammatory diseases ***(Grateau and Duruöz, 2010)***.

Previously, self-reactive T-cells were believed to be deleted in the thymus and to be present only when they arise following somatic mutation, producing "forbidden clones." The observation that autoimmune responses are not mono- or