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A Brief Review on Immune Mediated Diseases

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Abstract

The immune system of an organism protects against disease by identifying and killing pathogens and tumor cells. But sometimes it may over-react or start attacking the body and results in immune-mediated diseases. Autoimmune diseases like allergic diseases, Sinusitis, atopic dermatitis, allergic asthma, idiopathic dilated cardiomyopathy, rheumatoid arthritis and some HIV associated diseases are part of immune mediated diseases. In this review we highlight some of the immune mediated diseases along with their diagnostic methods and therapeutic approaches.

Introduction

Immune-mediated diseases are conditions which result from abnormal activity of the body's immune system. The immune system may over-react or start attacking the body. Autoimmune diseases are a subset of immune-mediated diseases. Allergy is a hypersensitivity disorder of the immune system, and is characterized by excessive activation of certain white blood cells called mast cells and basophils by a type of antibody known as IgE, resulting in an extreme inflammatory response. Common allergic reactions include eczema, hives, hay fever, asthma attacks, food allergies, and reactions to the venom of stinging insects such as wasps and bees [1]. Allergic diseases among children and youth are today one of the most common chronicle diseases in westernized countries and the prevalence has increased dramatically during the last decades [2,3]. The environmental and living conditions have been attributed to the increase in the percentage of allergic manifestations in infants and children. The "hygiene hypothesis" states that the lack of early childhood exposure to microbes increases susceptibility to allergic and infectious diseases [4-6].

The risk factors include host and environmental factors [7]. Host factors include heredity, gender, race, and age. Environmental factors include environmental pollution, allergen levels and dietary changes. Some people are sensitive to foods such as peanuts, poppy seeds, egg white proteins and milk. Natural latex is an important cause of allergy in individuals with risk factors. Neuromuscular relaxants together with natural latex are among the most studied agents responsible for pre-operative anaphylaxis. Allergic reactions to latex represents an immune response regulated by IgE antibodies (type I hypersensitivity). Several proteins have been identified from natural latex extracts that adheres to IgE. Ex: Hevein b 6 [8]. Hypersensitivity reactions to alcohol including anaphylaxis are well documented, however it is unclear what component causes these reactions, considering alcoholic drinks are exceptionally complex. There have been speculations on sensitivities to grains, yeast, sulphite additives and histamine. The natural history of these reactions is unknown. Anaphylactic reactions to alcohol may remit spontaneously [9,10].

Sinusitis

Sinusitis is inflammation of the paranasal sinuses, which may be due to infection, allergy, or autoimmune issues. Sinusitis affects 30 – 40 million people per year and is one of the most chronic illnesses [11]. Treatment of sinus problems may cost over $5.8 billion per year. Not only costly but it requires frequent antibiotic use for patients with sinusitis [12]. It has been reported that a total of 16 million office visits per year are due to sinusitis. Sinonasal complaints mainly include allergic rhinitis (AR) and chronic rhinosinusitis (CRS). Patients with CRS are phenotypically classified as CRS with nasal polyposis (CRSwNP) and CRS without nasal polyposis (CRSsNP). Atopy is an underlying etiologic factor in the development of CRS particularly CRSwNP. Many patients with CRS will have atopy. AR is observed in approximately 50% of CRS patients [13].

Atopic dermatitis

Atopic dermatitis (AD), also named atopic eczema (AE), is the most common inflammatory skin disorder often occurring within the first year of life and affecting up to 20% of children, the majority of whom outgrow the disease within a few years. As a result, and despite the occurrence of late-onset AD in some adults, the prevalence of AD in the adult population has been estimated to be much lower (2-9%) [14-16]. Multiple factors are involved in the pathogenesis of AE including genetic predisposition, impaired skin barrier function, microbial colonization and sensitization against environmental allergens. In addition, IgE antibodies reacting with human self-antigens are supposed to be involved in the pathogenesis of the disease. Up regulation of IgE-binding self-antigens in lesional skin of atopic eczema patients might further promote the existing inflammation and induce exacerbations of the disease in the absence of exposure to environmental allergens [17].

Allergic asthma

Allergic asthma is a chronic inflammatory disease of the lung driven by aberrant responses to normally innocuous environmental allergens. Disease is characterized by excessive IgE synthesis, eosinophilic pulmonary inflammation, mucus hypersecretion, airway remodeling and airway hyper responsiveness - all leading to the clinical features of disease - reversible episodes of coughing, shortness of breath and wheezing. While the excessive production of cytokines like IL-4, IL-5 and IL-13 by allergen specific-Th2 cells is sufficient to explain most

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features of allergic asthma, increasing evidence suggests that the Th2 paradigm does not explain the full spectrum of disease severity. In particular, severe asthmatics represent a small subset of asthmatics, in which disease is associated with more severe airway reactivity [18].

Diagnosis and treatment

Allergy tests: Serum analyses, Skin tests, Basophil activation tests are generally used. Basophil activation test (BAT) by flow cytometry is a recently developed in vitro test to predict the potential allergenic effect of a drug [19].

Traditional treatment and management of allergies consisted simply of avoiding the allergen in question or otherwise reducing exposure. For instance, people with cat allergies were encouraged to avoid them. In recent times, there have been enormous improvements in the medical practices used to treat allergic conditions. With respect to anaphylaxis and hypersensitivity reactions to foods, drugs, and insects and in allergic skin diseases, advances have included the identification of food proteins to which IgE binding is associated with severe reactions and development of low-allergen foods, improvements in skin prick test predictions; evaluation of the atopy patch test; in wasp sting outcomes predictions and a rapidly disintegrating epinephrine tablet for eosinophilic diseases [20]. Some common herpes virus infections have been linked to a reduced incidence of IgE sensitization and/or development of allergic disease, including HHV-6 and Epstein-Barr virus (EBV) [3,21,22]. Latex-free environment and gamma-irradiated devices were recommended for diagnosis of latex induced anaphylaxis [23].

Antihistamines are effective in reducing majority of symptoms of allergic rhinitis, but are ineffective for nasal congestion and nighttime symptoms. Montelukast have been found to provide quick relief. Montelukast combined with levocetirizine was effective in reducing daytime, nighttime, composite and daytime eye symptom score as compared to levocetrizine alone [24]. However, these drugs can only treat the symptoms of allergic disease. Immunotherapy, in which causative antigens of allergic diseases are injected, is believed to be the only curative approach to treat allergy. Therapeutic allergens (allergen vaccines) currently used for this purpose are naturally extracted. Allergen extracts, however, contain not only major allergens but also many allergenic and non-allergenic proteins. These proteins may result in anaphylaxis [25].

Sublingual immunotherapy (SLIT) has gained wide acceptance in many European countries and has raised the level of interest in immunotherapy among practicing allergists and primary care physicians. SLIT was firstly accepted as a viable alternative to subcutaneous immunotherapy (SCIT) in the World Health Organization (WHO) Position Paper, published in 1998, and then included in ARIA guidelines. Since 1986, 60 DBPC-RCT trials have been published. There seem to be 2 distinct and perhaps sequential immunologic responses to SLIT; generation of regulatory T- cells (Tregs) secreting interleukin (IL)-10 and transforming growth factor (TGF)-β and immune deviation from Th2 to Th1 responses. Subcutaneous allergen injection immunotherapy has been the principal immunotherapy approach in the treatment of allergic respiratory airway diseases [26,27].

Allergen immunotherapy has been reported to be effective in reducing allergic symptoms and drug consumption in cases of respiratory allergy. However, some concerns still exist about the relative safety of allergen immunotherapy. This form of therapy has a potential risk of serious systemic reactions. Allergen specific immunotherapy is effective and well tolerated treatment for allergic diseases. Allergen specific immunotherapy modifies the immunological response to allergens and induce a state of clinical tolerance [28-30]. SCIT was a safe treatment with a low risk to elicit severe systemic reaction, in which no fatality was observed. There are very few studies evaluating osteopathic treatment for sinus pain. Osteopathic sinus manipulative treatment functions to relieve sinus obstruction and pain; improve venous and lymphatic flow; affect reflex changes and improve mucociliary clearance [11].

Idiopathic dilated cardiomyopathy

Although idiopathic dilated cardiomyopathy (DCM) is the third most common cause of heart failure after coronary artery disease and hypertension, the etiology is largely unknown. One hypothesis is that immunological factors are responsible for disease development. Proinflammatory cytokines such as TNF-α and IL-6 have long been reported as elevated in plasma of patients with DCM and shown to correlate with heart dysfunction. These cytokines are today considered as a part of the heart failure syndrome [32-35].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a multi-factor disease with a key role of genetic component in its genesis. Development of osteoporosis and articular destruction is attributed with over expression of pro-inflammatory cytokines and reduced production of anti-inflammatory ones. Common variants of the IL-4, IL-6, IL-10, IL-18 and TNFα may significantly contribute to RA susceptibility [35].

Cystic lesions

Cells of immune system comprised of lymphoid series and myeloid progenitor series cells. Mast cells and tissue eosinophils both are granulocytes which come under myeloid progenitor series of immune cells system. The presence of mast cells in odontogenic cyst could contribute to their pathogenesis in several ways. Odontogenic cysts represent the commonest form of cystic lesions that affect the human skeleton. There are some common factors contributing to the pathogenesis of cystic lesion and in their subsequent enlargement [36,37].

Previous studies reported that polysaccharides have anti-tumor, immuno-stimulatory, and anti-oxidative effects. Recently, the non-starch polysaccharides have emerged as an important class of bioactive natural products [38-40]. In many Asian countries, several pharmaceutical agents derived from polysaccharides have been extracted such as lentinan, schizophyllan and krestin [41,42]. Saponins are natural products discovered in sea cucumbers and sponges, and possess a variety of biological and pharmacological activities [43,44], including antitumor, anti-bacterial, anti-microbial, anti-fungal, anti-yeast, and anti-inflammatory activities [45].

Selection of suitable antigens, preferably targets for cell mediated and humoral immune response is a critical step in the development of cancer vaccines. Cell surface proteins that are over-expressed in cancer cells thus constitute a very attractive class of antigens that can be targeted for effective cancer immunotherapy [46].

Cancer vaccines, activating the immune system against specific antigens, have demonstrated clinical benefit and an increasing number are now in development; however, one ongoing challenge is to identify the most appropriate antigenic targets. Although tumor antigens

were originally identified by cloning T cells that exhibited anti-tumor activity and then identifying the antigen to which the clones responded through genetic approaches, we have utilized a novel approach which exploits the differential expression of peptides displayed within the Major Histocompatibility Complex (MHC) [47] in tumors compared to normal cells [48]. Adoptive transfer of allochimeric MHC I-conditioned T cells promotes development of Treg cells and attenuates chronic rejection in rat cardiac model system [49].

HIV

Acquired immunodeficiency syndrome (AIDS) is a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive. It is caused by Human immunodeficiency virus (HIV) which is a lentivirus (a member of the retrovirus family) [50,51]. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (perinatal transmission). In 2005, it was estimated that HIV would infect 90 million people in Africa. According to UNAIDS the prevalence of HIV/AIDS in South Africa among 15-49 year olds was 17.8% at the end of 2009 [52]. In Tanzania, Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) remains a significant problem with an adult prevalence rate of 8.8% [53]. Patients infected with HIV typically seroconvert within weeks of primary HIV infection. In rare cases, patients do not develop antibodies despite demonstrable HIV infection by p24 antigen or viral load assays; a seronegative HIV [54].

Coinfection refers to two strains that appear to have been acquired at the same time (or too close to distinguish). Reinfection (or superinfection) is infection with a second strain at a measurable time after the first. Both forms of dual infection have been reported for HIV in both acute and chronic infection around the world [55,56]. Currently the global burden of both human immunodeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) is quite significant. HCV currently infects 3% of the world's population (greater than 170 million people), with approximately 38,000 new infections occurring annually in the United States alone [57]. Currently 33 million people globally are estimated to be living with HIV-1 [58]. Due to similar routes of transmission of these viruses, co-infection with the two is quite common. Intravenous drug use, in particular, has resulted in an increase in rates of HIV-1/HCV co-infection, with incidence reaching or exceeding 90% prevalence [59,60].

Histoplasmosis, caused by the fungus Histoplasmacapsulatum, is also known as Darling's disease. Disseminated histoplasmosis is associated with Acquired Immunodeficiency Syndrome (AIDS), involves different organ systems and may be fatal if untreated. Bone marrow histoplasmosis is a rare manifestation of disseminated Histoplasma infection presenting as pancytopenia. Disseminated TB is a close differential for histoplasmosis [61-63]. In HIV infected adults focal brain lesions (FBL) can be caused by opportunistic infections, neoplasms, or cerebrovascular diseases [64]. In developed countries, cerebral toxoplasmosis is the most frequently identified cause of HIV-associated FBL (HFBL), followed by primary CNS lymphoma [65]. The AIDS virus is a neurotropic virus and CNS involvement as the presenting complaint is seen in approximately ten percent of cases of HIV infection. The mechanisms of demyelination in HIV infection could be due to lesions directly related to infections of the nervous system by HIV itself, opportunistic infections and lymphomas, secondary to cell mediated immunodeficiency, and other general and systemic complications of HIV [66]. Rhabdomyolysis is a syndrome characterized by skeletal muscle breakdown, myoglobinuria, and creatine phosphokinase (CPK) elevation and can frequently lead to renal dysfunction. Numerous precipitating factors have been linked to rhabdomyolysis including trauma, seizures, drugs, toxins, metabolic derangements, severe exercise, and infections. Human immunodeficiency virus (HIV) infection has been associated with rhabdomyolysis [67-70]. Primary iliopsoas abscesses occur as a result of haematogenous spread of bacteria and are more frequent in established immunodeficiency states such as diabetes mellitus, renal failure, AIDS and with intravenous drug use [71]. Diagnosis of the abscess requires appropriate imaging (Computed tomography is the gold standard) as well as identification and antibiotic sensitivity determination of the causative organism through percutaneous drainage. Treatment consists of appropriate antibiotic cover with or without a drain remaining in situ to drain the abscess [72].

Incomplete immune reconstitution and persistent immune system hyperactivation in spite of highly active antiretroviral therapy continues to be a challenge. Both facts may lead to an increased risk for AIDS-defining and non AIDS-defining clinical conditions and may also promote atherogenesis and liver fibrogenesis in HIV and hepatitis C virus-coinfected patients. In spite of the fact that HAART allows the reconstitution of the immune system, which changes drastically the natural history of HIV infection, up to 30% of patients do not achieve a significant gain of CD4+ cell counts [73].

Diagnostic algorithm for HIV includes screening with ELISA or rapid tests and then confirmation using alternative screening tests, western blot test or a test to detect HIV RNA. The diagnosis of HIV infection by the detection of HIV- specific antibody is not possible if infected individuals do not produces HIV specific antibodies [54].

Chronic human immunodeficiency virus (HIV) infection is characterized by defects in the immune system including depletion of CD4+ T-cells and impaired T-cell function [74]. The CD4+ T-cell lymphocyte count (henceforth CD4+ count) is one of the most important prognostic factors for progression of HIV infection and forms the basis for International recommendations for antiretroviral treatment and prophylaxis [75]. However, comparative studies between African and European populations suggest that total lymphocyte count (TLC), including CD4+ count, is likely to vary significantly by ethnicity, in both, healthy [76] and HIV-infected individuals [77,78]. Total lymphocyte and CD4+ count is negatively affected by the poor nutritional status, and the prevalence of under-nutrition is generally higher in Asians [79,80]. Second, environmental factors including higher prevalence of background infections, such as Tuberculosis in Asian countries, may account for some of these differences [78,81]. World health organization (WHO) guidelines in 2010 [82] state that the total lymphocyte count (TLC) is no longer recommended to guide treatment decisions in adults and adolescents with human immunodeficiency virus (HIV). Recommendation to switch to CD4+ cell (CD4) counts will be more accurate, but it is more costly and difficult to monitor regularly [83].

Treatment: Successful antiretroviral therapy (ART) suppresses viral replication. The subsequent recovery of T-cell responses and the decline of opportunistic infections are well documented. Enfuvirtide, a 36-amino acid synthetic peptide, is the first antiretroviral drug that

inhibits the entry of HIV-1 into host CD4 lymphocytes [84]. Enfuvirtide is approved, in combination with other antiretroviral drugs, for the treatment of HIV infection [85]. Nucleoside reverse transcriptase inhibitors (NRTIs) are currently an essential part of highly active antiretroviral therapy (HAART) for the treatment of HIV. Since the introduction of protease inhibitors (PI) in highly active antiretroviral therapy (HAART) for HIV infection in the mid-1990s, HIV-related morbidity/mortality has decreased to one-fifteenth the level observed prior to the HAART era [86,87]. Amprenavir, the fourth PI to become available, offered some advantages over earlier PIs, including the option for once- or twice-daily dosing, minimal effect of food on its pharmacokinetics and a favorable resistance profile. Patients switched from equimolar doses of APV to FPV in HAART regimens with no other regimen changes, virologic suppression is maintained or improves and CD4+ counts increase over 24 weeks [88,89]. More than 1 million HIV-1 subtype C infected patients in South Africa are receiving antiretroviral therapy (ART) [90]. In 2004 a national treatment program was initiated, including a first-line regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI), either efavirenz or nevirapine, in combination with NRTI, stavudine or zidovudine, and lamivudine [91,92]. In 2004 fixed dose combination (FDC) tablets containing abacavir (ABC +lamivudine (3TC) (Kivexa®) and tenofovir (TDF) + emtricitabine (FTC) (Truvada®) were licensed. The long term safety and efficacy profile of these drugs in once-daily, FDC formulations is not known. In recent years particular attention has been drawn to the effect of antiretroviral (ARV) therapies on the incidence of serious non-AIDS events (SNAEs), including cardiovascular disease (CVD), end-stage renal disease, liver failure and fractures [93-95]. Recently, there has been an increased interest in the role of Herpes suppressive therapy in reducing the HIV-1 viral load of HIV positive individuals co-infected with HSV. With a few notable exceptions, no studies have found that acyclovir affects HIV-1 transmission, although it does reduce plasma, genital, rectal and seminal HIV-1 RNA concentrations in HSV co-infected individuals [96,97]. Concomitant antiretroviral therapy (ART) can be a factor leading to a lower efficacy of pegylated interferon (peg-IFN) plus ribavirin (RBV) in human immunodeficiency virus (HIV)/ hepatitis C virus (HCV)-coinfected patients. TDF plus lamivudine (3TC) or emtricitabine (FTC) is the first choice of NRTI combinations in coinfected individuals on treatment for HCV infection. However, there is currently little information about whether protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) which influence the rate of sustained virological response (SVR) in HIV/HCV-coinfected individuals [98-100].

Even with combination antiretroviral therapy (cART) regimen, the durability of HIV control is limited by many factors (adherence to treatment, drug toxicity, bioavailability, among the most important) [85]. Adherence is described as engagement and accurate participation of an informed patient in a plan of care [101]. Injection drug use (IDU) was the initial driving force for HIV spread in China and had contributed to over half of the total infections as of 2005. Risky drug use behaviors such as injection, as well as risky sexual behaviors such as having multiple sexual partners, can put drug users at risk of both acquiring and transmitting HIV and other blood-borne diseases [102]. Risk factors contributing to virologic failure and drug resistance in sub-Saharan Africa include incomplete adherence, treatment interruptions, low CD4 cell counts low body weight before ART initiation and prior exposure to single dose nevirapine (sdNVP) for prevention of mother-to-child transmission (pMTCT) and/or dual nucleoside treatment [92]. Some of the factors mentioned to constrain adherence include stigma, poor social support, wrong beliefs on HIV causation, lack of food, side-effects, inadequate counseling, long waiting time, costs related to transport and long distance to the facility. Factors promoting and/or facilitating adherence include adherence counseling, disclosure to the family members, social support, religion, good chain of drug supply, information and education [53].

Current highly active antiretroviral therapy (HAART) for the treatment of HIV infection is associated with long term side effects. Up to one third of patients treated with nucleoside reverse transcriptase inhibitors (NRTIs) experience peripheral neuropathic side effects. This distal symmetric polyneuropathy (DSP) is mainly caused by some dideoxynucleoside analogues such as didanosine and stavudine [103]. In a subset of patients, a favorable virological response to ART is accompanied by an atypical presentation of diseases associated with pre-existing opportunistic pathogens [104,105]. These are known as immune restoration disease (IRD) or immune reconstitution inflammatory syndrome (IRIS). NK cells may contribute to viral IRD [74]. Raltegravir, an integrase inhibitor approved for treatment of HIV infection and used in combination with other antiretroviral drugs has been associated with rhabdomyolysis [67]. IRIS is characterized by a paradoxical deterioration of clinical status after initiation of Anti-Retroviral Therapy (ART), despite improved immune function. It is caused by inflammatory response against the infectious antigen. IRIS typically occurs in patients with a low initial CD4 (usually <50) and a rapid decline in viral load [106,107]. HCV/HIV-coinfected individuals who received NVPbased ART showed lower plasma HCV-RNA levels than those who were treated with EFV- or PI-containing regimens. NVP use could be associated with lower HCV-RNA levels among HIV/HCV-infected patients [108,109]. Acetyl-L-Carnitine (ALCAR) has been investigated for the treatment of existing distal symmetric polyneuropathy (DSP) but the potential for ALCAR to prevent DSP is unknown. Acetyl-L-Carnitine has been shown to be an effective pathogenesis based therapy for the antiretroviral toxic neuropathy [110]. The potential for bioinformatics applications in the greater field of immunology is indisputable. Bioinformatic and phylogenomic methods have been and are being, used for the development of new vaccines and immune pharmaceuticals, and the mapping of epitopes [111].

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