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Alzheimer's Disease of the Immune System: A New Variant of Immune Deficiency

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Abstract

The interaction between infectious pathogens and the immune system has been a focus of research for many years. However, the failure of re-recognition or immune memory of infectious pathogen remains a clear mystery A memory B cell defect coupled with low levels of C1-INH and/or C1-INH function-failure of both the innate and adaptive immune components-may lead to persistent unresolved infection. Here we present 3 case studies that explore the abnormal immune response that may lead to persistent infection. These cases offer possible clarification of a longstanding clinical observation that some patients may develop a post infectious syndrome that includes various neurological symptoms and unusual fatigue. These patients may have positive serology seen only during acute infectious phase and have a documented positive PCR, suggesting active presence of the pathogen. The unusual presentation is prolonged and irreversible. We use the term "Alzheimer's disease of the immune system" to identify this subtype due to the memory defect of the immune system. As we identified 3 common immune defects in all cases, we suggest a new immune deficiency leading to the post infectious syndrome.

Introduction

The interaction between an infectious pathogen and the immune system has been a focus of research for many years. However, the failure of re-recognition or immune memory of infectious pathogens remains a mystery. In this case-based study, we describe some clinical and scientific observation that may explore the reasoning behind this "memory defect."

Toll-like receptors

The pathogen recognition receptors or toll-like receptors (TLR) in the innate immune system may explain some of its failure to recognize infectious pathogens. It has been suggested that repeated immune activation of certain TLRs early in life may "train" the immune response by binding and recognition of pathogenic or microbial molecular patterns. The resulting immune initiation was found to have an important role in shaping adaptive immune events. Repeated encounters with the same stimulatory antigen will gradually lead to an excessive Th2 response with the development of more severe forms of atopic disease; i.e. the atopic march. The early relationship of the TLR system with atopic cells may explain our observation that part of the "memory defect" is a partnership with atopic immune players [1,2].

Viral infections can upregulate TLR signaling; thus, innate immunity has a direct effect on immune response to viral infections. Antiviral innate effectors cells can control the immune response, as well as its quality [1,2]. The innate immune response provides sophisticated defense mechanisms to protect complex macroorganisms from attack of microorganisms. Among those, the complement system and TLRs are of paramount importance, having long been known to be major elements of innate immunity against infectious pathogens [3,4]. More recently, it has been observed that complement is also involved in the adaptive immune response and is considered a functional bridge between the innate and adaptive responses, making it an essential and efficient player in immune homeostasis and acquired immunity.

Complement proteins

The second player may be C1 esterase. This complement is also involved in the adaptive immune response and is considered to be a functional bridge between the innate and adaptive responses, making it an essential and efficient player in immune homeostasis and acquired immunity. Complement proteins form a trio of intersecting enzyme cascades that result in a number of protective mechanisms that bind to foreign surfaces and, thus, fight viruses, bacteria, and other foreign substances [5]. Once the complement cascade has been initiated, there are mechanisms that inhibit or slow down the process reaction at various steps. Without these checks in the system, uncontrolled complement activation can lead to inflammatory issues, autoimmune disorders, alterations of blood flow, and tissue destruction. C1 esterase inhibitor (C1-INH) is the major inhibitor of the classical pathway [6,7]. In addition to blocking activity of C1r and C1s, C1-INH has several non-complement target proteases, including factor XIIa and kallikrein of the kinin pathway, and plasmin and MASPs 1 and 3 of the lectin pathway [8]. C1-INH belongs to the family of serpins. Recent studies suggest some anti-inflammatory function for this molecule, possibly explaining the effects of C1-INH in diseases other than hereditary angioedema [9]. Acquired deficiency of C1-INH can accompany activation of complement, with consumption of C1-INH and hyper-activation of the classical pathway. This relationship has also been suggested with autoimmune (auto-antibodies against the inhibitor) or lympho-proliferative diseases [9].

In a previous article, we noted that a subset of patients with CVID had low C1-INH levels and/or C1-INH function. The clinical presentations of this subset of patients were extreme fatigue (90%), autoimmune presentation (80%), gastrointestinal issues (50%),

arthralgia (40%), neuropathy (20%), migraine (30%), and mild cognitive changes (10%) [10].

A memory B-cell defect coupled with low levels of C1-INH and/or C1-INH function-failure of both the innate and adaptive immune components–may lead to persistent unresolved infection.

Viruses

The Epstein-Barr virus (EBV) is a double-stranded DNA virus that is a member of the herpes family [11]. During their lifetime, approximately 95% of the world's adult population will become infected with EBV and will become lifelong carriers. EBV-infected individuals primarily exhibit subclinical infections or self-limiting acute infectious mononucleosis (IM) and a minority will present with fatal EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) [12]. Some patients will see a persistent presence of the virus and/or an acute IgM response. They may also clinically present with the spectrum known as chronic fatigue syndrome. EBV has been used as a paradigm for studying host virus interaction.

Autoimmune diseases comprise a heterogeneous group of conditions associated with a failure of the immune system to recognize self, and, consequently, create inflammatory disease. In contrast to allergic disease, it has generally been agreed that autoimmune conditions are mediated by an overactive Th1 arm of the immune system. More recently, there has been considerable debate about the role of Th2 in autoimmune conditions and the relative Th1/Th2 balance, especially in those mediated by autoantibodies such as systemic lupus erythematosis (SLE) and rheumatoid arthritis [13].

EBV infection is also known to be involved in the development of different autoimmune diseases. Several studies have brought forth evidence of connections between EBV and infection [14,15]. Researchers have even suggested a prognostic role of elevated anti-EBV antibody titers in the development of multiple sclerosis (MS) [16]. Toussirot et al. demonstrated serological differences in patients with systemic lupus erythematodes and rheumatoid arthritis in comparison to healthy controls, and confirmed the presence of viral DNA and RNA in disease-targeted tissue in patients with rheumatoid arthritis and Sjögren syndrome [17].

Mycoplasma pneumoniae (MP) is an extracellular pathogen that attaches to ciliated epithelial cells of the respiratory tract mucosa and causes damage [18,19]. Linkages between both atopy and immune deficiency and MP have been described in various studies [20-23]. A significant correlation between MP infection and IgE levels, which is associated with a Th1/Th2 cytokine imbalance, has also been established [24].

The relationship between MP infection and secondary allergic disease, as well as clarification of the associated mechanisms of inflammatory response, is not clear. MP patients with allergic conditions had increased serum IgE levels and increased IL-4/INF-γ ratio; IgE and Eosinophil Cationic Protein were further elevated in patients who eventually developed secondary asthma changes [25].

Parvovirus B-19 is a single strand DNA virus. Persistent parvovirus has been associated with various autoimmune diseases, suggesting a clear relationship with the immune system [26]. One common linkage to all infectious pathogens is the unknown reason that underlies the failure of the immune system to respond to the virus, thus leading to a "memory immune defect response." The potential partners that link the infectious pathogens to the immune system, and which may be involved in the "memory defect," are also unknown.

Immunity may also play a role in the "memory defect." Signals triggered during the innate immunity response to various infections can lead to the release of large numbers of migrating, high affinity IgE-derived precursors of the mucosal dendritic cells [27]. Furthermore, a history of atopic disease is associated with impaired TLR-4 mediated immune function in children (compared with non-atopic children). The immune response to various pathogens can determine the latency status, the immune response, and in some cases oncogenic ability. Immune response to DosR and Rpf antigens from Mycobacterium tuberculosis (Mtb) seems to be important for latency maintenance [28].

Here we present 3 case reports of patients who presented with a new subtype of CVID, which we refer to as "Alzheimer's disease of the immune system." All of these patients have a persistent IgM immune response and positive PCR to various pathogens. They also all have similar clinical presentations and common diagnostic findings; specifically, evidence of atopy, low C1-INH, low memory B-cells, low vitamin D3, decreased T- cell response to antigens, and low response to TLR3.

Case Report 1

An 18-year-old female presented to our clinic with a complex medical history that included malaise, extreme fatigue, and headaches along with positive IgE food allergies. She experienced chronic and recurrent infections that included sinusitis, otitis media, and bronchitis. Eighteen months prior to coming in, she had contracted EBV and missed 3 weeks of school as a result. IgM and PCR results were positive. Table 1 shows the results of clinical testing for the 3 patients we studied.

	PCR	TLR-3	Memory B	C1-INH	T-cell Antigens	Atopy
Case 1	Positive	Decreased	6.9(8-35%)	11 mg/dL	Decrease	Positive
Case 2	Mycoplasma PCR-positive	Decreased	12%	17	Decrease	Positive
Case 3	Parvo-PCR-positive	Decreased	8%	11	Decrease	Positive

Table 1: Clinical Finding for 3 Patients with CVID Subtype

Case Report 2

A 33-year-old female presented to our clinic with a medical history that included malaise, fatigue, and paresthesia. She had numerous respiratory infections leading to recurrent pneumonia, with no response to multiple courses of antibiotics. Evidence of chronic lung disease was found, based on pulmonary function testing, imaging, and other biomarkers, secondary to chronic infections. The patient displayed clinical arthralgias, fatigue, and skin rash, which are frequently seen in immunocompromised patients (Table 1).

Case Report 3

A 45-year-old female presented to our clinic with a history of seizure and fatigue and recurrent infections of prolonged course requiring multiple antibiotics. The majority of infections were gastrointestinal, with few respiratory infections. The patient noted many emergency room visits as a teenager and adult due to debilitating stomach pains that, at the time, were diagnosed as gastritis. Two months prior, she had experienced a seizure, which her neurologist treated with eslicarbazepine. The patient was tested for parvovirus B19, and the results were positive (Table 1).

All 3 patients were treated with CINRYZE® (C1 esterase inhibitor [human]) 1000 units BID for 3-6 months of them had been treated previously with intravenous immunoglobulin (IVIG) for 3 months. No clinical or serology changes occurred after treatment with IVIG, but C1 therapy was able to reverse the serology as well had a major impact on the clinical outcomes.

Discussion

The focus of the 3 cases was to explore the abnormal immune response that may lead to persistent infection based on IgM and PCR. We used 3 different pathogens, but the common linkage in all of the cases was the ability of the pathogens to have a unique interaction with the immune system and the common findings that may present a new immune deficiency described as "memory defect" or "Alzheimer's disease" of the immune system.

All of the patients had atopy, low C1-INH, low memory B cells, low response to T cells antigens, and decreased signaling to TLR-3. These cases offer possible clarification of a longstanding clinical observation that some patients may develop a post-infectious syndrome that includes various neurological symptoms and unusual fatigue. These patients may have positive serology seen only during acute infectious phase and have a documented positive PCR, suggesting active presence of the pathogen. The unusual presentation is prolonged and irreversible. We use the term "Alzheimer's of the immune system" to identify this subtype due to the memory defect of the immune system. As we identified 3 common immune defects in all cases, we suggest a new immune deficiency leading to the post-infectious syndrome and suggest their potential mechanism.

When it functions optimally, the immune system is alert to danger signals and provides protection against host invaders such as viruses, bacteria, and other pathogens. The immune system is divided into 2 interconnected subsystems–innate and adaptive [3]. Innate immunity is the first line of defense against pathogens and is composed of effectors that provide rapid, robust, nonspecific response [4], whereas adaptive immunity is a slower, fine-tuned response organized around 2 classes of lymphocytes, T- and B- cells, in which antigen-specific receptors allow identification and destruction of pathogens, as well as adaptive immune recognition that ensures tailored immune responses and long-term immunological memory against re-infection. Once thought to work independently, recent research shows a complex interaction and integration of innate and adaptive immunity.

The cases described here presented us with 3 common findings. Previously, we suggested that atopy may be one factor in the delayed maturation of the immune system, leading to transient hypogammaglobulinemia at early ages [29]. Delayed postnatal maturation of the immune system, including a delayed transition from Th2 to Th1 bias, is a risk factor for respiratory infections [30]. In a mouse model, after infection of the lungs with *Chlamydia muridarum*, IL-13, a Th2 cytokine, is rapidly produced and promotes susceptibility to infection, possibly related to impairment of macrophage phagocytic function [31]. Downregulation of TLRs may be responsible for increased susceptibility of asthmatics to mycoplasma infection, as mycoplasma clearance in an allergic mouse model has been demonstrated to be due to TLR2 down-regulation [32]. Another viral/immune example that may be related to the role of atopy is RSV [33].

An impaired innate immune response to RSV infection has been reported in adults with asthma and has been proposed to increase susceptibility to viral infections. Spann et al. demonstrated that airway and nasal epithelial cells in children with a history of wheeze and/or atopy have an intrinsic interferon (IFN)-independent defect in the antiviral response those results in elevated viral replication [34]. Impaired adaptive immune responses have also been described in patients with atopic dermatitis. It was found that children with moderate to severe eczema had significantly lower antibody responses to pneumococcal vaccination compared to control subjects with recurrent upper respiratory infections (17% compared to 57%) [35]. It was also determined that early onset atopic dermatitis increased the risk of developing autoimmunity later in life, suggesting a common immunological determinant [36].

The interaction of infectious pathogen(s) with the immune system leading to abnormal neurological disease was demonstrated many years ago. Pediatric acute-onset neuropsychiatric syndrome (PANS) is a broad diagnostic criterion for children with severe sudden onset of neuropsychiatric changes, most commonly, obsessive-compulsive disorder (OCD)/Tics, brought on by infectious agents [37]. Previously, the only infectious agent that was recognized for causing abrupt neuropsychiatric changes was group A beta-hemolytic *Streptococcus* (GABHS); patients with this presentation were diagnosed with PANDAS (pediatric autoimmune neuropsychiatric disorders associated with Streptococcal infections) [38]. Because it is often difficult to show a relationship between strep infections and OCD/Tic symptoms in PANDAS, the newer diagnosis of PANS was agreed upon by researchers and clinicians in 2010 in order to encompass the growing number of infectious agents that also caused acute-onset neuropsychiatric changes: *Mycoplasma pneumonia* causing pneumonia, Epstein-Barr virus; and *Borrelia burgdorferi* causing lyme disease, group A beta-hemolytic streptococci (GABHS). A diagnosis of PANS allows clinicians to focus on symptoms and not cause, and is based on history and physical examination. A significant finding that may suggest a relationship between a post-infectious response and behavioral changes revealed that antibodies to streptococcal proteins crossreacted with human brain tissue [39]. This may suggest a form of post-infectious autoimmunity through molecular mimicry. The possible crossreaction to brain tissue may also occur with other infectious agents because of sudden onset of behavioral changes. A recent paper by Hornig noted that some patients with Tourette

syndrome, OCD, and PANDAS show evidence of immune dysfunction [40]. Other studies show altered immunoglobulin profiles (IgM, IgG subclasses, IgA) and decreased levels of regulatory T-cells in PANS patients compared to healthy controls [41,42]. At the 2013 PANS Consensus Conference, it was recommended that PANS patients undergo immunodeficiency assessments [43].

Another aspect of innate immunity is the complement system that not only affects immunity against infectious pathogens, but is also: 1) a functional bridge between the innate and adaptive responses; and 2) a crucial player in immune homeostasis and adaptive immunity [3,44]. The links include enhancing humoral immunity, regulating antibody effectors mechanisms, and modulating T- cell function [4,45,46]. Uncontrolled complement activation can lead to inflammatory issues, autoimmune disorders, alterations of blood flow, and tissue destruction [6,7].

Common variable immunodeficiency disease (CVID) is comprised of a heterogeneous group of humoral immunodeficiencies of unknown etiology. It is characterized by infections, gastrointestinal disorders, autoimmune diseases, and increased susceptibility to malignancies [47]. A subset of patients with CVID have low C1-INH levels and/or C1-INH function. The clinical presentations of this subset of patients are extreme fatigue (90%), an autoimmune presentation (80%), gastrointestinal issues (50%), arthralgia (40%), neuropathy (20%), migraine (30%); and mild cognitive changes (10%) [10]. The inhibitory proteins responsible for confining activation to appropriate pathogenic surfaces to prevent collateral damage to the host are insufficient in quantity and/or function. This uncontrolled complement activation may be a contributing factor to these clinical presentations [6,7].

Although CVID is the most prevalent immune deficiency, its linkage to both autoimmunity and cancer is not clear. Warnatz et al. [48] suggested defining 2 groups of patients with CVID based on levels of switched memory B-cells, with group I consisting of patients with low levels of switched memory B-cells, and group II consisting of patients with normal levels of switched memory B-cells. These groups present differently, in that patients with normal levels of switched memory B-cells had a more normal course of the disease vs a higher morbidity for those patients with low levels of switched memory B-cells. We suggest that the new type of immune deficiency that includes low C1-INH as well low memory B cells, low response to T cell antigens, and atopy as a "silent partner."

The second important findings are the role of C1 from both diagnostic and therapeutic standpoints. We began therapy with IVIG as the patients were diagnosed with CVID, and this is the accepted therapy. Due to low C1-INH and some HAE-like symptoms, we added the C1 therapy. We believe that a synergistic effect may influence the memory defect that is leading to the persistent infections.

All cases have been treated with a C1 therapy due to HAE-like symptoms, specifically severe headache. In all cases, we saw a clear clinical improvement with a reversal of infection demonstrated by a negative PCR. Further studies are needed to determine if the synergy of IVIG and C1 therapy may be effective in this group of patients.

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