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EDITORIAL

Infectious Diseases and Their Role in Neuroimmune Disease

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ABSTRACT

Recent findings suggest a relationship between a post-infectious immune response and neurologic changes. These changes, manifesting as various neurological symptoms, including memory issues and cognitive alterations, may be linked to a form of post-infectious autoimmunity. We have coined the term "Alzheimer's of the Immune System," or AIS, to describe this syndrome and various immune partners that may play a role in this immune dysfunction have been identified. Here, we will discuss several clinical presentations that feed into the hypothesis of infectious-immune axis and its mechanism of action. We propose that these disorders fall under the umbrella of AIS and discuss the role of immuno therapy in their management.

First, we consider pediatric acute-onset neuropsychiatric syndrome (PANS), a broad diagnostic criterion created to describe children with severe, sudden onset of neuropsychiatric changes. Research exploring the link between immune dysregulation in PANS and its amelioration with intravenous immunoglobulin treatment strongly suggests the association of PANS with a pro-inflammatory state. Next, we delve into autism spectrum disorder (ASD), characterizing it as a neuroimmune disorder. ASD marked by communication and social skill deficits, as well as repetitive and stereotypical behaviors, is characterized by related but distinct profiles of immune dysregulation, inflammation, and endogenous autoantibodies that persist within the affected individual. Further definition of the role of immune dysregulation in ASD thus necessitates a deeper understanding of the interaction between both the mother's and child's immune systems, and their potential role in diagnosis and treatment. Lastly, we discuss post-viral fatigue syndrome in patients who have recovered from SARS-CoV-2 infection as another example of neuroimmune condition recently added to the growing list.

Further research is needed to validate our hypothesis of AIS, including large scale randomized control trials of different immuno therapies. By unravelling the infectious-immune axis and its mechanism of action, we equip physicians with valuable tools for identifying optimal forms of treatment and management for these conditions.

Editorial Commentary

The field of neuroimmunology has witnessed a significant upsurge in the prevalence of neuroimmune diseases. These conditions, often characterized by chronic pain, fatigue, and diverse neurological and psychiatric manifestations, arise from a complex interplay between infections and the immune response. Various infections, including Epstein Barr virus in multiple sclerosis, herpes simplex virus in Alzheimer's disease,[1, 2] and others associated with pediatric acute-onset neuropsychiatric syndrome (PANS),[3] Lyme disease[4], Kawasaki syndrome,[5] and autism,[6, 7] are now hypothesized to trigger neurological and cognitive changes.

Some similarities and differences in the characterization and immunology of PANS, autism, and post-acute COVID-19 syndrome (PACS) have been observed and reported.[3, 8, 9] These conditions arise due to the failure of the immune system to effectively combat a pathogen, resulting in a cytokine storm that affects various systems of the body, including the nervous system. For many years, we have investigated the relationship between infectious disease and immune responses. In an article published in 2016, we used the term 'Alzheimer's of the Immune System' (AIS) to describe this syndrome.[10] In certain patients' post-infectious disease, a memory defect of the immune system creates a neurological storm that includes mast cell activation; complement activation due to low levels and/or low function of C1-esterase inhibitor (C1-INH); decreased levels of immunoglobulin subclass 3; low response to T cell antigens; and a decrease in signaling of toll-like receptor. Here we discuss the infectious-immune axis as a driver of neuroimmune diseases and share our experiences of patients affected by these conditions.

PEDIATRIC ACUTE-ONSET NEUROPSYCHIATRIC SYNDROME

PANS is a broad diagnostic criterion created to describe severe, sudden onset of neuropsychiatric changes occasionally observed in children. The most common manifestation is obsessive-compulsive disorder (OCD) or tics brought on by an infectious trigger.[11, 12] The variety of neuropsychiatric symptoms was hypothesized to be a result of an immune response to the infection and subsequent inflammation and/or misdirected autoantibodies altering neuronal functions,[13] suggesting that antibodies to streptococcal proteins cross-react with tissue from human brain, causing a form of post-infectious autoimmunity through molecular mimicry.[14, 15] For many years, the only infectious agent that was recognized as causing abrupt neuropsychiatric changes was group A beta-hemolytic Streptococcus (GABHS) and patients with this presentation were given a diagnosis of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS). As it was often difficult to show a relationship between strep infections and OCD/tic symptoms in PANDAS, in 2010, researchers and clinicians agreed on a new diagnosis—PANS—that would encompass the growing number of infectious agents that were being recognized as causing acute-onset neuropsychiatric changes.[6]

In current clinical practice, PANS diagnosis is based on history and physical examination with focus on symptoms rather than the cause. Treatment options for PANS include psychiatric and behavioral interventions, as well as the use of nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotic therapy, corticosteroids, plasmapheresis, and intravenous immunoglobulin (IVIG). Current guidelines suggest oral or intravenous corticosteroids may be sufficient for moderate to severe PANS; however, IVIG is recognized as the preferred treatment for these patients by most members of the PANS Research Consortium.[16, 17]

In 1999, the first placebo-controlled study using IVIG treatment to treat post-GABHS neuropsychiatric symptoms (OCD and tics) demonstrated that the treatment was associated with symptom improvement.[18] Similarly, we conducted two clinical trials investigating the efficacy of IVIG infusions treatment in patients with moderate-to-severe PANS. Our first study showed for the first time that sequential infusions of IVIG successfully ameliorated psychological symptoms and dysfunction patients with PANS and these benefits were sustained for at least 8 weeks, and for up to 46 weeks after the final infusion in a subset of subjects.[19] Similar results were obtained in our recent study, enrolling 10 patients with moderate-to-severe PANS who received six infusions of IVIG (Octagam 5%) every 3 weeks.[20] Psychiatric measures and blood samples were obtained at Visits 1 (pre-treatment), 7, and 8 and flow cytometry was used to assess myeloid cell activation. IVIG treatment resulted in significant improvements based on psychometric assessments and parent questionnaires, and we showed that pro-inflammatory monocyte and dendritic cell levels decreased after IVIG treatment. The study results suggest IVIG treatment improves the pro-inflammatory profile and psychometric scores in PANS patients.[20]

Evidence is increasingly pointing to PANS as a post-infectious immunopsychiatric disorder,[3, 6, 21] and current research suggests that PANS is associated

with a pro-inflammatory state that improves after treatment with IVIG. Additional research is required, however, to elucidate the role of the immune system in PANS and the mechanism of action of IVIG in its regulation.

AUTISM AS A NEUROIMMUNE DISEASE

Autism spectrum disorder (ASD) is a group of heterogeneous neurodevelopmental conditions that typically manifest in early childhood as impaired social interaction, and repetitive behavior and interests.[7, 22] Despite extensive research, the etiology and pathogenesis of ASD remain largely unclear. The disorder may have a variety of causes, including environmental, neural, genetic, immune, and biochemical.[23] Structural abnormalities have been identified in areas of the autistic brain, with a pattern suggesting that a neurodevelopmental abnormality may have occurred.[24, 25] Research has suggested autoimmunity as a pathogenic factor in autism and a subset of the ASD population presents with immune dysregulation.[26, 27] Immunological abnormalities include depressed cell-mediated and antibody-mediated immunity, increased production of pro-inflammatory cytokines and chemokines, and the presence of autoantibodies against various neural tissues and antigens.[9, 28, 29]

While numerous studies have explored the role of IVIG therapy in patients with PANS,[18, 19, 30, 31] limited studies have investigated its role in patients with ASD. In our pilot study we investigated the efficacy and tolerability of IVIG infusion in children with ASD.[32] Participants were recruited based on a diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder not otherwise specified and, with evidence of immune dysfunction based on abnormal levels of specific biomarkers, including CD40 ligand (CD154), lymphocyte stimulation, and T or B cell dysfunction. Significant improvements from baseline to study endpoint were observed in standardized cognitive and behavioral tests, and significant reductions were also seen in numerous immunological biomarkers indicative of neuroinflammation.[32] A recent meta-analysis of 27 publications reporting on individuals with ASD treated with IVIG further supported the associations between IVIG treatment and improvements in total aberrant behavior, irritability, hyperactivity, and social withdrawal in ASD subjects.[33]

POST-ACUTE COVID-19 SYNDROME AS A NEUROIMMUNE CONDITION

The COVID-19 pandemic has added a new neuroimmune condition to this growing list. When symptoms of COVID-19 persist beyond 3 or 4 weeks, a patient is often diagnosed with post-acute COVID-19 syndrome (PACS), also known as "long COVID".[34] At this point, levels of SARS-CoV-2 are not detectable, but symptoms remain.[35] Between 32.6% and 87% of hospitalized patients report ongoing symptoms after COVID infection,[36, 37] and 30% of non-hospitalized patients report cognitive impairment.[38] Neuropsychiatric symptoms of PACS include depression, anxiety, post-traumatic stress disorder, sleep disorders, and cognitive disturbances.[39] Evidence suggests that a cytokine storm caused by COVID-19 may lead to a breach in the blood brain barrier, causing the SARS-CoV-2 and cytokines to enter the brain, and triggering a neuroinflammatory response.[37]

For many coronaviruses, there is no known mechanism for how they evade the host's innate immune system.[39] It is hypothesized that it is by either actively producing interferon antagonist proteins, using their own replicase proteins to modify host proteins, or by forming double membrane vesicles and compartmentalizing replication and potentially other coronavirus RNAs. The double membrane vesicles may serve to conceal the RNAs produced, protecting them from the host's RNA sensing machinery.[39] The rapid progression of lung involvement as well as the devastating effects of long COVID and lack of definitive, effective treatments make it imperative to develop efficient therapeutic management strategies for patients with PACS or long COVID. The point at which deterioration starts in patients with COVID-19 is a critical window of opportunity for intervention. It is important for all clinicians to be aware of the neurological effects experienced by some patients with long COVID and to continue to explore treatment options for this ever-increasing population.

Several studies have suggested that treatment with C1-INH, a member of the serpin family, can improve neurological functions by exerting an anti-inflammatory effect in brain ischemic injury.[40, 41] C1-INH is a major inhibitor of the complement system, which plays a vital role in the innate immune system.[42] The inhibitor binds and inactivates several proteases that are involved in the activation of the complement system, including C1r and C1s of the classical pathway,[43] and mannose binding lectin-associated serine proteases (MASPs) 1 and 2 of the lectin pathway.[44]

An ongoing, randomized, double-blind, placebo-controlled, cross-over, proof-of-concept study (NCT-04705831) aims to evaluate the impact of recombinant C1-INH on the neurological manifestations of post-SARS-CoV-2 viral fatigue syndrome. Adult participants with a previously confirmed diagnosis of SARS-CoV-2 and post-viral

fatigue syndrome more than 4 weeks after recovery from SARS-CoV-2 were included in the study and randomized to receive either weekly C1-INH or placebo infusions for 8 weeks. Preliminary, unpublished results have demonstrated promising trends indicating improvements in measures of cognitive changes, fatigue, and pain among participants receiving C1-INH compared with those receiving placebo. Moreover, for some patients, receiving C1-INH as the initial treatment provided a protective effect that persisted even after crossing over to placebo.

Another potential target for managing symptoms of PACS is alpha-1 antitrypsin (AAT), the most abundant serine protease inhibitor circulating in the blood. Recently, we have seen patients with post infectious neuroimmune presentations with AAT deficiency, which may play a key role in neurocognitive changes. AAT has long been thought of as an important anti-protease in the lung, where it decreases the destructive effects of major proteases such as neutrophil elastase.[45] In recent years, our understanding of this protein has expanded beyond this simple one-dimensional capacity as an anti-protease. AAT has significant anti-inflammatory properties affecting a wide range of inflammatory cells, leading to its potential therapeutical application in a number of important diseases.[45] Currently, the role of AAT as a partner in post-COVID neurological disease is being evaluated.

Conclusion

As the number of immune diseases in our population continues to rise, it is important to recognize the lingering effects of infectious diseases on immune function and their contribution to the neurological manifestations in disorders such as PANS, ASD, and PACS. Our ongoing work aims to validate our hypothesis of AIS, by elucidating the roles of the innate and adaptive immune responses in these post-infectious autoimmune conditions. While therapies like IVIG, C1-INH, and AAT show promise, further research, including randomized, blinded and placebo-controlled trials are needed to provide rigorous evidence and to guide clinical practice. Indeed, based on the positive preliminary results from previous studies, a large placebo-controlled phase 3 trial comparing the effect of IVIG versus placebo in patients with PANS is currently ongoing (NCT04508530), with estimated completion later this year. Understanding the infectious-immune axis and its mechanism of action will provide physicians with the tools to identify the best forms of treatment and management of these conditions and ultimately improve patient outcomes.

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