COVID-19 Evidence Accelerator Collaborative

Lab Meeting 47

Thursday, December 16th, 2021, 3 - 4:00 pm ET

Call Summary

Overview of Lab Meeting 47

Lab Meeting 47 featured two presentations on the intersection of COVID-19 and the immune system. First, Dr. Isaac Melamed of ImmunoHealth Centers and the University of Colorado presented research looking at the relationship between the neurological system and immune system and how COVID, in part, may be a neuroimmune disease. We then heard from Dr. Nehad Soloman of Arizona Arthritis & Rheumatology Associates discussed some initial findings about COVID-19 and its impact on his patients, and how concomitant use of immunomodulators may impact antibody levels post-vaccination.

Post-infectious Neuroimmune Disease – An Immune Memory Defect

Dr. Isaac Melamed, MD, University of Colorado School of Medicine

Neuro-Immune Disease

- Mental well-being has been understood to affect physical well-being has been since the 12th century
- Nervous and Immune system interact/affect one another in various ways
    - Cytoskeleton plays a role in signal transduction
    - Nerve Growth Factor (NGF) (nervous system) plays a role in signaling to B-Cells
    - Congenital insensitivity to pain with anhidrosis (CIPA) patients have mutation in NGF
    - NGF and the allergic cascade
- Epigenetics may make the immune system susceptible to an abnormal relationship with the nervous system
- Trends over the last several years show increases in allergic disease, immune-related disease, autoimmune disease, and neuro-immune disease
- Allergic and mental disorders have a bi-directional relationship
    - Allergic triggers --> neuro-immune inflammation with a direct effect on CNS/CNS stimuli
        - "Triggers" such as stress, anxiety, coupled with environmental factors release neuro-stimulants that impact allergic inflammation
    - Allergic disorders can lead to cognitive distortions
- Inflammatory Brain Disease --> post-infectious neuropsychiatric disease such as Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS) & Sydenham's Chorea Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)

PANS/PANDAS & Intravenous Immune Globulin (IVIG)

- Relationship between post-infection response and the sudden onset of neurologic symptoms exists and suggests a form of post-infectious autoimmunity through molecular mimicry
- Limited diagnostic ability to identify biomarkers of brain inflammation

- Found that about half of PANS patients had previous infection (HSV, EBV, Paro Virus, Lyme, etc.), 47% had developed Atopy and 85% had developed Immune Disease, 100% had a Neuro-Immune marker of brain inflammation (Cunningham, Neurozoom)

Study Overview

- Objective – Evaluate the benefit of Octagam 5% in subjects with PANS Syndrome
- Participants – Male and female children (ages 4-16 years old) with a diagnosis of PANS
- Design – A multi-site, open-label, pilot study
- Study Drug – 6 Infusions of Octagam 5% (1g/kg body weight) every 18-24 days
- 24 weeks of follow-up with patients

Results & Conclusions

- PANS questionnaire asking 58 questions related to symptoms (graded 0 to 4)
    - Clear change in symptoms observed infusion to infusion – Significant reductions in symptoms between 3rd and 6th infusion
    - Other assessments at baseline and visits 7/8/9 did not show the same results – outcomes are compelling and unique, showing steady improvement from infusion 1 to 6
    - Drawing samples pre-treatment and post-treatment showed change
- In PANS patients, all psychological endpoints studied exhibited statistically significant decreases following 6 infusions of IVG
- PANS is an autoimmune disease – innate immunity and the complement system may play a role in the pathogenesis of PANS
- Patients with PANS can benefit from a 6-cycle course of IVG – provisional late data demonstrate durability of the positive impact of IVG treatment

Common Variable Immunodeficiency (CVID) and Low C1-INH

- Chart review of 80 patients recently diagnosed with CVID
    - 30 patients had low levels of C1-INH protein, normal C4 levels
    - Clinical Presentation of these 30 patients – 90% had extreme fatigue, 80% had autoimmune disease, 50% had GI disorders, 40% arthralgias, 20% neuropathy, 30% migraines, and 10% had mild cognitive impairment
- Patients received IVIG 5% and 10%
    - Noted difference in neurologic AEs between 5% and 10% IVIG products
    - Explored further and found there was reduction in C-1 Esterase Inhibitor total and function
    - Hypothesis: could replacement with C-1 INH benefit patients experiencing neurologic AEs post-IVIG infusion?

Alzheimer's of the Immune System (AIS)

- Patients with chronic post-viral infectious conditions (EBV, Lyme, HSV, human parvovirus, etc.) with neurologic presentations have low levels of C1-INH/C1-INHF, are unable to clear the pathogens, and experience chronic inflammation leading to persistent infection
- Failure of re-recognition or immune memory of infectious pathogens, or AIS, may be caused by a failure of both the innate, complement, and adaptive immune components (memory B cell defect, low levels of C1-INH/INHF, Toll-Like Receptor (TLR))
- SARS CoV2 important focus when looking at AIS

Summary Points

- A relationship between infectious-immune response and neurologic changes may be a form of post-infectious autoimmunity that results in various neurological symptoms, such as memory issues and cognitive changes (AIS)
- Immune partners in this dysregulation include innate immunity mast cell activation, complement system and potential Alfa-1
- Both aspects of innate immunity (TLRs and the complement system) are key elements in the functioning of innate immunity against infectious pathogens
    - Both may play a role in the post-COVID neuro-immune disease.
- May be other epigenetic factors that impair the relationship such as diet, stress, implants, toxic environment, etc.
- Based on research & clinical observations:
    - Patients with immune memory failure experience a variety of neurological symptoms
    - Immune dysfunction is an inflammatory process related to the innate immune and complement systems
    - The inflammatory process is a failure of apoptosis and chronic activation of these systems
    - Named this AIS

COVID in Rheumatic Disease

Nehad Soloman, MD, Arizona Arthritis and Rheumatology Associates

Patient Population (3/2020 -- 11/2021)

- 39,000 patients with vaccination status including type, date booster
- 882 COVID-positive patients with detailed symptomology, 641 COVID-negative patients since Jan 2021
- 47 patients under Dr. Soloman's care -- 10 breakthrough vaccine patients (7 Pfizer patients 5 months post-2nd dose, 2 Moderna patients 8 months post-2nd dose
    - 37 sick prior to vaccination, 44 on immunomodulation (MTX, Humira, Enbrel, Orencia, etc.)
    - 10 patients sick post-vaccine, 9 on immunomodulation

Neutralizing Antibody Testing

- Tracking antibody (ab) levels post-vaccination among self and staff
- Notable difference in levels of ab were noted in individuals vaccinated at the same time with reproducible results – almost 4-fold more ab with Moderna compared to Pfizer

Interesting Findings

- Antibody responses pre- and post-boosters and post-vaccine COVID infection were comparable to levels that exceeded 25,000 units
- Rituxan patients seemed to have poor outcomes early in the pandemic prior to vaccines, found single-digit ab levels pre-booster (all were on drug prior to vaccination)
- Those who were vaccinated then went on drug mounted a response
    - Raises questions about whether they can mount a response if memory B-cell response would be effective enough to protect against infection

- Hybrid immunity – those infected pre-Pfizer vaccine hold ab levels at 2000 at 11-month mark, pre-Moderna vaccine hold ab levels at 5000 at 11-month mark, those with breakthrough infection post-vaccine hold levels >25,000 for at least 4-months
- Recent Moderna breakthrough cases Omicron-related or is this related to immunosuppressed state?