SATURDAY

447 Outcomes of T Cell Receptor Excision Circle (TREC) Based Severe Combined Immunodeficiency (SCID) Newborn Screening (NBS) in Michigan: 10 Year Data

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RATIONALE: TREC-based NBS for detection of primary immunodeficiency disorders was adopted in Michigan in October 2011. Our aim is to report the incidence of SCID and non-SCID/thymic related lymphopenia and their outcomes in the first 10 years of the TREC-based NBS in Michigan (1/2012-11/2021).

METHODS: This is an observational, descriptive study using a convenience sample of newborns with positive TREC-based NBS (birth dates: 1/2012-11/2021) obtained from the Michigan NBS Program. Maternal/infant demographics, clinical diagnosis, and available follow up information were collected.

RESULTS: Of the 1,086,388 Michigan infants screened, 1096 (0.1%) had abnormal TREC results. Of these, 502 (45.8%) were strong positive, 437 (39.9%) were borderline positive, and 157 (14.3%) were inconclusive. Of the strong positive results; 14 patients had SCID, 34 had 22q11 deletion syndrome, 7 had other syndromes with T-cell impairment, and 56 had secondary T-cell lymphopenia. 35% of patients with SCID had X-SCID. 11 typical SCID patients were successfully transplanted. Of the borderline results, none had SCID, 7 had 22q11 deletion syndrome, and 13 had secondary T cell lymphopenia. Most patients (n=365; 83.5%) with borderline results resolved on repeat screening.

CONCLUSIONS: A ten-year review of data from Michigan's TREC-based NBS revealed incidence, etiology and follow-up of T-cell lymphopenia in a large population. 14 SCID diagnoses were made with an incidence of 1.3:100,000. Most of the newborns with abnormal TREC screens had non-SCID/thymic related lymphopenia. TREC-based NBS led to earlier intervention and improved outcomes.

448 Anti-IgA Antibodies in CVID: Frequency, Severity, and Outcomes in a Large Cohort Study

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RATIONALE: Common Variable Immunodeficiency (CVID) patients have increased risk for autoimmunity. Patients who have anti-IgA antibodies may develop infusion reactions to immunoglobulin (Ig) replacement. However, the frequency of anti-IgA seropositivity and its consequences in CVID is not well-established.

METHODS: We conducted a retrospective chart review of 626 CVID patients followed at Mount Sinai Hospital and Memorial Sloan-Kettering Cancer Center since 1974. Infusion reaction severity was determined using Common Terminology Criteria for Adverse Events (CTCAE) criteria score.

RESULTS: The frequency of anti-IgA antibodies was 1.3% (8 in 626 patients). Diagnostic IgA was undetectable in all patients. Only one patient had concurrent hematologic autoimmunity. Two patients had a history of lymphoma after CVID diagnosis, and an additional 2 patients had concurrent lymphoproliferative disease. Four out of 8 patients (50%) developed anti-IgA antibodies 2-15 years (mean 9.5 years) after initiating Ig replacement. Reactions to Ig replacement therapy were generally mild (Grade 2 or lower) though one patient did experience an anaphylactoid reaction. Infusion reactions to IgA-containing Ig products were broad and included headache, fatigue, flushing, chills, shaking, nausea, emesis, localized erythema, conjunctivitis, and/or shortness of breath. The use of an IgA-depleted Ig product was effective in preventing further infusion reactions.

CONCLUSIONS: The overall incidence of anti-IgA antibodies in CVID is low in this large cohort and reaction severity to IgA-containing Ig products in affected patients is generally low. However, anti-IgA antibodies may develop over time. Thus, maintaining clinical awareness and re-testing in patients lacking endogenous IgA are essential, especially in those with new onset infusion-related symptoms.

449 Defining the role of Th2-associated cytokines in Aspergillus versicolor-induced pulmonary immune responses

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RATIONALE: *Aspergillus versicolor* is a fungal contaminant commonly found in damp indoor environments. Chronic exposure to *A. versicolor* is associated with Th2-mediated immune responses that can lead to allergy and other disease. The mechanistic role of Th2-associated cytokines, IL-4, IL-5, and IL-13, during fungal exposure needs further characterization.

METHODS: Mice (C57BL/6J, IL-5 neutralized, IL-13 knockout, IL-4 knockout, or RAG-2 knockout) were exposed biweekly to HEPA-filtered air, heat-inactivated *A. versicolor* spores, or viable *A. versicolor* spores ($3x10^5$) using an acoustical generator nose-only inhalation system for four or 13 weeks. IL-13, IL-4, and RAG-2 knockout animals were genetically modified strains. For IL-5 neutralization, anti-IL-5 antibody was administered to indicated groups on alternating days with exposures. Twenty-four to forty-eight hours following the last exposure, functional assessments and immunological responses were measured by antibody quantification, whole body plethysmography (WBP), flow cytometry, and histology.

RESULTS: C57BL/6J (wild type) mice exhibit pro-inflammatory responses following fungal exposure, which was significantly diminished in knockout mice. Exposure to *A. versicolor* led to a significant increase in total cells, eosinophils, and adaptive immune cells in wild-type mice. Exposure to both heat-inactivated and viable *A. versicolor* also resulted in a decrease in inspiratory time as measured by WBP.

CONCLUSIONS: Th2-associated cytokines drive the alterations in pulmonary function and immune responses elicited by fungal exposure. Understanding the immune response to fungal exposure is crucial for the development of tools to assess and treat fungal-related respiratory diseases.