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49 Individual Cytidine Deaminase and Adenosine Deaminase Variations in a Highly Immunologically Homogenous Group of Healthy Belarussian Adults

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RATIONALE: Cytidine deaminase (CDA) and adenosine deaminase (ADA) both have a role in immune responses and their regulation. Their activities may have high variability as individualized immunologic parameters.

METHODS: Using a homogeneous group of healthy volunteers from the Minsk, Belarus area without any systemic illnesses (n=33, age 18-31 mean 24±2, M:F ratio 4:1) serum CDA and ADA levels were assessed by the method of Guisti and Gallanti with prolonged incubation time. Also assessed were immunoglobulin heavy chain (IHC) gene rearrangement status by the Langerak and van Dongen method and CD8+, CD19+ cell numbers by flow cytometry.

RESULTS: On the background of normal CD8+ and CD19+ cell numbers and normal polyclonal IHC gene rearrangement status, the serum CDA level manifested itself as a highly variable parameter with vibration amplitude ranging from 0.58 IU/l to 4.91 IU/l (mean 1.82±0.36 IU/l) while the serum ADA level ranged from 4.01 to 25.97 IU/l (mean 11.94±1.92 IU/l).

CONCLUSIONS: Despite similar normal CD8+ and CD19+ cell numbers and normal polyclonal IHC gene rearrangement status there was more than a 6-fold variation in CDA and ADA serum levels. These enzymes may possibly be a biomarker of individually variable immune responses in patients with hidden immunodeficiency.

50 Pediatric Thymic Development of T Cells and Tregs

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RATIONALE: Thymic development of T cells and Tregs has not been well studied in human when compared to murine. It is not fully known whether markers seen in peripheral Tregs are expressed during thymic development and the association of Helios, BCL2 and BCL10 in survival.

METHODS: Fresh thymi obtained from cardiac surgery of pediatric patients (n=66) from 1 week to 14 years old with congenital heart defects were processed into cell suspension for FACS analysis. Patients with syndromes associated with immunodeficiency were excluded. Intracellular transcription factor staining was performed with eBioscience fix/perm buffers and protocol.

RESULTS: There was a major change in the frequencies of CD4/CD8 double negative (DN), double positive (DP) and single positive (SP) at <2weeks (n=18) vs. >2weeks (n=48) old. Foxp3-: DN* (5 vs. 2.4%), DP* (34 vs. 73%), CD4SP* (45 vs. 16%) and CD8SP* (13 vs 7%). Foxp3+: DN (1.4 vs. 1.4%), DP* (2.6 vs 0.8%), CD4SP (12 vs. 11%) and CD8SP (2.7 vs. 2.7%). >90% of Tregs were Helios+ with the greatest expression at the DP stage and unchanged with age. High expression of BCL2 and BCL10 was seen in Foxp3+DP, Foxp3+CD4SP, Foxp3-CD4SP and CD8SP, while Foxp3-DP had low expression. Tregs expressed CD39, CD134, CD137, CD278, CD279, CD25, CD152 and CD127 at both DP and SP stage. *p<0.001.

CONCLUSIONS: Helios, BCL2 and BCL10 are upregulated at the DP stage for Tregs, suggesting a survival and selection advantage. Early in the DP stage, Tregs expressed phenotypic markers. This study provides more insights into thymic development in human.

51 Newborn Screening for Severe Combined Immunodeficiency (SCID) in Ohio: Using Algorithms to Standardize Follow-up Limits the Number of False Positive Results

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RATIONALE: T cell receptor excision circle (TREC) analysis on newborn screening (NBS) dried blood spot specimens has proven to be a successful method of screening for Severe Combined Immunodeficiency (SCID). We hypothesized that standardized algorithms for follow-up of abnormal values would decrease the number of false positives results.

METHODS: TREC sequence and actin was amplified from NBS specimens using real-time PCR. Amplification values from samples of infants previously diagnosed with SCID and data from over 12,000 healthy newborns were used to establish a reference range suggestive of SCID. Immunologists in collaboration with the Ohio Department of Health created algorithms for follow-up on abnormal screens. Abnormal results were classified as moderate or elevated risk. Only infants in the latter category were recommended for immediate flow cytometry and consultation with an immunologist. NBS was repeated per the protocols for infants with moderate risk.

RESULTS: In the first year, approximately 140,000 infants were screened. There were 46 moderate risk infants and 4 elevated risk infants. Thirteen moderate risk infants died prior to follow-up and 31 infants "normalized" on repeat NBS. Two pre-term infants with abnormal repeat screens were eventually referred for flow cytometry and diagnosed with T cell lymphopenia but not SCID. Four elevated risk infants with no confounding factors had complete absence of TRECS: 3 have been diagnosed with SCID and 1 remains without a definitive diagnosis.

CONCLUSIONS: Algorithms created in advance were effective in standardizing follow-up protocols and minimizing the number of false positive results and infants referred for flow cytometry and immunology consultation.