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1. Back to Basics: Diagnosis of Lesch-Nyhan Syndrome in a Female via Karyotype Analysis

Joseph Biddle, Teresa Campbell, Alba Sanchis-Juan, Gabrielle Lemire, Lance Rodan, Melanie O'Leary, Christina Austin-Tse, Anne O'Donnell-Luria, Laurie Sadler

Lesch-Nyhan syndrome (LNS) is a rare X-linked disorder characterized by a deficiency of the hypoxanthine-guanine phosphoribosyltransferase (HPRT) enzyme. This enzymatic defect leads to systemic accumulation of uric acid, resulting in severe neurological and behavioral symptoms, including self-injurious behaviors, intellectual disability, and abnormal movements. Most individuals with LNS are males with a hemizygous pathogenic variant in the HPRT1 gene; however, females with a heterozygous HPRT1 pathogenic variant with LNS have also been reported due to skewed X-inactivation. We report a 6-year-old female with a classic clinical presentation of LNS caused by a balanced X-autosome translocation.

2. Macrophages, a therapeutic target for the rare disorder, Dense Deposit Disease (DDD)

Jessy J. Alexander

The complement field is currently experiencing an exciting period of growth, with its role being increasingly recognized across various medical conditions. With new complement therapeutics gaining FDA approval and research revealing novel functions for these proteins, there is increase in complexity of the field, and heightened interest in the field. Dense Deposit Disease (DDD) presents a rare challenge, stemming from the kidneys' susceptibility to complement-mediated changes, yet lacking effective therapies. The deficiency or dysfunction of the complement regulator, factor H (FH), underlies the kidney pathology in DDD and leads to organ loss, but the precise mechanisms remain elusive. Understanding these mechanisms is crucial for developing more targeted therapies and improving patient outcomes. Our research has uncovered significant macrophage infiltration in the DDD mouse model, with pathology alleviated upon macrophage depletion, highlighting the critical role of these immune cells. Macrophages, exhibiting dynamic inflammatory and restorative phenotypes, play a pivotal role in the disease process, but the exact phenotype or the imbalance of the phenotypes in the DDD setting, and the underlying mechanisms remain to be deciphered. Our studies show that FH participates in several noncanonical functions such as proliferation, migration, phagocytosis and metabolic programming. Our ongoing investigations focus on elucidating how FH modulates these macrophage functions, aiming to identify potential therapeutic targets for DDD.

3. Disproportionality Analysis of the FDA Adverse Event Reporting System (FAERS) Unveils Significant Pharmacovigilance Signal for Exposure to Hydroxychloroquine and the Adverse Event Pemphigus.

Justin Baroukhian, Kristina Seiffert-Sinha, MD, Animesh A. Sinha, MD, PhD

Identifying environmental factors that contribute to disease onset/activity in pemphigus adds relevant information as to potential risk factors and stands to improve clinical outcomes. Hydroxychloroquine (HCQ) is a 4-aminoquinolone anti-material also used in the treatment of various autoimmune and rheumatic diseases. Following reports of in vitro anti-viral activity against SARS-CoV-2, HCQ became the subject of widespread public intrigue and off-label adoption. Previously, a case of biopsy proven

pemphigus triggered by HCQ use and confirmed on clinical re-challenge has been reported in the literature. We set out to evaluate the association between HCQ use and the development of pemphigus using population level, FDA-generated data. This observational, retrospective, case-control, disproportionality analysis employed the validated tool OpenVigil 2.1 to query reports of drug associated adverse events in FAERS from 01/01/2020 to 11/13/2023. We identified a total of 2067 reports that included the adverse event pemphigus; among these, 77% of pemphigus reports (n=1603) included exposure to HCQ (ROR, 515.733; 95% CI, 464.802-572.245). When stratified by gender (77.54% females, 0.25% males, and 22.65% with no gender specified), we found that the association between the exposure and adverse event remained significant across genders. However, the magnitude of the effect sizes differed significantly, being over 100-fold greater among females (ROR, 725.942; 95% CI, 623.374-845.386) compared to males (ROR, 6.225; 95% CI, 2.309-16.785). A limitation of this study is that it cannot ascertain causality, nor can it identify individuals infected with and/or vaccinated against COVID-19. Nevertheless, the disproportionately elevated frequency of reports of the combination of pemphigus and HCQ supports an association between the two, corroborates previous case-report based evidence, and suggests that HCQ represents a possible trigger factor in pemphigus.

4. A Case of Clozapine-Associated Cecal Volvulus in a 58-Year-Old Female with Schizoaffective Disorder

Sharlo L. Bayless, MD, MS, Raphael J. Leo, MA, MD

Background: Clozapine is considered the gold standard for treatment-resistance schizophrenia. Impairment of gastrointestinal motility and constipation are common adverse effects associated with clozapine. Herein, a case of clozapine-associated cecal volvulus is described. To our knowledge, this has only been reported once previously.
Clinical Case: A 58-year-old female with schizoaffective disorder, bipolar type was hospitalized for constipation, abdominal distention, and bilious vomiting. Her medications included clozapine 575mg daily and diphenhydramine 50mg PO QID PRN. She was nonadherent to her bowel regimen of senna/docusate sodium 8.6/50 BID and polyethylene glycol daily. Computerized technology (CT) imaging of the abdomen/pelvis with rectal contrast showed progression of the contrast to the splenic flexure, and mesenteric swirling in the right lower quadrant adjacent to a dilated loop of bowel and extending to the left hemiabdomen with a large stool burden. Exploratory laparotomy confirmed cecal volvulus and tearing of the serosa of the intestine, indicating impending rupture. A right hemicolectomy was performed without complications. Bowel motility was restored, and she progressed well post-operatively.
Conclusion: Although constipation is a common adverse effect of clozapine, emergent surgical conditions can also result. Unrecognizied and untreated, cecal volvulus can lead to vascular strangulation, gangrenous intestines, or death. A low threshold of suspicion for potentially emergent surgical conditions is warranted in patients on clozapine who develop vomiting, severe constipation, or abdominal distention and pain. This case highlights that co-administered anticholinergic agents, i.e., diphenhydramine, and non-adherence with a bowel regimen may have had a cumulative effect on this patient's risk. It serves as a reminder of the seriousness of gastrointestinal complications that can develop from clozapine treatment and of actions that can reduce a patient's overall risk.

5. Heard of HARS?

Jamie Abbott, Christopher Francklyn, Victoria Siu, Tony Rupar

Human histidyl-tRNA synthetase (HARS) is an aminoacyl-tRNA synthetase (AARS) that catalyzes the attachment of amino acid histidine to histidyl-tRNA (tRNAHis) in a two-step reaction that is essential for protein translation. Mutations in the HARS gene have been associated with human disease. A homozygous founder mutation (HARS c.1361A>C, Y454S) was first reported in two Old Order Amish Patients in Pennsylvania, who were clinically diagnosed as having Usher Syndrome IIIB. Patients with Usher Syndrome IIIB lose their sight and hearing during their second decade of life, and clinicians have observed that the onset of deafness and blindness may be episodic and correlate with febrile illness. Furthermore, some USH3B patients present with a fatal form of acute respiratory distress. To date 23 additional cases in an extended Old Order Amish kindred in southern Ontario have been identified. Here we will describe the natural history of this condition, expand upon initial reported clinical features of those affected, to propose renaming the condition ""HARS syndrome"". We will also highlight biochemical approaches used to characterize this disease variant including enzyme kinetic analysis to monitor catalytic deficiencies, differential scanning fluorimetry (DSF) to evaluate structural instability, and cellular models to detect physiological effects of temperature on patient fibroblasts. This work demonstrates that Usher Syndrome IIIB is a complex syndrome and unlikely to be a consequence of a simple loss of HARS aminoacylation function. We believe that by understanding the biochemical basis of this inherited mutation and its link to Usher Syndrome, it may be possible to develop mechanism-based therapies to improve the quality of life for patients.

6. Uncovering the mechanisms of neural crest cell birth defects using human pluripotent stem cells

Maneeshi S. Prasad, Martin I. Garcia-Castro, and Rebekah M. Charney

Neural crest cells are a multipotent cell population which contribute to a diverse array of cell types including most of the craniofacial skeleton, neurons and glia of the peripheral nervous system, and melanocytes. Owing to their extensive contribution to derivatives throughout the body, many human health conditions are associated with the neural crest, including craniofacial malformations, rare syndromes, and cancer. Mowat-Wilson syndrome is a rare disorder characterized by craniofacial abnormalities, intellectual disability, and frequently heart defects and Hirschsprung's disease. We present a model of human neural crest development based on pluripotent stem cells, and utilize this model to examine the role of the Mowat-Wilson syndrome gene ZEB2 in human neural crest formation and differentiation. Our findings reveal the crucial role of ZEB2 in the establishment of the neural crest cell state and epigenetic landscape, and its requirement for the differentiation of osteoblasts, sensory neurons, and neuroglia. Finally, our results suggest that ZEB2 regulates early human neural crest specification in part by modulating proper levels of BMP signaling. These findings elaborate on the molecular defects underlying Mowat-Wilson syndrome.

7. Auricular Erythromelalgia: A Survey of Patient Experiences

Alaina Kenny BA BS, Alyssa Reese BA BS, Victoria Hoffman MS, Brianna Friend BS, Mark Burke MD

Auricular erythromelalgia and red ear syndrome (RES) are both characterized by recurrent episodes of erythema, warmth, and burning pain of the external ear. Despite the similarities in clinical presentation, the relationship between these two conditions remains unclear. The purpose of this study was to gain a better understanding of adult and pediatric experiences with auricular erythromelalgia and RES. A cross-sectional survey was shared to Facebook groups and Reddit communities for individuals with auricular erythromelalgia and/or RES. The survey consisted of questions about demographics, clinical features, medical history, and quality of life. Inclusion criteria were a diagnosis of auricular erythromelalgia or RES, either by a healthcare professional or self-diagnosis, and 18 years of age or above. Adult respondents could answer on their own or on behalf of a child under 18. Participants (N=60) were predominantly female (N=41, 68.3%), Caucasian (N=53, 88.3%) and aged between 4 and 76 with a mean age of 37.9 years. Most participants were adults with auricular erythromelalgia or RES (N=54, 90.0%), while 6 responses described pediatric cases (10.0%). Diagnosis of RES or auricular erythromelalgia was received by a medical professional in 51.7% of respondents (N=31). 38.3% waited 1 year or more for diagnosis after onset of symptoms (N=23). Most participants experience erythromelalgia in other areas of the body beyond the ears (N=37, 61.7%). 38.3% report coexisting autoimmune disease (N=23). Both auricular erythromelalgia and RES present with a wide range of clinical features, including age, severity, and comorbidities. This may explain the observed difficulties in diagnosis and treatment.

8. Farber Disease as a Cause of Severe Childhood Arthritis: A Case Report.

Nicole Gorski BS, Andrew Hurst MD, Kathleen Johnson NP, Briana Miskey DO, Victoria Sarata MD, Robert Welliver MD, Samara Appelstein DO, Rabheh Aziz MD

Farber Disease (FD) is a rare, recessive autosomal disorder characterized by a classic triad of joint involvement, subcutaneous nodules, and hoarse voice. However, numerous case reports have demonstrated the great variability in presentation of patients with FD. Here we report a case of an 11-month-old male who presented with polyarticular arthritis, hoarse voice, diffuse lymphadenopathy, severe malnutrition, and developmental regression. The presence of joint involvement and inflammatory markers raised suspicion for Juvenile Idiopathic Arthritis (JIA), however the patient’s young age and hoarse voice put FD at the top of the differential. After an extensive workup was nondiagnostic, genetic testing revealed two distinct mutations in the ASAH1 gene, confirming the diagnosis of FD. This case demonstrates the importance of considering FD as a differential diagnosis in young patients with polyarticular arthritis.

9. Postural orthostatic tachycardia syndrome and segmental dystonia as presenting features of Fabry disease in a female patient.

Aliya Hyman BS, Svetlana Blitshteyn, MD

Background: Fabry disease is a rare X-linked genetic disorder characterized by deficient Î±-galactosidase A activity, leading to the accumulation of globotriaosylceramide (Gb3) and related glycosphingolipids in

various tissues. The disease presents with a wide array of clinical manifestations, including renal impairment, cardiac complications, cerebrovascular events, and neurological symptoms such as small fiber neuropathy and autonomic dysfunction. Postural orthostatic tachycardia syndrome (POTS) in association with Fabry disease has not been typically encountered in clinical practice.
Methods: We present a case of a 19-year-old woman who initially presented with recurrent presyncope, migraine with aura, episodes of segmental dystonia, joint pain, and memory lapses. Results: Based on a tilt table test, the patient was diagnosed with POTS, but segmental dystonia and memory lapses were unusual features suggesting an additional diagnosis. Subsequently, the patient's father had an evaluation for neuropathic pain, which revealed a diagnosis of Fabry disease. Given her father's diagnosis, the patient was also tested for Fabry disease, which similarly revealed decreased serum alpha-galactosidase A activity. The patient was started on enzyme replacement therapy (ERT) with recombinant Î±-galactosidase A, which led to resolution of POTS symptoms, segmental dystonia and memory lapses.
Conclusion: This case underscores the significance of considering rare genetic disorders, such as Fabry disease, in the differential diagnosis of complex medical presentations, including patients with POTS who display unusual features. Additionally, Fabry disease should not be excluded in women simply because they have two X chromosomes. Early recognition and targeted treatment are paramount in managing patients with Fabry disease and improving or resolving its associated neurologic and autonomic manifestations.

10. An Overview of Merkel Cell Carcinoma (MCC) at Roswell Park Comprehensive Cancer Center

Joshua Kent, BA; Kelvin Anderson, BS; Justin Baroukhian, BA, BS; William J. Magner, PhD; Gyorgy Paragh, MD, PhD; Vishal Gupta, MD

Background: Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine tumor of the skin, most commonly on the head and neck. The incidence of MCC is approximately 0.7 per 100,000 in the US, making it challenging to study. Typically, primary MCC presents as a violaceous, painless, expanding exophytic nodule. Old age, fair skin tone, immunodeficiency, male sex, Merkel cell polyomavirus infection, and sun exposure are MCC's most well-documented risk factors. There has been limited research into how the primary head and neck subsite influences disease characteristics. Methods: Retrospective chart review to construct a database of all 155 MCC patients seen clinically from 2008-2024 at Roswell Park Comprehensive Cancer Center. Patient demographics, social history, medical history, family history, clinical staging at diagnosis, pathological features, radiation, immunotherapy, and treatment outcome data were collected with the help of nSight. Statistical analyses were performed with IBS SPSS v27.0.1.0. Nominal variables were analyzed with Pearson correlation, ordinal variables were analyzed with Spearman correlation, and scalar variables were compared using ANOVA with statistical significance set at $p<0.05$. Survival analysis was performed using Kaplan Meier.
Results: Survival was analyzed against anatomical location, gender, and diagnostic staging.

11. When Optic Neuritis is not MS, NMO, MOG..... ""The Others""

Norah Lincoff, Shefalika Prasad, Osman Farooq

The differential diagnosis of inflammatory autoimmune optic neuritis or neuropathy is extensive and often includes: MS, NMSOD, MOG, AARON, AON, CRION, RION and post infectious states. When the work up is negative initially, there is often treatment delay. Lab values can vary considerably depending on the time period of the exacerbation and can be normal at onset of disease. One often needs to treat on suspicion alone to protect the better seeing eye. Treatment modalities often include high dose steroids followed by disease modifying agents. We present 5 cases where the disease name became clear months to years after initial visual loss.

12. Characterization of Medication Complexity in a Metabolic Genetics Clinic

Mary Riedy PharmD, Jessica Briggs RD, Taosheng Huang MD, PhD

Introduction: The availability of FDA approved treatments for patients diagnosed with rare genetic metabolic disorders has expanded within the last decade. The complexity of medication use in this patient population has not previously been described. The primary objective was to characterize the complexity of medication acquisition and administration in patients with metabolic genetic disorders.
Methods: Retrospective, cross-sectional study. Patients with a confirmed diagnosis of a metabolic genetic disorder were included. Pregnant patients were excluded. Data was collected via manual chart review and consisted of diagnosis, medication use and laboratory data. The primary endpoint of medication complexity was defined as: requirement for prior authorization, use of specialty pharmacy, and/or manipulation of dosage forms. Costs were determined using the FDA RedBook. Descriptive statistics were utilized to characterize the data using Excel.
Results: Of 225 patients screened, 152 were included. Most patients were less than 21 years of age (n=93, 61.2%) and phenylketonuria was the most frequent diagnosis (n=63, 41.4%). 95 patients required 110 medications for treatment of their metabolic genetic disorder. Laboratory testing related to medication efficacy and safety was required in 90 patients with an observed compliance of 85.6% to any lab draw. The average annual cost per medication exceeded $100,000 in 47.2% of medications prescribed (n=51/108).
Conclusions: Treatment with at least one medication was required in 62.5% (n=95/152) of patients diagnosed with a metabolic genetic disorder seen at our clinic during the study period. One element of complexity was observed in 82.6% (n=90/109) of medications prescribed while 45.9% (n=50/109) required all three defined elements. Future research should explore the pharmacist's role in optimizing the complex, high cost pharmacotherapy utilized in this patient population.

13. Post-anoxic Myoclonic Eye Opening (PAMEO): A Polygraphic Study and Review

Margil Ranpariya, MD

Background: Post-anoxic myoclonic eye opening (PAMEO) is a poorly understood phenomenon defined as non-periodic jerky eye opening (EO) seen in comatose patients within 24-hours of cardiac arrest. In

this study, we aim to explore potential mechanisms of this rare phenomenon using EEG and surface-EMG (sEMG) data.
Methods: We studied 3 post-cardiac arrest patients with vEEG and sEMG covering various bulbar muscles, sternocleidomastoid and biceps. We analyzed the duration of EEG bursts, onset of myoclonus and EO in relation to the bursts using video and sEMG data and total duration of EO. We also analyzed the recruitment pattern of myoclonus using myogenic activity in sEMG, EKG and frontal EEG channels to characterize the myoclonus as cortical or reticular in origin. Correlational analysis was made using Pearson correlation coefficient, and literature review was performed.
Results: All 3 patients had a generalized burst-suppression pattern on EEG within 24-hours of cardiac arrest with myoclonus and EO time-locked to the bursts. In all patients, EO occurred after the onset of EEG bursts with an average latency of ~200-400ms. The total EO duration was ~1600-7500ms. In patients #1&3, there was a strong positive correlation between EEG burst duration and EO duration (r=.91 and .81 respectively). After analyzing sEMG data, we concluded that the myoclonus and EO were of cortical origin in patient #2, reticular in patient #3 and cortico-reticular in patient #1. In patients #1&2, there was a negative correlation between EEG burst duration and myoclonus/EO latency. In patient #3, there was a weak positive correlation instead. Extensive literature search found 12 previous published reports of eye opening in the setting of cardiac arrest (40 patients). All patients showed burst-suppression on EEG with onset of eye opening corresponding to the burst pattern, and 24 (60%) also reported additional non-ocular myoclonus. A total of 6 EEGs were analyzed further, showing onset of EO was 350 $\pm$ 180ms after burst onset, with EO duration of 500-4,100 msec. All subjects with PAMEO in the setting of burst suppression died.
Conclusion: PAMEO is associated with generalized burst-suppression pattern on EEG. The EEG burst and EO durations have a strong positive correlation. We propose that PAMEO and acute post-anoxic myoclonus can be cortical (descending volley) or reticular (ascending volley) or cortico-reticular in origin. Polygraphic analysis using sEMG electrodes covering various bulbar muscles can help localize the generator. Activation of the central caudal nucleus of the oculomotor complex in the midbrain is most likely responsible for the jerky EO. Levator palpebrae superioris contains unique fast-twitch fibers distinct from other extra-ocular muscles, causing myoclonic eyelid contraction, accounting for the jerky EO and slow-twitch fibers, are accounting for slow and longer duration of eye closer.

14. Physiological Approach to Studying Rare Corneal Dystrophy: New Insight on Effect of Ammonia on SLC4A11 Activity

Richard A. Pasternack, Bianca N. Quade PhD, Aniko Marshall, and Mark Parker, PhD

SLC4A11 is a unique protein in the SLC4 family, transporting protons instead of bicarbonate. SLC4A11 is expressed throughout the body, including corneal endothelial cells (CECs) and the vestibular portion of the inner ear. In the eye, SLC4A11 is thought to help prevent swelling of the corneal stroma, in addition to pH regulation of CECs. The physiological role of SLC4A11 in the inner ear is not well understood. Loss of function mutations in SLC4A11 cause a rare autosomal recessive disease called Congenital Hereditary Endothelial Dystrophy (CHED). CHED is characterized by corneal edema and opacification near or at the time of birth and is caused by a disturbed lining of CECs, which are vital to maintaining fluid balance in the cornea. As SLC4A11 is robustly expressed in CECs, a loss of transport function is paired with a permanent thickening of the cornea and the endothelial basement (Descemet's) membrane. The

transport substrate(s) and regulation of SLC4A11 is controversial. First thought to be a sodium-coupled borate transporter, studies over the last decade agree that protons (or hydroxide) are a primary transport substrate. Ammonia, known to stimulate currents in SLC4A11 expressing cells, is thought to either be a co-substrate with protons or an indirect allosteric activator due to its influence on pH1. We hypothesize that NH3 may be a direct allosteric activator. Understanding the effect of ammonia on SLC4A11 is important due to the presence of intracellular ammonia in CECs from metabolic processes such as glutaminolysis2. The activity of SLC4A11 at a constant extracellular pH can be modeled to fit a Hill curve with a known pK value3. Aiming to determine whether ammonia exerts any direct allosteric effect on human SLC4A11 protein, we generated Hill curves at various ammonia concentrations to determine if a measurable shift in pK is present.

15. Pediatric Large Vessel Occlusion in Setting of Endocarditis

Elizabeth Rosen, MD

BACKGROUND: Pediatric acute ischemic stroke (PAIS) can be very difficult to recognize given transient improvement of symptoms, and incidence of stroke mimics, particularly in the setting of the fever.[1] Pediatric patients with cardiac disease have a higher incidence of cardioembolic events than the general population.[2] While cardioembolic events are normally distributed bilaterally and more distally, they can present as large-vessel occlusions.[3] There is a lack of evidence supporting standardized management approaches for this vulnerable population.
METHODS: One 12-year-old male was followed from transfer from an outlying facility to our comprehensive stroke center, through his pediatric intensive care unit (PICU) admission.
CASE SUMMARY: This case report examines a 12-year-old male with a medical history of a bicuspid aortic valve with respective stenosis and pre-hospital modified Rankin Scale (mRS) of 0, who presented as a transfer from an outlying facility with acute onset right-sided weakness and expressive aphasia due to large-vessel occlusion (LVO) acute ischemic stroke (AIS) and fever. The patient had a late presentation due to transient improvement in symptoms, which delayed presentation to the emergency department. On presentation, perfusion imaging demonstrated a significant increased time to peak with corresponding decrease in cerebral blood flor and volume in the proximal superior M2 segment of the left middle cerebral artery (L-MCA). Echocardiogram demonstrated large vegetation on bicuspid, stenotic aortic value. MRI-Brain two days after initial presentation demonstrated a large area of restricted diffusion in the L-MCA distribution in addition to punctate changes in bilateral cerebellar hemispheres. Thrombolytics were not administered given unclear last known well time as well as presence of fever, and mechanical thrombectomy (MT) was not performed given large volume core on perfusion imaging. The patient underwent secondary stroke work up including trans-thoracic echocardiogram, which revealed a large vegetation (~10mm) on the aortic valve. Blood cultures returned positive for Gram-positive cocci in clusters within 30 hours of blood draw. Bacterial PCR returned positive for B. Henselae 4 days later. Anti-platelet and anticoagulation therapy were held. The patient was presented at cardiology surgical conference for valve replacement 6-8 months after insult.
CONCLUSION: Pediatric AIS is frequently clinically missed given high incidence of mimics, as well as delay in presentation. There are multiple risk factors in the pediatric population that are associated with higher incidence of stroke.[4] In addition, the more common infectious etiologies are not easily grown in culture and require more extensive infectious work up. More research is needed to better identify cardiogenic strokes in children as well as more standardized guidelines for pediatric patients with cardiac disease.

16. Disease-Promoting Cytokine Shifts Uncovered in Subjects Genetically Susceptible Towards Autoimmune Skin Disease

Rebekah R Schwartz; Kristina Seiffert-Sinha, MD; Animesh A. Sinha MD, PhD

Autoimmune diseases (AID) are defined by immune dysregulation characterized by specific humoral and/or cell mediated responses directed against the body's own tissues. Cytokines in particular play a pivotal role in the pathogenesis of AID, with proinflammatory cytokines contributing to the initiation and propagation of autoimmune inflammation, whereas anti-inflammatory cytokines facilitate regression of inflammation and recovery from acute phases of the disease. Parallel work by our group evaluating a comprehensive set of pro- and anti-inflammatory serum cytokines in Pemphigus vulgaris (PV) as well as Alopecia Areata (AA) uncovered a similar pattern of inheritance specific immune dysregulation in these two distinct autoimmune skin diseases. In AA, we found healthy control subjects who are blood related to AA patients exhibit the same cytokine dysregulation in Th1 and Th17 pathways as do patients with AA. In PV, patients as well as individuals who are healthy but carry specific PV-associated HLA alleles (HLA-matched controls) demonstrate cytokine upregulations similar to each other, but distinct from healthy controls who do not express these alleles. More specifically, HLA-matched controls and PV patients share immunological activation of pro-inflammatory cytokines IL-1a, IL-1b, IL-6, and TNF-a, Th17 cytokines IL-21 and IL-23, the Th2 cytokine IL-13, and the chemokine IL-8. Thus, in both AA and PV, we see cytokine profiles that are linked to genetic background. Our data underscore the known tendency of AID to cluster in families and support the notion of the shared genetic/ common cause hypothesis across multiple AID. The presence of disease promoting pathways in not only patients, but also genetically related, but healthy control individuals evokes the further hypothesis that there may be co-existing disease counteracting immune protective mechanisms at play in thwarting the threat of disease in genetically predisposed individuals who remain healthy.

17. Disease-related Variants at GluN1 Y647 Impair NMDA Receptor Gating Kinetics

Samantha R. Schwarz, Jamie A. Abbott, and Gabriela K. Popescu

N-methyl-D-aspartate (NMDA) receptors are glutamate-gated channels that mediate a substantial portion of excitatory transmission in the central nervous system and are essential for brain development and cognitive function. They assemble as heterotetramers of homologous GluN1 and GluN2 subunits. The agonist-controlled gate is formed by the intersection of a highly conserved sequence (SYTANLAAF) on the third (M3) transmembrane helix of each subunit. Within this motif, variations at the Y647 residue of the obligatory GluN1 subunit, Y647C and Y647S, are pathogenic. We hypothesize that these patient-derived variants cause neurological dysfunctions by disrupting the NMDA receptor gating mechanism. To investigate this hypothesis, we produced GluN1 subunits with Y647C, S, and L substitutions, co-expressed each of these with wildtype GluN2A subunits in HEK 293 cells, and recorded activity from individual channels with the cell-attached patch-clamp technique. Preliminary results showed that Y/C and Y/S substitutions produced channels with drastically reduced open probability relative to GluN1/GluN2A receptors (WT). In contrast, Y/L produced only minor changes, suggesting that the hydrophobic character of Y647 is essential in maintaining normal activity. Moreover, the gating deficit of Y/C and Y/S substitutions was entirely due to an increase in the mean duration of channel closures, with no substantial change in mean duration of openings. Further investigations with kinetic modeling will

identify the precise closed states whose stability depends on the hydrophobic moiety of GluN1 Y647, and will guide therapeutic interventions with positive allosteric modulators.

18. Inherent barrier defects of Friedreich's Ataxia blood-brain barrier model and rescue with Methylprednisolone

Frances M. Smith and Daniel J. Kosman

Friedreich's Ataxia (FRDA) is dually a rare pediatric disease and the most inherited ataxia, affecting ~1:50,000 US citizens. Molecularly, it is caused by a loss of the iron chaperone protein Frataxin (FXN). While patients have an early burst of neurodegeneration, progressive brain iron accumulation mirrors progression of disease, a phenotype seen consequent of blood-brain barrier (BBB) degradation in diseases such as Alzheimer's and Parkinson's. BBB cells rely on the cytoskeleton to anchor tight junction proteins for proper sealing of adjacent cells and the formation of a paracellularly impermeable barrier. In the early 2000s, cytoskeletal defects were identified in FRDA patient fibroblasts, but unfortunately the extent of the knowledge of how this affects cell pathology ended there. We have previously identified that Frataxin-deficient (shRNA) human brain microvascular endothelial cells (hBMVEC), an in vitro BBB model, do indeed display inherent barrier defects, including: 1) loss of whole-cell F-actin, 2) loss of F-actin at the cell membrane, 3) tight junction protein deficit, and 4) increased paracellular barrier permeability. Methylprednisolone (MPO) is a corticosteroid that stabilizes tight junctions, and treatment of our shFXN hBMVEC shows improvement of barrier physiology including: 1) increased tight junction production at both the transcriptional and translational levels, and 2) decreased paracellular permeability. We are particularly interested in MPO as a small clinical trial dosing FRDA patients with MPO reported clinical improvement in the timed 1-minute walk. Therefore, we propose that the FRDA BBB has inherent barrier defects, but treatment with MPO stabilizes BBB physiology, and is potentially neuroprotective.

19. SLC4A11 and lncRNA NEAT1: a link between Fuch's Endothelial Corneal Dystrophy

Jacob Tondreau, Regina Cooper, Sangita Patel, Mark Parker, Aniko Marshall, Bianca Quade

The cornea maintains a careful balance of ion gradients to regulate fluid exchange with the aqueous humor. Malfunction in the transporters and channels in the corneal endothelium that work to maintain osmotic balance can result in corneal dystrophies. SLC4A11, a H+ channel, is one such transporter. Loss of SLC4A11 causes congenital hereditary corneal dystrophy (CHED) but certain dominant mutations in SLC4A11 cause late-onset Fuch's endothelial corneal dystrophy (FECD) with corneal thickening in the 4th-5th decade of life. We recreated an FECD mutation in a mouse and observed characteristic progressive corneal thickening, offering insight into the mechanisms of the disease. Transcriptomic analysis reveals that Neat1, a long non-coding RNA, has 40% reduced expression in mice models heterozygous for the Slc4a11 mutation. Neat1 is responsible for paraspeckle formation and plays a key role in managing cellular oxidative stress response as an antioxidant. Lowering Neat1 expression may reduce the cell's ability to manage oxidative stress caused by UV exposure, compromising corneal integrity exacerbated by the loss of Slc4a11.

20. NMR Spectroscopy-Derived Serum Biomarkers of Metabolic Vulnerability are Associated with Disability and Neurodegeneration in Multiple Sclerosis

Taylor Wicks, Irina Shalaurova, Richard W. Browne, Anna Wolska, Bianca Weinstock-Guttman, Robert Zivadinov, Alan Remaley, James Otvos, Murali Ramanathan

Purpose: Metabolic vulnerabilities can cause weakness, fatigue, and decreased physical activity. The purpose was to evaluate whether blood biomarkers of inflammatory and metabolic vulnerability are associated with disability and neurodegeneration in multiple sclerosis (MS). Methods: Proton nuclear magnetic resonance spectra were obtained on serum samples from 153 healthy controls (HC), 187 relapsing-remitting MS (RRMS), and 91 progressive MS (PMS) patients. The spectra were analyzed to obtain concentrations of lipoprotein subclasses, glycated acute phase proteins (GlycA), and small molecule metabolites including leucine, valine, and isoleucine, alanine, citrate, beta-hydroxybutyrate, acetoacetate, and acetone. Composite indices for Inflammatory Vulnerability (IVX), Metabolic Malnutrition (MMX), and Metabolic Vulnerability (MVX) were computed. MS disability was measured on the Expanded Disability Status Scale (EDSS). MRI measures of lesions, whole brain and tissue-specific volumes were acquired. Results: Valine, leucine, isoleucine, alanine, beta-hydroxybutyrate, acetoacetate, IVX, MMX, and MVX differed between HC, RR-MS, and PMS groups in regression analyses adjusted for age, sex, and body mass index. EDSS was associated with small HDL particle levels, IVX and MVX. Timed ambulation was associated with beta-hydroxybutyrate, acetoacetate, IVX and MVX. Greater MVX and IVX were associated with lower gray matter and deep gray matter volumes, and greater lateral ventricle volume. Conclusions: Serum biomarker-derived indices of inflammatory and metabolic vulnerability are associated with disability and neurodegeneration in MS.

22. Disseminated Nocardia Ignorata Infection with Splenic and Brain Involvement in a Patient with Large B-Cell Lymphoma: A Case Report

Sherif Elbaz Younis, Mahmoud Ismail, Seth Glassman, Asmaa Badr, Eric John Dove

Nocardia bacteria, primarily affecting immunocompromised individuals, often presents as pulmonary infections or cerebral abscesses. This case report describes an unprecedented instance of disseminated Nocardia ignorata infection involving the spleen and brain in a 79-year-old Caucasian male with large B-cell lymphoma and chronic obstructive pulmonary disease (COPD). The patient's diagnosis was confirmed through microbiology and pathology assessments, revealing extensively necrotic CD20-positive large B-cell lymphoma in the spleen. The unique combination of brain and splenic dissemination in Nocardia infection adds complexity to the clinical presentation.