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Advisor(s): Khalid Iqbal and Riccardo Bianchi

Seizure susceptibility and hippocampal network hypersynchrony at young age in a triple transgenic mouse model of Alzheimer's disease

Alzheimer's disease (AD) patients are at an increased risk of developing seizures and the hypersynchronous network activity predisposing to seizures may be linked to AD pathology. It remains unclear if epileptiform activity precedes extensive disease pathology in AD and what are the underlying cellular mechanisms. Here, we evaluated seizure susceptibility and hippocampal network hypersynchrony at 3 weeks of age (prior to amyloid plaque deposition and neurofibrillary pathology) in a triple transgenic mouse model of familial AD (3xTg-AD mouse) that harbors mutated amyloid- β precursor protein (A β PP), tau, and presenilin 1 genes. We measured the incidence of seizures and death in animals after auditory stimulation, and recorded from hippocampal neurons in brain slices after pharmacological disinhibition (bicuculline). We also tested the effects of the mGluR5 selective antagonist, MPEP, and of passive immunization with a human A β PP/A β antibody (6E10). Audiogenic seizures were elicited in a higher proportion of 3xTg-AD mice compared with wild type (WT) controls. Seizure susceptibility in 3xTg-AD mice was attenuated by either MPEP or passive immunization with 6E10. In hippocampal slices from 3xTg-AD mice, prolonged (>1.5 s in duration; ictal-like) epileptiform discharges were observed in ~80% of the preparations following bicuculline application. In contrast, in WT slices, only short (<1.5 s; interictal-like) epileptiform discharges were observed after bicuculline application. The prolonged epileptiform discharges in 3xTg-AD slices were suppressed by MPEP. The ictal-like activity in hippocampal slices of 3xTg-AD mice that were immunized with 6E10 was reduced compared to that of untreated 3xTg-AD mice. Our data suggest that (1) neuronal hyperexcitability underlying seizure susceptibility precedes extensive amyloid β and tau pathologies in the triple transgenic mouse model of familial AD, and (2) A β PP/A β and mGluR5 may play a role in network hypersynchrony in AD.

Amit Bhanvadia

Advisor(s): Laura Martello-Rooney

Shifts in the Microbiota Following Antibiotic Therapy for Clostridium difficile Infection

C. difficile infection (CDI) is the leading health care-associated infection in the U.S. and a significant public health threat. Standard treatment for primary and recurrent CDI are suboptimal; however, restoration of a 'healthy' gut microbiome by fecal transplantation has been promising. It is understood that CDI occurrence and recurrence is linked to gut dysbiosis, however there is a paucity of data examining microbial signatures in relation to antibiotic therapy.

Our aim was to examine the microbiome in patients pre- and post-CDI treatment to determine microbial predictors of severity and response to specific therapeutic strategies.

We enrolled 18 patients prospectively at 2 hospital sites in Brooklyn. Patients were identified via toxin+/PCR+ samples and symptoms in keeping with guidelines. Samples were collected at 4 time intervals: Day 0 (diagnosis), T=2 days (post-treatment), T=7 days, and T=14-21 days. Samples were placed into RNAlater and stored at -80°C until analysis. Meta-data obtained at each time interval to assess clinical severity included vitals, abdominal pain/ distension, bowel movements, and components of the Hines VA criteria.

A general trend toward an increase in the relative abundance of Enterobacteriaceae was observed following therapy. We suggest that this clade is able to expand since a niche space previously occupied by sensitive strains is released upon antibiotic therapy. While this family-level classification is general and includes commensal species, it also boasts a variety of other pathogens such as Salmonella, Klebsiella, and Shigella.

The lack of targeted strategies in current CDI treatments fails to address the specific manner in which these therapies are effective. In this study, we identified a bacterial community that becomes abundant with treatment regardless of the regimen employed. The goal of this investigation is to put forth a model of bacterial identification that predicts future response to therapy.

Bhaveen Kapadia

Advisor(s): William Urban

Chronic Kidney Disease and Risk of Venous Thromboembolism or Periprosthetic Infection Following Total Hip and Knee Arthroplasty

Purpose Prevalence of end-stage renal disease (ESRD) and chronic kidney disease (CKD) has been increasing in addition to the incidence of total joint arthroplasties in this patient population. However, outcome data following surgery are lacking. The purpose of this study was to assess the risk of postop venous thromboembolism (VTE) and periprosthetic joint infection (PJI) among patients with CKD and ESRD who received primary total hip (THA) or knee arthroplasty (TKA).

Methods The NY Department of Health Statewide Planning and Research Cooperative System (SPARCS) was used to identify primary THA/TKA patients between 2005 and 2011. Patients with CKD, ESRD, and normal kidney function (NKF) were identified using ICD-9 codes. Logistic regression was used to calculate the age-adjusted odds ratio (OR) and 95% confidence interval (95% CI) of VTE within 90 days and PJI within 365 days of primary THA/TKA.

Results The study cohort consisted of 255,270 patients with THA or TKA, among which 2.4% (N=5,999) had CKD. The incidence of VTE within 90 days was 2.9% for CKD patients (N=176) compared to 1.9% (N=4,714) NKF patients (p<0.001). After adjusting for age, CKD patients were at 37% increased risk of VTE compared to NKF patients (OR=1.4; 95% CI=1.2-1.6; p<0.001). Incidence of PJI within 365 days was 1.4% for CKD (N=84) compared to 0.9% (N=2,220) for NKF patients (p<0.001). After adjusting for age, CKD patients were at 71% increased risk of PJI (OR=1.7; 95% CI=1.4-2.1; p<0.001). Among the subset of 547 ESRD patients, we observed 86% increased risk of VTE (p=0.044) and 168% increased risk of PJI (p=0.009) as compared to NKF patients.

Conclusion Patients who had CKD, particularly those with ESRD, were at increased risk of postop VTE and PJI following primary THA or TKA. This may be secondary to complications of renal dysfunction or associated comorbidities such as diabetes, glomerulonephritis, and hypertension, which are all independent risk factors for poorer outcomes.

Anthony D. Uglialoro

Advisor(s): John G. Kral

Weight-Supported (Anti-gravity) Treadmill Exercise in Caribbean-Black Obese Women

Background: Diabetes is prevalent in Caribbean-Black women in US inner-city environments with limited access to physical activity. Weight-bearing exercise is time-consuming, painful and difficult for obese people. In this pilot study 16 Caribbean-Black women aged 41 ± 11 y (mean \pm SD), mean BMI 35 Kg/m^2 (range: 28 -49.5) performed twice weekly 30-minute bouts of moderate exercise on an AlterG Anti-Gravity Treadmill™ at 70%, 65%, and 60% weight support and increasing levels of incline.

Methods: Anthropometry, oral glucose tolerance tests with plasma insulin, C-Protein and GLP-1, fasting adiponectin, ghrelin and Il-6, accelerometer testing with FitBit™ and socio-economic stress questionnaires. Treadmill distance and expended calories were recorded for each exercise session. Treadmill speed was the only parameter that was variable and adjusted by the participant depending on fatigue. Responders were defined as having improved 2-hr plasma glucose levels.

Results: Mean participation was 11 weeks (range: 8-20) amounting to mean 23 bouts (range 18-24). Three subjects had impaired glucose tolerance at entry (1 DM, 2 IGT), all of whom improved their area-under-the curve (AUC). 11/16 responders significantly reduced their AUC (p=0.0032). Mean s-triglycerides in the 16 subjects decreased from $71.0 \pm 27 \text{ mg/dl}$ to $62.9 \pm 22.4 \text{ mg/dl}$ (p=0.029). There were no statistically significant differences in before-after BMI.

Conclusion: An innovative and convenient moderate weight-supported (anti-gravity) treadmill exercise program improving mobility in this population is a feasible approach to improve metabolic fitness.

Jared Ditkowsky

Advisor(s): Tamar Smith-Norowitz and Stephan Kohlhoff

The Cost-Effectiveness of Varicella Zoster Virus Vaccination Considering Late Onset Asthma

Rationale: Cost-analysis models agree that the implementation of universal varicella zoster virus (VZV) vaccination has resulted in widespread cost savings. Recent studies in our laboratory reported that infection by VZV may lead to delayed onset of asthma in children/adolescents. This information could alter the cost-effectiveness of the program. We created a decision analysis model to estimate the costs and health-related effects of the U.S. VZV vaccination program, assuming VZV infection will delay asthma onset.

Methods: The Markov model (TreeAge Software) considered a birth cohort of 3,957,577 individuals entering the population from a societal perspective over a 20 year time frame. We predicted the number of asthma/VZV cases, asthma/VZV related mortality and costs associated with asthma/VZV. Comparison arms included: 1) VZV vaccination program with no delayed asthma onset 2) VZV vaccination program with delayed asthma onset and 3) no VZV vaccination program with delayed asthma onset. We considered delayed onset ranging from 3-12 years

Results: The vaccination program proved preferential across outcomes without an assumed delay in asthma onset. When the "Vaccination" and "No Vaccination" arms were compared assuming delayed asthma onset, the vaccination program remained less costly despite increased savings related to asthma without vaccination. Additionally, when the delayed onset was 9 years or greater, a comparison of the "Vaccination" and the "No Vaccination" arms revealed greater overall mortality with vaccination.

Conclusions: When there was delayed onset of asthma post-VZV infection, the VZV vaccination program proved less costly, although it resulted in increased asthma morbidity and an overall increase in mortality

Sam Decker

Advisor(s): Carl Paulino

Risk Factors for Cerebrospinal Fluid (CSF) Leak Following Anterior Cervical Discectomy and Fusion (ACDF): A Nationwide Database Study

Purpose Anterior cervical discectomy and fusion (ACDF) is a common spinal surgery. Cerebrospinal fluid (CSF) leak is a rare but serious complication of ACDF. We investigated the association between CSF leak and (1) demographic risk factors (age, sex, race); (2) comorbidities; (3) indications for surgery; (4) hospital stay; and (5) hospital charges.

Methods The Nationwide Inpatient Sample (NIS) was used to identify ACDF patients between 1998 and 2010. Among 1,261,140 patients we identified 3,048 (0.24%) who had postop CSF leak.

Results Mean age of patients with CSF leak was 54 years (95% CI=53-55), compared to 50.8 years (95% CI=50.7-50.9) in patients without CSF leak ($p<0.001$). We observed a 2% increase in risk for each additional year of age (OR=1.02; 95% CI=1.01-1.03; $p<0.001$), and a 50% increase among African Americans (OR=1.50; 95% CI=1.14-1.97; $p=0.004$), but no difference regarding sex ($p=0.19$), or Hispanic race ($p=0.7$). Obesity doubled the risk (OR= 2.05; 95% CI=1.5-2.7; $p<0.001$), while hypertension increased risk by 29% (OR=1.3; 95% CI=1.1-1.6; $p=0.01$). Indication of herniated disc was associated with a 25% decreased risk of CSF leak (OR=0.75; 95% CI=0.6-0.9; $p=0.049$), while indication of cervical spondylosis with myelopathy was associated with a 78% increase (OR=1.8; 95% CI=1.3-2.4; $p<0.001$). Hospital stay was 6 (95% CI=5.4-6.7) days among patients with CSF leak, compared to 2.1 (95% CI=2.09-2.12) days in patients without ($p<0.001$). Charges were \$76,856 (95% CI=69,152-84,560) in patients with CSF leak, compared to \$35,616 (95% CI=35,480-35,752) among patients without ($p<0.001$).

Conclusions Older age and black race had increased risk of CSF leak. These patients should be counseled of their tendency to this complication. Obesity and hypertension are modifiable comorbidities, thus patients may benefit from optimization of these conditions prior to surgery. CSF leaks also increased hospital stay and cost significantly.

Aditya Tarigoppula

Advisor(s): Joseph Francis

Reward Modulation in the primary primary motor and pre-motor areas of a naive monkey.

Reward modulated neural activity has been observed in multiple deep brain and cortical structures of the brain. Recently we found reward modulated neural signal in the primary motor cortex (M1) of the monkeys trained to perform a 'reward task' proficiently. Such a reward-like signal modulating in response to a rewarding or non-rewarding trial was observed in single/multi units as well as in local field potentials. The signal was observed irrespective of whether the monkey was performing the task manually or was passively watching the task being performed for it. These results lead to an interesting question - does the reward modulated signal in M1 show up in an untrained monkey, naive to the 'reward task', as it would have never got the opportunity to integrate the cursor on the virtual task plane into its motor map? An untrained non human primate was implanted in M1 and the pre-motor cortex (PMd) for this study. We demonstrate that a reward-like signal is observed in the M1 and PMd of a naive monkey where it was required to passively observe the 'reward task' being performed for it.

Meghan Walsh

Advisor(s): Mahmood Hussain

Microsomal triglyceride transfer protein determines plasma concentrations of ceramide and sphingomyelin but not of glycosylceramide

Sphingolipids are a large family of bioactive lipids that are implicated in stress responses, differentiation, proliferation, apoptosis, and other physiological processes. Aberrant plasma levels of sphingolipids have been implicated in metabolic disease, atherosclerosis, and insulin resistance. They are fairly evenly distributed in HDL and apoB-containing lipoproteins (Blps). Mechanisms involved in the transport of sphingolipids to the plasma are unknown. Here, we investigated the role of microsomal triglyceride transfer protein (MTP) in the transport of sphingolipids to the plasma. MTP is required for Blp assembly and secretion. We used LC-MS/MS to measure sphingolipids in the plasma of patients with Abetalipoproteinemia, a disease characterized by deleterious mutations in MTP and absence of Blps. Compared to controls, these patients had markedly reduced plasma sphingomyelin (SM) and ceramide, but normal hexosylceramide and lactosylceramide. Further, plasma levels of sphingolipids in liver and intestine specific MTP knockout (L,I-MTP^{-/-}) mice showed similar results, suggesting that MTP specifically plays a role in the regulation of plasma ceramide and SM. We hypothesized that MTP deficiency may affect either their synthesis or secretion. MTP deficiency had no effect on ceramide and SM synthesis, but it reduced secretion from primary hepatocytes and hepatoma cells. Further, synthesis of ceramide and SM in WT and L-MTP^{-/-} liver lysates were similar. Therefore, MTP is involved in ceramide and SM secretion, but not in their synthesis. To understand how MTP assists in the secretion of these sphingolipids, we determined whether MTP could transfer these lipids and observed that MTP transferred these lipids between vesicles in vitro. Therefore, we propose that MTP regulates plasma ceramide and SM levels by transferring these lipids to Blps in the liver and intestine for subsequent secretion into the plasma.

Aditi Khokhar

Advisor(s): Sheila Perez-Colon and Vatcharapan Umpaichitra

Septo-optic Dysplasia in Central Brooklyn Population

Background: Septo-optic dysplasia (SOD) is a rare condition (reported incidence 1/10,000 live births) defined by association of two out of three features: midline brain abnormalities, optic nerve hypoplasia (ONH) and hypothalamic-pituitary endocrine deficiencies. SOD is multifactorial with both genetic and environmental factors playing role in its pathogenesis. Genetic abnormalities are identified only in one percent of patients.

Objective:

-To describe varied clinical spectrum of SOD among five pediatric patients with different ethnic backgrounds living within same geographical area

-To report common maternal and environmental factors amongst the five patients

Method: Retrospective chart review

Results: Five pediatric patients (3 females and 2 males) were diagnosed with SOD over a period of 15 months at our institution. 3 patients were African American, 1 Asian and 1 Hispanic. All patients were first-born children. 4 patients were born full term. 4 mothers were primigravidae with age at childbirth ranging from 19 to 21 years. 2 patients were diagnosed at birth. Ages of diagnosis for the other 3 patients were 2, 3 and 7 years. 2 of the 5 patients developed pituitary hormone abnormalities. 3 patients had B/L ONH; 1 had U/L ONH. One patient had bilateral anophthalmia and SOX2 gene deletion. 4 of the 5 patients had corpus callosum or septum pellucidum hypoplasia.

Discussion: The increased incidence of SOD at our institution that we observed could be a reflection of increased awareness among physicians about this condition. We observed SOD to be more common in first-born children with young primigravida mothers. Central Brooklyn is a region with high population density, a setting that has been described to have higher incidence of SOD. The patients that did not have hypopituitarism might develop endocrine abnormalities later. These patients need to be followed periodically. Early diagnosis of this condition should decrease the disease related morbidity and mortality.

Mariebel Abelarde

Advisor(s): Meriam Caboral-Stevens

Use of Exparel in Ultrasound-guided Transverse Abdominus Block as an adjunct in Post Cesarean Delivery

Background: Post-operative pain relief is an interprofessional collaborative effort. Transversus abdominis plane (TAP) block, is a regional analgesia technique where local anesthetic is injected into the neurovascular plane of the abdominal wall. Exparel, a liposomal bupivacaine, is a new type of local anesthetic that can be delivered through TAP. There is paucity in research in the use of Exparel in cesarean section (C-Section). The purpose of this proposed research is to compare the efficacy of TAP ultrasound-guided block using Exparel as an adjunct to intravenous (IV) patient controlled-analgesia (PCA) morphine versus IV PCA morphine alone for pain relief following elective C-Section.

Theoretical framework: Kolcaba's Theory of Comfort guides the proposed study within the context of a woman's physical experience, prolong continuous relief using Exparel will better ease post-op pain and transcend above discomforts.

Method: A randomized controlled study design of 60 females aged 18-35 years of age categorized as American Society of Anesthesiologist (ASA) Class I or II, scheduled for elective C-Section using Pfannenstiel incision will be recruited from an urban institution in NY. Participants will be evenly divided to either Group A who will receive bilateral TAP block using Exparel as an adjunct to IV morphine PCA, or Group B who will receive IV morphine PCA alone. Numerical Rating Scale (NRS) will be used to assess post-operative pain and the opioid consumption will be based on PCA flow sheet. T-test will be used to compare the data with significance level set at 0.05.

Results: Findings from this study will provide information on the efficacy of using Exparel as an adjunct for post-op pain relief in elective C-section.

Implication: Effective post-operative pain control is critical to patient's health outcome. If this intervention is efficacious, the peri-operative team including Nurse Anesthetists will have a new approach to pain management.

Advisor(s):

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