PL1-1. Gene Therapy with AGIL-AADC in Children with AADC Deficiency Leads to De Novo Dopamine Production and Sustained Improvement in Motor Milestones Over 5 Years

Chien Y (Taipei, Taiwan), Lee N, Tieng S, Tai C, Conway A, Gruis K, Pykett M, Hwu W

Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare, genetic disorder of neurotransmitter synthesis in children. We evaluated biologic and clinical outcomes through 5 years following administration of AGIL-AADC, a recombinant adeno-associated virus containing human cDNA encoding the AADC enzyme, in children with severe AADC deficiency.

Methods: In two single-arm, open-label clinical studies, children with severe AADC deficiency received an AGIL-AADC total dose of 1.8×10^{11} vg as bilateral, intraputaminal, stereotactic infusions during a single operative session. De novo dopamine production was evaluated using FDOPA PET imaging. Clinical assessments included the achievement of motor milestones and adverse events (AEs). Data from AGIL-AADC patients were compared with a natural history cohort of severe AADC patients using Fisher exact test (p<0.05).

Results: Eighteen patients aged 21 months to 8.5 years were administered AGIL-AADC. At baseline, no patient had developed full head control or the ability to sit unassisted or to stand; these observations were consistent with the natural history cohort (N=82). Following AGIL-AADC administration, all patients had sustained de novo dopamine production. Of 15 patients evaluated 2 years post-treatment, 5 gained full head control (P<0.0001); 4 could sit unassisted (P=0.0004); and 1 could stand with support. Of 7 patients evaluated 5 years post-treatment, 4 gained full head control and the ability to sit unassisted (P<0.0001 each); 2 could stand with support (P=0.0054). Generally, AEs were associated with the disease.

Conclusions: AGIL-AADC is a potential gene therapy for children with severe AADC deficiency to enable achievement and maintenance of motor milestones.

Keywords: Movement Disorders, Rare Diseases, Cognitve/Behavioral Disorders

PL1-2. Gene Therapy for AADC Deficiency

Pearson T (St. Louis, MO), Gupta N, Viehoever A, Grijalvo-Perez A, Inamoura-Ching J, Seo Y, San Sebastian W, Bankiewicz K

Objective: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare autosomal recessive genetic disorder that causes impaired synthesis of dopamine and serotonin. It presents in infancy with hypotonia, hypokinesia, oculogyric crises (OGC), dystonia, autonomic symptoms, irritability, and motor delay. The objective of this trial is to investigate the safety and efficacy of adeno-associated virus serotype 2 (AAV2)-hAADC delivered by MR-guided infusion to the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA).

Methods: Three children (2 female, 1 male; ages 9, 8, and 5 years) were treated with a low dose of vector (1.3×10^{11} vector genomes) and have been followed for 6 to 12 months. Evaluations consisted of neurological examination, Gross Motor Function Measure-88, FDOPA-PET/ MRI scans and CSF analysis of neurotransmitter metabolites.

Results: MR data confirmed accurate targeting and 70-100% coverage of the SNc/VTA. No adverse events related to the surgical intervention occurred. Gene transfer resulted in complete cessation of OGC in 2/3 patients. Sleep, mood, and hyperhidrosis markedly improved in all subjects. Motor function improved by 4-5 points (GMFM-88 scale) at 6-12 months. One subject is able to sit independently, reach and grasp, and take steps with support. CSF homovanillic acid (HVA) increased in all subjects and FDOPA PET demonstrated increased uptake in the mid-brain, caudate and putamen. Subjects developed mild to moderate dyskinesia post-gene transfer, peaking in severity between 1-3 months.

Conclusions: AADC gene transfer to SNc/VTA is safe, and produces an improvement in dystonic symptoms, mood, and motor function in children with AADC deficiency.

Keywords: Movement Disorders, Translational/Experimental Therapeutics, Genetics

PL1-3. Lenti-D Hematopoietic Stem Cell Gene Therapy for the Treatment of Cerebral Adrenoleukodystrophy: Updated Safety and Efficacy Outcomes from an Ongoing Phase 2/3 Trial


Objective: Cerebral adrenoleukodystrophy (CALD) is characterized by inflammatory demyelination leading to progressive loss of neurologic function and death. Early diagnosis and treatment are key in ensuring optimal long-term outcomes.

Methods: Lenti-D Drug Product (DP) is an investigational gene therapy for the treatment of CALD. Boys with CALD (≤17 years) enrolled in an open-label phase 2/3 study of the safety and efficacy of Lenti-D DP underwent full myeloablation followed by infusion of autologous CD34+ cells transduced with elivaldogene tavalentivec (Lenti-D) lentiviral vector. The primary efficacy endpoint is the proportion of patients who are alive and free of major functional disabilities (MFD) at Month 24. The success criterion for the primary endpoint, defined from an observational study of the natural history of CALD and outcomes from allogeneic transplant, is met for the first 17 patients if the point estimate is ≥76.5% MFD-free survival at Month 24.
**Results:** As of August 2017, 15/17 (88%) patients with evaluable data at Month 24 remain alive and MFD-free with evidence of disease stabilization. One patient succumbed to disease progression; another was withdrawn from the trial due to radiographic evidence of disease progression. The safety profile has been consistent with myeloablative conditioning. As of April 2018, 29 patients will have received Lenti-D DP. The longest follow-up will be 54 months; 5 patients will have ≤3 months of follow-up. An updated efficacy and safety profile of Lenti-D DP will be presented.

**Conclusions:** Lenti-D DP is expected to meet its primary efficacy endpoint and appears to be a promising gene therapy for CALD.

**Keywords:** Rare Diseases, Demyelinating Disorders, Genetics

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**PL1-4. Identification of Compounds from a Novel Zebrafish Screen for Adrenoleukodystrophy**

**Bonkowsky J** (Salt Lake City, UT), **Freshner B, Stevenson T**

**Objective:** We have generated zebrafish mutants in ABCD1 that recapitulate key features of the human leukodystrophy ALD (X-linked adrenoleukodystrophy), including effects on myelin, oligodendrocytes, and elevated very-long-chain fatty acid (VLCPA) levels (Strachan et al., 2017). The mutants have impaired swimming behavior, which is present by 7 days post-fertilization (dpf) and that is rescued by expression of the human gene. Our goal was to screen for compounds that stopped or decreased disease effects, using the zebrafish ALD model.

**Methods:** We performed a primary compound screen of 2500 compounds from the Microsource Spectrum collection. Following the primary screen, promising hits were re-screened; and secondary assays were performed to assess biological activity and effects. In silico analysis was conducted to identify common features of positive hits.

**Results:** We identified 29 compounds that had significant improvements for the ALD mutants in the behavioral screen. Following the re-screen, 7 compounds had confirmed statistically significant effects. Secondary assays of oligodendrocyte counts; cell death in the CNS; and VLCPA (very-long chain fatty acid) levels; confirmed biological activity of three of the compounds.

**Conclusions:** We conducted a primary screen of compounds to treat ALD in a zebrafish model. The screen was conducted in less than 6 months, and identified several promising compounds, including two compounds from the same drug family that are FDA approved and not on patent. We are studying the biological effects of this compound family on oligodendrocytes, and our results suggest that clinical trials with this compound family may be indicated.

**Keywords:** Demyelinating Disorders

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**PL1-5. Trio-based Exome Sequencing Provides a Comprehensive and Dynamic Approach to Genetic Testing for Leukodystrophy**

**Zou F** (Gaithersberg, MD), **Zuck T, Downtain C, Zamora F, Retterer K, Scaffini J, McKnight D**

**Objective:** The objective of this study was to establish the positive diagnostic rate (PDR) for leukodystrophies by exome sequencing (ES) and provide evidence that evaluating multiple family members combined with a comprehensive gene list is an effective method.

**Methods:** We retrospectively reviewed the results of ES for 541 patients who had leukodystrophy reported as a clinical clue. A positive result was defined as the identification of one or two pathogenic or likely pathogenic variants, depending on the mode of inheritance expected for the disorder.

**Results:** Overall, ES yielded a positive result in 33% (176/541) of cases. In 51% (90/176) of positive cases, the causative gene was associated with an autosomal recessive (AR) disorder, 41% (72/176) were autosomal dominant (AD), and 8% (14/176) were X-linked (XL). Majority of patients diagnosed with an AD disorder (81%, 58/72) had de novo variants. Overall, pathogenic or likely pathogenic variants were reported in 133 different genes including most commonly reported genes: TUBB4A (3.4%), RNASEH2B (2.8%), GFAP (2.8%), EIF2B5 (1.7%), and POLR3A (1.7%). Interestingly, over 8% of genes with positive findings had been only described in connection with a specific disease within the last two years.

**Conclusions:** Overall, a trio-based comprehensive approach to genetic testing for leukodystrophies is a faster alternative to serial MRIs and biochemical tests and can help to identify a genetic etiology in at least one-third of cases. Furthermore, a significant portion of positive cases had diagnostic findings in newly described genes, underscoring the importance of a comprehensive and dynamic approach to gene sequencing for leukodystrophies.

**Keywords:** Genetics, Demyelinating Disorders

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**Singh K** (Worcester, MA), **Diggins E, Connors S, Zimmerman A**

**Objective:** Direct treatment of underlying mechanisms in ASD is limited. The “fever effect” in ASD, where febrile illness temporarily ameliorates disordered behavior, may offer a clinical clue. Fever stimulates heat shock proteins (HSP),
Nrf2 transcription and cell-stress responses (CSR), leading to improved synaptic function and long-range connectivity. Sulforaphane (SF), an isothiocyanate from broccoli sprouts, induces HSP, Nrf2 and CSR that may benefit ASD through common cellular mechanisms underlying heterogeneous phenotypes.

Methods: This is a phase-2 clinical trial to test safety and efficacy of oral SF in 50 children (age 3-12 years) with ASD. Treatment period is 30 weeks, with study-visits at screening, 7, 15, 22, 30 and 36 weeks. The first 15 weeks are randomized, double-blind, 1:1 placebo-controlled, the second 15 weeks open-label (all participants receiving SF), and last 6 weeks wash-out. Ohio Autism Clinical Impressions Scale (OACIS), Aberrant Behavior Checklist and Social Responsiveness Scale are administered and samples are collected for safety and research studies at each visit.

Results: We have completed enrollment; 32 participants have completed the trial, 16 are actively enrolled, with 2 drop-outs. A preliminary analysis of the OACIS showed: 23% participants were much/very much improved at 7 weeks, 31% at 15 weeks, 59% at 22 weeks, and 53% at 30 weeks (see Figure). Most adverse events so far are mild and transient [insomnia (28%), vomiting (19%), flatulence (17%), diarrhea (15%), and constipation (13%)]. Full results, including biomarker data, are expected after 07/2018.

Conclusions: Our preliminary results show that sulforaphane appears to be safe and effective in children with ASD.

Keywords: Cognitive/Behavioral Disorders, Translational/Experimental Therapeutics

PL1-7. Anticoagulation Use and its Associations with Etiology and Early Outcome of Childhood Cerebral Sinovenous Thrombosis: Findings from the International Pediatric Stroke Study

Felling R (Baltimore, MD), Hasanean S, Armstrong J, Aversa L, Billinghurst L, Goldenberg N, Lee J, Maxwell E, Noetzel M, Lo W

Objective: Cerebral sinovenous thrombosis (CSVT) affects 0.67 per 100,000 children and can have severe consequences including intracranial hypertension, venous infarction, and intracerebral hemorrhage. Anticoagulation is common based on extrapolation of adult guidelines. We investigated treatment practices and outcomes for childhood CSVT in the multinational prospective registry of the International Pediatric Stroke Study (IPSS).

Methods: We included patients enrolled in the IPSS registry with a diagnosis of CSVT at ≥28 days of age with radiological confirmation. Children with concomitant arterial ischemic stroke were excluded. Unfavorable outcome was defined as severe neurological impairment or death at discharge. Predictors were analyzed by ordinal regression.

Results: We included 410 children. Most (95%) had identifiable risk factors, and 82% received anticoagulation. In univariate analysis, we found lower odds of anticoagulation with decreased level of consciousness, seizure, hemiparesis, speech deficit, head trauma/intracranial surgery, intracerebral hemorrhage, and infant. Older age, papilledema, headache, and visual field deficits were associated with anticoagulation. In multivariable analysis, head trauma/intracranial surgery was the only significant predictor (OR 0.27, p=0.001). Intracerebral hemorrhage or venous infarct were associated with unfavorable outcome while older age and anticoagulation were associated with favorable outcome. In multivariable analysis, the use of anticoagulation and the presence of infarct retained significant associations (OR 0.33 p=0.027 and OR 3.03 p=0.017, respectively).

Conclusions: Within the multinational IPSS registry, children with head trauma or intracranial surgery were less likely to receive anticoagulation for CSVT. Anticoagulation was associated with favorable outcome at discharge. These findings are limited and warrant further investigation in randomized, case-controlled, prospective studies.

Keywords: Stroke, Critical Care

Platform Session 2
Wednesday, October 17
(8:30 am - 10:15 am)

PL2-1. A New Mouse Model of Congenital Zika Virus Infection Reveals Neurodevelopmental Pathways Disrupted in Congenital Zika Syndrome


Objective: Congenital Zika virus (ZIKV) infection causes severe neurological complications including microcephaly but its pathogenesis is not well understood and there is no effective intervention. We performed unbiased transcriptomic and proteomic analyses of the embryonic mouse brains of our new congenital ZIKV infection model to study its neuropathogenesis.

Methods: We infected wild-type mouse embryos in utero with ZIKV at embryonic day (E) 10.5. We performed RNA sequencing (RNAseq) and proteomic analysis of the ZIKV-infected and control bulk mouse brains at E14.5.

Results: RNAseq analysis identified 74 genes significantly downregulated and 507 genes significantly upregulated in the ZIKV-infected brains compared to controls. Forebrain development was the most enriched functional category among the downregulated genes. Proteomic analysis revealed that the
protein products of 29 of the 74 genes were also downregulated in the ZIKV-infected brains. These genes were also enriched for regulators of forebrain development including: 1) proneural gene Neurod2 and its downstream targets; 2) marker and regulator of intermediate neural progenitor cells, Tbr2; and 3) regulators of GABAergic interneuron development, Arx and Dlx2.

Conclusions: Our proteogenomic analysis implicated specific pathways that regulate neural cell fate and interneuron development as an underlying cause of congenital ZIKV syndrome. Abnormal interneuron development may also contribute to high epileptogenicity of the condition. Our new mouse model and unbiased proteogenomic approach are also expected to help therapy development for congenital ZIKV syndrome and may be applied studies of other congenital infections.

Keywords: Infections/Neuroimmunology, Rare Diseases

PL2-2. Early Changes in Cytokine Levels in Neonates with Encephalopathy Predict Remote Epilepsy
Numis A (San Francisco, CA), Foster-Barber A, Rogers E, Barkovich J, Ferriero D, Glass H

Objective: We aim to determine if levels of cytokines in neonates with brain injury are associated with the presence of acute symptomatic seizures or the development of remote epilepsy.

Methods: A cohort study of consecutive term newborns with encephalopathy at UCSF between 10/1993 and 1/2000 who had dried blood spots (DBS) obtained 24-120 hours after birth. DBS were analyzed for seven cytokines by immunoaffinity chromatography. Maternal, perinatal/postnatal, and neuroimaging variables were abstracted as previously described. In patients with >2 years of follow-up, epilepsy was determined by chart review. Univariate tests were followed by logistic regression to compare levels of cytokines with outcome variables while controlling for injury severity. P-values were adjusted for multiple comparisons using the false discovery rate correction.

Results: Twenty-eight of 62 (45%) newborns met inclusion criteria; 86% had evidence of NE, 10% stroke and 4% infection. Cytokine levels did not vary by sex, race, gestational age, maternal age, etiology, encephalopathy score, or MRI score. Eleven of 28 (39%) patients had acute symptomatic seizures. Diffuse alterations in cytokine levels were observed between those with and without acute symptomatic seizures (Figure 1). Seventeen of 26 (63%) patients had more than two years of follow-up and 4/17 (24%) developed epilepsy. Increased levels of IL-6, IL-9, and TNF-α were significantly associated with epilepsy (Figure 1).

Conclusions: Acute symptomatic seizures after neonatal brain injury result in diffuse changes in both pro-inflammatory cytokine levels. However, only increased levels

FIGURE 1: Cytokine levels in children without acute symptomatic/early seizures (n=11) compared to those with seizures (n=15). Abstract PL 2-2
of pro-inflammatory cytokines in the IL-1β pathway are associated with later development of epilepsy.

**Keywords:** Epilepsy, Neonatal Neurology, Infections/Neuroimmunology

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**PL2-3. Monocyte, T-cell, and B-cell Transcriptomes from Multiple Sclerosis Patients Treated with Vitamin D Highlight Metabolic Pathways Relevant to Immune Regulation**


**Objective:** Vitamin D status has been linked to an inexplicably wide range of disease states. Confusion over these apparent links could be due, in part, to our pre-existing assumptions of vitamin D’s physiologic roles. We sought an unbiased characterization of vitamin D’s in vivo effects on human immune cells in states of health and disease.

**Methods:** We generated discovery, validation, and placebo datasets using PBMC-derived human transcriptomes from 113 individuals in vitamin D trials (19 multiple sclerosis patients, NCT01024777; 94 pre-diabetic but otherwise healthy adults, NCT01771380). We characterized pathways using GSEA and Gene Ontology toolkits. We further validated our in vivo findings using in vitro studies of healthy human PBMCs.

**Results:** Unsupervised cluster and principal component analysis identified a well-delineated treatment effect. Our strongest pathway linkage indicated a treatment-related gain in OXPHOS coupling efficiency. In both pre-diabetic and multiple sclerosis-affected adults, in vivo vitamin D exposure inversely correlated with Hallmark pathways linked to metabolism (OXPHOS, Adipogenesis, Fatty acid metabolism, PI3K-AKT/MTOR), cell survival/cycle (MYC targets, NOTCH signaling), and inflammation (Inflammatory response). Pre-diabetic adults showed additional down-regulation in apoptosis and p53 pathways, while MS adults showed broader declines in inflammatory and oxidative stress pathways. Functional assays measuring survival and metabolism in healthy PBMCs confirmed these findings.

**Conclusions:** We find that vitamin D plays an unexpectedly prominent role in fuel dependency, energy efficiency, and cell survival in the human immune system. These findings offer new vantage points for understanding vitamin D’s role in human health and disease with particular relevance for disorders of fatty acid metabolism including X-linked adrenoleukodystrophy.

**Keywords:** Demyelinating Disorders, Infections/Neuroimmunology
PL2-4. A New Rodent Model of Dystonic Cerebral Palsy

Aravamuthan B (Boston, MA), Young A, Rutkove S

**Objective:** To develop an animal cerebral palsy (CP) model displaying quantifiable dystonia.

**Methods:** Since dystonic CP is associated with hypoxic-ischemic injury at term gestation, rats were variably exposed to graded global hypoxia for 10-15 minutes (anoxia and cardiac arrest by 11 minutes) between postnatal day (P) 6-8.5 (equivalent to human 36-38.5 post-conceptional weeks). Weekly motor assessment included gait analysis and rotarod acceleration. As qualitative differentiation between spasticity and dystonia is difficult, spasticity was instead quantified as soleus Hoffman (H) reflex suppression with 2Hz tibial nerve stimulation (diminished in spastic rats). Dystonia was quantified as tibialis anterior and triceps surae complex co-contraction frequency and coherence between 4-12 Hz (elevated in adults with dystonia).

**Results:** Pups survived 12 minutes of graded hypoxia between P7-8, but not afterwards. Earlier times of injury did not yield motor impairment. Hypoxia between P7-8 (n=15) produced the greatest motor impairment, which worsened through P28 before stabilization. Compared to sham-exposed pups (n=18), pups surviving 12 minutes of hypoxia had shorter stride length, worse rotarod performance, diminished H-reflex suppression, and increased hindlimb muscle co-contraction and coherence (p<0.05, 2-tailed, t-test). Two injured pups demonstrated hindlimb muscle coherence outside a 95% confidence interval of mean sham coherence.

**Conclusions:** We describe a novel clinically-relevant rat model of neonatal hypoxic-ischemic injury yielding motor impairment and quantifiable dystonia and spasticity. 15% of injured pups appeared to have a dystonic phenotype, comparable to the clinical frequency of dystonic CP for this injury mechanism. This model can be used to investigate the etiology and treatment of dystonic CP.

**Keywords:** Movement Disorders, Neonatal Neurology

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PL2-5. Evaluation of a Novel 18F-labeled Tryptophan Tracer for PET Imaging of Brain Tumors in a Medulloblastoma Mouse Model


**Objective:** Medulloblastoma is the most common malignant brain tumor of childhood. Despite major advances, long-term survival is hindered by relapse. Abnormal tryptophan metabolism, via the immunomodulatory indoleamine-2,3-dioxygenase (IDO)/tryptophan-2,3 dioxygenase (TDO)-mediated kynurenine pathway (KP), has been demonstrated in tumors, and is emerging as a valid target for immunotherapy and non-invasive tumor imaging. Both TDO and IDO are tissue-specific first step and rate-limiting enzymes of the KP of tryptophan metabolism. TDO2 and/or IDO1 mRNA expression was reported to be increased in 48/73 medulloblastoma samples across all 4 subgroups. Previously, α-[11C] methyl-L-tryptophan ([11C]AMT), a positron emission tomography (PET) tracer, was successfully used to evaluate the increased tryptophan metabolism and uptake through KP in gliomas. Nevertheless, the short half-life of [11C]AMT has limited its broad applications. In this study, we assessed tryptophan metabolism in a transgenic Sonic Hedgehog (Sonic) medulloblastoma in a Smo/Smo transgenic mouse; (B) a normal control mouse. PET images were taken 1 hour after injection of the tracer through tail vain. 18F-FETrp shows increased tumor accumulation compared to normal brain tissues. The abdomen in both animals shows physiologically high uptake. The color scale bar represents the SUV range 0-200,000 Bq/ml. Abstract PL 2-5
hedgehog (Shh) medulloblastoma subgroup mouse model using a novel PET tracer, 1-(2-[18F]fluoroethyl)-L-tryptophan (L-1-[18F]FETrp), with similar properties as [11C]AMT8.

Methods: PET imaging was performed on Smo-Smo transgenic mice bearing Shh medulloblastoma and normal control mice. Immunoblot and immunofluorescence were performed with tissue lysates.

Results: In Smo-Smo mice, PET imaging showed increased accumulation of L-1-[18F]FETrp in tumors (Image 1). Immunofluorescence and molecular analysis of tumor tissues obtained from Smo-Smo mice showed increased expression of TDO2, but not IDO1 (Image 2).

Conclusions: Our preclinical studies in Smo-Smo mice indicate that L-1-[18F]FETrp may be a suitable tracer for PET imaging of medulloblastoma tumors and could provide valuable information for non-invasive assessment of immunotherapy response and move towards targeted therapy.

Keywords: Brain Tumors/Oncology, Neuroimaging, Translational/Experimental Therapeutics

PL2-6. Age- and Sex-Dependent Dysregulation of KCC2 Co-transporter Expression by MTOR Pathway Activation

Jansen L (Charlottesville, VA), Hesse J, Zhong Q, Gunter S, Kelly K, Bur D, Talbot E, Shan S, Goodkin H

Objective: Reduced expression of the cation co-transporter KCC2 due to mTOR pathway activation has been identified in the mature brain. In this study, we examined the sex-dependent effects of excessive mTOR pathway activity on KCC2 expression in the immature brain.

Methods: Western blot and fluorescence immunohistochemistry determination of KCC2 expression was performed in brain specimens resected from children with intractable epilepsy, cultured mouse cortical neurons, and mice with heterozygous Tic2 loss-of-function.

Results: KCC2 expression was higher in infants with mTOR pathway activation than in age-matched controls. In contrast, KCC2 expression was reduced in the older epileptic children. In order to differentiate the effects of seizures from the effects of mTOR pathway activation itself, KCC2 expression was determined in immature cultured mouse cortical neurons expressing the constitutively active MTOR S2215Y mutation, and was again found to be increased. Finally, KCC2 protein measurements were performed in heterozygous Tic2+/- mice. At P5, cortical KCC2 levels were higher in mutant mice of both sexes than in wild-type littermates. However, at P14 and P21, sexually divergent effects were found, with male Tic2+/- mice still exhibiting elevated KCC2 expression, while female mutant mice transitioned to the mature pattern of reduced expression.

Conclusions: MTOR pathway activation in the immature brain increases KCC2 expression, which may cause an early shift in depolarizing to hyperpolarizing GABAergic neurotransmission, impairing synaptogenesis and network formation. This effect persists longer in males than females, and could contribute to sex-dependent developmental impairments.

Keywords: Genetics, Cognitive/Behavioral Disorders, Epilepsy
which were summed as a cumulative impact for the two football seasons. Players were also divided into “high intensity” and “low intensity” groups based on whether they sustained high g-force impacts in both seasons. Players completed assessments on a variety of outcomes before the 2016 season and after the 2017 season: neuropsychological test performance, symptom ratings, vestibular-ocular function, balance, parent-completed ADHD symptoms, and self-reported behavioral adjustment.

**Results:** Average cumulative impact was 6,920 (SD 4,553) g-forces combined for the two seasons and did not differ between age groups (p=0.66). Twenty-one players (38%) were classified as “high intensity” based on individual impacts. After correcting for multiple comparisons, neither cumulative impact nor impact intensity predicted change scores from pre-2016 season to post-2017 season on any outcome measures. Instead, younger age group and history of ADHD predicted worse change scores on several cognitive measures and ADHD symptom reporting.

**Conclusions:** Over two consecutive seasons of primary and high school tackle football participation, cumulative head impact burden and intensity of impacts were not found to be associated with changes in cognition, balance, vestibular function, or behavioral adjustment.

**Keywords:** Cognitive/Behavioral Disorders

| TABLE 1. Regression table depicting the results of three logistic regressions: depression, anxiety, and either depression or anxiety. Abstract PL 3-2 |
| --- | --- | --- | --- | --- | --- | --- |
| Category | Sub-Category | Factor | Depression | Anxiety | Depression and/or Anxiety |
| | | | OR [95% CI] | p-Value | OR [95% CI] | p-Value | OR [95% CI] | p-Value |
| Demographics | Age | Adolescent | 1.71 [0.66, 4.43] | 0.26 | 1.43 [0.70, 2.89] | 0.33 | 1.87 [1.00, 3.49] | 0.05* |
| | | Child | ref | --- | ref | --- | ref | --- |
| Geography | West | 2.08 [0.55, 7.93] | 0.28 | 0.75 [0.31, 1.79] | 0.52 | 1.05 [0.43, 2.52] | 0.92 |
| | Midwest | 1.7 [0.59, 4.90] | 0.32 | 0.85 [0.33, 2.15] | 0.73 | 0.97 [0.40, 2.34] | 0.95 |
| | Northeast | 0.4 [0.10, 1.58] | 0.19 | 1.12 [0.46, 2.73] | 0.81 | 0.95 [0.41, 2.20] | 0.8 |
| | South | ref | --- | ref | --- | ref | --- |
| | Sex | Male | 0.4 [0.14, 1.12] | 0.08 | 0.64 [0.33, 1.25] | 0.19 | 0.51 [0.27, 0.95] | 0.03* |
| | Female | ref | --- | ref | --- | ref | --- |
| Ethnicity | Hispanic | 0.38 [0.10, 1.41] | 0.15 | 0.35 [0.10, 1.19] | 0.09 | 0.29 [0.09, 0.95] | 0.04* |
| | Non-Hispanic | ref | --- | ref | --- | ref | --- |
| Race | White | 0.99 [0.28, 3.46] | 0.99 | 4.5 [1.25, 16.2] | 0.02* | 4.14 [1.35, 12.7] | 0.01* |
| | Other Race | 1.4 [0.27, 7.20] | 0.69 | 2.96 [0.67, 13.2] | 0.15 | 2.8 [0.78, 10.1] | 0.12 |
| | Black | ref | --- | ref | --- | ref | --- |
| Household Information | Highest Parent Education | High School or Less | 1.24 [0.37, 4.18] | 0.73 | 0.33 [0.14, 0.79] | 0.013* | 0.64 [0.30, 1.35] | 0.24 |
| | Greater than high school | ref | --- | ref | --- | ref | --- |
| Insurance | Any Public | 0.78 [0.19, 3.23] | 0.73 | 1.33 [0.52, 3.38] | 0.55 | 1.24 [0.53, 2.94] | 0.62 |
| | Uninsured | 1.23 [0.12, 12.3] | 0.86 | 0.4 [0.06, 2.86] | 0.36 | 0.29 [0.04, 2.13] | 0.22 |
| | Private | ref | --- | ref | --- | ref | ---

**PL3-2. Demographic Variables Associated with the Prevalence of Depression and Anxiety in a Nationally-Representative Sample of Children and Adolescents with Epilepsy**

LaGrant B (New York, NY), Grinspan Z

**Objective:** Anxiety and depression are common in children with epilepsy, but associated demographic, household, and health status factors are understudied.

**Methods:** We used the 2009-2010 National Survey of Children with Special Health Care Needs (NS-CSHCN) to identify children with epilepsy with and without depression and anxiety (Child and Adolescent Health Measurement Initiative, 2009-2010). We assessed factors associated with depression and anxiety using weighted multivariable logistic regression, allowing national estimates. Factors analyzed included age, race, ethnicity, region of United States, socioeconomic status (SES), type of health insurance, parent education level, epilepsy severity, and comorbidities.

**Results:** The final sample included 1,042 children over the age of five with epilepsy. Poverty was significantly associated with depression while white race and high parent education level were associated with anxiety. In a combined regression of both depression and anxiety, white race, non-Hispanic ethnicity, older age, female sex, and a greater...
number of medical comorbidities were significantly associated with anxiety and/or depression. Several psychiatric and neurologic comorbidities were also significantly associated with anxiety and/or depression. Neither epilepsy severity nor insurance status were related to depression or anxiety.

Conclusions: Sex, race, ethnicity, age, SES, and comorbidities are all crucial pieces of information for physicians to consider when treating children with epilepsy. Understanding these factors may have clinical relevance, in that they may help clinicians effectively determine who is most at risk for developing anxiety and depression, and intervene appropriately to screen for suicidality and/or reduced quality of life.

Keywords: Epilepsy

PL3-3. Risk Factors for Incomplete Response to Anti-seizure Medication in Neonates with Acute Symptomatic Seizures


Objective: To examine risk factors for incomplete response to anti-seizure medications in neonates with acute symptomatic seizures.

Methods: Prospective, multi-center cohort of neonates with acute symptomatic seizures due to hypoxic-ischemic encephalopathy (HIE), ischemic stroke, or intracranial hemorrhage (ICH) who received a loading dose of anti-seizure medication. A neonate was considered to have incomplete response if additional seizures were identified after the initial loading dose of medication as determined by chart review.

Results: Among 386 neonates with acute symptomatic seizures, the rate of incomplete response was 65%. There was no difference in the risk of incomplete response to the initial dose of medication by medication choice (phenobarbital 238/269 = 65%; levetiracetam 8/13 = 62%; fosphenytoin 4/4 = 100% incomplete response, p=0.3), term vs preterm birth (223/339 = 66% vs 27/47 = 57%, p=0.3), seizure etiology (HIE 133/217 = 62%, stroke 63/96 = 66%, ICH 52/73 = 71%, p=0.4), or initial loading dose of phenobarbital (Figure, p=0.1).

Conclusions: The risk of incomplete response to anti-seizure medication is similar across seizure etiologies and medication choices. Future clinical trials of novel anti-seizure medications should consider incorporating broad entry criteria rather than restricting to term neonates with HIE.

Keywords: Neonatal Neurology, Epilepsy, Critical Care

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<thead>
<tr>
<th>Category</th>
<th>Sub-Category</th>
<th>Factor</th>
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<th>Anxiety</th>
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<td></td>
<td>OR [95% CI]</td>
<td>p-Value</td>
<td>OR [95% CI]</td>
</tr>
<tr>
<td>SES</td>
<td></td>
<td>&lt; 100% FPL</td>
<td>9.28 [2.66, 32.4]</td>
<td>&lt;0.001***</td>
<td>1.02 [0.41, 2.56]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 100% FPL</td>
<td>ref</td>
<td>---</td>
<td>ref</td>
</tr>
<tr>
<td>Has Specialist Needs Met</td>
<td></td>
<td></td>
<td>0.3 [0.09, 1.06]</td>
<td>0.06</td>
<td>1.14 [0.27, 4.78]</td>
</tr>
<tr>
<td>Epilepsy Severity</td>
<td>Moderate Epilepsy</td>
<td></td>
<td>1.5 [0.54, 4.18]</td>
<td>0.44</td>
<td>1.29 [0.62, 2.68]</td>
</tr>
<tr>
<td></td>
<td>Severe Epilepsy</td>
<td></td>
<td>0.76 [0.24, 2.45]</td>
<td>0.65</td>
<td>0.9 [0.34, 2.34]</td>
</tr>
<tr>
<td></td>
<td>Mild Epilepsy</td>
<td></td>
<td>ref</td>
<td>---</td>
<td>ref</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Mental Retardation</td>
<td></td>
<td>0.66 [0.22, 2.00]</td>
<td>0.47</td>
<td>0.87 [0.32, 2.40]</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td></td>
<td>29.6 [10.5, 83.1]</td>
<td>&lt;0.001***</td>
<td>--</td>
</tr>
<tr>
<td></td>
<td>Behavior Issues</td>
<td></td>
<td>4.92 [1.72, 14.1]</td>
<td>0.003**</td>
<td>4.55 [1.74, 11.88]</td>
</tr>
<tr>
<td></td>
<td>Autism</td>
<td></td>
<td>1.24 [0.42, 3.64]</td>
<td>0.69</td>
<td>3.04 [1.43, 6.49]</td>
</tr>
<tr>
<td></td>
<td>ADHD</td>
<td></td>
<td>3.83 [1.65, 8.88]</td>
<td>0.002**</td>
<td>1.94 [0.82, 4.59]</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>Developmental Delay</td>
<td></td>
<td>0.51 [0.17, 1.53]</td>
<td>0.23</td>
<td>1.62 [0.64, 4.07]</td>
</tr>
<tr>
<td></td>
<td>Migraines</td>
<td></td>
<td>6.64 [2.34, 18.9]</td>
<td>&lt;0.001***</td>
<td>1.79 [0.84, 3.82]</td>
</tr>
<tr>
<td></td>
<td>Cerebral Palsy</td>
<td></td>
<td>1.1 [0.28, 4.35]</td>
<td>0.89</td>
<td>0.44 [0.20, 0.99]</td>
</tr>
<tr>
<td></td>
<td>Concussion</td>
<td></td>
<td>1.48 [0.37, 5.82]</td>
<td>0.58</td>
<td>0.57 [0.23, 1.42]</td>
</tr>
<tr>
<td></td>
<td>Down’s Syndrome</td>
<td></td>
<td>10⁻⁶ [10⁻⁷, 10⁻⁶]</td>
<td>&lt;0.001***</td>
<td>1.77 [0.12, 26.8]</td>
</tr>
<tr>
<td>Other Medical Conditions</td>
<td>Total Number of Conditions</td>
<td></td>
<td>1.05 [0.64, 1.73]</td>
<td>0.84</td>
<td>1.67 [1.18, 2.37]</td>
</tr>
</tbody>
</table>

Note: Significance levels of .05, .01, and .001 are indicated by *, **, and *** respectively.
PL3-4. Periods of Hyperglycemia During Neonatal Encephalopathy are Temporally Associated with Worse EEG Background
Pinchefsky E (Toronto, ON, Canada), Hahn C, Kamino D, Brant R, Chau V, Moore A, Tam E

Objective: To determine whether periods of hypo- and hyperglycemia in neonates with encephalopathy are associated with immediate changes in continuous electroencephalography (cEEG) background activity.

Methods: A cohort of term newborns with encephalopathy underwent continuous interstitial glucose monitoring (placed soon after birth) and cEEG monitoring. Episodes of hypoglycemia (≤2.8mmol/L) and hyperglycemia (>8mmol/L) were identified. cEEG background activity was classified in 5-min epochs. Generalized estimating equations were used to assess the relationship of hypo- or hyperglycemia with cEEG background scores, adjusting for clinical markers of hypoxia-ischemia (Apgar scores, umbilical artery pH and base deficit).

Results: 30 term newborns (median GA 40.1 wk) were included (17 males). Median of 49h of concurrent cEEG and continuous glucose monitoring were available per neonate, during which 9 events of hypoglycemia were detected in 5 neonates (median duration 45 min) and 14 events of hyperglycemia in 8 neonates (median 212.5 min). Epochs of hypoglycemia did not correlate with significant changes in cEEG background scores (p=0.239). Epochs of hyperglycemia were associated with worse cEEG background scores, including after adjusting for clinical markers of hypoxia-ischemia (1.621; 95% CI 0.663-2.579; p=0.039). A subgroup analysis was performed examining the association of hyperglycemia with cEEG background scores including only the 8 neonates that had episodes of hyperglycemia, and demonstrated epochs of hyperglycemia were still associated with worse background scores than epochs of normoglycemia (0.739; 95% CI 0.038-1.439; p=0.039).

Conclusions: Epochs of hyperglycemia are temporally associated with worse global brain function, even after adjusting for severity of hypoxia-ischemia. FUNDING: CIHR, Restracomp, Savoy Foundation. Equipment from Medtronic Canada

Keywords: Neonatal Neurology, Critical Care, Epilepsy
Objective: Describe the diagnosis, impairment, and treatment of Tourette syndrome (TS).

Methods: We analyzed data from the 2014 National Survey of the Diagnosis and Treatment of ADHD and Tourette Syndrome (NS-DATA). NS-DATA is a follow-back survey of parents/caregivers who reported “yes” on the 2011–2012 National Survey of Children’s Health to “has a doctor or other health care provider ever told you that your child had [attention-deficit/hyperactivity disorder or TS]?”. Descriptive analyses include percentages or means and standard deviations (SD). We calculated Fisher’s exact tests for severity comparisons.

Results: In this sample of 115 children ever diagnosed with TS (by parent report), the mean age of reported tic onset was 6.3 years (SD=2.6), mean age of TS diagnosis was 7.7 years (SD=2.7), and mean age when TS symptoms were worst was 9.3 years (SD=2.9). Most children (84.6%) had one or more co-occurring mental or developmental disorder(s). Most (77.2%) children had ever received any type of TS treatment; of those, 48.9% had received both medication and behavioral treatment. Three-quarters (73.0%) of parents/caregivers reported worst TS severity as “mild” or “moderate,” versus “severe” (27.0%). Tic-related impairment and treatment were associated with severity (figure 1, p<0.05). Experiences and activities had varying effects on tics (figure 1).

Conclusions: TS symptoms begin in childhood, are associated with varying impairment, and are influenced by co-occurring disorders and the environment. These findings support other research to increase understanding of TS and potential complexities regarding how best to support those living with TS and their families.

Keywords: Movement Disorders, Cognitive/Behavioral Disorders

FIGURE 1: Abstract PL 3-5

FIGURE 2: Abstract PL 3-5

Bitsko R (Atlanta, GA), Gupta P, Danielson M, Mink J

Objective: To describe healthcare expenditures associated with tic disorders (TDs).

Methods: Truven Health MarketScan® data comprised convenience samples of U.S. children aged 6-17 years in 2013 with public (Medicaid or Children’s Health Insurance Program, n=2,202,883) or commercial insurance (n=4,318,446). TDs were defined as having one inpatient claim or two outpatient claims at least seven days apart with ICD-9-CM code 307.2x. Outpatient, inpatient, drug, and total expenditures were calculated for children with and without TDs, matched on age, sex, and insurance type (capitated vs. fee-for-service). Log total expenditures from matched samples were adjusted for the presence of five co-occurring disorders (attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, autism spectrum disorder, anxiety disorder, and communication and language disorder), using the same algorithm as for TDs.

Results: Children with TDs had higher median total expenditures compared to those without ($1,648 vs. $477 for commercial insurance; $1,787 vs. $450 for public). Children with TDs had higher overall, drug, and inpatient expenditures, but lower outpatient expenditures. Children with TDs had incremental costs of $1,037 (commercial) and $1,001 (public) after matching. Co-occurring disorders were present in 70.9% (public) and 57.7% (commercial) of children with TDs. The incremental cost for TDs, after adjusting for co-occurring disorders, was $386 for commercial insurance; there was no longer a cost difference for Medicaid.

Conclusions: Higher overall healthcare expenditures among children with TDs compared to those without TDs were driven by higher drug and inpatient expenditures. Co-occurring disorders contributed a significant portion of the expenditures, and fully accounted for incremental costs of TDs in the Medicaid sample.

Keywords: Movement Disorders, Cognitive/Behavioral Disorders

PL3-7. Kennedy Krieger Institute’s Network for Early Childhood Telehealth (KKI-NECT): A Project ECHO Replication to Address the Workforce Shortage in Neurodevelopmental and Developmental and Behavioral Pediatrics

Leppert M (Baltimore, MD), Harrison J, Grace N

Objective: 15% of U.S. children have developmental (D) disorders, 11-20% have disorders of emotion (E) or behavior (B), and 15-40% have more than one of these disorders. A paucity of specialists, long waitlists and distances to specialists present barriers to consultation, and pediatric primary care clinicians (PPCC) are often called upon to diagnose and manage these children. KKI-NECT was the first multidisciplinary Project ECHO replication established to train PPCC’s on the identification and management of D/E/B disorders.

Methods: KKI-NECT replicates Project ECHO’s (Extension for Community Healthcare Outcomes) videoconference clinics, hosted weekly by Kennedy Krieger clinicians, and attended by PPCCs in rural and underserved areas of Maryland and West Virginia. Each clinic includes case based learning and didactic sessions aimed at guiding PPCC practice. The weekly didactic presentations are based on a multidisciplinary, multilevel curriculum designed and authored by KKI teaching faculty.

Results: To date, 42 virtual clinics with cases presented by PPCCs have been completed. 69% of cases had developmental concerns, 34.6% had emotional concerns (ACES), 96% showed behavioral concerns, and overall 69% had co-occurring concerns. All cases thus far have been managed in the Medical Home. Didactic sessions have progressed from novice level content to more specialized modules on treatment. Preliminary evaluation data indicates statistically significant improvement in PPCC knowledge and confidence surrounding evaluation and management of D/E/B disorders.

Conclusions: KKI-NECT provides an effective solution to the workforce shortage of Neurodevelopmental, Developmental and Behavioral and Child Psychiatry specialists by building PPCC knowledge and confidence in B/E/D disorders through case based and didactic learning.

Keywords: Cognitive/Behavioral Disorders, Teaching of Child Neurology