PLATFORM PRESENTATIONS

BRAIN TUMORS/ONCOLOGY

PL1. Biomarkers of CAR T cell neurotoxicity: CSF NFL and GFAP in an expansion cohort of pediatric ALL patients

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OBJECTIVE: Immunotherapy for hematologic malignancies with CD19-directed chimeric antigen receptor (CAR) T cells is complicated by neurotoxicity in approximately 40% of patients. We hypothesized that glial fibrillary acidic protein (GFAP) and neurofilament light chain (NFL) can predict neurotoxicity risk and measure severity of neuronal and glial injury. **METHODS:** We used the Mesoscale Discovery platform to measure CSF and serum NFL and GFAP levels on days -1, 10, and 21 after CD19-directed CAR T cell infusion in a consecutive cohort of 95 pediatric patients with B cell hematologic malignancies.

RESULTS: In the initial 43-patient cohort, CSF NFL levels prior to CAR T cell infusion positively correlated with the risk of subsequently developing severe neurotoxicity (no neurotoxicity, median 275pg/mL, mild 378pg/mL, severe 951pg/mL, P=0.0182 for severe vs none, P=0.0458 for severe vs mild). During neurotoxicity, mean CSF NFL levels increased to 1179pg/mL (mild neurotoxicity, P=0.0338) and 1345 pg/mL (severe neurotoxicity, P=0.0148), respectively. In serum, pretreatment NFL levels were highly abnormal in many patients (median 368pg/mL, range 10-56,321pg/mL; healthy control median 4pg/mL, range 1-7.5pg/mL). However, there was no correlation with neurotoxicity, history of CNS radiation, peripheral neuropathy, stem cell transplant, or number of prior chemotherapies. Day 7 serum NFL levels did not change significantly (median 439pg/mL, range 5-17,439pg/mL, P=0.3254). Analysis of the complete cohort's NFL and GFAP levels will be completed in the spring of 2020. **CONCLUSIONS:** We conclude that CSF NFL and GFAP may be promising biomarkers of CAR T neurotoxicity risk and severity. The abnormal baseline serum NFL concentrations remain unexplained and require further study.

KEYWORDS: Brain Tumors/Oncology, Infections/Neuroimmunology, Translational/Experimental Therapeutics

PL2. Impact of Molecular Subgrouping on Event-Free Survival (EFS): Results of a Children's Oncology Group (COG) Randomized Trial for Children with Medulloblastoma (MB); COG-ACNS 0331

Packer Roger (Washington, DC, United States) Michalski Jeff, Northcott Paul, Li Yimei, Billups Catherine, Smith Kyle, Burger Peter, Merchant Thomas, Gajjar Amar, Fitzgerald Thomas, Vezina Gilbert, Fouladi Maryam, Tarbell Nancy, Janss Anna

OBJECTIVE: To determine the impact of molecular subclassification of medulloblastoma on outcome in children treated on ACNS 0331

METHODS: 464 children with non-anaplastic , non-disseminated, and less than 1.5cm² residual disease post-operatively MB (average-risk MB), between 3 and 21 years of age, were prospectively randomized to treatment with either whole posterior fossa (PFRT) or involved field

(IFRT) radiotherapy. Those between 3 and 7 years underwent a second randomization between standard-dose (2400cGy) craniospinal RT (SDCSRT) and low-dose (LD) CSRT (1800cGy). Both groups received identical chemotherapy during and following CSRT. Patients were molecular subclassified as Group 1 (WNT-driven); Group 2 (SHH-driven), Group 3 and Group 4 by DNA methylation.

RESULTS: 362 of 464 children entered on study had sufficient tissue for methylation: 64 (17.7%) were Group 1; 66 (18.2%) were Group 2; 76 (21%) were Group 3 and 156 (43%) were Group 4. 5-year (5yr-EFS) was $82.5\pm2.7\%$ and $80.5\pm2.7\%$ for IFRT and PFRT, respectively (p=0.44). 5yr-EFS differed between SDCSRT ($82.9\pm3.7\%$) and LDCSRT ($71.4\pm4.4\%$), p=0.028. 5yr-EFS differed among subgroups with Group 3 having poorest outcome and Group 1 the best. In Group 2 (SHH), IFRT had better outcome than PFRT (p=0.018). Group 4 patients randomized to reduced dose CSRT had poorer outcome than those receiving SDCSRT (p=0.047). **CONCLUSIONS:** 5yr-EFS is poorer after LDCSRT than SDCSRT, especially in those with Group 4 MB. Approaches other than reducing CSRT are required to decrease treatment sequalae for average-risk MB. Molecular subclassification is clearly associated with 5yr-EFS and is mandatory for future prospective studies.

KEYWORDS: Brain Tumors/Oncology

COGNITIVE/BEHAVIORAL DISORDERS (INCLUDING AUTISM)

PL3. Clinical profile of children presenting with functional neurological complaints from a tertiary care center in north India

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OBJECTIVE: To describe the clinical profile of children presenting with functional neurological complaints from a tertiary care center in north India

METHODS: Clinical features, sociodemographic profile and management outcome of children diagnosed with functional neurological complaints between August 2017 and December 2019 in a tertiary care center were analyzed.

RESULTS: Total 317 children with functional neurological complaints were identified (192 children with psychogenic nonepileptic seizure (PNES), 71 children with psychogenic headache, 41 children with functional weakness and 3 children with functional

anesthesia/paresthesia. About 57% were girls, median age-10 years, IQR-8-13 years). 31% participants with PNES were already on antiepileptic drugs at presentation to our center.

Commonest Semiology of PNES was dialeptic (47 %), followed by nonepileptic aura (24 %) and motor (21%).

Predominant stressors identified were school related issues (49%), followed by family stressors (37%) and multiple stressors (27%). Most prevalent psychiatric co-morbidities were adjustment disorder (34%) and oppositional defiant disorder (25%). Predominant behavioral co-morbidities associated were somatic complaints (65%), attention problems (35%) and anxiety/depression (23%). 29%, 3% and 4% children had borderline ID, mild ID and SLD respectively.

On cognitive behavioral therapy, 63% were symptom free within 1 month and about 79% were asymptomatic on follow up at six months.

CONCLUSIONS: Psychogenic nonepileptic seizures and psychogenic headache were most common functional neurological complaints. Majority of children response favorably to cognitive behavioral therapy.

KEYWORDS: Cognitive/Behavioral Disorders (including Autism)

PL4. Increased Autoimmune Disease in Mothers of Children with Tourette Syndrome and Obsessive-Compulsive Disorder

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OBJECTIVE: Epidemiology, animal models and a growing understanding of the role of microglia in neurodevelopment implicate maternal immune activation as an epigenetic factor in the aetiology of neurodevelopmental disorders (1-3). Therefore, we hypothesised that children with Tourette syndrome (TS) and/or Obsessive-Compulsive Disorder (OCD) have a higher rate of maternal and familial autoimmunity than healthy and neurological autoimmune controls, and that children with a familial history of autoimmunity have distinguishing clinical features. **METHODS:** We performed a prospective case-control study of 200 children with tics/OCD review in a specialist clinic over an 18-month period, 100 healthy matched controls, and 100 children with neurological autoimmune conditions. A structured interview captured a family history of autoimmunity and clinical features of the child's TS/OCD.

RESULTS: Thirty-one percent of mothers of children with TS/OCD had autoimmune disease compared to 20% of mothers of neurological autoimmune controls (p>0.05) and 12% of healthy controls (p<0.005, adjusted OR 2.7, 95% CI 1.3-5.7). First-degree and maternal second-degree relatives of children with TS/OCD had higher rates of autoimmunity overall (Figure 1). Psoriasis was over-represented in mothers of children with TS/OCD compared to healthy controls (p=0.005) but reported autoimmune diseases were otherwise diverse (Figure 2). Children with a history of maternal autoimmunity were more likely to report a progressive course and improved symptoms with non-steroidal anti-inflammatory drugs (p<0.05).

CONCLUSIONS: Autoimmunity is more common in mothers and relatives of children with TS/OCD than in controls. These findings support further investigation into a possible role for maternal immune dysregulation in the aetiology of TS and OCD.

KEYWORDS: Cognitive/Behavioral Disorders (including Autism), Movement Disorders (including Cerebral Palsy), Infections/Neuroimmunology

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Figure 1. Frequency of autoimmune disease in the mothers and other first-degree and second-degree relatives of children with Tics/OCD compared to healthy and neurological autoimmune 'Neuroimmune' controls.



Figure 2. Percentage of mothers by autoimmune disease in each study group. Fourteen mothers in the Tics/OCD group had ≥ 2 autoimmune diseases, and three mothers in the 'Neuroimmune' group had ≥ 2 autoimmune diseases.

References

- Dalsgaard S, Waltoft BL, Leckman JF, Mortensen PB. Maternal History of Autoimmune Disease and Later Development of Tourette Syndrome in Offspring. J Am Acad Child Adolesc Psychiatry. 2015;54(6):495-501.
- 2. Salter MW, Stevens B. Microglia emerge as central players in brain disease. Nat Med. 2017;23(9):1018-1027.
- Gumusoglu SB, Stevens HE. Maternal Inflammation and Neurodevelopmental Programming: A Review of Preclinical Outcomes and Implications for Translational Psychiatry. Biol Psychiatry.2019;85(2):107-121.

PL5. The relationship between parental stress and mastery, forgiveness, and social support among parents of children with autism in a collectivistic and an individualistic society Mahajnah Muhammad (Hadera, Israel) Much Mays Abu, Weinberg Jacov, Akawi Ashraf,

Sharkia Rajech, Weinberg Michael

OBJECTIVE: Parents of children with autism have significantly more parenting-stress symptoms than parents of typically developing children. Therefore, the main goal of the present study was to examine the relationship between personal and social resources among multicultural families while coping with parental stress of children with autism

METHODS: Two hundred and nine (N=209) including Jewish (n=105) and Arab (n=104) participants completed demographic, mastery, forgiveness, social support and parental stress questionnaires. All participants, Jews and Arabs, are citizens of the State of Israel and are entitled to the same medical, social and psychological services. We examined the means (and their standard deviations) for the different variables and correlations between those variables (demographic, mastery, forgiveness, social support and parental stress).

RESULTS: The study findings demonstrated no significant differences between the groups regarding mastery, forgiveness, social support. However, a marginally significant difference was found with regard to the age at the time of diagnosis and parental stress. Arab children were diagnosed earlier and Arab parents reported higher parental stress. Hierarchal multiple regressions showed that among the Jewish sample age, education, financial situation, mastery, and social support contributed significantly to the explained variance of parental stress. Among the Arab sample, severity of autism, forgiveness, mastery, and social support significantly contributed significantly to the explained variance of parental stress.

CONCLUSIONS: The findings make an important contribution to our understanding of the differences and similarities in the factors predicting parental stress living in two different cultural contexts within the same society. Theoretical and clinical implications will be discussed. **KEYWORDS:** Cognitive/Behavioral Disorders (including Autism)

CRITICAL CARE

PL6. Prevalence of Prognostic Discordance for Infants in the Intensive Care Unit Bernstein Sarah (Durham, NC, United States) Farley Samantha, Barks Mary, Jiao Megan, Bansal Simran, Fisher Kimberley, Weinfurt Kevin, Ubel Peter, Lemmon Monica

OBJECTIVE: To 1) determine the prevalence of and factors related to prognostic discordance between parents and clinicians of infants with neurologic conditions and 2) characterize parent preferences for prognostic communication.

METHODS: We enrolled parents and clinicians caring for infants with neurologic conditions in advance of a family conference. Parent-clinician dyads completed a post-conference survey targeting expected motor, language, and cognitive outcome. Response items included a yes/no response with 3 degrees of confidence (6-item scale). Prognostic discordance was defined as a difference in yes/no prediction and further characterized as low, moderate, or high. Parents completed semi-structured interviews, which were analyzed using a rapid assessment approach. **RESULTS:** 56 parent-clinician dyads of 27 infants completed surveys; 41 parent interviews were analyzed. Parent-clinician discordance was typically moderate and most common in the motor domain (Figure 1). Discordance was more frequently due to differences in understanding (n=25/37, 68%) than to differences in belief (n=14/37, 38%). When discordance was present, parents were typically more optimistic than clinicians (n=32/37, 86%). In interviews, parents expressed that they valued 1) honest, direct, and consistent prognostic communication; 2) when prognostic communication balanced transparency with hope; and 3) their child's ability to lead a meaningful life, regardless of the presence of disability.

CONCLUSIONS: Differing perceptions about the prognosis of critically ill infants are common, and due to differences in both understanding and belief. These findings can be used to develop targeted interventions to improve prognostic communication.

KEYWORDS: Critical Care, Neonatal & Fetal Neurology, Palliative Care

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Figure 1: Presence and degree of prognostic discordance between parents and clinicians caring for infants with serious neurologic conditions.

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DEMYELINATING DISORDERS

PL7. Interim results from phase 2/3 (ALD-102) and phase 3 (ALD-104) studies of elivaldogene autotemcel (Lenti-D) gene therapy for the treatment of cerebral adrenoleukodystrophy

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OBJECTIVE: Preliminary results from ALD-102 study of elivaldogene autotemcel (eli-cel; Lenti-D gene therapy) showed that 88% patients with cerebral adrenoleukodystrophy (CALD) met the primary endpoint of survival free of major functional disabilities (MFD) at 24 months.

Here, we report updated results for the fully enrolled ALD-102 and preliminary data from study ALD-104 investigating an alternative myeloablative protocol that utilizes busulfan/fludarabine instead of busulfan/cyclophosphamide.

METHODS: Post-conditioning, patients with CALD (male, ≤ 17 years) received eli-cel (autologous CD34+ cells transduced with Lenti-D lentiviral vector encoding *ABCD1* cDNA). After ALD-102/ALD-104 (2 years), monitoring continues for additional 13 years in LTF-304. Data are median (min-max).

RESULTS: As of January 2020, 32 eli-cel-treated patients in ALD-102/LTF-304 had 30.0 (9.1–70.7) months follow-up. The primary efficacy endpoint was met in 20/23 (87%) evaluable patients; 2 withdrew and 1 died. Nine additional patients continue to be followed in ALD-102 (maximum follow-up 22.1 months) and 20 are enrolled in LTF-304; all but one show CALD stabilization.

As of February 2020, 13 patients were treated in ALD-104 with 6.1 (2.2-10.3) months follow-up. Two patients had delayed hematologic reconstitution; 13 achieved neutrophil and 12/13 platelet engraftment, to date.

In both studies, adverse events were generally consistent with myeloablation; no graft failure or graft-versus-host-disease occurred. One patient in ALD-102 had benign clonal dominance without clinical consequences at last visit (Month 60).

CONCLUSIONS: Eli-cel continues to show a favorable risk/benefit profile with up to 71 months follow-up in ALD-102/LTF-304. Evolving data from ALD-102 and ALD-104 will allow further insights into the clinical impact of eli-cel in CALD.

KEYWORDS: Demyelinating Disorders, Neurometabolic Disorders, Rare Diseases

PL8. Development of the PedsQL[™] Multiple Sclerosis Module items: Focus group and cognitive interviews

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OBJECTIVE: Health-related quality of life (HRQOL) is conceived as one of the most pertinent measures in evaluating the effectiveness of clinical treatments. Currently, there is a deficit in disease-specific outcome measures to assess the HRQOL of children, adolescents, and young adults with multiple sclerosis (MS). The purpose of this study was to develop items and support the content validity for the Pediatric Quality of Life InventoryTM (PedsQLTM) MS Module for children, adolescents, and young adults.

METHODS: The iterative process included multiphase qualitative methods. A literature review of pediatric MS QOL was conducted to generate domains for focus interviews. An expert panel, comprised of twelve pediatric MS specialists, participated in the development of interview questions. Patients under 21 years of age and their parents then participated in semi-structured focus group interviews (n = 15), think-aloud-cognitive interviews (n = 15), and pilot testing (n = 10).

RESULTS: Eighteen domains were derived from the qualitative methods. Once content saturation was achieved, 102 items were compiled. The domains composed included general fatigue, sleep/rest fatigue, tingling sensations, numbness sensations, physical weakness, pain, speech, balance, fine motor, vision, cognitive function, urination, constipation, bowel incontinence, anxiety, communication, treatment, and choice of medications.

CONCLUSIONS: Qualitative methods involving pediatric patients and their parents in the item development process support the content validity for the PedsQLTM MS Module. National validation and dissemination, using the large patient population from the US network of Pediatric MS centers, is forthcoming.

KEYWORDS: Demyelinating Disorders

PL9. Pediatric MOG antibody-associated syndromes: Description of a novel neuroimaging pattern

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OBJECTIVE: To describe findings of brain MRI lesions that might help to identify children with MOG antibody-associated syndromes (MAAS).

METHODS: This descriptive study identified 53 children with MAAS evaluated at a single referral center. All MRI scans (brain, brainstem and spinal cord) performed at presentation and at subsequent relapses were evaluated. Imaging findings and clinical data were associated to identify subgroups.

RESULTS: 327 MRIs were performed in 53 children with MAAS (49% girls), with a median age of 7 years (1.2-15) at clinical onset. Large hazy lesions with cystic changes involving the brain (85%) or cerebellar (15%) white matter were identified in 21/53 (40%) children, who were younger at clinical onset (median age 4.8 [1.7-13] years). Gadolinium enhanced MRI sequences revealed patchy, nodular or complete ring enhancement. Additional diffusion-weighted imaging revealed restricted diffusion, with reduced apparent diffusion coefficient.

This imaging pattern emerged in 17 children at first event with the following clinical phenotypes: ADEM 11, brain-brainstem-myelitis (BBM) 4, encephalitis 1, optic neuritis (ON) 1. It was additionally identified on the MRI scans of 22/86 (25%) relapses clinically presenting with: Encephalitis 9, ON-brain-myelitis 8, BBM 3, ADEM 2. Granulomatous disorders, encephaloclastic lesions, lacunar infarctions, primary and secondary neoplasms and infectious etiologies (cerebral abscess, cysticercosis, fungal cerebritis) were ruled out in every case. **CONCLUSIONS:** The novel neuroimaging finding of cystic changes inside large brain or cerebellar demyelinating lesions that we have described in this pediatric study group may contribute in distinguishing MAAS from other differential diagnosis.

KEYWORDS: Demyelinating Disorders, Neuroimaging, Infections/Neuroimmunology

PL10. Use of disease-modifying therapies in paediatric relapsing remitting multiple sclerosis in the UK: A multi-centre retrospective study

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OBJECTIVE: The approach to paediatric multiple sclerosis (MS) treatment is rapidly evolving, with 14 disease-modifying therapies (DMTs) licensed for adults. The first randomised controlled trial in paediatric MS has been recently published, assessing the efficacy and safety of a DMT (fingolimod) already licensed for adults. In this study, we aimed to describe the frequency of relapses and side effects in children on DMTs in a real-life cohort.

METHODS: Children (< 18yrs) with a diagnosis of RRMS, treated with DMTs, were identified from four UK tertiary paediatric neurology centres between 2012-2018. Annualised relapse rates (ARR) prior and on treatment were calculated.

RESULTS: Of 90 children included, 51 (56.7%) were treated with one DMT; 34 (37.7%) with two DMTs, and 5 (5.6%) with three or more DMTs. Side effects were reported in 40 (43.1%) children on first-line treatment and 11 (28.9%) children on second-line DMTs. In 4 patients, first-line DMTs were discontinued (n=2) or switched (n=3) due to side effects. ARR was reduced from 1.0 to 1.1 with interferon- β /glatiramer acetate (n=83, p< 0.001); 1.1 to 0.7 with dimethyl fumarate (n=10, p=0.27); 1.9 to 0.3 with fingolimod (n=14, p=0.01) and 1.7 to 0.3 with natalizumab (n=17, p= 0.004). Escalation from first to second-line DMTs resulted in a reduction of ARR from 1.7 to 0.2 (n=31, p< 0.001).

CONCLUSIONS: Newer second line DMTs are increasingly being used in paediatric MS. In this cohort, ARR reduction was observed with all DMTs. Escalating treatment to second-line DMTs such as fingolimod and natalizumab resulted in a large reduction of ARR. **KEYWORDS:** Demyelinating Disorders, Infections/Neuroimmunology, Rare Diseases



PL11. Time to Onset of Cannabidiol (CBD) Treatment Effect and Resolution of Adverse Events in the Tuberous Sclerosis Complex (TSC) Phase 3 Randomized Controlled Trial (GWPCARE6)

Joshi Charuta (Aurora, CO, United States) Cook Hannah, Wu Joyce, Devinsky Orrin, Miller Ian, Roberts Colin, Sanchez-Carpintero Rocio, Checketts Daniel, Sahebkar Farhad

OBJECTIVE: We conducted a post hoc analysis of the randomized, controlled GWPCARE6 trial (NCT02544763) in patients with TSC to estimate time to onset of CBD treatment effect and resolution of adverse events (AEs).

METHODS: Patients received highly purified CBD (Epidiolex[®]; GW Pharmaceuticals; 100 mg/mL oral solution) at 25 mg/kg/d (CBD25) or 50 mg/kg/d (CBD50), or placebo for 16 weeks. Treatment started at 5 mg/kg/d, reaching 25 mg/kg/d on Day 9 for CBD25 and 50 mg/kg/d on Day 29 for CBD50. Percentage reduction in TSC-associated seizures by cumulative day (i.e., including previous days) and timing of AEs were evaluated.

RESULTS: 224 patients were randomized to CBD25 (n=75), CBD50 (n=73), or placebo (n=76). Patients had discontinued a median of 4 antiepileptic drugs (AEDs) and were currently taking a

median of 3 AEDs. Differences in seizure reduction between CBD and placebo emerged on Day 6 (when titration reached 15 mg/kg/d) and became nominally significant (p<0.05) by Day 11 (CBD50) or Day 12 (CBD25). Over 90% of patients had an AE, with onset during the first 2 weeks of titration in 63%. AEs resolved within 4 weeks of onset in 42% of placebo and 27% of CBD patients and by end of study in 78% of placebo and 51% of CBD patients; most frequent AEs—diarrhea, somnolence, decreased appetite—resolved in 69–88% of CBD patients. **CONCLUSIONS:** Onset of treatment effect (efficacy and AEs) may occur within 2 weeks. AEs lasted longer for CBD vs. placebo but majority resolved during the trial. *Funding: GW Research Ltd*

KEYWORDS: Epilepsy, Rare Diseases, Critical Care

PL12. Long-Term Safety and Efficacy of Cannabidiol (CBD) Treatment in Patients with Lennox Gastaut Syndrome (LGS): 3-Year Results of an Open-Label Extension (OLE) Trial (GWPCARE5)

Patel Anup (Columbus, OH, United States) Gil-Nagel Antonio, Chin Richard, Mitchell Wendy, Perry M, Weinstock Arie, Checketts Daniel, Dunayevich Eduardo

OBJECTIVE: LGS is a treatment-resistant epileptic encephalopathy. Efficacy of CBD was demonstrated in the RCTs, with an acceptable safety profile. Here we assess long-term safety and efficacy of add-on CBD in patients with Lennox-Gastaut syndrome (LGS) in the third analysis of the open label extension (OLE; GWPCARE5) of two Phase 3, randomized controlled trials (RCTs), GWPCARE3 and GWPCARE4.

METHODS: Patients who completed either of the RCTs could enter this OLE trial (GWPCARE5/NCT02224573). Patients received plant-derived highly purified CBD (Epidiolex®; 100 mg/mL oral solution). Primary endpoint: safety. Secondary efficacy endpoints: median percentage change from baseline in drop and total seizure frequency.

RESULTS: Overall, 99% (366/368) of eligible patients with LGS entered the OLE. Median follow-up was 150 weeks (3 days to 179 weeks); 119 patients (33%) withdrew. Mean age: 16 years; $33\% \ge 18$ years; 54% male. Baseline median seizure frequency/28 days: 80 drop seizures; 168 total seizures. During the extended follow-up, the incidence of adverse events (AE) was 96%; serious AEs 42%; AEs leading to discontinuation 12%. Most common AEs ($\ge 20\%$): diarrhea, convulsion, pyrexia, somnolence, vomiting, upper respiratory tract infection, and decreased appetite. AEs of alanine aminotransferase increased occurred in 8% of patients. There were 11 deaths; none deemed treatment-related by the investigator(s). Median percentage reductions in seizure frequency (12-week windows over 156 weeks) was 48–71% for drop seizures and 48–68% for total seizures.

CONCLUSIONS: Long-term treatment with add-on CBD in patients with LGS produced sustained seizure reductions, with no new safety concerns.

Funding: GW Research Ltd

KEYWORDS: Epilepsy, Rare Diseases, Critical Care

PL13. Preventive antiepileptic treatment in infants with Tuberous Sclerosis Complex delays seizure onset and reduces epilepsy incidence and severity in a multi-center, randomized and observational EPISTOP trial

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OBJECTIVE: Epilepsy develops in 70–90% of children with Tuberous Sclerosis Complex (TSC) and is often resistant to medication. Recently, the concept of preventive antiepileptic treatment to modify the natural history of epilepsy has been proposed. EPISTOP was a clinical trial designed to compare the efficacy and safety of preventive versus conventional antiepileptic treatment in TSC infants.

METHODS: In this multi-center study, 94 infants with TSC without seizure history were followed with monthly video electroencephalography (EEG), and received vigabatrin either as conventional antiepileptic treatment, started after the first electrographic or clinical seizure, or preventively, when epileptiform EEG activity before seizures was detected. At six sites, subjects were randomly allocated to treatment in a 1:1 ratio in a randomized controlled trial (RCT). At four sites, treatment allocation was fixed, denoted an open-label trial (OLT). Subjects were followed until 2 years of age. The primary endpoint was the time to first clinical seizure. **RESULTS:** Fifty-three (56%) subjects were included in the RCT and 41 (44%) in the OLT. The time to the first clinical seizure was significantly longer with preventive than conventional treatment (RCT: 364 vs. 124 days, p=0.037; OLT: 426 vs. 106 days, p=0.001). At 24 months, our pooled analysis showed preventive treatment reduced the risk of clinical seizures (odds ratio [OR]=0.21, p=0.032), drug-resistant epilepsy (OR=0.23, p=0.022), and infantile spasms (OR=0, p < 0.001) (Fig.1). No adverse events related to preventive treatment were noted. **CONCLUSIONS:** Preventive treatment with vigabatrin was safe and modified the natural history of seizures in TSC, reducing the risk and severity of epilepsy. **KEYWORDS:** Epilepsy, Rare Diseases



PL14. Oligonucleotide STK-001 for the treatment of Dravet Syndrome: Cross-species pharmacology and efficacy in a mouse disease model

Ticho Barry (Bedford, MA, United States) Christiansen Anne, Han Zhou, Meena Meena, Ji Sophina, Borek Mylissa, Chen Chunling, Anumonwo Charles, Liu Chante, Zhao Nan, Ravipaty Shobha, Lin Qian, Leiser Steve, Isom Lori, Liau Gene

OBJECTIVE: These studies evaluated the pharmacology and efficacy of STK-001, an antisense oligonucleotide that is being developed for the treatment of Dravet syndrome (DS). DS is a severe developmental and epileptic encephalopathy that is primarily caused by heterozygous loss-of-function variants in *SCN1A*, which encodes the voltage-gated sodium channel, Nav1.1. STK-001 is designed to redirect RNA splicing to decrease the amount of non-

productive SCN1A messenger RNA (mRNA) and increase the level of

productive SCN1A mRNA, thus increasing the expression of Nav1.1 protein.

METHODS: STK-001 was administered via intrathecal administration (IT) in rats and NHP or via intra-cerebroventricular (ICV) administration in the neonate $Scn1a^{tm1Kea}$ DS mouse model. Nav1.1 protein was measured using a Mesoscale Discovery Electrochemiluminescence assay. STK-001 efficacy was evaluated by quantification of spontaneous seizures by electroencephalography and survival monitoring in $Scn1a^{+/-}$ DS mice.

RESULTS: Dose-dependent increases in Nav1.1 protein in brain were observed in rodent and NHP after single dose IT STK-001 administration. STK-001 administered ICV at postnatal day (PND) 2 resulted in an 80% reduction in spontaneous seizures detected between PND 22 and PND 46 in DS mice (p<0.05) and a 50% increase in the percentage of mice that were seizure-free during this observation period. STK-001 administration significantly improved survival in DS mice (33/34 survived up to PND 90, compared with 14/62 animals in PBS-treated group, p<0.0001).

CONCLUSIONS: These studies demonstrate pharmacologic effects of STK-001 in brains of rodents and NHP as well as efficacy in a DS mouse model and support initiation of a Phase 1/2a clinical trial with STK-001 for DS.

KEYWORDS: Epilepsy, Genetics, Translational/Experimental Therapeutics

PL15. Bridging the Childhood Epilepsy Treatment Gap in Africa (BRIDGE): A Protocol for a Cluster Randomized Clinical Trial of Task-Shifted Epilepsy Care in Three Northern Nigerian Cities

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OBJECTIVE: Conduct the first non-inferiority cluster randomized clinical trial (cRCT) of taskshifted epilepsy care to community health workers (CHWs) versus enhanced usual epilepsy care by physicians in sub-Saharan Africa.

METHODS: Among 399 eligible primary healthcare centers (PHCs) 60 were randomly selected (30 in Kano, 15 in Kaduna and 15 in Zaria); thirty participating PHCs were randomly assigned to a task-shifted protocol (figure 1; epilepsy diagnosis and treatment by CHWs), and thirty PHCs were randomly assigned to enhanced usual care (EUC) - physician epilepsy care plus primary care by epilepsy-trained CHWs. One hundred twenty CHWs, two for each of the sixty PHCs, completed a four-month epilepsy training program. Over 24 months about 1530 children with

previously untreated epilepsy identified in community-, clinic-, and school-based screenings will be enrolled in the cRCT, and will be assigned to the participating PHC closest to their home. Epileptologists who are blinded as to whether the study subjects are receiving task-shifted care or EUC, will evaluate each study subject at 1, 6, 18, and 24 months following enrollment. Electronic case report forms (CRFs) will be used for all study visits, with data

uploads to the data coordinating center at Vanderbilt (figure 2).

RESULTS: The primary outcome will be the percent of children seizure-free in each arm of the cRCT. Implementation and cost-effectiveness of task-shifted care will be studied.

CONCLUSIONS: When completed, this tack-shifted epilepsy care cRCT, regardless of outcome, will inform efforts to provide epilepsy care to about 50% of the world's children with epilepsy who are currently without treatment.

KEYWORDS: Epilepsy



Figure 2. Overall BRIDGE Cluster Randomized Controlled Trial Design

A non-inferiority cRCT of a task-shifted epilepsy care system

			Outcome Measures by Blinded
		30 Primary Healthcare Centers	Neurologist @ 1, 6, 12, 18, and 24 months
		Task-shifted (to CHEWs) epilepsy care	Primary outcome Seizure-free
		~ 765 CWE enrolled	
	60 Randomly Selected	across 30 task-shifted PHC sites	Secondary outcomes
	Primary Healthcare Centers		 Dx accuracy (CHEW vs.
	~ 1530 CWE enrolled		 75% reduction in sz
	across 60 PHC sites	~ 765 CWE enrolled	frequency
		across 30 "enhanced usual care" PHC s	First AED response
		30 Primary Healthcare Centers	Mortality
		"Enhanced Usual Care" - Routine Referra	al to • Status Epilepticus
		Physician for epilepsy care; enhanced by	primary • Morbidity
K		care follow-up by CHEW	 AED adverse events
	CHEW = community health extens	 Hospitalizations 	
	cRCT = cluster randomized control	led trial	 Diagnostic tests ordered
	CWE = children with epilepsy		 CHEWs Protocol adherence (by coordinating center)

PL16. Diagnostic and prognostic utility of outpatient short term video EEG records in children with seizures: experience from a tertiary care center in north India.

Panda Prateek (Rishikesh, India) Lourembam Radhapyari, Sharma Vishakha, Mohan Latika, Sharawat Indar

OBJECTIVE: To evaluate the diagnostic and prognostic utility of outpatient short term video EEG records in children with seizures.

METHODS: All short term video EEG records of children <18 years presenting with seizures between September 2019 and January 2020 were reviewed. Both the frequency of epileptic discharges, slowing/electrodecremental response following epileptic discharges and background abnormality was graded from 0 to 3 by an experienced pediatric neurologist. Epilepsy severity was determined by early childhood epilepsy severity score(E-CHESS), with suitable adaptation for elder age groups. Agreement between most plausible clinical diagnosis before EEG and final electroclinical syndrome after reviewing the EEG was determined.

RESULTS: Total 285 EEG records (154 sleep and 141 awake EEG records, 6.43±1.27 years, 203 boys, 69%) were included in the analysis. Out of these, 96 did not show any abnormality, 128 and 61 records had focal and generalized discharges, 7 records had classic/modified hypsarrhythmia, 19 records had features of LGS (slow spike wave and paroxysmal fast activity), 11 records had electrical staus epilepticus in slow wave sleep. Primary generalized epilepsy (17), absence epilepsy (9-1 Jeavon syndrome, 2-Tassinari syndrome), BCECTS (29), selflimited occipital epilepsy (15) were other electroclinical syndromes identified. Yield of sleep EEG was more than awake EEG (p=0.04). Cohens kappa coefficient of agreement between plausible clinical diagnosis and final electroclinical syndrome was 0.71. There was strong positive correlation between EEG severity score and epilepsy severity score by E-CHESS (correlation coefficient, r=0.73).

CONCLUSIONS: Short term video EEG is a robust and useful diagnostic technique with fair prognostic value, which complements existing resources.

KEYWORDS: Epilepsy

PL17. Epilepsy with Myoclonic Atonic Seizures (Doose Syndrome): A Severe Epileptic Encephalopathy with a Positive Outlook?

Nickels Katherine (Rochester, MN, United States) Joshi Charuta, Kossoff Eric, Eschbach Krista

OBJECTIVE: EMAS (Epilepsy with Myoclonic Atonic Seizures, or Doose syndrome) is a rare epileptic encephalopathy with variable outcome. Seizure control may lead to improved cognitive outcomes. However, there is no consensus regarding most effective treatments. This large multicenter study examines the treatments and outcomes of EMAS.

METHODS: Records of children with EMAS treated at each author's institution were retrospectively reviewed.

RESULTS: 1) 133 children identified 2) Developmental regression is common: 54% with regression (44% global) Final: 51% with delays (40% global) 3) Epilepsy course: a) Epilepsy is medically refractory early: Response (>50% seizure reduction) to first treatment: 17% Second: 21% Third: 32% 66% moved from second to third medication within 3 months b) Epilepsy may be self-limited:

Seizures resolved in 61%; If seizure free, 72% were seizure-free by age 6 years 4) Ketogenic diet efficacy greater than medications (Figure 1): a) Medication efficacy (>50% seizure reduction):

Levetiracetam: 17% Valproic acid: 27% Other medication: 25% b) Ketogenic diet efficacy (>50% seizure reduction): 71% 5) Seizure freedom correlates with final development (Figure 2) : Seizure free: 35% with delays (22% global) Not seizure free: 77% with delays (67% global) **CONCLUSIONS:** This is the largest EMAS cohort reported. Unlike other epileptic encephalopathies, seizure freedom and nearly normal development was obtained in over 1/2 of patients. Seizure freedom correlated with final development. Few experienced seizure reduction or freedom with medications; response to ketogenic diet was significantly greater than medications. Ketogenic diet should be considered early in the course. **KEYWORDS:** Epilepsy, Rare Diseases





PL18. Electroclinical spectrum of childhood epilepsy secondary to neonatal hypoglycemic brain injury in a low resource setting: A 10 year experience

Patra Bijoy (Delhi, India) Kapoor Dipti, Sharma Suvasini, Yadav Sidharth Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020 **OBJECTIVE:** Neonatal hypoglycemic brain injury (NHBI) is being increasingly recognized as an important cause of refractory childhood epilepsy in low resource settings. The objective of the present study is to analyse the electro-clinical spectrum of epilepsy in children secondary to NHBI.

METHODS: This was a retrospective study of children enrolled in the Epilepsy Clinic from January 2009 to August 2019. Data of children who had developed epilepsy after documented symptomatic neonatal hypoglycemia was collected. Details of clinical profile, seizure types, neurodevelopmental co-morbidities, EEG, neuroimaging findings and seizure outcomes were noted.

RESULTS: One hundred and seventy children were enrolled. The mean age at seizure onset was 10.3 months (SD 0.5 months). The seizures types were epileptic spasms (76.5%), focal with visual auras (11.2%), bilateral tonic clonic (7.1%), myoclonic (3.5%) and atonic seizures (1.8%). The EEG findings included classical hypsarrythmia (64.6%), hypsarrythmia variant (35.4%), focal occipital or temporo-occipital spike wave discharges (10.6%), multifocal discharges (4.7%), diffuse slow spike and wave with bursts of fast rhythms (2.4%), continuous spike waves during sleep (1.2%) and normal EEG (4.7%). MRI showed gliosis with or without encephalomalacia in the occipital lobe with or without parietal lobe in 96.5% of the patients. Comorbidities included global developmental delay (91.2%), cerebral palsy (48.7%), vision impairment (48.2%), microcephaly (38.2%), hearing impairment (19.4%), and behavioural problems (16.5%). Refractory epilepsy was seen in 116 (68.2%) patients.

CONCLUSIONS: Our study highlights the varied electroclinical and radiological spectrum and the adverse epilepsy and neurodevelopmental outcomes associated with NHBI. **KEYWORDS:** Epilepsy, Neuroscience, Neuroimaging

PL19. Provider attitudes toward sexual and reproductive healthcare for young women with epilepsy and intellectual disabilities

Kirkpatrick Laura (Pittsburgh, PA, United States) Collins Amy, Sogawa Yoshimi, Kazmerski Traci

OBJECTIVE: Explore attitudes and practices of pediatric neurologists and epileptologists regarding sexual and reproductive healthcare (SRH) for adolescent and young adult women with co-morbid epilepsy and intellectual disabilities.

METHODS: Individual semi-structured interviews were conducted with pediatric neurologists and epileptologists regarding their attitudes and practices with SRH for adolescent and young adult women with co-morbid epilepsy and intellectual disabilities. Interviews were audiorecorded and transcribed. Qualitative analysis was conducted using thematic analysis. **RESULTS:** Six child neurologists and 10 epileptologists participated. Specific themes included: (1) SRH provision and counseling is variable among providers. While some providers never discuss SRH with women with intellectual disabilities, others address this topic more comprehensively compared to those without disabilities. (2) Topics frequently addressed with women with intellectual disabilities included menstrual hygiene and suppression, bone health, and the risk of sexual abuse. (3) Providers reported they are more likely to discuss long-term contraception, including sterilization, for patients with intellectual disabilities. However, some

contraception, including sterilization, for patients with intellectual disabilities. However, some raised ethical and/or legal questions about this practice. (4) Providers often addressed sexual

activity and childbearing as never occurring voluntarily for women with intellectual disabilities, including women with mild disabilities.

CONCLUSIONS: This is the first study to assess attitudes and practices of pediatric neurologists and epileptologists regarding SRH for adolescent and young adult women with epilepsy and co-morbid intellectual disabilities. Our findings suggest that practice among providers is highly variable and many providers wrestle ethically with providing SRH to this population. More tailored clinical guidelines on SRH needs of this population may be beneficial. **KEYWORDS:** Epilepsy

PL20. Role of immunotherapy in children with new onset refractory status epilepticus (NORSE): Hit early and hit hard.

Patel Harshkumar (Ahmedabad, India) Kharod Prarthana

OBJECTIVE: New-onset refractory status epilepticus (NORSE) is defined as a clinical condition, with new onset status epilepticus without a clear metabolic, structural, infective of toxic cause in a patient without any pre-existing neurological disorder or epilepsy. In majority of the cases of NORSE either proven or possible autoimmune or immune mediated etiopathogenesis is suspected. Our aim of study is to describe clinical profile of children with NORSE presented to our centers between July 2017 to December 2019 and discuss the implications of early immunotherapy in children with NORSE.

METHODS: During study duration total 18 children with NORSE were included. Their clinicobiochemical, radiological, electrophysiological and treatment details were recorded and short term neurological follow up was obtained.

RESULTS: Out of total 97 children with status epilepticus 18 were presented with NORSE. Mean age was 7.4 years. History of preceding or current febrile illness was seen in 4 (22%) patients. None of 18 were positive for HSV PCR or autoimmune serology. Four children (22%) had abnormal MRI study. All 18 children had abnormal EEG. All the patients were given immunotherapy and median duration for termination seizures was 7 days. Out of 18 ,10(55%) children have epilepsy and six of them have persistent neurobehavioral deficits in follow-up. In Subgroup analysis 4 out of 18 received immunotherapy within 48 hours of presentation and achieved seizure termination with median duration of 4 days.

CONCLUSIONS: Immunotehrapy has beneficial role in management of children with NORSE. Early immunotherapy (within 48 hours of presentation) can achieve faster seizure freedom and lesser neurological impairments.

KEYWORDS: Epilepsy, Infections/Neuroimmunology

PL21. Update on a sponsored no-cost epilepsy gene panel for seizure onset between 2–4 years of age: Results from 682 tests

Pang Tiffany (Novato, CA, United States) Leal-Pardinas Gernanda, Bailey Mitch, Koh Sookyong, Millichap John, Truty Rebecca, Wirrell Elaine, Aradhya Swaroop

OBJECTIVE: Neuronal Ceroid Lipofuscinosis Type 2 (CLN2) disease often presents with epilepsy at approximately three years of age accompanied by a history of language delay. Behind the Seizure® (BTS) is a US-based, sponsored, no-cost, targeted, next-generation sequencing epilepsy gene panel for children suspected to have genetic epilepsy. The goal is to utilize BTS to lower the age of CLN2 disease diagnosis.

METHODS: Eligibility criteria were: age-at-test-order between 24-60 months and unprovoked seizure onset >24 months. BTS uses an epilepsy gene panel of 180+ genes with the option to include preliminarily associated genes.

RESULTS: Non-BTS epilepsy gene panel testing, which includes no limitation for age-at-testorder and age-of-seizure-onset, has shown a 15.5% (n=1234/7939) molecular diagnostic yield (MDx) overall and 0.05% specifically involving *TPP1* gene(CLN2 disease). Within the BTS program, the overall MDx was 6.74% (n=46/682). However, the yield of *TPP1* positives was 0.88%, representing a 17.6-fold increase in comparison to non-BTS cohort. Age of CLN2 disease diagnosis was earlier than as described in the literature (3.89-year versus 5-year). CLN2 disease was not a suspected diagnosis for 5 out of 6 individuals tested using BTS. Other genes that contributed to positive molecular diagnoses in the BTS program included *CACNA1A*, *CHD2, EHMT1, FOXG1, FRRS1L, GRIN2A, IQSEC2, KANSL1, KIAA2022, MECP2, PACS1, PCDH19, PPT1, PURA, SCN1A, SCN2A, SLC6A1, STX1B, SYNGAP1, TSC1* and *ZEB2*. **CONCLUSIONS:** The BTS program has facilitated earlier CLN2 disease identification. These findings indicate that broad epilepsy gene panel tests can increase diagnostic yield for CLN2 disease and simultaneously identify other genetic causes of epilepsy. **KEYWORDS:** Epilepsy, Genetics, Rare Diseases

PL22. Management practices for West syndrome in South Asia: a survey study and metaanalysis

Madaan Priyanka (Chandigarh, India) Chand Prem, Linn Kyaw, Wanigasinghe Jithangi, Mynak Mimi Lhamu, Poudel Prakash, Riikonen Raili, Kumar Amit, Dhir Pooja, Negi Sandeep, Sahu Jitendra

OBJECTIVE: To study the management practices for West syndrome (WS) in South Asia. **METHODS:** An online questionnaire was sent to 223pediatric neurologists/pediatricians in India, Pakistan, Myanmar, Sri Lanka, Bhutan, Nepal, and Bangladesh. Responses were evaluated and supplemented by meta-analysis of the existing literature.

RESULTS: One-hundred-twenty-five responses were received (Response-rate:56%). Around 60% of responders observed male preponderance and lead-time-to-treatment (LTTT) of 4-12weeks. The commonest etiology observed was a static structural insult (88.6% of responders). Preferred first-choice drug(country-wise): India-corticotropin (ACTH, 50%); Pakistan-oral steroids (45.5%); Myanmar, Sri Lanka, and Nepal-oral steroids (94.4%); Bangladesh-ACTH (2/2); Bhutan-vigabatrin(3/5). ACTH and vigabatrin are not available in Myanmar and Nepal. The most common regime for ACTH was maximal-dose-at-initiation-regime in India, Sri Lanka, and Bangladesh and gradually-escalating-regime in Pakistan. Maximum dose of prednisolone was variable- most common response from India:3-4mg/kg/day; Pakistan, Bhutan, and Bangladesh:2mg/kg/day; Sri Lanka, Nepal, and Myanmar:5-8mg/kg/day or 60mg/day. The total duration of hormonal therapy ranged from 4-12 weeks (59/81). Most responders (106/125) advised electroencephalography to check for hypsarrhythmia resolution. Difficult access to pediatric EEG in Bhutan and Nepal is concerning. More than 95% of responders felt a need for more awareness. The meta-analysis supported preponderance of male gender[68%(C.I.:64-73%)], structural etiology[80%(C.I.:73-86%)], longer LTTT[2·4months(C.I.:2·1-2·6months)], and lower response-rate to hormonal therapy(ACTH-17%; prednisolone-28%) in WS in South Asia.

CONCLUSIONS: This study highlights the practices and challenges in management of WS in South Asia. These include a penchant for oral steroids, longer LTTT, a preponderance of structural etiology, difficult access to pediatric EEG, non-availability of ACTH and vigabatrin in some countries, and lower effectiveness of hormonal therapy in this region. **KEYWORDS:** Epilepsy





PL23. Hemodynamic responses to interictal epileptiforme discharges and clinical prognosis in childhood epilepsy with centrotemporal spikes

Coan Ana Carolina (Campinas, Brazil) Cavalcante Charlington, Campos Brunno

OBJECTIVE: Despite overall good prognosis, some children with childhood epilepsy with centrotemporal spikes (CECTS) have larger number of seizures and cognitive comorbidities. We aimed to evaluate the patterns of interictal epileptiform discharges (IEDs)-related hemodynamic responses of children with CECTS and their association with different seizure control and cognitive outcomes.

METHODS: Eight consecutive children with CECTS underwent concomitant electroencephalography and functional MRI. Twenty-four minutes of echo-planar and volumetric T1-weithed images were acquired in a 3T scanner with concomitant 64-MRI compatible EEG electrodes. The instants of visually detected IEDs were used to look for blood oxygen level dependent (BOLD) changes. Second level analysis compared IEDs-related hemodynamic Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020 responses of: i) children with more or up to ten seizures; ii) children with or without learning disabilities (Two-sample T-tests, p<0.001, minimum of 40 contiguous voxels).

RESULTS: All patients presented perirolandic discharges, which resulted in positive BOLD changes in ipsilateral supplementary motor area, rolandic opercular region, postcentral, inferior temporal and fusiform gyri; contralateral precentral gyrus; bilateral precuneus and medium occipital gyri. Compared with those with learning disabilities, children without learning disabilities showed bilateral perirolandic positive BOLD changes (Figure 1). There were no differences between children with more or up to ten seizures.

CONCLUSIONS: We observed diffuse brain network activation related to IEDs in CECTS. In children without learning disabilities, activations were restricted to perirolandic area. We hypothesized that the diffuse IEDs-related BOLD changes might contribute to worse clinical and cognitive outcome in some children with CECTS.

KEYWORDS: Epilepsy, Neuroimaging

Figure 1: Comparison of interictal epileptiform discharges-related hemodynamic changes in children with childhood epilepsy with centrotemporal spikes with and without learning disabilities. Those without learning disabilities presented positive hemodynamic changes restricted to perirolandic areas. (Two-sample T-tests, p<0.001, minimum of 40 contiguous voxels).



PL24. Perspectives on Preferred Practices for Rescue Therapies in Epilepsy: Gaps or Agreement?

Shafer Patricia (Wilmington, MA, United States) French Jacqueline, Santilli Nancy, Buchhalter, Hirsch Lawrence, Nasuta Mary, Gilchrist Brian

OBJECTIVE: To examine agreement between pediatric and adult health care providers (HCP) on recommended practices for rescue therapies (RT) in epilepsy. Previous literature identified gaps between HCP, patients, and caregivers. Gaps between adult and pediatric providers is unknown

METHODS: A multidisciplinary group of experts and stakeholders participated in a consensus process led by the Epilepsy Foundation. A modified Delphi technique was used to seek consensus from participants using an online survey. Items reached agreement when 80% or more of respondents rated an item between 6 and 8 on a 0-8 Likert scale. Results were sent to a diverse group of HCPs between November 2019 and January 2020.

RESULTS: 368 responses were received: 46% school nurses, 24% physicians, 12% advanced practice providers, 13% hospital/clinic nurses. 62% of providers practiced 11 years or more. The majority (62%) cared for children/youth with epilepsy. Agreement on preferred practices fell into 4 areas: when to use RTs, importance of a common language, assessing need, and RT education. A revised definition of cluster seizures reached agreement by all groups. The need for providers to individualize use of RTs was consistent. Agreement on preferred practices was analyzed for 1) HCPs who assess/prescribe RTs compared to those who educate others or give RTs; 2) between pediatric and adult HCPs.

CONCLUSIONS: Despite different provider roles, consensus in many areas was achieved for use of RTs in epilepsy. Understanding perspectives between pediatric and adult HCPs and those who prescribe or educate others about RTs, will assist in developing appropriate interventions and education.

KEYWORDS: Epilepsy, Rare Diseases

PL25. Medically intractable myoclonic epilepsy, intellectual disability, and dysmorphism in a teenage girl caused by a novel variant in NEXMIF

Herman Isabella (Houston, TX, United States) Sully Krystal

OBJECTIVE: Myoclonic epilepsy is characterized by myoclonic seizures, generalized tonicclonic seizures (GTCs), and absence seizures. Several genetic etiologies have been linked to myoclonic epilepsy, including 22q11 del, GABA(A)R, CLN6, and the x-linked gene NEXMIF in males. Here, we report a teenage girl with early childhood onset myoclonus, GTCs, absence seizures, intellectual disability (ID), and dysmorphism due to a novel missense variant in NEXMIF (c.1381 C>T).

METHODS: The GeneDX comprehensive epilepsy panel was utilized to evaluate a potential genetic etiology for myoclonic epilepsy. MRI and EEG were previously performed as part of a comprehensive seizure workup.

RESULTS: Testing revealed a novel missense variant in *NEXMIF* (c.1381 C>T) previously not reported in the literature. Further analysis revealed that this variant is absent from healthy populations (gnomAD), has a high predictability of deleteriousness (CADD score 25.1), and its genetic location is highly conserved among different species. Other variants in *NEXMIF* have previously been shown to cause ID, dysmorphism, autism, and epilepsy in males.

CONCLUSIONS: We report a novel variant in the x-linked gene *NEXMIF* as the likely etiology of medically intractable myoclonic epilepsy, ID, and dysmorphism in a teenage girl with early onset childhood myoclonic epilepsy. *NEXMIF* has been shown to cause severe epilepsy and ID in boys, however, less is known about its pathogenicity in females. Further studies are needed to determine the functional role of *NEXMIF* (c.1381 C>T) in females.

KEYWORDS: Epilepsy, Genetics, Rare Diseases

PL26. High dose diazepam treatment for Electrical Status Epilepticus in Sleep (ESES): Is it effective?

Gorodetsky Carolina (Toronto, Ontario, Canada) Go Tina, Weiss Shelly

OBJECTIVE: Epileptic encephalopathy with ESES is a pediatric epilepsy syndrome with sleep induced epileptic discharges and acquired impairment in cognition, language and/or behavior. Treatment of ESES is assumed to improve cognitive outcome. Despite the widespread use of high dose diazepam, there is limited research on its efficacy.

METHODS: Single-center, retrospective, consecutive case-series of children presenting with cognitive/ language regression and ESES from 2014-2019. Children underwent overnight EEG followed by Diazepam (1mg/kg) administered per rectum, and continuation of 0.5 mg/kg of oral Diazepam for 3 months. Follow up EEGs performed following first dose and after 6-9 weeks of treatment.

RESULTS: 23 children included [male 14 (60%); mean age 7 years (4 -12)]. Epilepsy syndromes included: 15 (65%) Continuous Spike and Wave During Sleep, 6 (26%) atypical Childhood Epilepsy with Centro-Temporal spikes and 2 (8%) Landau Kleffner syndrome. Prior to treatment 18 (78%) had clinical seizures, 20 (87%) had intellectual disability. 10 children (45%) had symptomatic epilepsy (defined by abnormal MRI and/or genetic

evaluation). Decrease in more than 25% of the spike activity noted in 18 (78%). Effect sustained in 11 children (47%) after 6 weeks. 6 (60%) children from the symptomatic group had EEG response, while 11 (91%) responded from the idiopathic group. 5 children (21%) had clinically significant cognitive/ language improvement (4 from idiopathic group).

CONCLUSIONS: Treatment with high dose Diazepam reduces epileptiform activity in ESES in majority of children, especially the idiopathic cohort. Despite the reduction of the epileptiform activity only minority of patients experience clinically significant cognitive improvement. **KEYWORDS:** Epilepsy

	Age (yea rs)/ Gen der	Typ e of epile psy	Prese nce of seizur es prior to DZ treat ment	Cogni tive level prior to DZ treat ment	AED' s prior to DZ treat ment	Etiology (MRI findings)	Initial SWI → 1- day post treat ment	SWI 6-9 weeks post treatm ent	Develop mental response	Dura tion of follo w up (year s)	Adve rse event s
	6F	LKS	none	ID	none	Idiopathic (normal)	80% →20 %	none	Language improve ment	6 mont hs	none
8	3M	LKS	none	GDD	none	N/A	60% → 20%	Intermi ttent spike (no ESES)	No cognitive change	10 mont hs	none
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Table 1- Detailed clinical information and response to treatment in the individual patients

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6F	CS WS	yes	ID	VPA	Symptomati c (encephalo	81% → 37%	ESES	No cognitive	5 years	None
					malacia)	5770		change		
4.5 M	AR	yes	GDD	LEV	Idiopathic (normal)	85% → 1%	ESES	Cognitive improve ment	5 years	None
4F	CS WS	yes	GDD	LEV, CLB	Symptomati c (encephalo malacia)	90% →80 %	ESES	No cognitive change	5 years	None
8F	CS WS	yes	ID	LEV, CLB	Idiopathic (normal)	100% →18 %	Slowin g (no ESES)	No cognitive change	5.5 years	None
8M	CS WS	none	ID	LEV	Idiopathic (normal)	85% →20 %	ESES (75%)	No cognitive change	5.5 years	None
12F	AR	yes	Norm al	VPA	Idiopathic (normal)	92% → 24%	Intermi ttent spikes (no ESES)	No cognitive change	5.6 years	Sleepi ness
7F	AR	yes	Norm al	VPA	Idiopathic (normal)	84% →50 %	ESES (95%)	Cognitive improve ment	5.8 years	None
7F	AR	yes	ID	VPA	Idiopathic (normal)	85% → 50%	Norma 1	No cognitive improve ment	5.5 years	None

Abbreviations: AR- Atypical Rolandic epilepsy (childhood epilepsy with centro-temporal spikes), AED's- anti-epileptic drugs, CSWS- continues spike and wave , during sleep, CLB-Clobazam, DZ- Diazepam, ETX-Ethosuximide, ESES- electrical status epilepticus in sleep, GDD- global developmental delay, ID- intellectual disability, LEV- Levetiracetam, LTM-Lamotrigine, LKS- Landau Kleffner syndrome, PMG- polymicrogyria, PVL- periventricular leukomalacia, N/A- not available, SUL- Sulthiame, VPA- Valproic acid, WM- white matter

CCEX



PL27. Thalamocortical Loop Models as an Integrative Framework for Epileptiform Activity.

Knox Andrew (Madison, WI, United States) Scott Dillon, Tononi Guilio

OBJECTIVE: Epilepsy is a heterogeneous disease in which a multitude of varied underlying pathologies lead to a limited number of seizure types and EEG findings. Mechanistic frameworks explaining the emergence of epileptiform activity from specific pathologies are lacking. Computer thalamocortical loop models with biophysical correlates may serve as such a framework. We hypothesize that simulating several different underlying pathologies by varying corresponding parameters in a thalamocortical loop model will lead to a common set of epileptiform abnormalities.

METHODS: We studied the effects of network parameter changes in a thalamocortical loop model developed by Hill and Tononi¹ to study features of slow wave sleep. We employed a parameter search of network variables that directly correspond to changes in ligand gated ion channels (GABAA, AMPA, and NMDA conductance), changes in network connectivity, and indirectly corresponding to changes in voltage gated ion channels (sodium or potassium channelopathies).

RESULTS: A variety of propagating waves of synchronous neuronal activity were observed. Simulated local field potentials suggested common EEG features seen in epilepsy, including spike and wave discharges, polyspike and wave discharges, polyspikes, paroxysmal fast activity, high frequency oscillations, tonic seizures, and delta activity seen during focal seizures with associated standing spiral waves. Multiple single-parameter changes led to common epileptic features (for example, increased AMPA conductance, decreased GABAA conductance, and increased membrane excitability all led to spike and wave discharges). **CONCLUSIONS:** Biophysical thalamocortical loop models hold promise as integrative frameworks that can show how underlying pathology leads to the emergence of epileptic phenotypes.



KEYWORDS: Epilepsy, Neuroscience

Figure 1 – Epileptiform Abnormalities Simulated in Hill-Tononi Network. The first row shows simulated local field potentials; each plot has a time scale of 1-2 seconds. The second row shows the membrane potential of a single neuron from the simulation; all plots have a time scale of 200-500ms except for the focal seizure, which shows 1.5 seconds. The third row shows the membrane potential of all neurons in a single cortical layer at the time point indicated by the red line on the plot of the local field potential, with warmer colors representing increased depolarization.

PL28. Efficacy of Combined Therapy of ACTH plus Vigabatrin compared to ACTH alone for treatment of Infantile Spasm- A Randomized controlled trail

Sumi Samsun (Dhaka, Bangladesh) Saha Narayan, Hoque Azimul, Islam Ariful, Debnath Bithi, Choudury Yamin, Sumi Sufia, Chandra Mohua, Choudury Shahjahan, Habib Ahsan

OBJECTIVE: To determine whether combined treatment of ACTH plus vigabatrin is superior to ACTH alone in the treatment of infantile spasm.

METHODS: Randomized controlled trial enrolled 50 patients of 2 to 24 months having clinical diagnosis of infantile spasm and hypsarrhythmia in EEG from Dept. of Paediatric Neurology, National Institute of Neurosciences and Hospital, Dhaka, largest neurology hospital in Bangladesh during the period of 1st June, 2017 to 31st May, 2018. Tuberous sclerosis, neurometabolic diseases were excluded. One group (25 children) was treated with high-dose natural ACTH (150 IU/m²/d in BD for 2 weeks, taper off for another 2 weeks). Another group was treated with high dose ACTH plus Vigabatrin simultaneously. Vigabatrin was given in 100mg/kg for three months, tapering for another 1 month. Follow up was done at day 7, 15, 43.and 91 of starting treatment.

RESULTS: The primary outcome was cessation of spasms (from 14 to 42 days after initiation of therapy) occurred in 18 (72%) children in combination therapy and 11 (44%) children in hormonal therapy. Treatment response was faster in combination therapy. During follow-up period for 3 months, more children became spasm free in combination therapy (48%) than ACTH alone (32%). EEG became normal in 60.0 % children in combination therapy and 32.0 % children in hormonal therapy after 2 weeks of treatment.

CONCLUSIONS: Combination therapy of ACTH plus vigabatrin was superior than ACTH alone in cessation of spasms along with electrographic remission. Treatment response was also faster in combination therapy.

KEYWORDS: Epilepsy, Neuroscience, History of Child Neurology Table 1: Cessation of spasm (n=50)

Cessation of	Group					6	
spasm $(14 - 42)$ days	Hormonal therapy N (%)	Combined therapy N (%)	<i>x</i> ²	df	OR (95%CI)	P value	
Responder	11 (44.0)	18 (72.0)	4.023	1	0.306 (0.094-0.992)	0.045	
Non responder	14 (56.0)	7 (36.0)					

Chi square test was done to measure the level of significance

Table 2 : Time of Cessation of spasn	n (response to treatment)	to the patients in groups
(n=50)		

	Gro	oup			
Cessation of spasm	Hormonal therapy n (%)	Combined therapy n (%)	t	df	P value
2 – 6 days	16 (64.0)	21 (84.0)			
7 – 14 days	8 (32.0)	4 (16.0)			
>14 days	1 (4.0)	0 (0.0)			
Mean ±SD days	5.88 ± 2.83	3.72 ± 1.64	3.296	48	0.001

Unpaired t test was done to measure the level of significance

PL29. Thrombocytopenia in pediatric patients on concurrent cannabidiol and valproic acid *McNamara Nancy (Ann Arbor, MI, United States) Ziobro Julie, Fedak Romanowski Erin, Smith Garnett, Carlson Martha, Robertson Patricia, Leber Steven, Joshi Sucheta, Dang Louis, Shellhaas Renee*

OBJECTIVE: In January 2019 a new plant-derived purified cannabidiol preparation, approved by the U.S. Food and Drug Administration (FDA), became commercially available for patients \geq 2 years with Lennox-Gastaut syndrome (LGS) or Dravet syndrome. Among our patients who were prescribed the FDA-approved cannabidiol formulation, we observed several cases of thrombocytopenia and therefore embarked on this urgent systematic chart review.

METHODS: We conducted a single-center systematic chart review of all pediatric patients (\leq 21 years) who were prescribed cannabidiol from January to August 2019.

RESULTS: Eighty-seven patients (age 1.2 to 19.8 years) were included (Table 1). Among the 28 who took a combination of anti-seizure medications that included valproic acid and cannabidiol, 9 (32%) developed thrombocytopenia (defined as platelets <110,000/ μ L; platelet nadir range: 17,000-108,000; Table 2). Five of these 9 also had abnormalities in a second cell line (white blood cell N=2; hemoglobin N=3). Four of the 9 children also had documented thrombocytopenia during the year prior to initiating cannabidiol. Total valproic acid dose, free and total valproate levels were not different between children who developed thrombocytopenia and those who did not (p>0.3 for all comparisons). No children on cannabidiol without valproic acid (0/59) developed thrombocytopenia.

CONCLUSIONS: We report a novel and clinically important side effect of thrombocytopenia in one third of pediatric patients treated concurrently with pharmaceutical grade cannabidiol and valproic acid. Frequent monitoring for thrombocytopenia should be considered for patients treated with the combination of valproic acid and cannabidiol.

KEYWORDS: Epilepsy

Table 1: Demographic and clinical profile of 87 patients treated with cannabidiol (CBD)*						
Demographics						
Age	9.7±5.0 years (range 1.2 – 19.8 years)					
Sex	48 (55%) female					
Epilepsy Characteristics						
Epilepsy Syndrome						
- Lennox-Gastaut Syndrome	75 (86.2%)					
- Dravet Syndrome	6 (6.9%)					
- Other treatment-resistant epilepsies	6 (5.7%)					
Number of ASMs used prior to CBD	Median 4, IQR 2-6					
Number of concurrent ASMs at the time of CBD initiation	Median 3, IQR 2-4					
Concurrent valproic acid and CBD	28 (32.2%)					
Valproic acid dose	26.2±15.0 mg/kg/day					
Baseline total valproic acid level prior CBD	101±35 µg/mL					
Response to Cannabidiol						
Highest CBD dose	Mean 13.4±5.0 mg/kg/day					
Did CBD improve seizures?	Yes = 38 (50%)					
Side effects attributed to CBD						
- Sedation	23 (25%)					
- Behavior change	13 (14%)					
- Agitation	5 (5%)					
- Other	9 (10%)					
Children treated with concurrent clobazam	57 (65.6%)					
Need to wean clobazam (Y/N)?	33 (58%)					
If weaned clobazam, by how much	Median 33% (IQR 25-50%)					
(% of baseline dose?)						

Table 2: Laboratory abnor	malities were common	among children who were p	rescribed a						
combination of valproic acid and cannabidiol*									
Baseline labs (N=83*)	N=28 on	N=59 on CBD+other	p-value						
	CBD+VPA	ASM**							
- WBC	6.6 ± 2.1	7.3 (2.1)	0.20						
- HGB	13.0 (1.0)	13.6 (1.4)	0.06						
- PLT	218.2 (90.5)	269.3 (94.7)	0.03						
- AST	37.8 (22.7)	33.0 (26.1)	0.43						
- ALT	27.2 (26.9)	26.9 (28.2)	0.96						
1-month labs (N=55*)									
- WBC	7.6 (3.7)	7.2 (2.6)	0.66						
- HGB	17.7 (21.0)	13.4 (1.6)	0.41						
- PLT	200.5 (85.7)	279.1 (66.3)	0.0009						
- AST	53.5 (32.8)	27.7 (10.2)	0.004						
- ALT	45.7 (35.9)	21.5 (9.2)	0.01						
3-month labs (N=42*)									
- WBC	7.9 (3.2)	8.3 (4.0)	0.78						
- HGB	12.7 (1.3)	13.9 (1.5)	0.01						
- PLT	223.6 (112.5)	271.9 (65.4)	0.14						
- AST	53.4 (32.1)	24.8 (7.0)	0.003						
- ALT	42.8 (42.8)	20.4 (8.2)	0.05						
6-month labs (N=24*)									
- WBC	6.1 (1.9)	7.3 (2.5)	0.25						
- HGB	12.6 (1.7)	14.0 (1.6)	0.07						
- PLT	222.7 (115.1)	263.4 (69.4)	0.29						
- AST	48.3 (26.3)	30.1 (10.3)	0.15						
- ALT	27.8 (16.7)	24.6 (10.1)	0.59						
Thrombocytopenia	9 (36%)	0 (0%)	< 0.0001						
[PLT ever < 110 (N, %)]									
Lowest recorded PLT	193.7 (96.8)	250.1 (82.7)	0.006						

*Data are presented as mean \pm standard deviation or N (%), unless otherwise indicated ASM = anti-seizure medication; CBD = cannabidiol

*Data are presented as mean ± standard deviation unless otherwise indicated

*Not all children had labs at every time point as these were ordered at the clinicians' discretion. **Two children were treated with CBD monotherapy

ASM = anti-seizure medication

CBD = cannabidiol

WBC = white blood cell count (K/ μ L)

HGB = hemoglobin (g/dL)

PLT = platelets $(K/\mu L)$

AST = aspartate aminotransferase (IU/L)

ALT = alanine aminotransferase (IU/L)

PL30. Long-Term (2-Year) Safety and Efficacy of Adjunctive ZX008 (Fenfluramine Hydrochloride Oral Solution) for Dravet Syndrome: Interim Results of an Ongoing Open-Label Extension Study

Sullivan Joseph (San Francisco, CA, United States) Auvin Stéphane, Pringsheim Milka, Knupp Kelly, Wirrell Elaine, Farfel Gail, Galer Bradley, Morrison Glenn, Lock Michael, Gammaitoni Arnold, Thiele Elizabeth

OBJECTIVE: To evaluate the long-term safety and efficacy of adjunctive fenfluramine for controlling seizures in patients with Dravet syndrome enrolled in an open-label extension (OLE) study at treatment durations of up to 2 years.

METHODS: Patients who completed Phase 3 controlled studies enrolled in an OLE study (NCT02823145). Patients started at 0.2 mg/kg/day fenfluramine and were titrated to effect (maximum: 26 mg/day, or 17 mg/day with stiripentol). Seizure frequency was captured via handheld e-diary. Effectiveness and safety were assessed at each office visit (monthly for the first 3 months, then every 3 months).

RESULTS: At time of analysis (2/15/2019), 330 patients were enrolled (mean±SD age: 9.0±4.6 years old [y/o]; 55% male; 28% <6 y/o), with a median treatment duration of 445 days (range: 7-899 days). Over the entire OLE, median monthly convulsive seizure frequency (MCSF) change was -63% compared with pre-randomization baseline (P<0.001). Over the entire OLE, 62% of patients experienced clinically meaningful (\geq 50%) reductions in MCSF and 37% experienced profound (\geq 75%) reductions in MCSF. The most common (\geq 15%) non-cardiovascular adverse events were nasopharyngitis (23%), pyrexia (23%), decreased appetite (21%), and diarrhea (15%). At the most recent visit, 8% of patients experienced \geq 7% weight loss while 39% gained \geq 7% weight vs pre-randomization baseline. There were no echocardiographic or clinical observations of valvular heart disease or pulmonary hypertension at any time.

CONCLUSIONS: Fenfluramine provided durable, clinically meaningful reduction in MCSF for up to 2 years of treatment and was generally well tolerated. Fenfluramine may represent an important new treatment option for patients with Dravet syndrome.

KEYWORDS: Epilepsy



FIGURE 1: Significant reduction in MCSF over time during 24 months fenfluramine treatment in an open-label extension study.

MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

PL31. Number Needed to Treat (NNT) With Fenfluramine to Achieve a Clinically Meaningful Reduction in Convulsive Seizure Frequency in Patients With Dravet Syndrome

Sullivan Joseph (San Francisco, CA, United States) Dlugos Dennis, Nabbout Rima, Haney Douglas, Morrison Glenn, Farfel Gail, Galer Bradley, Gammaitoni Arnold

OBJECTIVE: Prior Dravet syndrome (DS) antiepileptic-drug studies report a number needed to treat (NNT) of 5-6 to achieve \geq 50% reduction in monthly convulsive seizure frequency (MCSF). We determined the NNT with fenfluramine to achieve "clinically meaningful" MCSF reductions in a pediatric DS population, as determined by Clinical Global Impression of Improvement (CGI-I) ratings and improvement on Behavior Rating Inventory for Executive Function (BRIEF[®]2) Index Scores.

METHODS: Using data from a Phase 3 and long-term extension study for adjunctive fenfluramine (NCT02682927/NCT02826863/NCT02823145), we assessed: (1) degree of seizure frequency reduction associated with "Very much improved" caregiver CGI-I ratings via receiver operating characteristic (ROC) analysis and (2) proportion of patients with clinically meaningful, \geq 10-point improvement on BRIEF[®]2 index scores (Behavior, Emotion, Cognition, Global), comparing patients with <25% (negligible) vs \geq 75% (profound) MCSF reduction via 2-sided Mann-Whitney-U test. NNT was calculated: 1/((Experimental-Responder Rate)-(Control-Responder Rate)).

RESULTS: ROC analysis of CGI-I ratings identified a clinically meaningful threshold of $\geq 60\%$ MCSF reduction. There was $\geq 60\%$ MCSF reduction in 60%, 28% and 5% of patients in fenfluramine 0.7 mg/kg/day (NNT=2), fenfluramine 0.2 mg/kg/day (NNT=4) and placebo groups (Figure). Patients with $\geq 75\%$ MCSF reduction were significantly more likely to achieve ≥ 10 -point improvements in Emotion Regulation and Global BRIEF[®]2 Index Scores at Year 1; 45%, 20%, and 2% of patients in fenfluramine 0.7 mg/kg/day (NNT=2), fenfluramine 0.2 mg/kg/day (NNT=6), and placebo groups achieved $\geq 75\%$ MCSF reduction (Figure 1).

CONCLUSIONS: Fenfluramine treatment (0.7 mg/kg/day) resulted in NNT=2 to achieve either clinically meaningful (\geq 60%) or profound (\geq 75%) MSCF reductions; profound reductions were associated with executive-function improvements.

KEYWORDS: Epilepsy

SCEPTEN



FIGURE 1: Responder analysis.

FFA, fenfluramine; MCSF, monthly convulsive seizure reduction frequency; NNT, number needed to treat; OLE, open label extension.

PL32. POTENTIAL MECHANISMS OF SUDEP IN MOUSE MODEL OF ALTERNATING HEMIPLEGIA OF CHILDHOOD

Elliott Courtney (Chapel Hill, NC, United States) Hunanyan Arsen, McCall Angela, Kherallah Bassil, Sinden Daniel, Pitt Geoggrey, Elmallah Mai, Mikati Mohamad

OBJECTIVE: Sudden unexpected death due to epilepsy (SUDEP) can affect up to 1 in 1000 patients with epilepsy. The aim of this study is to investigate the potential mechanisms of SUDEP in the *Mashl*^{+/-} mouse model of Alternating Hemiplegia of Childhood (AHC), which manifests both epilepsy and SUDEP.

METHODS: We studied *Mashl*^{+/-} mice with the knock-in D801N *ATP1A3* mutation, the most common mutation causing AHC. To assess for abnormalities in the control of breathing, awake, spontaneously breathing mutants and wild type littermate controls underwent whole body Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020

plethysmography recordings at baseline and during a respiratory challenge (FiO₂: 0.10; FiCO₂: 0.07; nitrogen balance). To assess for abnormal cardiac rhythms, mutants underwent EKG recordings at baseline and during seizures. After baseline, mice received injections of a convulsive dose of kainic acid, to induce seizures, directly into the amygdala and both EEG and EKG were recorded until death occurred during the ongoing seizure activity.

RESULTS: Breathing studies demonstrated mutant mice had a significantly decreased tidal volume (p=0.02), peak expiratory flow (p=0.02), and active respiratory cycle time (p=0.01) during respiratory challenge compared to their wild type counterparts (figure 1). The EKG recordings showed that, compared to controls, mutant mice at baseline had significantly increased heart rates, prolonged QRS s, PR and QTc intervals (p<0.05 in all comparisons) (figure 2). During seizures mutants developed JT segment abnormalities, atrioventricular block and then sinus arrest with apnea.

CONCLUSIONS: We demonstrated that both respiratory control and cardiac rhythm abnormalities occur the $Mashl^{+/-}$ model. This supports the hypothesis that SUDEP mechanisms may be multifactorial.



PL33. Improving folate supplementation counseling for adolescent females with epilepsy. *Fridinger Sara (Philadelphia, PA, United States) Gonzalez Alexander, Fitzgerald Mark, Melamed Susan, DiGiovine Marissa, Dlugos Dennis, Kessler Sudha, Abend Nicholas, Helbig Ingo*

OBJECTIVE: Despite the American Academy of Neurology quality measure recommending folate supplementation counseling be performed at office visits for women >/=12 years with epilepsy, we found that this counseling was addressed (counseling documented or prescription given) at only 22% of our visits. Our SMART aim is to increase the percentage of office visits for females with epilepsy >/=12 years at which folate counseling is addressed from 22% to 50% by September 2020.

METHODS: We reviewed charts to determine rates of folate counseling among a subset of pediatric neurology providers (n=9). We interviewed providers following applicable visits to assess barriers (Figure 1). We implemented countermeasures including an embedded question about folate counseling in our epilepsy office visit Epic SmartForm, provider education, and an after-visit summary dotphrase. We tracked performance using a statistical process control chart (Figure 2).

RESULTS: The largest barriers to folate counseling were insufficient time and lack of provider knowledge. Although a definite centerline shift has not yet occurred, there has been evidence of special cause variation in a positive direction since interventions were implemented.
Performance dropped during the 11/25-12/18/19 weeks, likely due to a co-occurring epilepsy conference.

CONCLUSIONS: We have seen signals of improvement in our practice of folate counseling following implementation of embedded electronic medical record prompts, provider education, and an after-visit summary dotphrase. We expect ongoing efforts to result in a sustained centerline shift towards our goal, thus improving our practice gap for folate counseling. We expect this approach may subsequently help address other practice gaps in patient counseling. **KEYWORDS:** Epilepsy



Figure 1. Pareto chart illustrating barriers to folate supplementation counseling during visits for adolescent females with epilepsy \geq 12 years based on provider responses during brief interviews conducted after applicable visits.

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Figure 2. Statistical process control chart (p-chart) showing percentage of office visits for females with epilepsy \geq 12 years at which folate supplementation counseling was done per 2 week time block.

PL34. Worldwide short course education programmes in paediatric epilepsies – improving knowledge and changing attitudes and practice.

Gifford Alison (Dundee, United Kingdom) Rodie Philippa, Wilmshurst Jo, O'Callaghan Finbar, Griffiths Mike, Kirkpatrick Martin

OBJECTIVE: The PET (Paediatric Epilepsy Training – BPNA) programmes, with 14,000 participants across five continents, include a one-day standardised course promoting evidence-based, safe practice delivered by a trained faculty to a target audience. The objective was to measure improvement in paediatric epilepsy knowledge and change in attitude and clinical practice after course attendance.

METHODS: An identical true/false knowledge quiz with clinical management scenarios was performed at the beginning of and immediately after 24 courses in 2018. Between April 2018 and March 2019, an "Attitudes and Practice" survey was sent to 1,361 attendees 6-months after their course.

RESULTS: 762 participants completed a pre/post quiz (93% response rate in high-income countries (HIC), 79% in low- and middle-income countries (LMIC)). The knowledge gain was much greater in LMIC (66%-pre to 85%-post versus 85 to 91% HIC). 365 responses were received to the "Attitudes and Practice" survey (21% response rate in HIC, 24% in LMIC). 76% report PET changed their personal practice moderately or significantly (88% from LMIC). 81%

were prompted to improve their clinical service for children with epilepsies; 16% from LMIC creating dedicated epilepsy clinics. Practice change varied: 46% in LMIC no longer prescribed anti-convulsant prophylaxis for febrile seizures compared to 2% in HIC and 52% used status epilepticus guidelines for the first time compared to 6%.

CONCLUSIONS: PET is improving knowledge and changing clinicians' attitudes and practice with the largest gains in LMIC. This data provides evidence for the effectiveness of short-course epilepsy education to improve the lives of children with epilepsies globally.

KEYWORDS: Epilepsy, Teaching of Child Neurology

Submitted on behalf of the British Paediatric Neurology Association (BPNA)

PL35. Neuroimaging for Non-Index Seizures in Pediatric Emergency Rooms

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OBJECTIVE: Determine risk factors for abnormal head imaging and acute management changes (ACM) in patients presenting to pediatric emergency departments (PED) with non-index (non-first time) seizures (NIS).

METHODS: For this retrospective cohort study, patients were included if they presented to a large PED from 2008-2018 with a chief complaint of NIS, excluding repeat febrile seizures, and also had head imaging ordered in the PED. Clinical characteristics were extracted from the electronic medical record. The primary outcome was abnormal head imaging that resulted in an ACM.

RESULTS: We identified 391 patients with 450 encounters. Ages ranged from 1.7 months to 18.9 years. Head imaging revealed a newly identified finding in 19% (85/450) of encounters, such as hemorrhage, stroke, or ventricular enlargement, and an ACM in 5.3% (24/450) of encounters including admissions (22), neurosurgical interventions (6), and new non-seizure medications (5). Factors predicting an ACM included new seizure semiology (OR 3.3, 1.3-8.4), new focal exam finding (OR 4.1, 1.5-10.9), and altered mental status (OR 4.0, 1.4-11.2). A patient with 2 or more risk factors had an OR 9.1 (2.7-30.1) for an ACM. Two percent (4/200) of patients with no risk factors had imaging that lead to observation only.

CONCLUSIONS: We identified risk factors for patients with NIS that may stratify patients in the PED as high or low risk for ACM based on imaging. Validating these risk factors may allow for a prediction tool for NIS in emergency rooms where resource utilization, reduced exposure to ionizing radiation, and sedation are critically important.

KEYWORDS: Epilepsy, Neuroimaging

Encounters Where Head Imaging led to an Acute Change in Management

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Age, sex	Seizure History and Etiologies	New seizure semiology	Increased seizure freg or duration	AMS present	New focal neurologic deficit	Presence of VPS	Head trauma	Imaging finding	Acute change in management
18 F	Provoked seizures, Lupus Cerebritis	Unclear	Yes	Yes	Yes	No	No	Cerebral edema, cortical necrosis	Admission, new med (immune)
15 M	Epilepsy	No	Yes	Yes	No	Yes	No	Ventricular enlargement	Admission
17 M	Epilepsy	Yes	Yes	No	No	Yes	No	Ventricular enlargement	Admission, NSGY intervention
15 F	Epilepsy, cavernomas	Yes	Yes	No	No	No	No	Hemorrhage	Admission, NSGY intervention
6 F	Epilepsy	No	Yes	No	Yes	Yes	No	Ventricular enlargement	Admission, NSGY intervention
6 M	Provoked seizures	Yes	Yes	No	No	No	No	Nonspecific white matter changes	Admission
11 M	Epilepsy	No	No	Yes	Yes	No	No	Brainstem infarct	Emergent intubation, admission
6 F	Epilepsy	Yes	Yes	No	No	Yes	No	Shunt discontinuity	NSGY intervention
17 M	Epilepsy, MS	No	Yes	No	No	No	No	New MS lesion	New medication (immune)
4 F	Epilepsy	No	Yes	Yes	No	Yes	No	Ventricular enlargement	Shunt tapped
4 F	Epilepsy	Yes	Yes	Yes	Yes	No	No	Restricted diffusion	Admission, new med (Abx)
9 F	Epilepsy	No	No	No	No	No	Yes	Occipital bone fracture, hemorrhage	Admission
6 M	Provoked seizures, brain tumor	No	Yes	Yes	No	No	No	Cerebral edema, Ventricular enlargement	Admission
3 <u>mo</u> F	Abnormal EEG	No	Yes	No	No	No	No	Cortical dysplasia	Admission
3 F	Epilepsy, Vein of Galen	Unclear	Yes	Yes	Yes	No	No	Hemorrhage, ventricular enlargement	Admission, NSGY intervention
2 <u>mo</u> M	Epilepsy, cortical malformations	No	Yes	Yes	Yes	Yes	No	Sinus vein thrombosis	Admission, New medication (Heparin)
4 mo. M	Abnormal EEG	Yes	Yes	No	No	No	No	Ventricular enlargement	Admission, NSGY intervention
15 F	Provoked Seizures	Yes	Yes	Yes	No	Yes	No	Ventricular enlargement	Admission, NSGY intervention
4 M	Provoked Seizures	Yes	No	Yes	No	No	Yes	Subdural hemorrhage, encephalomalacia	Admission, AHT evaluation
8 M	Epilepsy, Alpers Syndrome	Yes	Yes	Yes	Yes	No	No	Metabolic stroke vs PRES	Admission
13 M	Epilepsy	No	Yes	No	No	No	Yes	Subarachnoid hemorrhage	Admission
2 F	Provoked seizures, craniotomy for tumor resection	Yes	No	Yes	Yes	No	No	Bilateral subdural hematomas	Admission
6m0 M	Provoked seizures, multiple shunt infections	Yes	Yes	No	No	Yes	No	Ventricular enlargement	Admission
3 F	Epilepsy	No	Yes	No	No	Yes	No	Ventricular enlargement	Admission
3mo F	Provoked seizures, lacticacdemia	No	Yes	No	No	No	No	Cerebral edema	Admission

Age in years, mo= months EEG= electroencephalogram, MS= Multiple Sclerosis, AHT- Abusive Head Trauma, NSGY = Neurosurgery, PRES = Posterior reversible encephalopathy syndrome

ETHICS

PL36. Decision-Making for Infants with Neurologic Conditions

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OBJECTIVE: To 1) Characterize shared decision-making for infants with neurologic conditions and 2) Determine the frequency of shared decision-making elements in parent-clinician conferences about decisions.

METHODS: We enrolled infants, parents, and clinicians in a longitudinal mixed-methods study of decision-making for infants with neurologic conditions. We audio-recorded family

conferences and analyzed conferences that included a decision about life-sustaining treatment. We iteratively adapted existing paradigms of shared decision-making and applied them to the data using a directed content analysis approach.

RESULTS: We enrolled 27 infants and 42 parents, who participated in 49 family conferences. Twenty-five conferences contained decisions about life-sustaining treatment (Table 1). Most conferences were multi-disciplinary, with a median of 5 team members (range 2-14). We identified four non-linear communication phases: medical information exchange, values-based Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020 information exchange, team-family relationship building, and integration of values into decisions (Figure 1). Medical information exchange frequently included clinician description of the clinical nature of a decision (n=24/25, 96%) and parental perspective on the infant's clinical course (n=15/25, 60%). Exploration of values and preferences occurred in the majority of conferences (n=18/25, 72%); this discussion was typically parent-initiated (n=15/18, 83%). Integration of family values and preferences into decision-making occurred in approximately half of conferences (n=12/25, 48%).

CONCLUSIONS: The decision-making process for critically ill infants is non-linear. Clinical information exchange includes both clinician and parent contributions. Discussion of values is common and typically parent-initiated. This framework characterizes how clinicians and parents balance clinical information and values as they make decisions for infants with neurologic conditions.

KEYWORDS: Ethics, Neonatal & Fetal Neurology

Table 1: Infant and parent characteristics

Characteristic	Median (Range)
	Or n (%)
Infant Characteristics (n=12)	
Gestational age at birth wk	35 (23-39)
Age at enrollment wk	8 (0-33)
Sex. Female	8 (67)
Medical conditions	
Prematurity	7 (58)
Seizures	6 (50)
Genetic or metabolic disease	5 (42)
Congenital heart disease	4 (33)
Intraventricular hemorrhage	4 (33)
Brain malformation	3 (25)
Hypoxic ischemic encephalopathy	3 (25)
Parent characteristics (n=21)	
Age, y	29 (20-38)
Sex	. /
Female	12 (57)
Male	8 (38)
Other/not reported	1 (5)
Race and ethnicity	
White	6 (29)
African American	12 (57)
Asian	2 (10)
More than one race	1 (5)
Level of education	
Less than high school	2 (10)
High school/GED	8 (38)
Some college	6 (29)
Bachelor's degree	2 (10)
Graduate or professional degree	3 (14)
Annual household income	
Less than \$25,000	9 (43)

\$25,000-\$34,999	4 (19)
\$35,000-\$49,999	2 (10)
\$50,000-\$74,999	2 (10)
\$150,000 or more	4 (19)
Previous involvement in family member's intensive care	10 (48)

Table 1: Meeting Characteristics (n=25)	NS
Characteristic	Median (Range)
Number of meetings per case	$\frac{\text{Or n}(\%)}{2(1-7)}$
Meetings with decisions per case	2(1-7) 2(1-6)
Meeting length minutes	2(1-0) 49(15-78)
Family members	4) (15-70)
Mother present	25 (100)
Father present	20 (80)
Total family members present	3 (1-7)
Team members	
Clinician type present ^a	
Neonatologist	23 (92)
Neurologist	14 (56)
Palliative care clinician	12 (48)
Other specialists ^b	10 (40)
Resident	8 (32)
Medical student	6 (24)
Unit staff present	
Bedside nurse	9 (36)
Social work	19 (76)
Physical, occupational, and/or speech therapy	4 (16)
Total team members present	5 (2-14)

^aClinician type includes attending physicians, fellows, and advanced practice providers. ^bOther consulting specialists include pulmonologists, cardiologists, neurosurgeons, and geneticists.



PL37. The expressions of microRNAs in febrile seizure

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OBJECTIVE: Febrile seizure (FS) is the most common neurological disorder of childhood. The exact pathophysiology of FS is unknown. The alteration in the expression levels of specific microRNAs has been described as a possible cause in the pathophysiology of different diseases such as cancer, Parkinson's disease and epilepsy The present study aimed to investigate expression levels of microRNAs in children with FS.

METHODS: This prospective multicenter study examined representative populations in eight different cities in Turkey. The study was conducted with 30 children with FS and 30 febrile controls. Blood samples were taken from all children at presentation. The expression levels of miR-146a, miR-155, miR-181, miR-223 and their correlation between tumor necrosis factoralpha (TNF- α), interleukin 1 beta (IL-1 β), and interleukin 6 (IL-6) levels were searched. **RESULTS:** MicroRNA expression analysis revealed an alteration in children with FS as compared with controls. The expression levels of miR-146a and miR-155 were significantly increased in febrile seizure patients. Serum TNF- α , IL-1 β , IL-6 levels were higher in FS group than the controls. The results of statistical analysis showed that there were correlations within microRNA expressions in children with FS.

CONCLUSIONS: microRNAs 146a, 181a, 155 and 223 may be involved in febrile seizure pathogenesis. Altered micro-RNA expression levels might be an adaptive response to inflammation. New therapeutic approaches based on microRNA expression may provide new perspectives for FS treatment.

KEYWORDS: Ethics

	Febrile Seizure Group	Control Group	p value
	Median (min-max)	Median (min-max)	
MicroRNA-181	-0.4240 (-1.50-1.57)	-0.1490 (-1.77-2.17)	0.32
MicroRNA-155	-0.6200 (-1.92-0.88)	-0.0150 (-2.69-1.57)	0.077
MicroRNA-146a	-1.0600 (-2.39-1.60)	-0.0980(-1.66-2.68)	0.034
MicroRNA-223	-0.4010 (-1.69-2.15)	-0.0820 (-2.04-2.39)	0.62
TNF-α (ng/ml)	515.58 (31.96-1127.71)	212.58 (39.27)	0.009
IL-1β (pg/L)	3923.54 (280.83-8220.80)	1747.13 (221.48-7817.39)	0.021
IL-6 (ng/ml)	326.79 (13.64-728.53)	109.59 (21.42-610.72)	0.008

Table. The expression level of microRNAs

GENETICS

PL38. Episodic hemiplegia secondary to channelopathies: clinical spectrum and genotypephenotype correlations

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OBJECTIVE: Episodic hemiplegia occurs in many channelopathies. While genotype-phenotype correlations are well-described in *ATP1A3*-related disorders, they are less recognized in *CACNA1A*, *SCN1A*, *ATP1A2*, and *PRRT2*-related disorders. This presents a major prognostic challenge for clinicians, patients and their families.

METHODS: A retrospective chart review was performed by searching for all encounters with a diagnosis of "hemiplegic migraine" and/or "monoallelic mutation

of *ATP1A2*, *CACNA1A* or *SCN1A* gene." Patients with *CACNA1A*, *SCN1A*, *ATP1A2*, or *PRRT2* variants and a personal or family history of episodic hemiplegia were included. Patients with benign variants were excluded.

RESULTS: Sixteen individuals met criteria and are summarized in Table 1. Developmental disorders were common (11/16). Five patients had severe attacks (defined by duration longer than a week with or without residual disability). While cerebral edema frequently accompanied attacks, cerebral atrophy was seen in only three patients after severe attacks, all of whom had lasting disability. Fourteen variants were identified in *CACNA1A* (7), *ATP1A2* (6) and *PRRT2* (1) (Table 2). Two unrelated patients shared the *ATP1A2* c.2438T>A variant and had an atypical phenotype resembling alternating hemiplegia of childhood. Additionally, we describe the fourth individual with a *CACNA1A* c.4151A>G variant and a severe phenotype (GDD/ID, hypotonia, cerebellar ataxia and episodic hemiplegia).

CONCLUSIONS: Even in this small cohort some genotype-phenotype correlations were suggested, including an association between the *CACNA1A* c.4151A>G and *ATP1A2* c.2438T>A variants and severe disease. Additionally, an association between cortical atrophy after severe attacks and persistent deficits was observed. These observations may aid prognostication in patients with episodic hemiplegia secondary to channelopathies.

KEYWORDS: Genetics, Headache/Migraine

CEPTER

Case	Phenotype	Gene	Variant	Protein	Classification	on CADD Allele frequency (gnomAD)		Previously reported	De novo?
1	SHM	CACNA1A	c.2815G>C	p.G939R	VUS	14.17	0.0000366	Yes	Unk
2	SHM	CACNA1A	c.5899C>T	p.R1967W	VUS	32	-	No	No
3	FHM	CACNA1A	c.1588T>C	p.F530L	VUS	27.8	-	No	Unk
4	FHM	CACNA1A	c.1997C>T	p.T888M	Pathogenic	25.2	-	Yes	Unk
5	SHM	CACNA1A	c.4151A>G	p.Y1384C	Pathogenic	28.5	-	Yes	Unk1
6	SHM	CACNA1A	c.806C>T	p.P269L	VUS	23	-	No	Unk
		CACNA1A	c.3043G>A	p.E1015K	VUS	9.075	0.0000138	Yes	Unk
7	Single severe attack	ATP1A2	c.2522T>C	p.L841P	Likely pathogenic	29.3	-	No	Yes
8	Atypical AHC	ATP1A2	c.2438T>A	p.M813K	Likely pathogenic	27	-	Yes	Yes
9	Atypical AHC	ATP1A2	c.2438T>A	p.M813K	Likely pathogenic	27	- / /	Yes	Yes
10	Speech delay ¹	ATP1A2	c.2723G>A	p.R908Q	Pathogenic	33	- X X	Yes	No
11	FHM	ATP1A2	c.841C>T	p.P281S	VUS	26.5	0.0000398	Yes	Unk
12	FHM	ATP1A2	c.2288G>A	p.R763H	VUS	32	0.0000398	No	Unk
13	FHM	ATP1A2	c.2723G>A	p.R908Q	Pathogenic	33	-	No	Unk
14 ²	FHM	ATP1A2	c.2782T>C	p.W928R	VUS	31	V -	No	Unk
15 ²	FHM	ATP1A2	c.2782T>C	p.W928R	VUS	31	-	No	Unk
16	SHM	PRRT2	c.769_778del	p.E257KfsX53	Pathogenic		-	Yes	Unk

Table 1: Clinical Features

CADD score (https://cadd.gs.washington.edu/), Allele frequency in gnomAD database (https://gnomad.broadinstitute.org/), 1 = presumed *de novo* based on history, parents not available for testing, VUS = variant of unknown significance, SHM = sporadic hemiplegic migraine, FHM = familial hemiplegic migraine, AHC = alternating hemiplegia of childhood.

Case	Phenotype	Variant	Age of onset (year)	Current Age	Frequency	Duration	Development	Seizures	Imaging abnormalities	Other features
1	SHM	CACNA1A c.2815G>C	8	11	Few per year	<24 hr	Normal	No	No	
2	SHM	CACNA1A c.5899C>T	8	15	Weekly to monthly	Hours to two days	GDD	Yes	No	Prolonged Todd's paralysis, CVS, POTS
3	FHM	CACNA1A c.1588T>C	3	8	Every few years	1 hr	Speech delay	No	No	Bifid uvula
4	FHM	CACNA1A c.1997C>T	8	11	Every month	Hours to several days	Normal	No	Unilateral cerebral edema, cerebellar atrophy	
5	SHM	CACNA1A c.4151A>G	3	14	Single attack	Days	GDD	Yes	Unilateral cerebral edema, cerebellar atrophy	Hypotonia, ataxia
6	SHM	CACNA1A c.806C>T, c.3043G>A	4	14	1-2 per month	Hours to a week	GDD	No	No	Congenital CMV, microcephaly
7	Single severe attack	ATP1A2 c.2522T>C	5	6	Single attack	Severe attack with lasting disability	GDD	Yes	Unilateral cerebral edema, cerebellar atrophy	Regression
8	Atypical AHC	ATP1A2 c.2438T>A	1	3	Monthly	<1 hr; rare severe attacks with lasting disability	Speech delay	Yes	Unilateral cerebral edema followed by cerebral atrophy	Regression, chorea, myoclonus, MRE, autonomic dysfx
9	Atypical AHC	ATP1A2 c.2438T>A	1	10	Few attacks per month	<1 hr; rare severe attacks with lasting disability	GDD	Yes	Unilateral cerebral edema followed by cortical atrophy	Regression, myoclonus, MRE
10	Speech delay	ATP1A2 c.2723G>A	-	4		-	Speech delay	No	No	FHx of HM, epilepsy
11	FHM	ATP1A2 c.841C>T	9	11	Two events	Hours	Normal	No	No	
12	FHM	ATP1A2 c.2288G>A	12	18	A few attacks	Hours to days	Normal	Yes	Unilateral cerebral edema	
13	FHM	ATP1A2 c.2723G>A	3	15	Several per year	Hours to days	GDD	Yes	Unilateral cerebral edema	
141	FHM	ATP1A2 c.2782T>C	3	22	2-3 per month	Hours to days; rare severe attacks with lasting disability	GDD	Yes	Unilateral cerebral edema followed by cerebral atrophy	Rare severe attacks with slow recovery; residual hemiplegia and hypertonia
15 ¹	FHM	ATP1A2 c.2782T>C	5	22	2-3 per month	Hours to days; rare severe attacks with lasting disability	GDD	Yes	Unilateral cerebral edema	Rare severe attacks with slow recovery
16	SHM	PRRT2 c.769_778del	12	14	Every two months	Hours	Normal	No	No	

1 = fraternal twins, GDD = global developmental delay, FHx = family history, CVS = cyclic vomiting syndrome, POTS = postural orthostatic tachycardia syndrome, MRE = medically refractory epilepsy. *Note: no patients with SCN1A variants and a personal or family history of episodic hemiplegia were identified.

Table 2: Summary of variants identified

PL39. Variability in diagnostic yield of exome sequencing by clinical phenotype: Review of 977 cases from a single center

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OBJECTIVE: Exome sequencing (ES) has become an important element of the evaluation of many pediatric patients with undiagnosed neurologic diseases. We report our institutional experience regarding diagnostic yield in relation to neurologic phenotypes.

METHODS: Retrospective review of clinical data collected on patients who underwent clinical ES between May 2015 and January 2020 at the Washington University Undiagnosed Mendelian Disorders Exome Clinic and were consented for research analysis of ES and clinical data. ES data was generated as part of routine clinical care by GeneDx and other diagnostic laboratories. Patients were referred primarily by clinical geneticists, child psychiatrists, and pediatric neurologists.

RESULTS: A total of 977 patients were included. Of these, 237 (24.3%) had genetic variants reported clinically as having a definitive relationship to phenotype and were considered "solved" for purposes of this study. Developmental delays in gross motor, fine motor, and speech domains were all associated with significantly higher solve rates. Of 11 neurologic signs and symptoms evaluated, only hypotonia was associated with significantly higher solve rates. Cerebral atrophy was the only structural brain abnormality associated with increased solve rate. While microcephaly trended toward increased solve rate, there was no significant change associated with head circumference.

CONCLUSIONS: ES is a useful tool for the evaluation of patients with a variety of clinical phenotypes of unclear etiology. This study suggests that variable diagnostic yield may be expected based on clinical phenotype. Further investigation into additional phenotypes may help to guide clinical decisions on when to pursue ES for patients with unknown diagnoses. **KEYWORDS:** Genetics

PL40. Pediatric 50K (P50K) Heredigene Project: Whole Genome Sequencing Initiative for 50,000 Children: Integrating Genomic Testing and Data with Longitudinal Pediatric Clinical Outcomes and Treatments in an Integrated Healthcare System

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OBJECTIVE: The clinical integration of genetic and genomic information for pediatric medicine has been under-addressed. Unmet clinical needs encompass relatively common conditions such as epilepsy, as well as rare, orphan, and undiagnosed diseases disproportionately affecting infants and children. The objective of our project was to implement a coordinated effort to understand the global landscape of genetic disease burden in children, including a focus on neurological diseases.

METHODS: Here we describe: 1) a population-based approach to pediatric personalized health with unique resources including a vertically integrated medical record system and population pedigree information, 2) strategies for testing, data collection, and outcomes tracking, and 3) results of pilot trials including in epilepsy, congenital heart disease, and the Newborn Intensive Care Unit (NICU). Finally, we describe the launch of the genetic and genomic P50K component, for whole genome sequencing of 50,000 pediatric patients and children.

RESULTS: Our findings include development of novel WGS algorithms for diagnosis in epilepsy and leukodystrophies; predictive utility of genetic testing in new-onset pediatric seizures; and clinical and cost utility of rapid whole genome sequencing (WGS) in NICU infants. Finally, we discuss logistics and initial results from the launch of whole genome sequencing in 50,000 children.

CONCLUSIONS: The P50K program is the largest effort in the world of whole-genome sequencing and population health for pediatric patients. It has a further unique opportunity because it can be combined with granular, longitudinal clinical data and near complete clinical ascertainment in an integrated healthcare system; and a state-wide genetic pedigree database. **KEYWORDS:** Genetics, Rare Diseases, Epilepsy

PL41. Human Genetic Risk and Protective Factors In Congenital Zika Syndrome

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OBJECTIVE: Neurodevelopmental disorders, including brain malformations, epilepsy and intellectual disability can result from extra-neuronal insults by neurotropic viruses, including Zika virus. Our overarching hypothesis is that Zika virus infection affects neural environment by perturbing shared genetic pathways.

METHODS: Our multicentered nested case-control association study seeks to identify maternal and fetal genetic risk factors in Congenital Zika Syndrome (Fig.1,2). We performed in-silico analyses of putative neurodevelopmental and viral-responsive genes that might be interacting with Zika virus. We then performed whole exome sequencing on mother-infant dyads in Colombia and Brazil, where infants had 1) Congenital Zika Syndrome (clinical diagnosis), 2) severe brain malformations, or 3) mild imaging changes. We developed a cerebral organoid tissue culture system and performed transcriptomic profiling for candidate gene validation. **RESULTS:** We identified 3098 neurodevelopmental candidate genes; 49 of these genes (1.5%) are associated with 10 or more different neurodevelopmental disorders. Transcriptomic profiling showed that 2968/3098 (96%) of disease-associated candidate genes are expressed in cerebral organoids. Preliminary analysis of sequencing data revealed likely pathogenic variants in 6 genes, including 3 candidate neurodevelopmental genes.

CONCLUSIONS: Our finding might explain how Zika virus infection can affect the neural environment and lead to different brain malformations in different people. This work is foundational for the Zika Genetic Consortium as we build a biobank of 5,000 mother-infant dyads from 15 international health centers in 7 countries in collaboration with the NIH and CDC. We are leveraging these datasets to identify vulnerabilities or resiliencies in the neural environment toward neuroprotective therapies to prevent brain injury.

KEYWORDS: Genetics, Infections/Neuroimmunology, Neonatal & Fetal Neurology



PL42. Characterization of PTEN-associated cortical malformations and associated clinical phenotype

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OBJECTIVE: We aimed to systematically characterize brain malformations in patients harboring *PTEN* pathogenic variants and assess the relevance of their brain malformations to clinical presentation.

METHODS: We systematically searched a local radiology database for patients with pathogenic *PTEN* variants who underwent brain MRIs. We used targeted sequencing in 3 individuals to confirm that there were no other germline variants that were likely to explain their cortical malformation. EEG data and the electronic medical record were reviewed to assess rates of epilepsy and developmental delay.

RESULTS: In total we identified 22 patients with *PTEN* pathogenic variants with brain MRIs (age range 2 year 10 months – 17 years). Of these subjects, 12 (54%) have structural malformations of cortical development including 10 with polymicrogyria (PMG). Interestingly, epilepsy was present only in 1 out of 11 patients with PMG when associated

with *PTEN* mutations. We found nominally higher rates of GDD, ID, and motor delay in subjects with cortical abnormalities, though the small cohort limited statistical significance.

CONCLUSIONS: Malformations of cortical development and PMG in particular are an underrecognized phenotype associated with *PTEN* pathogenic variants and may be associated with cognitive and motor delays. Epilepsy was infrequent in this cohort compared to high risk of epilepsy in patients with PMG of any cause.

KEYWORDS: Genetics, Neuroimaging, Epilepsy

PL43. Diagnostic yield of genetic testing in infants with congenital hypotonia

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OBJECTIVE: Hypotonia presents a common diagnostic challenge and use of genetic testing is crucial in diagnosing underlying disorders. However, the overall diagnostic rate of genetic tests for this common condition remains unclear. This study aims to determine the diagnostic yield of genetic testing in congenital hypotonia.

METHODS: We conducted a retrospective chart review of infants with hypotonia, seen at a tertiary children's hospital over a course of five years (2014 - 2019). Data collected included demographics, clinical presentation, ancillary and genetic testing.

RESULTS: Out of 496 patients reviewed, 324 (65.3%) underwent genetic testing. Out of 324 patients, 171 (52.7%) were males and 153 (47.2%) females. Hypotonia was axial in 92 (28.3%), peripheral in 20 (6.1%) and diffuse in 212 (65.4%) patients. The median age of presentation was 5.3 ± 4.0 months. 147 (45.3%) patients underwent karyotype, 248 (76.5%) microarray, 127 (39.1%) targeted testing (Prader-Willi syndrome, spinal muscular atrophy etc.), 35 (10.8%) targeted gene panels and 157 (48.4%) whole exome sequencing. The diagnostic yield was 48 (32.6%) for karyotype, 48 (19.3%) for microarray, 31 (24.4%) for targeted tests, 13(37.1%) for targeted gene panels and 57 (36.3%) for whole exome sequencing. 18 of the variants identified by exome sequencing were novel pathogenic variants.

CONCLUSIONS: Our results show that targeted analysis remains the most efficient way of approaching congenital hypotonia, but without specific clinical cues, whole exome sequencing can identify an etiology in one-third or more of the infants. Statistical analysis of this dataset is ongoing for further markers that may increase diagnostic yield of genetic testing. **KEYWORDS:** Genetics, Neuromuscular Disorders, Neonatal & Fetal Neurology

INFECTIONS/NEUROIMMUNOLOGY

PL44. Common autoantigen identified in a cohort of ROHHAD-NET patients, supporting ROHHAD as a novel paraneoplastic neurological disorder

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OBJECTIVE: The rare and devastating pediatric disorder, ROHHAD ((rapid-onset obesity (RO) with hypothalamic dysregulation (H), hypoventilation (H), and autonomic dysregulation (AD)), is strongly associated with neuroendocrine tumors (ROHHAD-NET), suggesting it may be an autoimmune paraneoplastic neurological disorder. However, the location of the inflammation (hypothalamus/pituitary), lack of a detectable autoantibody and rarity have made the etiology elusive. We used a new approach to identify a potentially diagnostic autoantibody for ROHHAD-NET syndrome.

METHODS: Antibodies from sera and cerebrospinal fluid from ROHHAD-NET patients (n=6) were screened using a programmable phage display of the human peptidome (PhIP-Seq) within one year of diagnosis. Antibody profiles from ROHHAD patients were compared to autoantibody profiles from non-inflammatory controls (NIC) and from patients with opsoclonus-myoclonus syndrome (OMS). Candidate autoantibodies were validated using a radioactive ligand binding assay (RLBA). Expression of candidate antigens in ROHHAD associated neuroendocrine tumor tissue was confirmed using commercial antibodies. Public datasets were utilized to confirm expression of candidate antigens in brain.

RESULTS: Our screening method identified antibodies to ZSCAN1, a human-specific zinc finger/SCAN domain protein, in 6/6 ROHHAD-NET patients, but not in NIC (0/100) or OMS (0/25) controls. Specificity of anti-ZSCAN1 antibodies in ROHHAD-NET patients were validated by RLBA. ZSCAN1 protein expression was confirmed in ROHHAD-associated neuroendocrine tumor and heathy human brain tissue.

CONCLUSIONS: Our results indicate that anti-ZSCAN1 antibodies fulfill the criteria for an authentic paraneoplastic-associated autoantigen in ROHHAD-NET syndrome. Species-specific and brain region-specific expression of ZSCAN1 likely explains the previous inability of standard molecular approaches to detect ROHHAD-NET autoantibodies.

KEYWORDS: Infections/Neuroimmunology, Neurometabolic Disorders



Graphic 1: (A) Cohort-level PhIP-Seq analysis comparing ROHHAD-NET (n=6) to non-inflammatory controls (n=100). Each dot represents the mean number of sequencing reads for each protein in the phage display library for each cohort. Note specific enrichment of ZSCAN1 in ROHHAD-NET (labeled in red, pointed to with arrows) (B) ZSCAN1 antigen detection by immunohistochemistry of ROHHAD neuroganglioma tissue using commercial antibody to ZSCAN1. DAPI marks nuclei. ROHHAD-NET = Rapid-Onset Obesity with Hypothalamic Dysregulation Hypoventilation and Autonomic Dysregulation with presence of neuroendocrine tumor. NIC = Non-inflammatory controls

PL45. Think AFM: many patients with acute flaccid myelitis are misdiagnosed

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OBJECTIVE: Acute flaccid myelitis (AFM) is a polio-like illness that has both acute and long-term complications if not promptly recognized. We aim to highlight misdiagnosis in AFM with the goal to improve future identification, monitoring and treatment.

METHODS: Retrospective chart reviews of children (<18 years) meeting 2018 CDC case definition for AFM in 2014-2018 were performed at 13 institutions in the US and Canada. Patients were considered misdiagnosed if they were given an alternative diagnosis(es) prior to AFM and/or were evaluated by a medical provider (outpatient or emergency) and discharged home without acute care admission (n=137). This cohort was compared to children who were not misdiagnosed at presentation (n=38).

RESULTS: 175 children were included, 78% of whom were misdiagnosed. Amongst those given alternative diagnoses, half were given non-neurologic diagnoses (28% of all). Misdiagnosed children had higher rates of ICU admission and need for invasive or non-invasive ventilation of 53% and 31% respectively, compared to 37% and 16% for patients promptly diagnosed, though not statistically significant. Time from onset of weakness to treatment with any immunomodulatory therapy was 5 days for the misdiagnosed group compared to 3 days for the promptly diagnosed (p=0.019).

CONCLUSIONS: Most patients with AFM were not initially recognized which can have serious clinical consequences. While some were diagnosed with similar conditions such as transverse myelitis and Guillain Barré syndrome; many patients were also thought to have benign non-neurologic conditions. First line providers should consider a diagnosis of AFM when evaluating children with new onset weakness.

KEYWORDS: Infections/Neuroimmunology, Neuromuscular Disorders, Critical Care

PL46. Validity of the clinical diagnostic criteria for anti-N-methyl-D-aspartate receptor encephalitis in Japanese pediatric patients

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OBJECTIVE: In 2016, a study in *Lancet Neurology* proposed that at least four of six symptom groups are required for probable diagnosis of anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis. Here, we tested this proposition in a Japanese pediatric cohort.

METHODS: We retrospectively reviewed clinical information of pediatric patients with neurological symptoms whose cerebrospinal fluids were analyzed for NMDAR antibodies (Ab) in our laboratory from January 1, 2015, to March 31, 2019.

RESULTS: Overall, 139 cases were included. Of 41 cases diagnosed as probable anti-NMDAR encephalitis ("criteria positive") according to the criteria, 13 were positive and 28 negative for anti-NMDAR Ab. Among the 98 criteria-negative cases, three were positive and 95 negative for anti-NMDAR Ab. The sensitivity of the criteria was 81.2% (95% confidence interval [CI]: 54.4–96.0%), specificity was 77.2% (95% CI: 68.8–84.3%), positive predictive value (PPV) was 31.7% (95% CI: 18.1–48.1%), negative predictive value was 96.9% (95% CI: 91.3–99.4%), and the diagnostic odds ratio was 14.7. Compared to the true-positive group, the false-positive group contained more males than females (male/female 4/13 in the true positive vs 19/28 in the false-positive group, p = 0.0425). The majority of the cases with false-positive diagnoses were associated with autoimmunity.

CONCLUSIONS: The clinical diagnostic criteria are sufficiently reliable for deciding to start immunomodulatory therapy in the criteria-positive cases. However, the low PPV from our study suggests that criteria positivity does not guarantee the diagnosis of NMDAR encephalitis. Physicians should continue differential diagnosis, especially focusing on other forms of encephalitis.

KEYWORDS: Infections/Neuroimmunology

PL47. Comparison of Seizure Type and EEG findings in Autoimmune Encephalitis: A Multicenter Sample

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OBJECTIVE: Autoimmune encephalitis is an increasingly recognized class of inflammatory diseases of the brain that can present with seizures. The purpose of this study was to compare seizure type and EEG findings in pediatric versus adult patients diagnosed with autoimmune encephalitis.

METHODS: This was a retrospective review of clinical and EEG data from pediatric and adult patients with a diagnosis of autoimmune encephalitis from three medical centers. Patients with positive CSF autoantibody results and autoantibody-negative but probable autoimmune encephalitis were included utilizing criteria from a recent position paper on a clinical approach to the diagnosis of autoimmune encephalitis (Lancet Neurology 2016).

RESULTS: There was a total of 102 patients, of whom 67 were pediatric (65.7%). Seizures were a presenting symptom in 54 (53%) patients, classified as focal (66.7%), generalized (16.7%), or undetermined (16.7%). Status epilepticus was present in 15% of patients. EEG findings including diffuse slowing (49%), focal spikes (22.9%), focal slowing (14.6%), or delta brush (1%). EEG was normal in 12% of cases. Pediatric patients had a higher incidence of focal seizures and status epilepticus compared to adult patients (p<0.05). Patients with positive CSF anti-neuronal antibody results were more likely to have seizures and focal slowing on EEG, compared to autoantibody-negative patients (p=0.04). (Figure 1)

CONCLUSIONS: Autoimmune encephalitis is more likely to present with focal seizures and status epilepticus in children. Positive autoantibody status is associated with seizures and focal slowing on EEG. Further study is being performed to explore the prevalence of chronic epilepsy in this subset of patients.

KEYWORDS: Infections/Neuroimmunology



PL48. Clinico-radiological profile of children with acute necrotizing encephalopathy of childhood (ANEC) associated with dengue fever: A case series *Patel Harshkumar (Ahmedabad, India)*

OBJECTIVE: Acute necrotizing encephalopathy of childhood (ANEC) is a rare but distinct clinico-radiological condition mainly thought to be secondary to viral (eg influenza, HHV 6) infections and even specific genetic mutations (RANBP2) have also been implicated. Various neurological manifestations have been described with dengue as dengue encephalopathy or dengue encephalitis but reports of ANEC in children with dengue is very scarce. Here we are describing clinical profile of children with ANEC associated with dengue, might be largest case series till date to best of our knowledge.

METHODS: From July 2018 to December 2019 total 8 children with ANEC associated with dengue infection were included. Their clinical, CSF parameters, radiological and treatment details were recorded and short term neurological follow up was obtained.

RESULTS: Mean age of children was 5.5 years and out of 8,5 (63%) were female and 3(37%) were boys. All children presented with acute onset encephalopathy, seizures and recurrent posturing. All but one were seropositive for dengue. Three children had normal CSF study while

5 had abnormal CSF study with one was positive for dengue PCR.All children had symmetric bilateral thalami lesions with variable midbrain and pons involvement on MRI, while 4 had associated supratentorial and two had cerebellar involvement.Median hospital stay was 17 days. Two children died while 4 of them had sever neurological impairments and only 2 of 8 were recovered fully.

CONCLUSIONS: ANEC with dengue infection is to be considered as severe CNS manifestations of dengue which is likely para infectious immune mediated process instead of direct viral invasion.

KEYWORDS: Infections/Neuroimmunology, Neuroimaging, Critical Care





Figure 1: This FLAIR(up) and DWI(below)(diffusion weighted) images shows classical symmetrical thalami and significant pons and midbrain involvement c/w ANEC



Figure 2: This DWI images shows apart from thlami lesions involvement of supratentorial and cerebellar involvement.

PL49. GAD65 Antibody Encephalitis presenting as treatment resistant temporal lobe epilepsy and peripheral neuropathy in a pediatric patient

Nabavi Nouri Maryam (London, Ontario, Canada)

OBJECTIVE: To review the clinical presentation, EEG abnormalities, MRI features and treatment response in a child presenting with treatment resistant temporal lobe epilepsy (TLE) and peripheral neuropathy associated with high titers of anti-glutamic acid decarboxylase (anti-GAD65). Combination of TLE and demyelinating neuropathy has not been previously reported in a pediatric patient with anti-GAD65 in absence of diabetes.

METHODS: Case-report

RESULTS: This is a previously healthy and developmentally normal 15-year-old male who presented with a two-month history of recurrent spells of tachycardia, chest tightness and confusion in the context of severe anorexia. These spells were captured on EEG and were consistent with left temporal lobe seizures. Brain MRI revealed T2 hyperintensity in the hippocampus bilaterally. CSF was remarkable for elevated CSF proteins (0.69g/L) and high levels of anti-GAD65 (>25000units/mL). Multiple anti-seizure medications provided only transient improvement. First and second line immunotherapy (IV methylprednisolone and IVIG) followed by rituximab, mycophenolate mofetil and cyclophosphamide failed to control his seizures. With disease progression, he developed demyelinating sensorimotor polyneuropathy. During his treatment course, his MRI normalized but no change was observed in CSF anti-

GAD65 levels. He was started on plasmapheresis for treatment of his seizures and neuropathy with no clear response.

CONCLUSIONS: This case broadens the phenotypic variability of GAD65 antibody in the pediatric population with demonstration of both central and peripheral nervous system involvement. Despite early initiation of immunotherapies, our patient did not respond favourably to conventional treatments. Questions still remain about early biomarkers of treatment response and underlying mechanisms of GAD autoimmunity.

KEYWORDS: Infections/Neuroimmunology, Epilepsy, Neuromuscular Disorders

PL50. Acute Encephalitis in the Pediatric Population of Western Pennsylvania

Mack Meghan (Pittsburgh, PA, United States) Thakkar Kavita

OBJECTIVE: We aimed to categorize the etiologies, demographic, clinical, diagnostic, and prognostic features of acute encephalitis in the pediatric population at our institution. **METHODS:** Children between ages 6 months and 18 years who were clinically diagnosed with encephalitis from January 2009 to January 2020 were included. Known epilepsy, metabolic, toxic, neoplastic, and genetic etiologies were excluded.

RESULTS: 95 of 937 children were included. 53(56%) were male. Median age at diagnosis was 9.5years. There was no seasonal predilection. Antecedent illness of the upper respiratory tract and/or fever was noted in 75(79%). Elevated CSF WBC (>5cells/mm³) was seen in 60(63%), and elevated protein (>45gms/dl) was noted in 32(34%). Etiologies included infectious encephalitis 29(31%), ADEM 19(20%), and autoimmune encephalitis 7(7%). 40(42%) had no etiology identified. Infectious etiologies included viral 21(72%) and bacterial 8(28%) and were seen at a median age of 10.5 years. Patients with ADEM presented at a median age of 6 years. Those with unknown etiology had a median age of 10 years and lower mean CSF WBC (88cells/mm³) than those with an indentified etiology (mean CSF WBC 370cells/mm³). 51(54%) received steroids, IVIG or plasma exchange either in combination or by itself. 6 month follow up was available in 65; 38(58%) made full recovery, 24(37%) made partial recovery and 3(5%) made no recovery. There were no deaths.

CONCLUSIONS: Infections and ADEM remain the predominant causes of childhood encephalitis. More than a third of the patients do not have an identified etiology. Further characterization of these undiagnosed cases will help expand the etiological spectrum. **KEYWORDS:** Infections/Neuroimmunology

MOVEMENT DISORDERS (INCLUDING CEREBRAL PALSY)

PL51. The effect of intrathecal baclofen in dyskinetic cerebral palsy (IDYS trial): a multicentre, randomised, double-blind, placebo-controlled trial

Bonouvrie Laura (Amsterdam, Netherlands) Becher Jules, Vles Hans, Vermeulen R. Jeroen, Buizer Annemieke

OBJECTIVE: Patients with severe dyskinetic cerebral palsy (DCP) experience extensive motor disabilities. Treatment options are limited. Intrathecal baclofen (ITB) treatment is used for the

treatment of dystonia in DCP. The primary aim of this study was to provide evidence for the effect of ITB treatment on individual goals in patients with severe DCP.

METHODS: This multi-centre, randomised, double-blind, placebo-controlled trial was performed at two University Medical Centres in the Netherlands. Patients with severe dyskinetic CP (Gross Motor Functioning Classification System level IV-V), aged 4 to 24, eligible for intrathecal baclofen treatment, were included. Patients were assigned by block randomization (2:2) for treatment with intrathecal baclofen or placebo during three months via an implanted micro-infusion pump. The primary outcome was Goal Attainment Scaling of individual treatment goals (GAS T-score). A linear regression model was used for statistical analysis with study site as a covariate. Safety analyses were done for number and type of (serious) adverse events. The trial is registered with the Dutch Trial Register, NTR3642.

RESULTS: Thirty-six patients were recruited from January 1st 2013 to March 31st 2018. Data for final analysis were available for 16 patients in the placebo group and 17 in the ITB group. Mean (SD) GAS T-score at three months was 38.9 (13.2) for ITB and 21.0 (4.6) for placebo (regression coefficient 17.8, 95% CI 10.4 to 25.0, p<0.001). Number and types of (serious) adverse events were similar between groups.

CONCLUSIONS: Intrathecal baclofen treatment is superior to placebo in achieving treatment goals in patients with severe dyskinetic cerebral palsy.

KEYWORDS: Movement Disorders (including Cerebral Palsy), Neurorehabilitation

PL52. Stereotypies have lower burden of comorbidity compared to tics

Dean Shannon (Baltimore, MD, United States) Mink Jonathan

OBJECTIVE: Tics and stereotypies are common pediatric movement disorders and share some common comorbidities. We sought to evaluate differences in comorbidity burden, resource use, and need for intervention.

METHODS: We did a retrospective chart review of typically developing children diagnosed with stereotypies (n=63) or tics (n=63) at the University of Rochester Child Neurology Clinic between 2003 and 2016. We extracted the total number of visits, comorbidities diagnosed, and any interventions recommended. We also conducted a follow-up survey with 23 subjects with stereotypies.

RESULTS: Children with stereotypies were younger at first (mean 5.6 vs 7.1yrs) and last visit (6.5 vs 9.8yrs), and had fewer total visits (1.8 vs 4.5) compared to children with tics. They also had fewer total neuropsychiatric comorbidities 0.7 vs 1.9 /person), lower rates of ADHD(27% vs 48%), OCD(8% vs 41%) and anxiety(21%vs63%)), and were less likely to have pharmacologic (21% vs 51%) or behavioral intervention (21% vs 41%) recommended for comorbidies. In order to control for less frequent visits, we also compared this data to that seen in our follow-up survey. Survey respondents with stereotypies were less likely to have the three most common comorbidities (0.8/person) than documented in children with tics (1.5/person).

CONCLUSIONS: Children with stereotypies are seen less often by a neurologist than those with tics, and are less likely to have an intervention for comorbidity recommended. This is not simply because they are first seen at a younger age before comorbidities manifest, but likely also a reflection of a lower comorbidity burden overall.

KEYWORDS: Movement Disorders (including Cerebral Palsy)

PL53. Anxiety symptoms in youth with and without tic disorders

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OBJECTIVE: To evaluate anxiety symptoms in youth with tic disorders and to evaluate if youth with tics have a similar anxiety symptom profile to youth without tics.

METHODS: We evaluated the impact of tic disorders on children, families, and communities in a cross-sectional, multisite study. We analyzed data on anxiety-related symptoms for this study and compared anxiety severity in youth with tic disorders and community controls. We also evaluated archival data on anxiety severity from the Child/Adolescent Anxiety Multimodal Study (CAMS), the largest randomized controlled trial of childhood anxiety. We compared our sample of youth with tic disorders to the CAMS participants.

RESULTS: We analyzed data from 176 youth with tic disorders, 93 control subjects, and 488 CAMS participants. Youth with tic disorders had significantly higher anxiety symptom severity compared to control subjects (p<0.0001). Total anxiety severity was similar between the tic disorder and CAMS groups (p=0.13) but youth with tic disorders had higher physical anxiety (p<0.0001) and separation anxiety (p=0.0003) symptom severity. Increased separation anxiety was associated with younger age in CAMS participants but there was no relationship between age and anxiety symptom severity in youth with tic disorders.

CONCLUSIONS: Anxiety severity was higher in youth with tic disorders compared to community controls and similar to treatment-seeking youth with anxiety disorders. Youth with tic disorders may have higher separation anxiety severity which may also be more likely to persist with increasing age. This may have important implications for targeting treatment of anxiety in youth with tic disorders.

KEYWORDS: Movement Disorders (including Cerebral Palsy)

PL54. Improved Motor Function in Children With AADC Deficiency Treated with Eladocagene Exuparvovec (PTC-AADC): Interim Findings from a Phase 2 Trial

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OBJECTIVE: Aromatic L-amino acid decarboxylase (AADC) deficiency is a rare genetic disorder caused by mutations in *DDC*, resulting in missed motor milestones. We report interim findings from a phase 2 study on gene therapy with PTC-AADC.

METHODS: Eight children underwent bilateral intraputaminal injection of PTC-AADC $(1.8 \times 10^{11} \text{ vg for } \ge 3 \text{ years and } 2.4 \times 10^{11} \text{ vg for } < 3 \text{ years of age})$. Endpoints are described in table 1. Mean follow-up was 11.5 months.

RESULTS: Patients received doses of 1.8×10^{11} vg (n=3; mean age, 55.0 months) or 2.4×10^{11} vg (n=5; mean age, 24.8 months). Baseline PDMS-2 and AIMS total scores were low. At 1 year, some patients had achieved motor milestones (table 2). Increases from baseline in PDMS-2, AIMS, and Bayley-III total scores at 1 year were statistically significant (*P*<0.0001, *P*≤0.0016, and *P*≤0.0004 respectively, both doses). Mean body weight increased from baseline to year 1 in both groups. The number of patients with hypotonia, oculogyric crises, and limb dystonia decreased during the first year. No viral shedding was detected. No differences were observed in the safety profiles for the doses. All patients experienced ≥1 TEAE, most of mild intensity; none

were definitely related to treatment. Mild dyskinesia episodes were considered possibly related to therapy. Of 21 serious AEs, all resolved and were considered unlikely to be related to study treatment.

CONCLUSIONS: Children with AADC deficiency achieved meaningful gains in motor function 1 year after PTC-AADC. No new safety signals were observed.

KEYWORDS: Movement Disorders (including Cerebral Palsy), Neuromuscular Disorders

Primary efficacy endpoint	 Proportion of patients achieving key milestones at 12 months compared with a historical control group (n=82) Measured by the Peabody Developmental Motor Scale, Second Edition (PDMS-2) 			
Secondary efficacy endpoints	 Changes in PDMS-2 Alberta Infant Motor Scale (AIMS) Bayley Scales of Infant Development, Third Edition (Bayley-III) scores Body weight Neurologic examination findings related to AADC deficiency symptoms 			
Dopamine production assessment	• Putaminal L-6-[¹⁸ F] fluoro-3,4-dihydroxyphenylalnine (¹⁸ F-DOPA) uptake on positron emission tomography (PET) was evaluated as an objective measurement of <i>de novo</i> dopamine production			
Safety endpoints	 Treatment-emergent adverse events (TEAEs) Viral shedding 			

Table 1. Endpoints and Assessments

Table 2. Patients Achieving Motor Milestones at 12 Months

Milestone	Low-dose group (n=3)	High-dose group (n=4)	Total (N=7)
Full head control, n	1	3	4
Sitting unassisted, n	0	1	1

PL55. High-throughput Screen For Small Molecules That Modulate Protein Trafficking In Adaptor Protein Complex 4 (AP-4) Associated Hereditary Spastic Paraplegia

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OBJECTIVE: Bi-allelic variants in subunits of the adaptor protein complex 4 (AP-4) lead to childhood-onset hereditary spastic paraplegia (SPG47, SPG50, SPG51, SPG52). Aims: 1) To develop a high-throughput phenotypic screening assay in patient-derived cells; 2) To screen libraries of known bioactive compounds.

METHODS: A combination of patient-derived cells and automated high-content imaging. **RESULTS:** We investigated 20 patient-derived fibroblast lines and six lines of iPSC-derived neurons covering a wide range of AP-4 variants. All patient-derived cells showed reduced levels Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020 of the AP4E1 subunit, a surrogate for levels of the AP-4 complex. The autophagy protein ATG9A accumulated in the trans-Golgi network. Western blot analysis demonstrated a 3–5-fold increase in ATG9A expression in patient lines. ATG9A was redistributed upon re-expression of the missing AP4 subunit. We adapted the ATG9A mislocalization assay as a surrogate for AP-4 deficiency in a high-throughput format using automated confocal microscopy. Conventional statistical measures for assay sensitivity and reliability showed a robust performance with a Z' score of >0.0 and SSMD value of >3. We screened three libraries of known bioactive molecules (Biomol 4 – FDA Approved Library, NINDS Custom Collection 2, LDDN-CNS) and identified 13 compounds that decreased ATG9A fluorescence at the trans-Golgi network and/or increased ATG9A fluorescence in the cytoplasm.

CONCLUSIONS: We establish ATG9A mislocalization as a key marker of AP-4 deficiency in patient-derived cells, including the first human neuron model of AP-4-HSP, and demonstrate its use in a phenotypic small molecule screen. The identified lead compounds provide novel insights into AP-4 biology and opportunities for drug development.

KEYWORDS: Movement Disorders (including Cerebral Palsy), Translational/Experimental Therapeutics, Rare Diseases

PL56. Improved Motor Function in Children With AADC Deficiency Treated With Eladocagene Exuparvovec (PTC-AADC): Compassionate Use Study

Hwu Paul Wuh-Liang (Taipei City, Taiwan) Chien Yin-Hsiu, Lee Ni-Chung, Tseng Sheng-Hong, Conway Anne Marie, Pykett Mark, Tai Chun-Hwei

OBJECTIVE: AADC deficiency is caused by mutations in the gene for AADC. This study evaluated efficacy and safety of PTC-AADC, a recombinant adeno-associated virus containing cDNA encoding AADC, in children with AADC deficiency for 5 years.

METHODS: This observational study evaluated data from a single-arm, compassionate-use trial enrolling children >2 years of age with AADC deficiency (n=8) who received intraputaminal PTC-AADC. Primary efficacy endpoint was the proportion achieving key milestones using the Peabody Developmental Motor Scale, Second Edition (PDMS-2), compared with a historical control group (n=82). Secondary endpoints included changes in PDMS-2, Alberta Infant Motor Scale (AIMS), and Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT) scores and body weight. Pharmacodynamic endpoints included putaminal ¹⁸F-DOPA uptake on positron emission tomography (PET). Safety endpoints included treatment-emergent adverse events (TEAEs) and viral shedding. Mean follow-up duration was 62.5 months.

RESULTS: PTC-AADC increased motor milestone achievement (table). Mean PDMS-2, AIMS, and CDIIT total scores (all *P*<0.0001) and mean body weight (*P*=0.027) increased from baseline to 5 years. Putaminal ¹⁸F-DOPA PET uptake increased over time (*P*=0.0134) (figure). All patients experienced \geq 1 TEAE, none considered PTC-AADC related and most of mild/moderate intensity. Eight patients experienced 9 possibly/probably treatment-related dyskinesia episodes, generally in the first few months and resolving within 4 months. Seven patients experienced \geq 1 serious AE, none PTC-AADC related. No deaths occurred during the study. No viral shedding was detected.

CONCLUSIONS: Children with AADC deficiency achieved sustained improvements in motor function after PTC-AADC, with increased putaminal dopamine production. No new safety signals were identified.

KEYWORDS: Movement Disorders (including Cerebral Palsy), Neuromuscular Disorders

Motor Milestone	Timepoint	PTC-AADC Group (n=8)	Historical Control Group (n=82)	<i>P</i> Value
	Baseline	0	_	_
	1 year	4	_	-
Full head control	2 years	4	-	- 6
	5 years	4	0	0.002
	Baseline	0	-	-
Sitting upperiated	1 year	2	_	-
Sitting unassisted	2 years	4	-	-
	5 years	4	0	0.002
	Baseline	0	-	-
Standing with	1 year	0	-	-
support	2 years	0	-	-
	5 years	2	0	0.0454
	Baseline	0		-
Walking with	1 year	0	0	_
assistance	2 years	0		_
	5 years	0	0	N/A

Table: Number of Patients Achieving Key Motor Milestones

Figure: Putaminal ¹⁸F-DOPA PET Uptake





The black arrows mark the signal observed in the putamen.

NEONATAL & FETAL NEUROLOGY

PL57. Lateralized neonatal EEG response to maternal voice exposure as a predictor of language outcome

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OBJECTIVE: Enriched language exposure through maternal voice recordings may benefit infants in the neonatal intensive care unit (NICU). We evaluated how neonatal EEG coherence changes in response to maternal voice exposure may predict language development. **METHODS:** In a level IV NICU, convalescent neonates underwent 12-hour polysomnography. Continuous playback of a recording of the mother reading children's books was randomized to the first or second 6 hours. Children were evaluated with Bayley-III at 18-months. To compare functional connectivity for left and right hemispheres, we calculated the imaginary coherence (ICOH) between EEG leads and computed a bootstrap estimate of its mean across frequencies. We then calculated the Spearman correlation between ICOH and Bayley Language scores. **RESULTS:** Thirty-six neonates were included (N=19 33-to-<35 weeks gestation, N=17 \geq 35 weeks). Predictive value of ICOH during neonatal quiet sleep was lateralized and varied with gestational age and voice playback. ICOH in the left-hemispheric (C3-Cz) channels across multiple EEG frequency bands was associated with 18-month language scores (rho= -0.3 to -0.6, p<0.05; figure). However, right hemisphere ICOH (C4-Cz) was not associated with language outcome. The effect was isolated to neonates born at <35 weeks gestation and most pronounced during maternal voice exposure (table).

CONCLUSIONS: Patterns of EEG functional connectivity during neonatal quiet sleep show early signs of physiologic asymmetry that may predict language development. In the absence of strong predictive value from neurologic exam scores and objective clinical studies of neonates, we speculate that digital analyses of the sleep EEG could have unique prognostic value. **KEYWORDS:** Neonatal & Fetal Neurology, Critical Care

Figure: Among 36 neonates, the imaginary component of the coherence (ICOH) between left central EEG electrodes (C3-Cz) was predictive of 18-month language outcome, especially during playback of a maternal voice recording (Panels A and B). There were no such associations of right central (C4-Cz) ICOH and outcome, with or without maternal voice playback (Panels C and D).



Association between LEFT hemisphere ICOH (C3-Cz EEG electrodes) during neonatal quiet	
sleep and 18-month language outcomes	

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EEG	Maternal	C3-Cz ICOH all		C3-Cz ICO	H	C3-Cz ICOH	
Frequency	Voice	subjects		GA 33 to <.	35 weeks	GA ≥35 weeks	
	Playback						
		rho p-value		rho	p-value	rho	p-value
2-4 Hz	off	-0.43	0.01	-0.36	0.13	-0.47	0.056
4-8 Hz	off	-0.25	0.15	-0.27	0.26	-0.25	0.34
8-12 Hz	off	-0.40	0.017	-0.56	0.013	-0.073	0.78
12-16 Hz	off	-0.32	0.057	-0.57	0.012	0.060	0.82
2-4 Hz	on	-0.49	0.004	-0.45	0.060	-0.49	0.066
4-8 Hz	on	-0.32	0.072	-0.48	0.043	-0.025	0.93
8-12 Hz	on	-0.41	0.017	-0.65	0.004	0.066	0.81
12-16 Hz	on	-0.44	0.011	-0.65	0.003	-0.11	0.69

Association between RIGHT hemisphere ICOH (C4-Cz EEG electrodes) during neonatal quiet sleep and 18-month language outcomes

Steep und to month language outcomes							
EEG	Maternal	C4-Cz ICOH all		C4-Cz ICOH		C4-Cz ICOH	
Frequency	Voice	subjects		GA 33 to <35 weeks		GA ≥35 weeks	
	Playback	-					
		rho	p-value	rho	p-value	rho	p-value
2-4 Hz	off	-0.08	0.63	-0.11	0.66	-0.15	0.57
4-8 Hz	off	-0.29	0.07	-0.16	0.51	-0.31	0.23
8-12 Hz	off	-0.24	0.16	-0.24	0.32	-0.17	0.51
12-16 Hz	off	-0.31	0.07	-0.45	0.05	-0.12	0.64
2-4 Hz	on	-0.17	0.36	-0.19	0.45	-0.12	0.68
4-8 Hz	on	-0.28	0.12	-0.20	0.44	-0.30	0.28
8-12 Hz	on	-0.14	0.44	-0.24	0.34	0.01	0.73
12-16 Hz	on	-0.12	0.28	-0.35	0.15	0.16	0.57

Association between LEFT hemisphere ICOH (C3-Cz EEG electrodes) during neonatal quiet sleep and 18-month language outcomes

	steep und 10 month hanguage outcomes								
	EEG	Maternal	C3-Cz ICOH all		C3-Cz ICOH		C3-Cz ICOH		
	Frequency	Voice	subjects		GA 33 to <35 weeks		GA ≥35 weeks		
		Playback							
	•	\mathbf{C}	rho	p-value	rho	p-value	rho	p-value	
	2-4 Hz	off	-0.43	0.01	-0.36	0.13	-0.47	0.056	
	4-8 Hz	off	-0.25	0.15	-0.27	0.26	-0.25	0.34	
	8-12 Hz	off	-0.40	0.017	-0.56	0.013	-0.073	0.78	
	12-16 Hz	off	-0.32	0.057	-0.57	0.012	0.060	0.82	
-	2-4 Hz	on	-0.49	0.004	-0.45	0.060	-0.49	0.066	
	4-8 Hz	on	-0.32	0.072	-0.48	0.043	-0.025	0.93	
	8-12 Hz	on	-0.41	0.017	-0.65	0.004	0.066	0.81	
	12-16 Hz	on	-0.44	0.011	-0.65	0.003	-0.11	0.69	

Association between **RIGHT** hemisphere ICOH (C4-Cz EEG electrodes) during neonatal quiet sleep and 18-month language outcomes

EEG	Maternal	C4-Cz ICOH all		C4-Cz ICOH		C4-Cz ICOH	
Frequency	Voice Plavback	subjects		GA 33 to <35 weeks		GA ≥55 weeks	
		rho	p-value	rho	p-value	rho	p-value
2-4 Hz	off	-0.08	0.63	-0.11	0.66	-0.15	0.57
4-8 Hz	off	-0.29	0.07	-0.16	0.51	-0.31	0.23
8-12 Hz	off	-0.24	0.16	-0.24	0.32	-0.17	0.51
12-16 Hz	off	-0.31	0.07	-0.45	0.05	-0.12	0.64
2-4 Hz	on	-0.17	0.36	-0.19	0.45	-0.12	0.68
4-8 Hz	on	-0.28	0.12	-0.20	0.44	-0.30	0.28
8-12 Hz	on	-0.14	0.44	-0.24	0.34	0.01	0.73
12-16 Hz	on	-0.12	0.28	-0.35	0.15	0.16	0.57

PL58. Duration of Anti-seizure Medication Treatment and 2-Year Outcome After Acute Symptomatic Neonatal Seizures – a Neonatal Seizure Registry study

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OBJECTIVE: To assess whether anti-seizure medication (ASM) treatment duration after acute symptomatic neonatal seizures alters risk of epilepsy, cerebral palsy (CP), or functional neurodevelopment at age 2-years.

METHODS: The *Neonatal Seizure Registry* presents a prospective, 9-center, observational comparative effectiveness study of ASM duration for infants with acute symptomatic neonatal seizures born 7/2015-3/2018. Propensity for ASM at discharge was defined by multivariable logistic regression.

RESULTS: Characteristics of the first 230 children with 2-year follow-up are presented (Table). ASMs were prescribed at discharge for 64% and continued for median 4 (IQR 3, 8) months, with a higher propensity in those with high seizure burden, complex clinical course, and abnormal discharge neurological examination. The risk of epilepsy was similar for children whose ASM was discontinued before neonatal discharge vs. maintained (unadjusted 11% vs 12%, p=0.9; propensity adjusted OR 0.6, 95% CI 0.2-1.5, p=0.3), as was age of epilepsy onset (adjusted HR 0.97, 95% CI 0.4-2.4, p=0.95). The risk of CP was similar by ASM duration (10% vs 16%, p=0.2; adjusted OR 1.3, 95% CI 0.5-3.1, p=0.6). Functional neurodevelopment (WIDEA scores) was also similar between groups (adjusted difference -2 points, 95% CI -11-7, p=0.7).

CONCLUSIONS: Discontinuing ASM prior to discharge for infants with acute symptomatic neonatal seizures does not increase risk of epilepsy/CP/functional development at 2-years. Results from this large, prospective, and multicenter study support discontinuing ASM after resolution of acute symptomatic seizures prior to hospital discharge, which reflects a change in practice at many centers.

KEYWORDS: Neonatal & Fetal Neurology, Epilepsy

Table: Clinical and seizure characteristics considered for propensity adjustment for 230 children with acute symptomatic neonatal seizures and discharge home on or off anti-seizure medications (ASM).

	Home on ASM	Home off ASM	p- value
Total N=230	194 (64%)	108 (36%)	4
Clinical Characteristics		•	
Gestational age at birth* - <28 weeks - 28 - <32 weeks - 32 - <37 weeks - <u>></u> 37 weeks	3 (2%) 1 (2%) 18 (13%) 118 (84%)	4 (4%) 3 (33%) 5 (6%) 78 (87%)	0.1
Male	77 (55%)	44 (49%)	0.4
5-minute Apgar	8 (5.5, 9)	6 (4, 9)	0.006
Participant location at the time of seizure evaluation - NICU - PICU - CICU - Other	122 (87%) 4 (3%) 13 (9%) 1 (1%)	85 (94%) 3 (3%) 2 (2%) 0	0.16
Seizure and EEG Characteristics			
Seizure etiology* Hypoxic-ischemic encephalopathy Ischemic stroke Intracranial hemorrhage Other 	57 (41%) 38 (27%) 22 (16%) 23 (16%)	50 (56%) 19 (21%) 11 (12%) 10 (11%)	0.18
 Worst EEG background during the 1st 24hrs at study center* Normal Mild/moderately abnormal Severely abnormal (burst suppression, depressed/undifferentiated, flat tracing) Electrographic status epilepticus at onset of recording Cannot assess 	7 (5%) 93 (66%) 24 (17%) 14 (75%) 2 (1%)	12 (13%) 62 (69%) 11 (12%) 5 (6%) 0	0.09
EEG seizure frequency at the study center - None - Few (<7) - Many isolated (≥7) - Frequent recurrent - Status epilepticus - Documentation inadequate	20 (14%) 35 (25%) 30 (21%) 36 (26%) 18 (13%) 1 (1%)	23 (26%) 29 (32%) 17 (19%) 12 (13%) 9 (10%) 0	0.08
Days of EEG seizures*	2 (1, 2)	1 (0, 2)	0.003
Initial loading anti-seizure medication (ASM) - Phenobarbital - Levetiracetam - Fosphenytoin - No loading dose	128 (91%) 9 (6%) 1 (1%) 2 (1%)	79 (88%) 2 (2%) 2 (2%) 7 (8%)	0.03
Incomplete response to initial loading dose of medication	93 (66%)	47 (53%)	0.08
Received ≥2 ASM	79 (56%)	36 (40%)	0.015
Clinical course			
Complex medical diagnosis (congenital heart disease, ECMO, congenital diaphragmatic hernia)	20 (14%)	7 (8%)	0.1
Therapeutic hypothermia*	35 (25%)	37 (41%)	0.01
Abnormal exam at discharge*	51 (36%)	16 (17%)	< 0.002

Data presented as n (%) and median (IQR)

*Included in the final propensity model

PL59. Short-Term Seizure Recurrence In Neonates With Acute Symptomatic Seizures: Early Vs Late Discontinuation Of Anti-epileptic drugs: A Randomized, Controlled, Non-Inferiority Trial

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OBJECTIVE: The data on optimal duration of anti-epileptic drugs (AEDs) in neonates with acute symptomatic seizures is scarce, and current treatment practices mostly based on expert consensus.

METHODS: Study design: Randomized, controlled, open label, non-inferiority trial. We compared short-term seizure recurrence, developmental delay, readmission rate and mortality between"early" (at or within 7 days of discharge) Vs "late" (one month or later i.e. current protocol) discontinuation of AEDs, among neonates (³ 34 weeks) with acute symptomatic seizures.

RESULTS: Of 246 neonates with seizures during the study period, 31 were excluded initially, and 27 were excluded later. Transient metabolic disturbances (hypocalcemia, dyselectrolytemias etc,) were excluded. Of 188 enrolled neonates, 178 were randomized and were included in final analysis: 86 in 'early discontinuation' group and 92 in 'late discontinuation' group. The commonest causes of seizures were hypoxic-ischemic encephalopathy, hypoglycemic brain injury, and CNS infections. At 4 months, a total of 25 infants (14%) had seizure recurrence: 8 of 86 in 'early discontinuation' group and 17 of 92 in 'late discontinuation' group [9.3% Vs 18.4%; p value: 0.52), and the difference was not statistically significant. Developmental delay (10.4% Vs 17.3%; p=0.68), rates of hospital readmissions (9.3% Vs 5.4%; p=0.19) and mortality (5.3% Vs 1.7%; p=0.29) were similar between the groups.

CONCLUSIONS: Early AED withdrawal is not inferior to late withdrawal in terms of shortterm seizure recurrence, developmental delay, hospital readmission rates and mortality among neonates with acute symptomatic seizures. Given the adverse effects, it is recommended to discontinue anti-epileptic drugs early in neonatal period.

KEYWORDS: Neonatal & Fetal Neurology, Epilepsy

PL60. Effect of therapeutic hypothermia and pattern of injury on neurodevelopmental outcomes at 1-2 years in a prospective cohort of neonatal encephalopathy

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OBJECTIVE: To evaluate the association of therapeutic hypothermia (TH) and magnetic resonance imaging (MRI) findings in term neonatal encephalopathy (NE) with neurodevelopment at 1-2 years.

METHODS: Cross-sectional analysis of neurodevelopment at 30mo (IQR:18.9-31.4) in a prospective cohort of NE imaged with diffusion-weighted MRI 4d (IQR:3-6) after birth (2002-2017). MRI injury pattern was classified as normal, watershed (WS) or basal ganglia/thalamus (BG/T) by a blinded pediatric neuroradiologist. Outcomes were assessed with the Bayley-II (abnormal<70) or Bayley-III (abnormal<85). Descriptive statistics, and multivariable logistic

regression with a propensity score for TH were used to evaluate the association of TH and MRI with outcomes.

RESULTS: Follow-up was available in 308 (71%) children with NE, of whom 150 (49%) received TH. TH-treated children less commonly had abnormal motor (9%-vs-34%, P<0.01) and cognitive (4%-vs-24%, P<0.01) scores. Adjusting for quintiles of treatment propensity, TH was independently associated with decreased odds of abnormal motor (OR 0.21, 95%-CI 0.09-0.45, P<0.01) and cognitive (OR 0.14, 95%-CI 0.05-0.37, P<0.01) outcomes. This association was mildly diminished with adjustment for injury pattern. Abnormal MRI was associated with increased odds of abnormal cognitive (Figure 1a) and motor (Figure 1b) outcomes, with attenuation after adjusting for TH and propensity for TH. TH lowered the sensitivity of abnormal MRI for abnormal motor (33%-vs-91%) and cognitive (67%-vs-95%) outcomes (Figure 2). **CONCLUSIONS:** TH is associated with lower rates of adverse outcomes at 1-2 years after accounting for treatment propensity and injury pattern. TH attenuates the effect of injury on MRI

and normal MRI is less reassuring in the setting of TH. **KEYWORDS:** Neonatal & Fetal Neurology, Neuroimaging Figure 1.



* Adjusted for TH, MRI pattern of injury, and propensity for TH (Apgar<5 at 10 minutes of life, need for intubation at resuscitation (resuscitation score ≥5), pH<7 on initial blood gas, presence of moderate-to-severe encephalopathy (encephalopathy score ≥4), and presence of seizures in the first 24 hours of life)

Figure 2.

Predictive Value of Abnormality on MRI								
	Sensitivity	Specificity	PPV	NPV				
Untreated subjects								
Abnormal cognitive outcome	0.95	0.34	0.32	0.95				
Abnormal motor outcome	0.91	0.43	0.46	0.90				
TH-treated subjects								
Abnormal cognitive outcome	0.67	0.63	0.08	0.98				
Abnormal motor outcome	0.33	0.61	0.08	0.90				

PL61. Placental abnormalities in a large cohort of neonatal hypoxic-ischemic encephalopathy (HIE)

Goodman Amy (San Francisco, CA, United States) Redline Raymond, Comstock Bryan, Juul Sandra, Chang Taeun, Wu Yvonne

OBJECTIVE: Placental histology may provide clues to HIE etiology. We aimed to describe placental histologic findings in neonates enrolled in a multicenter phase 3 trial testing erythropoietin for HIE (HEAL, NCT02811263).

METHODS: Of 500 cooled newborns \geq 36 weeks gestation with moderate/severe HIE, 304 (61%) underwent placental histology. A placental pathologist reviewed reports for acute chorioamnionitis and subacute/chronic lesions. Associations between placental findings and maternal complications were determined.

RESULTS: 186 of 304 (61%) placentas had abnormalities including acute histologic chorioamnionitis only (27%), subacute/chronic lesions only (22%), or both (13%). Subacute/chronic lesions included maternal vascular malperfusion (25%), villitis of unknown etiology (8%), and fetal vascular malperfusion (5%). 13% of patients harbored a high-grade subacute/chronic lesion, a finding associated with lower birthweight (2926±532 vs. 3427±566 g, P<0.001) and smaller head circumference (33.3±1.6 vs. 34.5±1.7 cm, P<0.001). 35% of patients with histologic chorioamnionitis had clinical chorioamnionitis, whereas 84% of clinical chorioamnionitis was accompanied by histologic chorioamnionitis. Histologic chorioamnionitis was higher in vaginal (59% vs. 31%, P<0.001) and primiparous (50% vs. 24%, P<0.001) deliveries. Subacute/chronic placental lesions and histologic chorioamnionitis were higher at ≥41 weeks gestation (28% vs. 11%, P<0.01) and in males (16% vs. 8%, P=0.04). Acute sentinel events were common (37%), both with subacute/chronic lesions (33%) and histologic chorioamnionitis (31%). The majority (59%) of patients with subacute/chronic lesions were exposed to acute sentinel events and/or histologic chorioamnionitis.

CONCLUSIONS: Histologic chorioamnionitis (39%) and maternal vascular malperfusion (25%) were the most common placental abnormalities. Our findings suggest the importance of placental insults occurring at multiple time points in HIE.

KEYWORDS: Neonatal & Fetal Neurology

PL62. Advanced genetic analysis in fetuses and term neonates with idiopathic cerebral hemorrhage

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OBJECTIVE: To investigate the role of rare genetic variants in fetuses and term neonates with cerebral hemorrhage with unidentifiable etiology

METHODS: Twenty-seven cases (10 diagnosed prenatally, 5 underwent termination of pregnancy) of perinatal cerebral hemorrhage with no identified etiology per clinical history, laboratory workup and radiological findings and their parents underwent advanced genetic analysis using whole-exome sequencing. Nonsynonymous rare variants (less than 1% mean allele frequency) in potential candidate genes that encode proteins involved in inflammatory response regulation, coagulation, and vascular integrity were curated

RESULTS: Seventeen patients were diagnosed postnatally (mean age -1.78 days). IVH was the most common hemorrhage type (18 patients, 63%), followed by subpial hemorrhage and parenchymal hemorrhage (4 patients (15%) each). The mean patient's age at the last follow-up was 67 months. only one patient had a recurrent episode of cerebral bleeding. Pathogenic/ likely pathogenic variants were identified in 11 patients (40%) in six genes implicated in inherited bleeding disorders [FBG, FGG (associated with congenital disorders of fibrinogen), ABCG5, ACTN1 (associated with macrothrombocytopenia), GP1BA (associated with heterozygous Bernard Soulier syndrome) VKOC1 (associated with carboxylation of vitamin K–dependent proteins), and in 4 genes associated with extracellular matrix integrity (FN1, VEGFA, COL4A2, COL5A1).

CONCLUSIONS: Advanced genetic analysis in patients with perinatal ICH reveals potential candidate genes associated with genetic bleeding disorders and vessel wall integrity. As none of the patients had abnormal bleeding function tests and the recurrence rate was extremely low, we speculate that complex environmental-genetic interactions in the perinatal period might contribute to the heightened vulnerability to cerebral bleeding.

KEYWORDS: Neonatal & Fetal Neurology, Genetics, Stroke (including other Vascular Disorders)

PL63. Hyperglycemia in term neonatal encephalopathy associated with increased risk for neonatal seizures

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OBJECTIVE: Identify the characteristics of glucose derangements with seizures in neonatal encephalopathy.

METHODS: Prospective cohort study of newborns \geq 36 weeks PMA recruited within 6 hours of life underwent Medtronic iProTM 2 continuous glucose monitoring, therapeutic hypothermia and brain monitoring (aEEG followed by cEEG). Seizures were identified clinically and electrographically. Average interstitial glucose levels every 5 minutes were supplemented with blood levels obtained prior to monitoring. Association between hypoglycemia (\leq 50mg/dL) or hyperglycemia (>144mg/dL) and presence of seizures was compared using logistic regression, adjusting for 5-minute Apgar score and umbilical artery pH.

RESULTS: 25(54%) subjects had hyperglycemia, 21(46%) has hypoglycemia; and 10 (22%) had both. Of 15 subjects with seizures confirmed with monitoring, 10 subjects had clusters of seizures spanning at least 15 minutes, for a total of 15 clusters of seizures within 6 hours apart. The remaining 5 had only brief, single seizures lasting under 10 minutes. Hyperglycemia was associated with 10.5-fold increased odds for monitoring-confirmed seizures (P=0.007). All 10 subjects with prolonged seizure clusters had hyperglycemia. Of the 15 clusters, 7 spanned periods of hyperglycemia, 3 starting before and 4 starting during hyperglycemia. 4 clusters started within 24 hours of hyperglycemia and 4 after that period. Hyperglycemia was not associated with clinical seizures before monitoring (P=0.65). Hypoglycemia was not associated with seizures before (P=0.22) or after (P=0.42) monitor initiation.

CONCLUSIONS: In newborns with therapeutic hypothermia, EEG-confirmed seizures are strongly associated with hyperglycemia. Targeted EEG monitoring of neonates with hyperglycemia may facilitate timely seizure identification and management.

KEYWORDS: Neonatal & Fetal Neurology

NEUROMETABOLIC DISORDERS

PL64. Persistent treatment effect of cerliponase alfa in children with CLN2 disease: A >4 year update from an ongoing multicenter extension study

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OBJECTIVE: An open-label study demonstrated that intracerebroventricular (ICV) infusion of 300 mg cerliponase alfa (rhTPP1 enzyme) every other week for 48 weeks slowed deterioration in motor and language function in children with CLN2 disease. We report additional safety and efficacy data for at least 216 weeks.

METHODS: Subjects who completed the initial study continued receiving 300 mg cerliponase alfa q.o.w. in an extension study. Cumulative data from both studies were used to evaluate long-term safety and efficacy (assessed by changes in the CLN2 clinical rating scale motor and language (ML) domains).

RESULTS: 24 subjects were treated with cerliponase alfa in the open-label study (9 male, 15 female, mean (SD) age 4.3 years (1.24)); 23 enrolled in the extension study and 19 continued on study at time of analysis (≥216 weeks). The most common adverse events (AEs) were URTI, pyrexia and vomiting. Twenty-one (88%) subjects experienced serious AEs including hypersensitivity and device-related infections. Rate of decline in ML score (mean (95% CI): 0.24 (0.16, 0.32) points/48 weeks, p<0.0001) was significantly attenuated compared with a rate of decline of 2.0 points/48 weeks in untreated patients, and has improved since prior analysis at 48 weeks (0.40 points/48 weeks). A Cox proportional hazards model of time to unreversed 2-point decline or score of zero in ML score demonstrated an 8-fold reduction in the likelihood of ML decline compared to untreated patients (hazard ratio, 0.12; 95% CI, 0.05 to 0.29; p<0.0001). **CONCLUSIONS:** Cerliponase alfa has an acceptable safety profile and a sustained treatment effect.

KEYWORDS: Neurometabolic Disorders, Rare Diseases

PL65. Reduction of Rate of Severity Increment in a Cohort of Patients with Niemann-Pick Type C1 (NPC1) Treated Long-Term With Intrathecal Adrabetadex

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OBJECTIVE: To compare pre- and post-treatment rates of severity increment in a large cohort of patients on long-term treatment with intrathecal adrabetadex

METHODS: For each patient in a combined cohort (N=47) from RUMC (expanded access) and NIH (phase 1/2a open label trial) treated for over a year, the Annual Severity Increment Score (ASIS) pre-treatment was calculated by dividing the NPC Neurological Severity Scale (NPC-NSS) score and the 5 Domain Subscale (core NPC features – ambulation, fine motor, cognitive, speech, swallow) scores at baseline by age. Annual rate of progression (increment) after starting treatment was calculated as change in scores divided by length of treatment. Patients with maximal scores in any domain at baseline (N=7) were eliminated from analyses.

RESULTS: The 40 patient analysis cohort had average age 14.1 ± 11 (range 1-44 years), length of treatment 2.9±1.8 (1-6 years), baseline NPC-NSS score 13.4 ± 8 (0-31) and 5-Domain score 8.5±5.1 (0-19). Pre-treatment NPC-NSS ASIS in the cohort was 1.54 ± 1.77 and post- treatment annualized increment 0.8 ± 2.77 5 (p=0.12). Pre-treatment 5 Domain ASIS was 1.11 ± 1.61 and post- treatment annualized increment 0.26 ± 1.42 (p=0.0065). Adjustment for age and/or length of treatment did not alter results.

CONCLUSIONS: Long-term treatment with intrathecal adrabetadex significantly reduced the pre-treatment annual rate of severity increment in a 2-site cohort of patients with NPC1 in the core 5 Domain score, despite the calculated ASIS being a low pre-treatment estimate of rate of decline. New models such as this, comparing trajectories pre- and post-treatment are needed to evaluate novel treatments for rare slowly progressive neurological diseases.

KEYWORDS: Neurometabolic Disorders, Translational/Experimental Therapeutics, Rare Diseases



PL66. Development of the "Hamburg Best Practice Guidelines for intracerebroventricular (ICV)- enzyme replacement therapy (ERT) in CLN2 Disease" based on 5 years treatment experience in 48 patients

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OBJECTIVE: ICV ERT therapy for CLN2 disease represents the first approved treatment for NCL diseases. The mode of administration every other week by ICV infusion via an implanted Rickham device, combined with a 4 hour infusion time, represents a therapeutic challenge due to
the potentially greater risk of infection compared with other intravenously applied ERT. Our objective was to develop best practice guidelines in order to reduce the risk of side effects during treatment.

METHODS: At the beginning, a literature search was carried out and all standard operation procedures (SOPs) at our hospital regarding ERT and the use of intraventricular catheters were evaluated. Multidisciplinary board meetings were conducted. After agreeing on and using the first version of our guideline, we performed regular multidisciplinary board meetings for re-evaluation and improvement of our technique.

RESULTS: The NCL Specialty Clinic (Hamburg, Germany) was the first study site worldwide to perform ICV ERT for CLN2 and has performed more than 3000 ICV s to date. Strictly adhering to our guidelines has led to a very low rate of device-related adverse events (0.35%) and low infection rate (0.36%) compared with the literature (33%) and (27%), respectively. **CONCLUSIONS:** The ICV application is a safe and practical way to deliver ERT if only a small expert group is allowed to access the device and high standards are implemented throughout the procedure, including surgery and puncture. By sharing our internal procedural guidelines, we would like to support and improve standardization and patient safety of ICV ERT for CLN2 disease.

KEYWORDS: Neurometabolic Disorders, Rare Diseases

PL67. Single-dose AAV9-CLN6 gene transfer stabilizes motor and language function in CLN6-type Batten disease: interim results from the first clinical gene therapy trial *de los Reyes Emily (Columbus, OH, United States) Meyer Kathrin, Lehwald Lenora, Albright*

Charles, Rogers David, Castelli Jeff, Jiang Hai, Reha Allen, Barth Jay

OBJECTIVE: To evaluate the interim safety and efficacy of the first clinical gene therapy trial for CLN6-type Batten disease, a fatal neurodegenerative disorder for which there is no treatment. **METHODS:** The ongoing study is an open-label, single-site phase 1/2 trial of adeno-associated virus serotype 9 (AAV9)-mediated *CLN6* gene transfer in children (\geq 1 year) with CLN6-type Batten disease (ClinicalTrials.gov: NCT02725580). Patients received a single intrathecal injection of AAV9-CLN6 into the subarachnoid space. Key efficacy assessments include the Hamburg Motor and Language (HM+L) Score (range: 0-6).

RESULTS: At study entry, 12 patients ranged from 19-79 months of age and had a median (range) HM+L score of 4 (3-6). At data cutoff (July 2019), duration since gene transfer ranged from 8 to 41 months. Most adverse events (AEs) were mild and unrelated to treatment. Nine Grade 3 (severe) AEs (all SAEs) were reported in 4 patients; 4 SAEs were considered possibly related to treatment (vomiting [2], epigastric pain [1], fever [1]; all recovered) and there were no life-threatening AEs or death. Most treated patients with \geq 12-month data demonstrated stabilization in HM+L score (Figure 1) and better scores relative to untreated siblings and natural history patients matched by age and HM+L baseline score. For treated sibling pairs, younger siblings demonstrated better outcome than older siblings.

CONCLUSIONS: Intrathecal administration of AAV9-CLN6 is well tolerated. Efficacy results demonstrate meaningful treatment effect in motor and language function in patients with CLN6-type Batten disease. There may be potential benefit of early intervention of AAV9-CLN6 gene therapy. Updated results will be presented.

KEYWORDS: Neurometabolic Disorders, Rare Diseases, Translational/Experimental Therapeutics

Figure 1. Individual Hamburg Motor and Language Aggregate Score, Motor Subscore, and Language Subscore of AAV9-CLN6 Gene Therapy-treated Patients.



PL68. Increased intracranial pressure in pediatric patients with Spinal Muscular Atrophy receiving nusinersen via lumbar puncture

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OBJECTIVE: Nusinersen is an intrathecally delivered antisense oligonucleotide approved by the FDA for treatment of Spinal Muscular Atrophy (SMA). It is delivered via lumbar puncture in four loading doses followed by maintenance doses every 4 months. Side effects for nusinersen are class specific including thrombocytopenia, coagulopathy, and glomerulonephritis. We noticed increased opening pressures on lumbar puncture and have been trending this phenomenon. Hydrocephalus has since been added to the nusinersen medication insert. **METHODS:** This is a review of patients with SMA receiving nusinersen administration via lumbar puncture in a single tertiary center. Patients underwent lumbar puncture per standard protocol. Opening pressures were obtained in the normal course of the procedure prior to nusinersen administration.

RESULTS: 40 patients have received nusinersen in our program since it was commercially approved. We noticed that some patients had rapid flow of CSF leading to assessment of opening pressure. Monitoring opening pressure has since become standard. 52% of our patients receiving nusinersen via lumbar puncture have increased opening pressure (31-52 cm water.) Onset was 5^{th} to 12^{th} dose. Age range is 2 years to 15 years. There is no correlation between type of SMA (Type 1=1 (4%), Type 2=7 (33%), Type 3=3 (14%)) and increased intracranial pressure. Interestingly, only 2 females (9%) have increased intracranial pressure which is out of proportion

to our female population with SMA (38%).

CONCLUSIONS: Opening pressures need to be monitored in patients receiving nusinersen via lumbar puncture. Consider ophthalmology evaluation and neuroimaging in selected patients. **KEYWORDS:** Neuromuscular Disorders

PL69. Ataluren delays loss of ambulation and decline in pulmonary function in patients with nmDMD

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OBJECTIVE: Duchenne muscular dystrophy (DMD) is a fatal, X-linked disease characterized by progressive muscle weakness. Loss of ambulation (LoA) and decline in lung function are prognostic of mortality. Approximately 10–15% of cases of DMD are caused by a nonsense mutation (nmDMD) in the dystrophin gene. Oral ataluren (10, 10, 20 mg/kg [morning, midday, and evening]) enables the formation of a full-length, functional dystrophin.

This phase 3, ~ long-term safety study enrolled 95 nmDMD patients from prior ataluren clinical trials, and evaluated whether nmDMD patients receiving ataluren + standard of care (SoC: corticosteroid or palliative therapies) had delayed LoA and a slower decline in pulmonary function, compared with matched DMD patients receiving SoC in CINRG DNHS Study (CINRG DNHS; NCT00468832).

METHODS: Propensity score matching (1:1) identified ataluren and CINRG DNHS patients with comparable indicators of disease severity: corticosteroid type and duration of use, and age at first symptoms. Kaplan–Meier analyses estimated the age at LoA and at decline in forced vital capacity (FVC) to <60%- or <50%-predicted or <1L.

RESULTS: Age at LoA was delayed by ~2.5 years in nmDMD patients receiving ataluren vs patients in CINRG DHNS (median 15.5 years vs. 13 years; p=0.0079 [each n=60]; Figure 1a). Ataluren was also associated with delayed decline to %-predicted FVC <60% in non-ambulatory patients by ~2.5 years (median 18.1 years vs. 15.5 years; p=0.0376 [each n=45]; Figure 1b) **CONCLUSIONS:** Ataluren + SoC delay LoA and may reduce pulmonary function decline in nmDMD patients compared with DMD patients receiving SoC.

KEYWORDS: Neuromuscular Disorders, Genetics, Rare Diseases

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Figure 1. Age at **a)** loss of ambulation and **b)** %-predicted FVC < 60% for propensity-score matched patients with nmDMD receiving ataluren plus standard of care in Study 019 vs patients with DMD receiving standard of care in the CINRG DNHS.



Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD, Duchenne muscular dystrophy; FVC, forced vital capacity; nmDMD, nonsense mutation Duchenne muscular dystrophy.

PL70. Onasemnogene Abeparvovec-xioi Gene Therapy for Spinal Muscular Atrophy Type 1 (SMA1): Phase 3 Study Clinical Update (STR1VE-EU)

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OBJECTIVE: Onasemnogene abeparvovec-xioi (formerly AVXS-101), a one-time intravenous adeno-associated virus serotype 9–based gene therapy, addresses the genetic root cause of SMA.

We report preliminary data from the phase 3 STR1VE-EU (2017-000266-29/NCT03461289) study evaluating efficacy and safety of onasemnogene abeparvovec infusion in infants with SMA1.

METHODS: STR1VE-EU is an ongoing, multicenter, open-label, single-arm, single-dose study in patients with SMA1 aged <6 months (biallelic survival motor neuron (*SMN*) 1 mutations, 1–2xSMN2). Outcomes: independent sitting for ≥ 10 seconds throughout 18 months; survival (no death/permanent ventilation) at 14 months.

RESULTS: Enrollment in STR1VE-EU is complete (31 May 2019; N=33, all 2x*SMN2*). Mean age at dosing: 4.1 (1.4–6) months. Mean baseline Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score: 28 (14–55). Mean length of time in study: 4.8 (0.4–9.2) months. At baseline, 9/33 (27%) patients required nutritional support and 7/33 (21%) required ventilatory support. Relative to baseline, mean CHOP INTEND score increased 6.4, 10.6, and 12.3 points at 1, 3, and 5 months post-dosing, respectively. Overall, 32 patients were surviving without permanent ventilation, including 9/10 patients who reached 10.5 months of age or experienced an event. One patient died at age 6.8 months (hypoxic-ischemic brain injury secondary to respiratory tract infection due to SMA). Treatment-related treatment-emergent adverse events were reported in 11 (48%) patients (8 March 2019).

CONCLUSIONS: Interim data from the ongoing STR1VE-EU study show that a single intravenous onasemnogene abeparvovec infusion has therapeutic benefit in patients with SMA1 compared to natural history.

KEYWORDS: Neuromuscular Disorders

PL71. Nusinersen in Infantile-onset Spinal Muscular Atrophy: Results from Longer-term Treatment from the Open-label SHINE Extension Study

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OBJECTIVE: To present interim results from the SHINE open-label extension study (NCT02594124) for participants with infantile-onset SMA who transitioned from previous nusinersen trials.

METHODS: Participants from CS3A, ENDEAR and EMBRACE could transition to SHINE.Following protocol amendment, all receive the Modified Maintenance Dosing Regimen (MMDR; 12mg nusinersen every 4 months). Previous ENDEAR participants initiated MMDR at the end of the SHINE blinded loading dose period or 120 days after last loading dose. CS3A and EMBRACE participants directly entered the MMDR period or if already in SHINE transitioned to MMDR at their next study visit. Endpoints will be assessed from MMDR Day 1. **RESULTS:** 65 participants from the ENDEAR nusinersen-treated and 24 from the shamprocedure group transitioned to SHINE. Based on the 15 October 2018 datacut, 21/59 (36%) participants who received nusinersen in ENDEAR/SHINE achieved the WHO motor milestone sitting without support, 5 (8%) standing with assistance, and 3 (5%) walking with assistance at MMDR Day 1. None of those randomized to sham-procedure in ENDEAR and nusinersen in SHINE (n=22) achieved these milestones. Mean (\pm SD) HFMSE score at MMDR Day 1 was 7.3 (6.82) for the nusinersen in ENDEAR/SHINE group (n=50) and 0 for the sham-procedure in ENDEAR/nusinersen in SHINE group (n=17). Data from the 2019 SHINE datacut for this cohort

and participants who transitioned from the CS3A and EMBRACE studies, and updated safety data, will be presented.

CONCLUSIONS: Continued analysis of SHINE study data will increase the information available on the long-term safety/tolerability and efficacy of repeated nusinersen doses in patients with infantile-onset SMA.

KEYWORDS: Neuromuscular Disorders

PL72. Nusinersen in advanced-stage patients with spinal muscular atrophy type1. Kotulska Katarzyna (Warsaw, Poland) Chmielewski Dariusz, Tomaszek Katarzyna, Pierzchlewicz Katarzyna

OBJECTIVE: Nusinersen has been approved for spinal muscular atrophy (SMA1) treatment regardless of the disease type, severity of symptoms and age of the patients. In the clinical trials in SMA1, only infants below 6 months of age were included and the efficacy of treatment of more severely affected SMA1 patients is not clear. The aim of this study was to analyze the safety and efficacy of nusinersen treatment in older or more severely affected children with SMA1.

METHODS: Eligibility criteria included: definite SMA1 diagnosis, at least one year of nusinersen treatment, age>3 years or CHOP-INTEND <15 points at treatment onset. The clinical data, including survival, respiratory, feeding, and motor functions of the patients were evaluated. **RESULTS:** Of 70 patients who received nusinersen in our hospital, 21 met the eligibility criteria (3 patients were younger than 3 years of age but had baseline CHOP-INTEND score of 2-13

points, and 18 patients were older than 3 years). Mean baseline CHOP-INTEND score was 19. 9 patients had tracheostomy, 5 had non-invasive ventilation and 10 had gastrostomy. No patient died or required new ventilation support during the study. After one year of treatment, 20 (95%) patients improved in CHOP-INTEND (mean improvement: 7 points), and 1 patient remained stable.

CONCLUSIONS: Our findings indicate that nusinersen treatment improves the functional status of SMA1 patienst even in the more advanced stages of the disease. **KEYWORDS:** Neuromuscular Disorders

PL73. One-Time Administration of AVXS-101 IT for Spinal Muscular Atrophy: Phase 1/2 Study (STRONG)

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OBJECTIVE: AVXS-101 intrathecal (IT) addresses the genetic root cause of spinal muscular atrophy (SMA), biallelic survival motor neuron 1 gene (*SMN1*) deletion/mutation. STRONG is a phase 1/2 study (NCT03381729) that assessed the safety/tolerability, optimal dose, and efficacy of AVXS-101 IT.

METHODS: Patients (biallelic *SMN1* loss, 3xSMN2) aged $\geq 6-<60$ months who could sit but not stand/walk received a single, one-time AVXS-101 IT dose (dose A: 6.0x10e13; B: 1.2x10e14; C: 2.4x10e14 vg). Primary endpoints: safety/tolerability, optimal dose, unsupported standing of ≥ 3 seconds ($\geq 6-<24$ months), and change in baseline Hammersmith Functional Motor Scale Expanded (HFMSE) score from baseline ($\geq 24-<60$ months) at 12 months post-dose.

RESULTS: As of 31 May 2019, 31 patients were enrolled (dose A, complete: n=3; dose B, complete: n=25; dose C: n=3). As of 8 March 2019 (30 patients), no fatal treatment-emergent adverse events (TEAEs) have occurred; 7 serious TEAEs occurred in 4 patients. HFMSE increased a mean 5.9 points from baseline at most recent visit in patients aged \geq 24–<60 months (mean [range] duration of follow-up, 9.3 [7.2–11.9] months). Eighteen motor milestones were gained following treatment in 7/16 (44%) patients aged \geq 6–<24 months (doses A and B), including 2 who stood independently. In patients aged \geq 24–<60 months (dose B), 3/12 (25%) gained motor milestones following treatment. End of study data from dose A and B will be presented.

CONCLUSIONS: Interim data from the ongoing STRONG study demonstrate improvements in motor milestones and functional achievements in sitting but non-ambulatory SMA patients. **KEYWORDS:** Neuromuscular Disorders

PL74. Longer-term Nusinersen Treatment According to Age at First Dose: Results From the SHINE Study in Later-onset Spinal Muscular Atrophy (SMA)

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OBJECTIVE: To assess motor function with longer-term nusinersen treatment by age at first dose in children with later-onset SMA.

METHODS: SHINE (NCT02594124) is an open-label extension study for participants who completed previous nusinersen trials. These analyses focus on participants with later-onset SMA who received nusinersen or sham procedure in CHERISH (NCT02292537) and transitioned to SHINE. Following a protocol amendment, all participants receive nusinersen 12mg maintenance doses every 4 months in SHINE. Motor function data (15 October 2018 interim analysis) were analyzed in three groups by age at first nusinersen dose ($\geq 2.0-<3.5$ years[n=35]; $\geq 3.5-<5.0$ years[n=41]; $\geq 5.0-<9.5$ years[n=34]) in participants reassessed for CHERISH inclusion criteria with a value windowed to Day 690 regardless of treatment group.

RESULTS: At SHINE Day 690, mean[SD] change in HFMSE total score from baseline improved in those youngest at first dose (+8.9[5.7]), improved then stabilized in those of intermediate age (+3.1[4.3]), and stabilized in children who were older at first dose (-2.1[4.2]). Mean (SD) change from baseline to Day 690 in RULM total score also improved over time in those who were youngest (+8.0[5.1]) or of intermediate age (+3.6[3.3]) at first dose, and was stable in those older at first dose (+0.5[2.9]). The youngest participants at first dose achieved the most gains in WHO motor milestones. Data from the 2019 SHINE interim analysis for these participants and those who transitioned from CS2/12 and EMBRACE will be presented. **CONCLUSIONS:** Among individuals with later-onset SMA, the youngest participants at first nusinersen dose showed the greatest improvement in motor function.

KEYWORDS: Neuromuscular Disorders

PL75. Pulmonary function in non-ambulatory patients with nmDMD: Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry and CINRG DNHS matched cohort analysis

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OBJECTIVE: STRIDE (is an ongoing, multicentre, observational registry providing data on ataluren use in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) in clinical practice. We examined whether patients with nmDMD receiving ataluren+standard of care (SoC; corticosteroid or palliative therapies), who were non-ambulatory by their last assessment, experienced a lesser decline in pulmonary function vs matched patients with DMD receiving SoC alone (Cooperative International Neuromuscular Research Group Duchenne Natural History Study [CINRG DNHS]). Data cut-off was 31 January 2019.

METHODS: Propensity score matching was performed to identify non-ambulatory patients with nmDMD from STRIDE and the CINRG DNHS with comparable predictors of disease progression: age at first symptoms; age at first corticosteroid use, and duration of deflazacort or other corticosteroid use. Kaplan–Meier analyses estimated age at loss of ambulation (LOA) and age at pulmonary function decline.

RESULTS: Median age at LOA (95% confidence interval [CI]) for the matched STRIDE vs CINRG DNHS cohorts (each n=22) was 12.4 (10.7,12.9) years vs 11.1 (10.0,12.5) years. Mean (95% CI) ataluren exposure for patients in STRIDE up to LOA was 302 (163,440) days. Median (95% CI) age at which patients reached %-predicted forced vital capacity (FVC) <60% (each n=22) was delayed for patients from STRIDE vs the CINRG DNHS (18.7 [17.7,18.7] years vs 15.6 [13.2,16.7] years). Mean (95% CI) ataluren exposure for patients in STRIDE up to %-predicted FVC <60% was 661 (495,826) days.

CONCLUSIONS: These data suggest that ataluren plus SoC treatment slows pulmonary disease progression in non-ambulatory patients with nmDMD.

KEYWORDS: Neuromuscular Disorders, Rare Diseases, Genetics

Figure 1. Age at predicted FVC < 60% for propensity-score matched non-ambulatory patients from the STRIDE Registry and CINRG DNHS.

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CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

PL76. Beyond the Muscle: The Expanding Mutational and Phenotypic Spectrum of Disease Due to Mutations in the MICU1 gene (mitochondrial calcium uptake 1)

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OBJECTIVE: To describe the phenotypic spectrum, molecular and biochemical characteristics of patients with mutations in MICU1.

METHODS: We identified 25 children with a primary muscle phenotype with mutations in MICU1. Data collected retrospectively included demographics, muscle phenotype, presence of a movement disorder, biochemical, radiological and other features.

RESULTS: Onset of features ranged from infancy to 8 years. A history of motor delay and proximal weakness was present in 21 patients. A degree of mild to moderate learning difficulties was present in all patients. A prominent movement disorder characterised by choreiform movements in around half of the patients with some having facial dyskinesia's. 6 patients had a history of episodic ataxia. 15 had relative short stature and 4 had distinct dysmorphic features. Almost all patients had raised creatine kinases (CK) with a mean of 2600iu/l(range 300-12900). The commonest mutation was a biallelic *c.1078-1G*>*C* most prevalent in those of South Asian ethnicity in 14 patients.

The majority had a static or slowly progressive course, with a small number demonstrating improvement in muscle strength over time (GMFCS I=10,II=14,III=1). Stroke-like episodes where noted in two patients with subsequent resolution of symptoms. Muscle biopsy findings were available for around half of the patients included dystrophic changes, regenerative fibres and myopathic changes.

CONCLUSIONS: Mutations in MICU1 present with distinct phenotypes presenting in the first few years of life with motor delay, a raised CK with varying degrees of proximal weakness. It should be suspected in such children who may also manifest with an evolving movement disorder and episodic ataxia.

KEYWORDS: Neuromuscular Disorders, Movement Disorders (including Cerebral Palsy), Genetics

PL77. Onasemnogene Abeparvovec-xioi Gene Therapy in Presymptomatic Spinal Muscular Atrophy: SPR1NT Study Update

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OBJECTIVE: Spinal muscular atrophy (SMA) is caused by biallelic survival motor neuron 1 gene (*SMN1*) deletions/mutations. Copies of *SMN2* modify disease severity. SPR1NT (NCT03505099) evaluates safety/efficacy of onasemnogene abeparvovec-xioi (formerly AVXS-101) in presymptomatic SMA patients.

METHODS: SPR1NT is a multicenter, open-label, phase 3 study. Asymptomatic patients with genetically confirmed SMA (2–3x*SMN2*, \leq 6 weeks) receive a one-time intravenous onasemnogene abeparvovec infusion and are assessed through 18/24 (2x*SMN2*/3x*SMN2*) months. Primary outcomes: sitting \geq 30 seconds/standing unassisted (2x*SMN2*/3x*SMN2*). Exploratory outcomes: Children's Hospital of Philadelphia Infants Test of Neuromuscular Disease (CHOP INTEND).

RESULTS: As of 31 May 2019, 23 infants were dosed (8–43 days of age [mean: 24.7]; 2xSMN2/3xSMN2/4xSMN2, n=10/12/1). All patients are alive and none required ventilatory support as of last visit. Among 2xSMN2 patients, 7 achieved a full/near-full CHOP INTEND score of 60–64; 6 achieved sitting (all within the WHO 1st–99th percentile range [3.9–9.2 months]); 3 achieved standing with assistance (mean [range]: 10.1 [8.8–12.3] months). Among 3xSMN2 patients, 2 sat (6.3–9.0 months); 1 crawled/stood with assistance (9.0 months). No patient is delayed in standing alone or independent sitting. All patients (2x–3xSMN2) with a 6month evaluation (12/12) had normal swallowing. As of 8 March 2019, 13/18 patients experienced ≥ 1 treatment-emergent adverse event (TEAE); treatment-related TEAEs were reported in 7/18 patients; 4/18 patients experienced TEAEs of special interest. **CONCLUSIONS:** Data show improvements in presymptomatic SMA patients dosed with onasemnogene abeparvovec vs SMA type 1 natural history, underscoring the importance of early

treatment. Updated data will be presented.

KEYWORDS: Neuromuscular Disorders

PL78. Nusinersen Effect in Infants Who Initiate Treatment in a Presymptomatic Stage of SMA: NURTURE Results

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OBJECTIVE: Present interim results from the ongoing NURTURE study (NCT02386553) examining the efficacy and safety of intrathecal nusinersen initiated in presymptomatic infants with 2 or 3 *SMN2* copies.

METHODS: Enrolled infants were ≤ 6 weeks at first dose, clinically presymptomatic, and genetically diagnosed with SMA. The primary endpoint is time to death or respiratory intervention (≥ 6 hours/day continuously for ≥ 7 days or tracheostomy).

RESULTS: NURTURE has enrolled 25 infants (2 *SMN2*, n=15; 3 *SMN2*, n=10). As of 29 March 2019, the median age at last visit was 34.8 (range 25.7–45.4) months. All infants were alive and none required permanent ventilation. Four infants (all with 2 *SMN2* copies) required respiratory intervention over the course of the study, with all cases initiated during an acute reversible illness. Median time to death or respiratory intervention could not be estimated because of too few events. All 25 infants achieved the WHO motor milestone of sitting without support, 23/25 (92%) achieved walking with assistance, and 22/25 (88%) were walking alone. Most children achieved these motor milestones (21/25 [84%] sitting without support, 15/23 [65%] walking with assistance, and 16/22 [73%] independent walking) within the 99th percentile age window established by the WHO for healthy children. Nearly all children reached the maximum score on the CHOP INTEND scale. No new safety concerns were identified. Results from a new, Spring 2020 interim analysis will be presented.

CONCLUSIONS: These data demonstrate the continued benefit to infants who initiated nusinersen before symptom onset, emphasizing the value of newborn screening and early treatment.

KEYWORDS: Neuromuscular Disorders

PL79. Long-Term Follow-Up of Onasemnogene Abeparvovec-xioi Gene Therapy in Spinal Muscular Atrophy Type 1 (SMA1)

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OBJECTIVE: Onasemnogene abeparvovec-xioi (formerly AVXS-101), a one-time intravenous adeno-associated virus serotype 9–based gene therapy, is designed to address the genetic root cause of SMA1. In the phase 1 trial (START; NCT02122952), SMA1 patients who received a high-dose onasemnogene abeparvovec infusion (Cohort 2, n=12) demonstrated significantly improved outcomes versus untreated natural history. Here, we evaluate long-term safety and efficacy of onasemnogene abeparvovec in patients previously treated in START Cohort 2.

METHODS: START patients could electively enroll into a long-term follow-up study (LT001, NCT03421977). Primary objective: long-term safety. Patients have annual visits (5 years) followed by annual phone contact (additional 10 years). Assessments include medical history and record review, physical examination, clinical laboratory evaluation, pulmonary assessments, and evaluation of developmental milestone maintenance.

RESULTS: Thirteen patients (Cohort 1, n=3; Cohort 2, n=10) enrolled (31 May 2019). All Cohort 2 patients have survived and are free of permanent ventilation (mean [range] age at last Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020

follow-up: 4.2 [3.7–5.0] years; mean [range] time since dosing: 3.9 [3.5–4.6] years). No developmental milestones were lost; 2 patients have newly achieved standing with assistance. Of the 10 enrolled Cohort 2 patients, 6 require no regular, daily respiratory support and 7 are not receiving concomitant SMN2 upregulating therapy. As of 8 March 2019, no new treatment-related serious adverse events occurred.

CONCLUSIONS: Data from LT001 continue to suggest that one-time intravenous administration of high-dose onasemnogene abeparvovec demonstrates durable efficacy with new milestone development in START patients. Updated data will be presented. **KEYWORDS:** Neuromuscular Disorders

PL80. Georgia state SMA newborn screening (NBS) pilot: clinical outcomes and way forward

Elkins Kathryn (Atlanta, GA, United States) Bhalla Sonam, Wittenauer Angela, Phan Han, Sekul Elizabeth, Wilcox William, Verma Sumit

OBJECTIVE: Clinical, functional, electrophysiological outcomes among SMA newborn screen (NBS) positive infants

METHODS: Pilot testing for SMA was added to Georgia NBS in 2019. Infants screened positive for SMA on NBS had confirmatory testing which determined the number of SMN2 copies for each patient. Retrospective review of the electronic medical records performed for baseline and follow-up neuromuscular examination, CHOP-INTEND results, EMG/NCS data, and outcomes. Descriptive statistics used.

RESULTS: Nine SMA NBS positive babies identified between February 2019 to January 2020. SMN2 copy numbers as follows: 22% (n=2) 1 copy, 33% (n=3) 2 copies, 33% (n=3) 3 copies, and 11% (n=1) 4 copies. Mean time of positive NBS since birth was 4.6 days, confirmatory testing from positive NBS was 4.8 days. Two subjects admitted to NICU and remainder seen in clinic at an average age of 36.3 days (Table 1). On examination, 56% (n=5)

were *symptomatic* and remaining 44% (n=4) were *pre-symptomatic*. CHOP-INTEND scores and motor CMAPs from EMG/NCS were available in 66% (n=6) and 33% (n=3) of subjects, respectively. In the *symptomatic* group 80% (n=4) of patients died and did not receive intervention; 20% (n=1) received AAV9 SMN gene therapy and is alive and improving. In *pre-symptomatic* group 20% (n=1) received gene therapy (Table 2). None of the subjects received intrathecal nusinersen.

CONCLUSIONS: Early genetic confirmation, improved neurology clinic access, availability of SMA therapeutic programs and patient education in *symptomatic* infants may decrease mortality. Further long-term follow-up studies are needed to understand the success and challenges of SMA NBS.

KEYWORDS: Neuromuscular Disorders, Genetics

Table 1: Timeline of subjects with SMA newborn screen (NBS) positive results.

Subject number	SMN2 copy number	Age of positive NBS report (days)	Age when confirmatory testing collected (days)	Age at time of neurologic examination (days)
1*	1			**
2	3	5	8	36
3	2	4	10	33

4	2	3	22***	34
5	3	5	6	45
6	3	5	6	45
7	4	6	11	39
8	2	5	8	22
9	1	4	4	**

Mean age at time of positive NBS reporting was 4.6 days (range 3-6 days).

Mean age when confirmatory testing sent was 9.4 days (range 4-22 days), which indicates mean time between NBS reporting and confirmatory testing was 4.8 days.

Two subjects (1 and 9) were admitted to NICU and remaining seen in neurology clinic at an average age of 36.3 days.

* Ages for when NBS and confirmatory testing resulted for subject 1 are unknown.

**Subjects 1 and 9 were hospitalized in NICU after birth and both died after family decided to withdraw care.

***Delay in time between NBS report and confirmatory testing for subject 4 attributed to family initially not wanting confirmatory testing.

PL81. Intravenous (IV) Onasemnogene Abeparvovec-xioi Clinical Development Programs in Spinal Muscular Atrophy (SMA): Integrated Safety Report

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OBJECTIVE: To describe the safety of IV onasemnogene abeparvovec-xioi in spinal muscular atrophy patients across 4 clinical trials.

METHODS: Symptomatic or presymptomatic SMA patients (biallelic *SMN1* mutations, 2–4X*SMN2*) received a single IV onasemnogene abeparvovec infusion. Adverse events (AEs) were assessed per CTCAE and monitored/reported in accordance with study protocols.

RESULTS: Seventy-five patients received the therapeutic dose (1.1e14 vg/kg) of IV onasemnogene abeparvovec (8 March 2019). Mean age at dosing: 2.5 (0.3–7.9) months. Mean weight: 5.3 (3.0-8.4) kg. One patient, aged 7.8 months, died of respiratory arrest 5.7 months post-dosing (deemed unrelated to treatment). One patient, aged 6.8 months, died of hypoxicischemic brain injury secondary to respiratory tract infection due to SMA.Sixty-four (85%) patients reported ≥ 1 AE; 33 (44%) patients had ≥ 1 treatment-related AE; 29 (39%) patients had \geq 1 serious AE. Vomiting and pyrexia were reported as treatment-emergent AEs at rates >5% in the clinical development program (considered treatment-related). Pyrexia was reported in 30 (40%) patients (9 patients ≤ 1 week after dosing) and was considered treatment-related in 4 (5%) patients. Increased liver transaminase (>upper limit of normal) were observed in 8 (11%) patients (considered treatment-related, clinically asymptomatic, and generally resolved with prednisolone). Transient thrombocytopenia was reported, without clinically significant bleeding or bruising. There is no evidence of cardiac safety findings of concern associated with onasemnogene abeparvovec. Updated safety data (31 Dec 2020 datacut) will be presented. **CONCLUSIONS:** IV onasemnogene abeparvovec treatment maintains an overall favorable safety profile and monitoring continues across multiple settings.

KEYWORDS: Neuromuscular Disorders

PL82. Edasalonexent Treatment in Young Boys with Duchenne Muscular Dystrophy is Associated with Age-Normative Growth and Normal Adrenal Function

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OBJECTIVE: Edasalonexent is being investigated as a potential foundational therapy for DMD patients regardless of mutation. Edasalonexent was designed to inhibit NF- κ B and does not impact the glucocorticoid receptor. The MoveDMD Phase 2 trial was designed to assess efficacy and long-term safety in 31 steroid-naïve 4-7 year-old boys (<8th birthday) with DMD treated with edasalonexent for up to 150 weeks.

METHODS: Efficacy evaluations included muscle function and MRI assessments. Safety measures included assessments of growth and impact on adrenal function (ACTH and cortisol). Fractures were recorded as part of safety monitoring.

RESULTS: Edasalonexent was well-tolerated. Diarrhea was the most common treatment-related AE, generally mild and transient, and there were no serious AEs on edasalonexent. There was no evidence of adrenal insufficiency with no clinically significant changes in either cortisol or ACTH. In over 60 patient-years of exposure, two fractures were reported (radius and metatarsal), none with minimal trauma. Height increased along expected growth curves for unaffected boys and weight increase resulted in overall normalized BMIs. Efficacy evaluations showed slowing of disease progression compared to an off-treatment control period.

CONCLUSIONS: In this trial, edasalonexent was well tolerated and associated with favorable growth patterns without negative impact on bone health or adrenal function. Edasalonexent has the potential to be disease-modifying in DMD patients and in this Phase 2 trial did not demonstrate adverse effects associated with high-dose steroids. An ongoing, fully enrolled Phase 3 trial of edasalonexent, PolarisDMD, is further assessing safety and efficacy in young boys with DMD.

KEYWORDS: Neuromuscular Disorders, Rare Diseases

PL83. Systemic Gene Transfer with rAAVrh74.MHCK7.SGCB Increased β-sarcoglycan Expression in Patients with Limb Girdle Muscular Dystrophy Type 2E (LGMD2E)

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OBJECTIVE: We present findings of a phase 1 multiple ascending-dose gene transfer trial of \leq 9 LGMD2E patients (β -sarcoglycan [SGCB] deficiency) who received rAAVrh74.MHCK7.SGCB (NCT03652259).

METHODS: Participants age 4-15y, SGCB mutation (both alleles), no rAAVrh74 antibodies, >40% on 100-meter timed test (100m). Cohort 1 (n=3): single IV infusion of $5x10^{13}$ vg/kg rAAVrh74.MHCK7.SGCB. All patients: prednisone 1 mg/kg/day initiated 1d before gene delivery (30-d taper). Primary endpoints: \geq 20% SGCB-positive fibers (Day-60 muscle biopsy); safety. Secondary endpoints: CK decrease; functional endpoints (1-y).

RESULTS: For 3 patients in Cohort 1 (age 13, n=2; age 4, n=1), robust SGCB expression observed by immunohistochemistry: mean 51% SGCB positive fibers (range 42-63%) expressing mean 47% intensity (38-57%). Co-localization of α -sarcoglycan observed. Western blot showed

mean 36.1% SGCB expression vs normal (34.5-39.2%). Mean CK levels at 1 year reduced from baseline by 72%, suggesting slowed muscle destruction. All patients showed improvements in functional measures from baseline (NSAD, Time-to-rise, 4-stair climb, 100m, 10m walk run); mean change from baseline in NSAD at 1 year of 5.7 points. As of Jan 15, 2020, 2 patients had elevated liver enzymes, 1 with transient increase in bilirubin and related SAE of liver inflammation after steroid taper, which returned to normal limits within 30d. One patient experienced vomiting (no correlation with liver enzyme elevations/other abnormality). No other clinically significant lab findings. Cohort 2 (n=3) received single IV infusion of $2x10^{14}$ vg/kg. **CONCLUSIONS:** Efficient skeletal muscle transduction and robust β -sarcoglycan protein expression post-infusion with rAAVrh74.MHCK7.SGCB resulted in CK reductions and functional improvements, suggesting improvement against disease-mediated muscle damage. **KEYWORDS:** Neuromuscular Disorders, Genetics, Rare Diseases

PL84. Systemic Gene Transfer with rAAVrh74.MHCK7.micro-dystrophin in Patients with Duchenne Muscular Dystrophy

Mendell Jerry (Columbus, OH, United States) Sahenk Zarife, Lehman Kelly, Nease Carrie, Lowes Linda, Miller Natalie, Iammarino Megan, Lewis Sarah, Church Kathleen, Shell Richard, Potter Rachael, Griffin Danielle, Pozsgai Eric, Hogan Mark, Rodino-Klapac Louise

OBJECTIVE: Gene transfer therapy is promising for Duchenne muscular dystrophy (DMD). We designed an adeno-associated virus vector (rAAVrh74) containing codon-optimized human micro-dystrophin transgene driven by muscle-cardiac specific promoter, MHCK7. Findings from 4 patients in our open-labeled, single-dose, Phase I/IIa trial (NCT03375164) are presented.

METHODS: Ambulatory boys (4-7y) with confirmed *DMD* mutations, creatine kinase (CK) >1,000 U/L, \leq 80% predicted 100-meter timed test (100m), no AAVrh74 antibodies, and stable steroid dosing (\geq 3 mo) received IV 2.0x10¹⁴ vg/kg rAAVrh74.MHCK7.micro-dystrophin. Prednisone (1 mg/kg/d) was initiated 1d before gene delivery, tapering after 30d. Primary endpoint: safety. Secondary and exploratory endpoints: micro-dystrophin expression by western blot (WB) and immunohistochemistry (IHC); functional outcomes by North Star Ambulatory Assessment (NSAA), 100m, Time-to-Rise, 4-Stair Climb; and CK.

RESULTS: No serious adverse events observed by serum chemistry. Three patients had transiently elevated gamma-glutamyl transpeptidase (resolved with steroids). No adverse immune responses observed. Robust transgene expression observed in all: mean 81.2% muscle fibers expressing micro-dystrophin (mean intensity 96% at the sarcolemma by IHC). WB showed mean micro-dystrophin expression of 74.3% without fat/fibrosis adjustment and 95.8% when adjusted (Day 90). All patients had confirmed vector transduction and robust CK reductions (mean change from baseline to 1y: -67.3%). Motor function improved in all, with increased ambulatory function (100m), increased muscle strength (Time to Rise, 4-Stair Climb), and overall motor abilities (NSAA). All 4 patients had clinically meaningful improvement on NSAA as early as Day 90.

CONCLUSIONS: rAAVrh74.MHCK7.micro-dystrophin infusion was well-tolerated, demonstrating successful systemic micro-dystrophin transgene delivery and targeted expression of functional micro-dystrophin protein.

KEYWORDS: Neuromuscular Disorders, Genetics, Rare Diseases

NEUROREHABILITATION

PL85. Development and Evaluation of a low-cost working memory intervention kit for cognitive deficits in children with epilepsy: a pilot study

Anand Aakanksha (New Delhi, India) Sharma Suvasini, Mukherjee Sharmila OBJECTIVE: To develop an indigenous working memory intervention using a mobile-based application and activity booklet with simple play materials to improve the working memory deficits in children with epilepsy.

METHODS: In Phase I, the intervention was developed. Fifteen children aged 6-15 years with idiopathic generalized epilepsy and IQ > 70 were enrolled in Phase II. They underwent baseline cognitive evaluation using Working memory index from Weschlers Intelligence Scale -IV for Children, Color cancellation task and Parent's rating from the Conners' ADHD/DSM-IV Scale. Seguin Form Board Test and Malin's Intelligence Scale for Indian Children were used for IQ Assessment. The children underwent working memory intervention under the supervision of the psychologist. At the end of 8 weeks the scores of above mentioned on tests were evaluated. **RESULTS:** There was a statistically significant improvement in all the working memory parameters: digit span forward (baseline median 3 (IQR 2-5) to 6 (IQR 4-7); p<0.01),letter number sequencing (baseline median 9 (IQR 5-10) to 12 (IQR 7-13);arithmetic (from baseline median 4 (IQR 4-7) to 6 (4-9).

CONCLUSIONS: In conclusion, we developed a low-cost working memory intervention kit, using a combination of mobile-based application and activity based booklet with simple play materials (with bilingual instructions in Hindi and English) to help improve working memory deficits in children with epilepsy. This was found to be feasible and efficacious in improving working memory deficits in a pilot study. This intervention now needs to be tested in a randomized controlled trial in children with epilepsy to confirm the efficacy. **KEYWORDS:** Neurorehabilitation, Epilepsy

PL86. Efficacy of abobotulinumtoxinA in reducing upper-limb spasticity in children with cerebral palsy: Results from a Phase 3, pivotal study

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OBJECTIVE: Assess the reduction in upper-limb spasticity following abobotulinumtoxinA injections in children with cerebral palsy (CP).

METHODS: Double-blind, repeat-treatment (≤ 4 cycles over 1y) study (NCT02106351). Children (2-17y) with spasticity in ≥ 1 upper-limb were randomized (1:1:1) to Cycle-1 injections of abobotulinumtoxinA 8U/kg, 16U/kg or 2U/kg (control) into the primary target muscle group (PTMG; elbow or wrist flexors). The PTMG could change in cycles 2-4, when children received 8U/kg or 16U/kg.

RESULTS: 212 children were randomized and 180 completed the study. Changes in the Modified Ashworth Scale (MAS) of the PTMG from Baseline to Cycle-1/Wk6 (primary-endpoint) were significantly different for the 8U/kg and 16U/kg abobotulinumtoxinA groups versus 2U/kg control (mean reductions from baseline of -2.0 and -2.3 vs. -1.6, respectively) and statistical difference was maintained at Wk16. All three groups showed improvement from Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020

baseline in Tardieu Scale parameters in the PTMG. For PTMG elbow flexors, significant improvements ($p\leq0.05$) for the 8U/kg and 16U/kg dose groups versus the 2U/kg control group were seen at Wk6 for the angle of catch (X_{V3}) and spasticity angle (X). For PTMG wrist flexors, the 16U/kg dose (but not the 8U/kg dose) was significantly superior (p<0.001) to the 2U/kg dose at Wk6 in X_{V3} and X. Benefits were sustained over one year with repeat abobotulinumtoxinA injections (8U/kg or 16U/kg).

CONCLUSIONS: AbobotulinumtoxinA administered at doses of 8U/kg or 16U/kg in the upperlimb significantly reduced spasticity compared to the 2U/kg control dose. Therapeutic benefits were sustained with repeat injections of 8U/kg or 16U/kg over one year.

KEYWORDS: Neurorehabilitation, Movement Disorders (including Cerebral Palsy)

NEUROSCIENCE

PL87. Dysfunction of D2 dopamine receptor neurons underlies select manic-like behaviors in SHANK3 overexpressing mice

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OBJECTIVE: We previously described the *SHANK3* duplication syndrome and reported mice modeling this disorder have multiple behavioral abnormalities including hyperactivity and accentuated amphetamine induced hyperactivity (AIH). SHANK3 is a scaffolding protein in the post-synaptic density of excitatory synapses. *Our objective was to discover the abnormal behaviors mediated by dysfunction of the striatum.*

METHODS: Measurements of synaptic activity were determined in *Shank3* overexpressing mice (*Shank3* TG mice). *Shank3* TG mice were treated with two novel D2 dopamine receptor (D2dr) antagonists developed as potential anti-psychotics. To further explore the necessity of Shank3 overexpression in these neurons for hyperactivity phenotypes, we created mice with a floxed *Shank3*TG allele (conditional rescue mice). These mice were crossed with mice expressing Cre recombinase only in D2 dopamine receptor neurons to normalize *Shank3* expression.

RESULTS: Frequency of miniature excitatory post-synaptic currents (mEPSCs) was significantly elevated in medium spiny neurons of the striatum in *Shank3* TG mice while amplitude was unchanged. Furthermore, only D2dr positive neurons have elevated mEPSC frequency while D1 dopamine receptor neurons are normal. Sub-acute treatment of *Shank3* TG mice with D2dr antagonists rescued hyperactivity and accentuated AIH while other abnormal behaviors are unchanged. Similarly, normalization of Shank3 abundance in D2 dopamine receptor neurons rescued baseline hyperactivity as well as accentuated AIH without altering other behaviors.

CONCLUSIONS: Together these data demonstrate that dysfunction of D2dr neurons in *Shank3* TG mice contributes to their baseline hyperactivity as well as accentuated AIH. These data also suggest a potential personalized therapy for individuals with genomic duplications involving *SHANK3*.

KEYWORDS: Neuroscience, Cognitive/Behavioral Disorders (including Autism), Genetics

RARE DISEASES

PL88. The natural history of fatty acid hydroxylase-associated neurodegeneration (FAHN).

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OBJECTIVE: Fatty Acid Hydroxylase-Associated Neurodegeneration (FAHN) is an autosomal recessive childhood onset complex spastic-ataxic neurodegenerative disorder. A subset of patients demonstrate brain iron accumulation or leukodystrophy on neuroimaging. The detailed natural history of FAHN is unknown.

METHODS: Patients with a genetic confirmation of FAHN were recruited via patient-led family organizations, and international collaborators.

When possible, patients were seen in clinic or via video for interview and examination. All other patients were entered into a standardized clinical reporting form by the collaborating neurologist/geneticist.

RESULTS: Our study cohort included 30 new patients and updated information from 6 previously reported patients. All children were initially developmentally normal. Motor regression was the initial symptom in all patients, affecting lower extremities first, at an average age of 4.7 (SD 3.4). This was followed by dysarthria in 28 (82%), at an average age of 7.3 (SD 3.1), dysphagia in 26 (77%), at an average age of 13.8 (SD 8.4), and cerebellar involvement in 26 (81%), at an average age of 6.9 (NA). Patients were non-ambulatory by the median age of 6.8 (95%CI 4.0 - 8.3). (Figure 1). No extra-CNS symptoms were present in our patient cohort.

CONCLUSIONS: FAHN is complex spastic-ataxic syndrome with relentless motor degeneration with accompanying dysarthria, dysphagia, dystonia and cerebellar involvement. Understanding this natural history is paramount to allow for disease modifying therapies to be accurately and safely introduced. Further research is underway to follow the natural history prospectively and look for potential imaging and biochemical biomarkers.

KEYWORDS: Rare Diseases, Movement Disorders (including Cerebral Palsy), Genetics Figure 1. Unadjusted Kaplan-Meier curves (with 95%CI) of time to aid/walker and wheelchair use

CEPTER



PL89. Efficacy and safety of arimoclomol in patients with Niemann Pick Type C: Results from a double-blind, randomised placebo-controlled trial with a novel treatment

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OBJECTIVE: Niemann Pick Type C (NPC) is a rare, relentlessly progressive neurological disease with underlying mutated NPC protein and lysosomal dysfunction. Most patients debut in childhood with early fatal outcome. To assess efficacy and safety, a 12-months multi-national, double-blind, randomised, placebo-controlled trial with the heat shock protein (HSP) amplifier, arimoclomol, was conducted.

METHODS: NPC patients, 2-18 years of age, who had at least one neurological symptom and preserved ability to walk with assistance were eligible. Patients were maintained on routine clinical care. The primary endpoint was change in disease severity based on the 5-domain NPC-severity score (NPCCSS). The 5 domains included: ambulation, fine motor skills, speech, swallowing, and cognition.

RESULTS: 50 patients were enrolled (39 on miglustat); 34 treated with arimoclomol and 16 with placebo. 43 patients completed the trial. Baseline demographics and characteristics were comparable between treatment groups. Arimoclomol was well tolerated. Benefit of arimoclomol over placebo was established on the 5-domain NPCCSS score with a treatment effect of -1.34

(95% CI: -2.71, 0.02), p=0.0536, corresponding to 63% relative reduction of disease progression adjusted according to baseline values of both treatment groups. Supplementary analyses based on genotyping and pre-specified subgroups will be presented.

Arimoclomol treatment significantly increased HSP70 levels in peripheral blood mononuclear cells (PBMC), reduced accumulation of un-esterified cholesterol in PBMC and decreased serum cholestane-triol.

CONCLUSIONS: Arimoclomol reduced the annual disease progression by 63% compared with placebo on the 5-domain NPCCSS (primary endpoint). Also, biomarker analysis confirmed the pharmacological effect of arimoclomol as a HSP amplifier.

KEYWORDS: Rare Diseases, Translational/Experimental Therapeutics, Neurometabolic Disorders

STROKE (INCLUDING OTHER VASCULAR DISORDERS)

PL90. Harnessing Multimodal Neuroimaging to Predict Higher-Order Language Outcome Post Neonatal Stroke: An In Vivo Model of Neuroplasticity

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OBJECTIVE: Network reorganization following early brain insults may inform models of developmental neuroplasticity. The aim of the study is to utilize multimodal neuroimaging to investigate how patterns of functional and structural connectivity following Neonatal Arterial Ischemic Stroke (NAIS) correlate with higher-order language outcomes.

METHODS: A cross-sectional study of fourteen children with left (n=8; 2M; 11.1 ± 2.2 years) or right (n=6; 3M; 12.4 ± 4 years) middle cerebral artery (MCA) NAIS, as well as seven neurotypical children (5M; 13.4 ± 2.7 years), was conducted. Children listened to correct/incorrect syntactic stimuli while MEG was recorded, and task-related functional connectivity was determined. Structural connectivity was investigated using DTI tractography, and language outcomes were assessed using neuropsychological tests.

RESULTS: A network-based analysis of syntactic language processing (4-7 Hz, 1.2-1.4s) revealed a dysfunctional bilateral frontal-temporal network involving language areas in patients (p=0.01). Patients also showed significant reductions in bilateral frontal structural connectivity compared to controls (p<0.05). A combined model of functional and structural left intraconnectivity accounted for 70.2% of the variance in language outcome in patients with right-MCA stroke (p=0.037). This model performed better than either measure alone. For patients with left-MCA stroke, bilateral structural connectivity negatively correlated with outcome, while bilateral functional connectivity, or right-hemispheric functional connectivity, positively correlated with language skills (p<0.05).

CONCLUSIONS: The findings suggest that contralesional or bilateral reorganization of functional and structural networks may account for frontal-temporal impairments. Measures of combined functional and structural connectivity may be useful biomarkers for language development and brain network neuroplasticity following early injury.

KEYWORDS: Stroke (including other Vascular Disorders), Neuroimaging, Neonatal & Fetal Neurology

PL91. Robotic sensorimotor assessment of children with perinatal stroke and hemiparesis following intensive motor learning and neuromodulation

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OBJECTIVE: Perinatal stroke is the leading cause of hemiparetic cerebral palsy (CP). Limited therapies for sensorimotor dysfunction exist however intensive motor learning and neurostimulation have demonstrated potential. The KINARM exoskeleton robot provides an objective, quantitative assessment of upper limb sensorimotor function. We aimed to characterize sensorimotor functional changes after intensive motor therapy.

METHODS: This project is a component of a randomized, sham-controlled, double-blind, phase III neuromodulation clinical trial (ClinicalTrials.gov:NCT03216837). School-aged participants with hemiparetic CP and MRI-confirmed unilateral perinatal stroke completed a 2 week, goal-oriented, peer-supported intensive motor learning therapy camp. A validated,

normalized KINARM robot protocol was performed to assess visually guided reaching, position matching, and kinesthesia at baseline, 1 week (post), and 6 months retention (RT). Z-scores were compared for the three time points (one-way or Friedman rmANOVA on ranks).

RESULTS: Twenty-six participants were analyzed (median age 10.7yo, range 7-19, 42% female). In visually guided reaching, both the affected and unaffected limbs demonstrated significantly faster reaction times from post to RT (p=0.014 and 0.019, respectively). In Kinesthesia, initial direction error significantly improved from baseline to post (p=0.028) and RT (p=0.018). In the Kinesthesia task at RT, initial direction error z-scores correlated with clinical motor outcomes including the Assisting Hand Assessment (r=-0.434, p=0.027) and Box and Blocks (r=-0.410, p=0.037).

CONCLUSIONS: Intensive motor therapy may have a lasting impact on sensorimotor function in children with hemiparetic CP. The KINARM is a valuable tool to assess sensorimotor changes associated with intensive motor therapy and potentially help quantify mechanisms of interventional sensorimotor plasticity.

KEYWORDS: Stroke (including other Vascular Disorders), Movement Disorders (including Cerebral Palsy)

PL92. Regional thalamic dysrhythmia and connectivity abnormalities relate to motor performance in children with perinatal stroke

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OBJECTIVE: To use resting-state functional MRI to identify differences in brain activity and characterize the relationship with clinical symptoms in children who have had a periventricular venous infarct (PVI).

METHODS: Twenty-three children with left PVI (13M; mean age = 11.9y) and 22 age, sexmatched typically developing children (TDC) (11M, mean age = 12.7y) completed resting-state functional MRI scans. Brain activity was assessed using: 1) Amplitude of Low Frequency Fluctuation (ALFF), 2) Regional Homogeneity (ReHo), and 3) Degree Centrality (DC). Using the Box and Block Test (BBT), motor function in the affected (BBTA) and unaffected (BBTU)

hands was evaluated. Non-parametric permutation testing (5000 iterations) identified brain regions that showed group differences between PVI and TDC. Subsequent regions were masked and regressed against BBTA and BBTU scores.

RESULTS: Children with PVI showed greater oscillatory activity (ALFF) in the ipsilesional thalamus, lower bilateral thalamic connectivity (DC) to the rest of the brain (DC) (p<0.05, FWE-corrected) but no ReHo differences compared to TDC. Greater oscillatory activity in the dorsomedial thalamus was highly correlated with BBTA (rho = -0.65, p<0.05 FWE-corrected) but not BBTU (p>0.05).

CONCLUSIONS: This work suggests that altered connectivity between the thalamus and the rest of the brain, as well as thalamic dysrhythmia, may be functionally relevant to unilateral motor impairments in children with PVI.

KEYWORDS: Stroke (including other Vascular Disorders), Neuroimaging

PL93. Posterior Choroidal Artery Collaterals Predict Ischemic Event Recurrence and Response to Revascularization Surgery in Childhood Moyamoya

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OBJECTIVE: Collaterals have been shown to predict outcome in adult moyamoya. Our objective was to assess how collateralization patterns predict ischemic risk and outcome in childhood moyamoya.

METHODS: Pre- and post-surgical cerebral angiograms were reviewed in children with moyamoya disease (MMD) and moyamoya syndrome due to neurofibromatosis type 1 (MMS-NF1). Collaterals ere grouped into four categories: (1) pial collaterals (ACA-MCA, ACA-PCA, PCA-MCA, Anterior choroidal artery (AchoA)-MCA), (2) dural collaterals (posterior collaterals, STA-ACA, MMA-ACA, tentorial ICA branches, ophthalmo-ethmoidal branches), (3) anterior deep collaterals (lenticulostriates; AchoA collaterals) and (4) posterior deep collaterals (posterior communicating artery (Pcomm) collaterals, thalamoperforators, posterior choroidal arteries (PchoA)). Clinical features at presentation, motor Pediatric Stroke Outcome Measure (PSOM) at last follow-up, ischemic event recurrence, and angiographic response to surgery were assessed. Statistical analysis were performed comparing affected cerebral hemispheres using Chi-square and Fischer's Exact tests (p<0.05).

RESULTS: Eighty-nine affected hemispheres were identified (MMD=67; MMS-NF1=22). MMS-NF1 were less likely to have anterior deep collaterals (72% MMS-NF1 vs 92% MMD, p=0.0238). Pial collaterals on initial angiography were associated with better motor PSOM at last follow-up (98% Normal/Mild vs 33% Moderate/Severe, p<0.0001). PchoA collaterals were associated with ischemic event recurrence (63.89% vs 38.89%, p=0.0309), silent infarct recurrence (81.82% vs 44.30%, p=0.0252) and good surgical response (61% good vs 21% poor, p=0.0352).

CONCLUSIONS: Collateralization pattern in childhood moyamoya affects outcome and response to revascularization surgery. PchoA collaterals are associated with higher risks of ischemic event recurrence, but good surgical response, while pial collaterals are associated with a better PSOM at last follow-up.

KEYWORDS: Stroke (including other Vascular Disorders), Neuroimaging

PL94. Perinatal infections: an important etiological risk factor for Mineralizing angiopathy in children

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OBJECTIVE: Though mineralising angiopathy is increasingly being recognised as an important cause of ischemic stroke in young children, it's cause is not clear. One of the suggested aetiology is perinatal infections. We intended to look at the prevalence of perinatal infection in children with mineralising angiopathy and compare it with stroke secondary to focal cerebral arteriopathy and non-stroke patients.

METHODS: This study was conducted at the Child development clinic of a tertiary care hospital. Data of patients with stroke in the last two years was retrieved. Sixteen children with mineralising angiopathy, 14 children with focal cerebral arteriopathy were enrolled and forty children who visited the hospital for non-neurological complaints and on thorough examination who didn't have any neurological or developmental abnormality were taken as non-stroke controls. Detailed parental interview was done to look for perinatal infection. Premature rupture of membranes (PROM) was taken as a surrogate marker for chorioamnionitis and perinatal infection. Fisher exact test was used for statistical analysis. P value of < 0.05 was considered significant.

RESULTS: Perinatal infection (PROM in 8 and documented neonatal sepsis in 2) was seen in 8 patients (68.2%) with mineralising angiopathy and none of the children with focal arteriopathy. Only 3 (7.5%) of non-stroke patients had history of perinatal infection. This difference was statistically significant (p=0.0003).

CONCLUSIONS: PROM history is more common in children with mineralising angiopathy and PROM may predispose them to develop mineralising angiopathy which later presents as stroke following minor trauma.

KEYWORDS: Stroke (including other Vascular Disorders), Trauma, Infections/Neuroimmunology

PL95. Intracranial and extracranial vascular stenosis as risk factors for stroke in sickle cell disease

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OBJECTIVE: Prevalence and contribution to stroke risk of intracranial and extracranial stenosis were assessed prospectively in adults and children with sickle cell disease (SCD). **METHODS:** Adults and children ages 6-40 years with SCD phenotypes HbSS or HbS β^0 underwent neurological exam, brain MRI, and MRA of head and neck. Two neuroradiologists recorded patterns of infarct and identified the presence of arterial stenosis. Demographic variables and stroke outcomes were compared between participants with and without stenosis. Logistic regression analyses were performed to describe the association of variables of interest with stroke outcomes.

RESULTS: Of 167 participants, 20 (12.0%) had intracranial stenosis and nine (5.4%) had concurrent extracranial stenosis. No participants had isolated extracranial stenosis (Figure). Participants with intracranial stenosis were more likely than those without stenosis to have an overt stroke (70% vs. 5%, p<.001), silent cerebral infarct (SCI) (95% vs. 35%, p<.001) or any stroke defined as overt stroke or SCI (100% vs. 39%, p<.001) (Table 1). There were no Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020

significant differences in demographics or stroke outcomes between participants with and without extracranial stenosis. In logistic regression models, intracranial stenosis was a strong predictor of all types of stroke, and age was a significant predictor of SCI and any stroke. **CONCLUSIONS:** Intracranial stenosis was the strongest predictor of stroke studied, with prevalence similar to prior estimates in SCD of 10-15%. Extracranial stenosis was present in only 5% of participants and only concurrent with intracranial stenosis. Imaging protocols to specifically detect extracranial stenosis may be unnecessary. Other modifiable risk factors were not significant in this sample.

KEYWORDS: Stroke (including other Vascular Disorders)



Figure. Flow diagram for vascular imaging and stenosis findings. Diagram shows numbers of participants that received relevant vascular imaging studies (MRA head and neck) and presence and absence of stenosis.

	Intracranial	No intracranial	p-value
	Stenosis Present	stenosis present	
n	20	147	
Age, years	23.3±9.0 (22.0)	$18.9 \pm 9.0 (17.5)$.039*
Children <18 years	5/79 (6.3%)	74/79 (93.7%)	.033*
Male sex	10 (50.0%)	68 (46.3%)	.753
Moyamoya	14 (70%)	0	N/A
Any stroke	20 (100%)	57 (38.8%)	<.001*
experienced			
Overt stroke	14 (70.0%)	8 (5.4%)	<.001*
experienced			
Silent cerebral infarct	19 (95%)	52 (35.4%)	<.001*
experienced			
Smoker, ever	0	16 (10.9%)	.222
Diabetes	0	2 (1.4%)	.774
Hypertension	3 (15.0%)	13 (8.8%)	.413
BMI	$22.5 \pm 4.5 (22.3)$	20.5±4.8 (20.5)	.082
Hemoglobin	8.8 ± 1.3 (9.0)	9.5 ± 6.3 (9.1)	.626
Hematocrit	$25.4 \pm 3.6 (25.5)$	25.8 ± 3.9 (25)	.649

Table 1. Summary statistics for participants with and without intracranial stenosis. Values are shown as mean \pm standard deviation (SD) with median in parentheses for continuous variables, and number of participants with percent (%) of group in parentheses for categorical variables. Categorical variables used a χ^2 test if expected values were >5, and a Fisher's exact test if expected values were <5. Continuous variables used an unpaired *t*-test. * = statistical significance, *p*<.05.

PL96. Cerebral venous sinus thrombosis in infants after surgery for congenital heart disease

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OBJECTIVE: Children with congenital heart disease (CHD) are at increased risk for cerebral sinus venous thrombosis (CSVT). The incidence of CSVT in neonates undergoing repair of CHD may be as high as 28%. However, the incidence of CSVT in this population is not well-established. We hypothesize that the incidence of CSVT in infants with CHD is lower than previously reported.

METHODS: Infants who had CHD repair prior to 90 days of age followed by a post-operative brain MRI were identified from an institutional database. Clinical data was obtained from a cardiac surgery database and the medical record. Imaging was reviewed by a pediatric neurovascular neuroradiologist.

RESULTS: 315 infants who had repair of CHD from 2008-2019 had a post-operative brain MRI. 7 (2%) had a CSVT; 4 (57%) had transposition of the great arteries (TGA), 2 (29%) had an Proceedings of the 16TH INTERNATIONAL CHILD NEUROLOGY VIRTUAL CONGRESS October 2020

interrupted aortic arch (IAA), and 1 (14%) had aortic coarctation (CoA). Among patients without CSVT, 36 (12%) had TGA, 7 (2%) had IAA, and 30 (10%) had CoA. CSVT involved the transverse sinus in all patients. 5/7 (71%) patients were anticoagulated. All patients had complete or partial resolution of thrombosis, regardless of treatment. No patient experienced complications.

CONCLUSIONS: Infants with CHD undergoing surgery prior to 90 days of age have a low incidence (2%) of CSVT. All CSVTs were asymptomatic and found only in patients with TGA, IAA, and CoA. Recanalization was universal. Further studies are needed to establish best practices for surveillance, prevention, and treatment of CSVT in this population. **KEYWORDS:** Stroke (including other Vascular Disorders), Neuroimaging, Critical Care

TEACHING OF CHILD NEUROLOGY

PL97. Quality Improvement Measures in an Academic Pediatric Neurology Outpatient Practice

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OBJECTIVE: Quality Measures (QM) are important markers to identify gaps and assess outcomes in patient care. Our goal was to simplify the tracking of quality measures for physicians working in a busy academic outpatient pediatric neurology practice by integrating them into an existing electronic medical record (EMR) workflow. By initiating PDSA cycles, we planned to increase tracking QM by 50%.

METHODS: Compliance with quality measures had not been routinely assessed in the past. EMR templates for new and follow up visits were reorganized to integrate QM checklists covering 8 categories based on diagnosis. These categories were chosen based on AAN/CNS national guidelines. Compliance with documentation was tracked over a one year time period. After reassessment, a second PDSA cycle with 12 total categories is currently in progress for further improvement.

RESULTS: At the beginning of the PDSA cycle analysis, tracking of QM was averaged at a baseline of 30% over all categories. By the end of the year, 11,495 patient visits over a one-month time period were assessed. Compliance with tracking quality measures had increased to an average of 60% across all categories.

CONCLUSIONS: Integration of checklists into the EMR template has increased adherence to quality measures. Further modification of templates may continue to improve ease of compliance as well as patient care outcomes.

KEYWORDS: Teaching of Child Neurology

PL98. Adoption of Telemedicine within Pediatric Neurology of the MGH Healthcare System before and during the COVID-19 Pandemic

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OBJECTIVE: Real-time virtual communication technologies are poised to revolutionize access to health care. We set out to examineexamined the adoption of telemedicine before and during the COVID-19 crisis pandemic at a single center and compared the use of this technology by adult neurologists, pediatricians, and pediatric neurologists.

METHODS: We extracted pulled the number of completed telemedicine visits documented in EPIC for providers in neurology, pediatrics, and pediatric neurology from October 2019 through until March April 2020 at the Massachusetts General Hospital (MGH).

RESULTS: Before March 2020, the average number of scheduled telemedicine visits per month was 66±15 in pediatric neurology, 215±33 in adult neurology, and 73±11 in pediatrics. In March 2020, numbers escalated over the mean 7.6-fold in pediatric neurology, 4-fold in adult neurology, and 11-fold in pediatrics (Figure 1). In addition to scheduled telemedicine visits, practitioners began utilizing phone-only and impromptu telemedicine visits during the COVID-19 pandemic (168 in pediatric neurology, 662 in adult neurology, and 1,556 in pediatrics). **CONCLUSIONS:** The adoption of telemedicine at MGH in all three departments was dramatically accelerated during the COVID-19 pandemic. Phone-only visits, utilized as a temporary measure of providing patient care under the extreme circumstances, may translate into further increased utilization of telemedicine visits in the future. **KEYWORDS:** Teaching of Child Neurology



Figure 1. Number of scheduled telemedicine visits completed in the departments of pediatric neurology, adult neurology, and pediatrics at MGH between October 2019 and March 2020.

TRANSLATIONAL/EXPERIMENTAL THERAPEUTICS

PL99. Transpher A, an open-label, multicenter, single-dose, dose-escalation, Phase 1/2 Clinical Trial of gene transfer of ABO-102 in Sanfilippo Syndrome type A (Mucopolysaccharidosis IIIA): Safety, tolerability, biopotency and neurocognitive data

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OBJECTIVE: Study the safety and efficacy of intravenous ABO-102 (AAV9-based gene vector expressing the human *SGSH* gene) in children with Sanfilippo syndrome type A (MPS IIIA). **METHODS:** Transpher A is a Phase 1/2 clinical trial of ABO-102 in children with MPS IIIA receiving 0.5 X 10^{13} vg/kg (Cohort 1, n=3), 1 X 10^{13} vg/kg (Cohort 2, n=3) or 3 X 10^{13} vg/kg (Cohort 3, n=8). Evaluations include serial measures of general safety, biomarkers, liver and brain volumes and neurocognitive development.

RESULTS: Fourteen patients have been enrolled. Cohorts 1 and 2 and 4 patients in Cohort 3 have completed 24 months follow-up, while the remaining 4 patients have been followed to a mean 19.4 months (range 15.4-22.4 months). No serious drug-related adverse events have been found. Signals of biological efficacy include a rapid, sustained and dose-dependent reduction in CSF heparin sulfate as well as reductions in liver volume as early as 30 days post-treatment, sustained up to month 24. Children younger than 30 months (n=3) at treatment have demonstrated development progress within normal population variance at 18 and 24 months follow-up - deviating from the natural course in untreated disease.

CONCLUSIONS: Intravenous administration of ABO-102 in children with MPS IIIA shows a favorable long-term safety profile and leads to durable and dose-dependent improvement in disease biomarkers and liver volume. Patients treated before 30 months of age show development tracking in the normal range, providing evidence of neurological benefit when treatment is initiated early, before neurodegeneration is advanced.

KEYWORDS: Translational/Experimental Therapeutics, Rare Diseases, Neuromuscular Disorders

TRAUMA

PL100. Cerebral blood flow predicts outcome in children with persistent post-concussion syndrome

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OBJECTIVE: Persistent post-concussion symptoms (PPCS) following pediatric mild traumatic brain injury have been associated with differential changes in cerebral blood flow (CBF). We aimed to examine how CBF changes during recovery in children with PPCS.

METHODS: A prospective cohort study was performed in children (ages 8 to 18 years) with PPCS recruited from a convenience sample enrolled in the Play Game trial (NCT01874847). Exclusion criteria included assault, alcohol or drug use, significant past medical or psychiatric history (except attention disorders), a previous concussion within the last three months, and the use of psychoactive medications. 3D pseudo-continuous arterial spin labelled MRI (pCASL) was performed at 5 and repeated at 10 weeks post-injury. Clinical recovery was determined by return

to baseline (pre-injury) level symptoms on the Post-Concussion Symptoms Inventory (PCSI). Pre-processing and statistical analysis was performed using Statistical Parametric Mapping software.

RESULTS: Sixty-one participants (mean age 14 (SD 2.6) years; 41% male) had repeated pCASL imaging, and 23 participants had recovered at the time of the second scan (M=70 SD=6.6 days post-injury). Relative and mean global CBF was higher in those participants with good recovery, 50.08 (95%CIs: 48.66, 51.49) compared to those who remained symptomatic, 44.92 (95%CIs: 43.65, 46.19) ml/min/100g grey matter tissue. Using logistic regression, mean global CBF at 4-6 weeks post-injury significantly predicted recovery in 80% of children with PPCS (Odds Ratio 1.47, 95%CIs: 1.20, 1.81).

CONCLUSIONS: Cerebral blood flow is a promising predictive biomarker in children with PPCS. Further validation studies are required to confirm these findings.

KEYWORDS: Trauma, Neurorehabilitation, Neuroscience



Mixed effect linear model of cerebral blood flow changes between session 1 (4 to 6 weeks post injury) and session 2 (8 to 10 weeks post-injury) in those children with persistent post-concussion symptoms who recovered (blue) and those who did not recover (red).