Multi-scale computational modelling of neuronal dynamics in genetic epilepsies

RE ROSCH1,2, M HEILBRON1, C PETERS3, P RUBEN3, M LIM4,5, D PAL4,5, S Goyal6, E HUGHES4, T BALDEWEG3, KJ FRISTON1
1Wellcome Trust Centre for Neuroimaging, University College London, UK; 2UCL Great Ormond Street Institute of Child Health, University College London, UK; 3Department of Biomedical Physiology and Kinesiology, Simon Fraser University, Burnaby, BC, Canada; 4Department of Paediatric Neurology, Evelina London Children’s Hospital, GSTT NHS Foundation Trust, London, UK; 5Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King’s College London, UK; 6Department of Clinical Neuropsychology, Evelina London Children’s Hospital, GSTT NHS Foundation Trust, London, UK

There has been a recent increase in our ability to identify ‘epilepsy genes’, particularly in childhood. Many are directly important for synaptic function. Yet even in well delineated genetic epilepsies, such as those caused by mutations in SCN1A, or GRIN2A, the mechanistic link between molecular disruption and paroxysmal phenotypes is not well understood.

Computational modelling allows in silico simulations of specific abnormalities at different spatial and temporal scales, allowing inference on hidden pathophysiological mechanisms. Using two case studies, we illustrate how computational neuronal models can be used to identify dynamic neuronal dysfunction in the context of an epilepsy syndrome with known molecular cause.

In the first, ‘bottom-up’ example, we focus on a specific mutation in the SCN1A gene causing a temperature-sensitive epilepsy in the Dravet-syndrome spectrum. Using patch-clamp recordings at different environmental temperatures, we identify specific gating abnormalities introduced by the mutation. A computational model of the neuronal membrane is used to show how these gating abnormalities allow abnormal tolerance to high input currents, thus linking molecular abnormality and observed phenotype (Peters et al. 2016 Sci Rep 6, 31879).

The second, ‘top-down’ example explores abnormal sleep dynamics in a child with a familial GRIN2A mutation and an epilepsy-aphasia spectrum phenotype. Using dynamic causal modelling of sleep-EEG, observed spectral changes are modelled as fluctuations in neuronal coupling. The electromagnetic model is then used to identify which changes in thalamocortical coupling underlie the observed sleep abnormalities using Bayesian model comparison.

The examples used here illustrate two contrasting, but complementary approaches to the computational modelling of pathophysiology in genetic epilepsies; namely (1) using models to simulate emergent properties, and (2) fitting models to empirical data (i.e., dynamic causal modelling). These are flexible and scalable, allowing for the integration of existing knowledge and empirical evidence to develop a patient-specific understanding of neurological abnormalities.
Objective: Children with epilepsy (CWE) often have cognitive impairment. The pathophysiology behind these impairments remains uncertain. Slow EEG background activity is often associated with developmental delay. We hypothesize that EEG networks are predictive of impairments in CWE.

Methods: Routine EEG data collected from newly diagnosed CWE (n=51, age<3) were analyzed using a custom Fieldtrip processing pipeline in MATLAB. Raw EEG data was split into short epochs (2 seconds), and band-pass filtered with artifacts removed prior to network analysis in narrow bans of 2 Hz. Binarised networks were obtained via the minimum spanning tree (MST) and clustering span threshold (CST) coupling, assessed with the phase-slope index (PSI) and the weighted phase-lag index (WPLI) for each child. Independent network metrics from these analyses were then correlated with z-scores from age-appropriate assessments of intelligence, carried out within 2 months of epilepsy diagnosis, using Kendall’s tau.

Results: Both MST and CST analysis showed correlation in lower frequencies (<11 Hz) with intelligence assessed via the PSI. In the MST, intelligence positively correlated (tau=0.22) with the diameter and negatively correlated (tau=-0.21) with the maximum betweenness centrality (mBC) of the network at 9–11 Hz. In the CST, intelligence positively correlated (tau=0.20) to only the mBC, at 5–7 Hz. The CST showed correlations to intelligence for WPLI as well. Using WPLI, intelligence was negatively correlated (tau=-0.24) to both the clustering coefficient and the average variance in degree of the network at 1–3 Hz.

Conclusions: Significant correlations exist between specific network metrics and cognitive z-scores in CWE. Advanced network analysis tools like MST and CST provide a potential means to extract EEG markers sensitive to cognitive impairments, which could be used as biomarkers in CWE.

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Aetiology and subcortical structure volume are associated with subsequent cognitive deficits in children following convulsive status epilepticus (CSE)

KH BENNETT1,2, SS PUJAR3, MM MARTINOS2, MM YOONG1,2,*, RF CHIN1,2,4,5,*
1Muir Maxwell Epilepsy Centre, Child Life and Health, University of Edinburgh, Edinburgh, UK; 2Developmental Cognitive Neurosciences Unit, UCL Institute of Child Health, London, UK; 3College of Medicine and Veterinary Medicine, University of Edinburgh, Edinburgh, UK; 4Institute of Child Health, University College London, London, UK; 5Department of Paediatric Neurosciences, Royal Hospital for Sick Children, Edinburgh, UK

Objective: Childhood CSE is associated with poorer neuropsychological outcomes with aetiology as a significant risk factor. In a recent systematic review we showed a wide spectrum of decreased subcortical structure volumes associated with lower IQ in childhood epilepsy. We hypothesise that in childhood CSE, aetiology and decreased subcortical structural volumes are associated with full-scale intelligence quotient (FSIQ).

Methods: Structural MRI scans (Siemens Avanto, 1.5T) and FSIQ (Wechsler Preschool and Primary Scale of Intelligence) were collected from age and gender matched controls and patients at a mean 8 years post-CSE (Prolonged Febrile Seizures (PFS), n=30; Symptomatic, n=30; and Other, n=12). Scans underwent quantitative volumetric analysis (KHB, MMY) using FSL (Analysis Group, FMRIB, Oxford) to provide subcortical structure volume, grey/white matter volume, and intracranial volume (ICV). Multivariable linear regression was performed for each subcortical structure of patients to identify significant predictors of FSIQ, whilst correcting for aetiology, age, and ICV; Bonferroni correction was applied. Due to significant collinearity between structures, an additional multivariable analysis was used with total subcortical structure volume instead of individual subcortical structures, whilst additionally correcting for white/grey matter volume.

Results: 72 controls (12 ± 2.95SD years; 43 male) and 72 patients (11.7 ± 3.45SD years; 36 male) underwent analysis. Aetiology is an independent determinant of FSIQ: PFS=9-point decrease FSIQ (p=0.003), Symptomatic CSE=14-point decrease FSIQ (<0.001), Other=15-point decrease FSIQ (p=0.001). Only volumes of left putamen and pallidum significantly correlated with FSIQ (p < 0.005). In the final model, total subcortical volume was independently associated with FSIQ (B=0.001, p < 0.001).

Conclusions: Our findings suggest that in addition to aetiology, decreased volumes of the left putamen and pallidum are associated with cognitive deficits following CSE. This, along with our findings with total subcortical volume, indicates that a subcortical network rather than individual structures may be associated with FSIQ. Further analysis is ongoing.

Defining nodding syndrome: contrasting nodding syndrome in South Sudan, North Uganda & Tanzania

MA ATIM-OLUK1
1Pediatric Department, Morriston Hospital, Swansea, UK

Objective: Nodding Syndrome (NS) in South Sudan (SS) & North Uganda (NU) presented in the late 1990’s as an emerging seizure disorder occurring in children previously resident in Internal Displacement camps due to war, associated with multiple seizure types, intellectual disability and stunting. NS in Tanzania is an endemic seizure disorder associated with resolution of head nodding. Following the WHO international conference on NS in 2012, investigators defined NS in SS/NU and NS in Tanzania as the same condition. However data suggests otherwise and the cause remains unknown. I aim to compare and analyse the epidemiological and clinical data of NS in SS/NU and NS in Tanzania with the intention of improving research agenda.
Method: Literature review comparing studies regarding NS in SS/NU with studies of NS in Tanzania

Results: There are 3 published, 4 partially published and 2 unpublished case control studies comparing NS cases against matched controls in SS/NU. There have been less than 5 case series investigating the natural history of NS in SS/NU and no prospective longitudinal studies. Characterisation of head nodding (HN) between regions is variable. HN in SS/NU is a seemingly progressive emerging paediatric neurological disorder presenting with multiple seizure types including spasms, cognitive impairment, metabolic acidosis, abnormal interictal EEGs and cerebral/cortical atrophy. All data regarding NS in Tanzania originates from a cohort of 62 patients. The disease can occur in adults, represents an endemic seizure disorder without cognitive impairment in which the majority of cases undergo remission of HN

Conclusion: NS in SS/NU and Tanzania should be regarded as a separate entity. There have been a tiny number of studies researching NS in SS/NU and Tanzania. Existing research needs to be published and more research is urgently needed to detail the natural history and investigate causality of NS in both SS/NU and Tanzania

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Neurological outcome among the survivors of possible severe neonatal infections in coastal Kenya

SM GEORGE1,2, B NEVILLE2, CRJC NEWTON1,2,3, A SEAL1,2, J BERKLEY1,4, AA ABUBAKAR1

1KEMRI-Wellcome Trust Collaborative Research Programme, Kilifi, Kenya; 2Clinical Neurosciences, Institute of Child Health, University College London, London, UK; 3Nuffield Dept of Medicine, Oxford University, Oxford, UK; 4Department of Psychiatry, University of Oxford, Oxford, UK

Introduction: Serious neonatal infections including pneumonia, sepsis and meningitis account for a third of neonatal deaths around the world. However data on neuro-cognitive impairment after neonatal infection, particularly following clinical diagnosis of possible serious bacterial infection (pSBI) used to guide empiric treatment are lacking.

Methodology: This prospective study included 102/196 children born in a rural hospital in Kenya who survived neonatal pSBI (excluding those with confirmed meningitis) and 94/196 well neonates born in the same hospital. Children had neurodevelopmental assessments (including vision, hearing & motor impairment and epilepsy) at between 18 to 36 months. Odds of developing impairment were compared between the two groups using penalised multiple logistic regression. These comparisons were adjusted for birth weight, gestational age, clinical diagnosis of hypoxic-ischaemic encephalopathy and bacteraemia.

Results: Children who had neonatal pSBI had a higher risk of developing neurodevelopmental impairment (18/102, 17.6%; Odds ratio (OR) 1.78, 95% confidence interval (CI) 1.60–1.99) compared to those without pSBI (5/94, 5.3%). Speech and language (13/102, 12.7% vs 3/94, 3.2%; OR 4.14, 95%CI 1.29–1.56) and neuro-motor domains (11/102, 10.8% vs 4/94, 4.3%; OR 1.38, 95%CI 1.22–1.58) were most commonly affected domains.

Those who were exposed had a significantly higher risk of developing epilepsy (3/102, 2.9% vs 0/94; OR 1.83, 95%CI 1.56–2.19).

Conclusion: Neonatal pSBI (excluding cases of confirmed meningitis) caused significant neurodevelopmental impairment in children after adjusting for confirmed bacteraemia. This has important implications for improving prevention, supporting effective neonatal care and managing the long-term consequences of neonatal infection in resource-poor settings.

Long-term outcomes of NMDAR-Ab encephalitis cases from three U.K. centres

SK WRIGHT1, Y HACOHEN2, E KONSTANTOULAKI4, A ALMOYAN3, A VINCENT4, C HEMINGWAY2, M LIM3, E WASSMER1

1Department of Neurology, Birmingham Children’s Hospital, Birmingham, UK; 2Neurology Department, Great Ormond Street Hospital, London, UK; 3Children’s Neurosciences Centre, Evelina Children’s Hospital, London, UK; 4Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK

Objectives: NMDAR-Ab encephalitis is a well recognised neuro-immunological syndrome. The majority of patients (81%) diagnosed and treated promptly have a good outcome at 24 months (Titulaer 2014). Here we report longer-term clinical data of UK paediatric patients (>2 years follow-up) in relation to known predictors of good outcome.

Methods: Anonymised audit of patient records was carried out in 3 UK tertiary paediatric neurology hospitals. Data collection concentrated on potential prognostic factors (time to diagnosis and treatment, PICU admission, teratoma) as well as long term co-morbidities (epilepsy, cognitive, behavioural), relapses, medications and overall outcome.

Results: 27 case notes were studied, all patients (age range 0.75–17 years) had at least 2 years follow-up (range 2–10 years). 55% of patients had residual disabilities (15/27; MRS Grade 2: 11/15 (mild), MRS Grade 3: 3/15 (moderate), MRS Grade 5:1/15 (severe)); the remaining 44% of patients had a complete/near-complete recovery (12/27 MRS grade 0–1). 7 patients remained on regular medications, anti-epileptic drugs being most common (5/7); 4 patients were on 2 or more medications (range 2–8). Of the 6 patients treated late (>6 months), 5 had mild to moderate disability (83%). Seven patients required PICU, 5 made a complete or near-complete recovery (MRS 0–1), as did the 2 patients with ovarian teratomas.

Conclusions: Recovery from NMDAR-Ab encephalitis can be prolonged (>18 months, Titulaer 2014), however this study confirms that delayed acute treatment is a poor prognostic factor even in long-term follow-up. Ovarian teratoma patients made an excellent recovery, and PICU admission did not predict a poor long-term outcome in our cohort. Patients and parents in the acute phase of the illness need to be counselled on the significant long-term risks of co-morbidities. Establishment of large patient registries with standardised data sets will enable identification of accurate predictors of long-term outcomes in affected paediatric patients.
Clinical features and outcome of optic neuritis in children with relapsing demyelinating syndromes of the central nervous system

M EYRE1, S WRIGHT2, M LIM3, E WASSMER2, C HEMINGWAY3, Y HACOHEN1
1Department of Neurology, Great Ormond Street Hospital for Children, London, UK; 2Paediatric Neuroscience, Evelina Children’s Hospital, (g) Guy’s and St Thomas’ NHS Foundation Trust, Kings Health Partners Arcade, London, UK; 3Department of Paediatric Neurology, Birmingham Children’s Hospital, Birmingham, UK

Background: Optic neuritis (ON) is a common presentation of relapsing demyelinating syndromes (RDS) in children. The pattern of ON may assist in the differential diagnosis. In addition to the diagnostic implications, ON may lead to irreversible visual loss. We studied a cohort of children with RDS and ON to evaluate their clinical, ophthalmological, radiological characteristics, and visual outcome.

Methods: 42 children with RDS and one or more episodes of ON were identified at Great Ormond Street Hospital, Evelina London Children’s Hospital and Birmingham Children’s Hospital. Twenty two children (52%) had a diagnosis of MS, 16 (38%) MOG-Ab-associated disease and 4 (10%) AQP4-Ab NMOSD. Clinical characteristics, laboratory investigations, neuroimaging and ophthalmological evaluations at ON onset and follow-up were retrospectively reviewed.

Results: Children with a diagnosis of MS (n=22) were compared to children with antibody-associated disease (n=20). Older age at onset of ON was associated with MS compared to Ab-associated disease (median age 13 years vs 8 years, p < 0.0001). Gender, ethnicity, ocular pain, bilateral involvement, and severity of acute visual loss did not differ between groups. Complete visual recovery occurred in 60% of children and did not differ between groups. Children with Ab-associated disease were more likely to suffer recurrent ON (75% vs 27%, p=0.005), and suffered a higher rate of optic nerve atrophy (85% vs 55%, p=0.05). Abnormal intracranial MRI at time of ON was observed in 95% of MS cases compared to 10% of Ab-associated cases (p < 0.0001).

Conclusion: Children with RDS presenting with ON have a 40% risk of permanent visual impairment. Clinical features at presentation with ON were not predictive of the underlying diagnosis in our cohort, however abnormal intracranial MRI was highly predictive of MS. Children with Ab-associated disease were more likely to follow a course of recurrent ON and optic nerve atrophy.

When positive is positive: medium-term cognitive outcomes in paediatric autoimmune encephalitis comparing N-methyl-D-aspartate receptor antibody positive (NMDAR Ab+) and neuronal surface antibody negative (Ab-) patients

I GARROOD, A ALMOYAN, E KONSTANTOULAKI, J GADIAN, M ABSOUD, M LIM
Children’s Neurosciences, Evelina Children’s Hospital, London, UK

Objective: Retrospective neuropsychological data from a single centre was used to compare the outcomes between NMDA-R antibody positive and neuronal surface antibody negative patients.

Methods: Fifty consecutive patients with definite and probable autoimmune encephalitis (Graus et al., 2016 Lancet Neurology; 15(4): 391–404) were identified between 2006 and 2016. Routine neuropsychological or multidisciplinary assessment was undertaken in 25 patients, typically 12–18 months post diagnosis. All had an age appropriate IQ measure calculated and most completed additional testing of specific cognitive domains e.g. episodic memory, executive functioning.

Results: 11/22 NMDAR-Ab+ patients and 14/28 Ab- had cognitive assessments (mean age=10;3 years, range=3;9–17;1 years, females=16). There were no differences in clinical or behavioural concern characteristics between those tested and not tested. Comparison of the Full Scale IQ between groups revealed significantly better functioning in the NMDAR-Ab+ group compared to Ab- (mean(SD)-92(15) vs 76(15) p=0.01). 7/11 the NMDAR-Ab+ patients had a FSIQ in the normal range (i.e. > 85) compared to 4/14 in the Ab- group. The FSIQ difference was mainly accounted for by differences in the Verbal Comprehension Index (significant at p=0.004).

Comparison of other areas of cognitive functioning revealed impaired scores in only a third of NMDA-R Ab+ group, with no consistent domain identified. The Ab- group had greater difficulties across all domains. Cognitive outcome was not predicted by age at onset, initial disease severity (PICU admission, seizures) or disability level (MRS level).

Conclusion: In our study, children with NMDAR encephalitis have better cognitive outcomes compared to the children where no neuronal surface antibodies were identified. These outcomes appear better than the literature reports of adult patients with NMDAR encephalitis and children with a range of other infective encephalitides.

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Intracerebroventricular cerliponase alfa (BMN 190) in children with CLN2 disease: Results from a Phase 1/2, open-label, dose-escalation study

P GISSEN1, A SCHULZ2, N SPECCHIO3, E DE LOS REYES4, R WILLIAMS5, H CAHAN5, P SLASOR6, D JACOBY6
1Great Ormond Street Hospital for Children, London, UK; 2University Medical Center Hamburg-Eppendorf, Hamburg, Germany; 3Bambino Gesù Children’s Hospital, IRCCS, Rome, Italy; 4Nationwide Children’s Hospital, The Ohio State University, Columbus, OH, USA; 5Guy’s and St Thomas’ NHS Foundation Trust, London, UK; 6BioMarin Pharmaceutical Inc

Objectives: CLN2 disease, a rare, inherited, pediatric-onset, neurodegenerative lysosomal storage disorder caused by TPP1 enzyme deficiency, is characterized by seizures, ataxia, rapid loss of language and motor functions, blindness and early death. Cerliponase alfa (BMN 190) is a recombinant human TPP1 enzyme. This phase 1/2, multi-center, open-label, dose-escalation study evaluated the safety, tolerability and efficacy of every other week intracerebroventricular (ICV) infusions of cerliponase alfa in children with CLN2 aged 3–16 years.
Methods: The first ten subjects were assigned to one of three cohorts in a dose escalation period (30 mg, 100 mg, 300 mg). All subjects were subsequently administered a stable dose of cerliponase alpha (300 mg every other week) for at least 48 weeks. Efficacy was evaluated by monitoring changes in motor and language functions using a CLN2 clinical rating scale.

Results: 24 subjects (9 male, 15 female, mean age 4.3 years [median: 4 years; range: 3–8 years]) enrolled in the study. Almost all subjects (96%) had adverse events (AEs) assessed as study drug-related, the majority of which were Grade 1–2 and included pyrexia (46%), hypersensitivity (33%), seizure (33%), and epilepsy (17%). Serious adverse events (SAEs) assessed by the investigator as study drug-related were reported in seven (29%) subjects. There were no anaphylaxis/anaphylactoid reactions, study drug discontinuations or deaths due to AEs. The mean (SD)/median rate of decline in CLN2 score of 21 evaluable subjects was 0.43 (0.84)/0.00 units/48 weeks, in contrast to the 2.09 (0.97)/1.87 units/48 weeks rate of decline observed in 41 natural history patients.

Conclusions: Enzyme replacement therapy with ICV-administered cerliponase alpha is well-tolerated and slows the progression of functional decline in children with CLN2.

A novel manganese transporter defect caused by mutations in SLC39A14 leads to parkinsonism-dystonia and neurodegeneration that is treatable with disodium calcium edetate

K TUSCHL1,2, E MEYER1, LE VALDIVIA2, PT CLAYTON1, PB MILLS1, MA KURIAN1, SW WILSON2
1UCL GOS Institute of Child Health, London, UK; 2Department of Cell and Developmental Biology, University College London, London, UK

Objective: This study set out to identify the disease gene in a cohort of nine children with early-onset parkinsonism-dystonia associated with hypermanganesaemia and hyperintensity of the globus pallidus on T1-weighted MRI.

Methods: Whole exome sequencing in combination with autozygosity mapping and Sanger sequencing was used for gene identification. Manganese levels were determined using inductively-coupled plasma mass spectrometry. A zebrafish model was generated using CRISPR/Cas9 genome editing.

Results: A affected child presented with loss of developmental milestones, progressive pharmacoresistant dystonia and bulbar dysfunction at ages six months to three years. MR brain imaging was characteristic of manganese deposition with T1-hyperintensity of the globus pallidus, striatum, and white matter including the cerebellum, spinal cord and dorsal pons, with sparing of the ventral pons. Post mortem studies revealed marked neuronal loss in the globus pallidus and dentate nucleus, and a vacuolated myelopathy in the cerebral and cerebellar white matter. Homozygous loss-of-function mutations in SLC39A14 were identified in all patients. SLC39A14 is a divalent metal transporter facilitating uptake of manganese, zinc, iron and cadmium at the cell membrane. Blood metal analysis in affected children found an increase in manganese levels alone. Overexpression of mutant SLC39A14 in HEK-293 cells confirmed impaired manganese uptake. Loss-of-function of slc39a14 in zebrafish led to manganese accumulation, increased sensitivity to manganese toxicity and impaired motor activity. Chelation with disodium calcium edetate significantly lowered manganese levels in fish and led to striking clinical improvement in one patient who regained the ability to walk.

Conclusions: The manganese transporter SLC39A14 joins SLC30A10 as a crucial regulator of manganese transport. Mutations in these genes impair hepatic manganese excretion with subsequent manganese accumulation in the brain causing parkinsonism-dystonia that is treatable with chelation therapy.

Acknowledgements: We thank our many collaborators on this project who are not listed but will be acknowledged when presented.

Aetiological investigations in early developmental impairment (EDI): which tests help make a diagnosis?

M ATHERTON1, S BARFIELD1, S SIMPSON1, R SHARMA2, MJ PARKER3, DJA CONNOLLY4, AR HART5
1Department of Paediatrics, Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK; 2Department of Paediatric Neurodisability, Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK; 3Department of Clinical Genetics, Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK; 4Department of Paediatric Radiology, Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK; 5Department of Paediatric Neurology, Sheffield Children’s Hospital NHS Foundation Trust, Sheffield, UK

Objective: To evaluate how frequently investigations performed in EDI identify an aetiology.

Methods: Children referred to Sheffield Children’s Hospital between January 2010 and December 2015 for evaluation of EDI were identified from clinic letter databases. Case notes and investigations were retrospectively reviewed. Participants were excluded if the cause of EDI was clear from initial history and examination. Participants were divided into EDI with no additional features and EDI with additional features. Referral to Clinical Genetics was part of the guideline, where appropriate, so directed genetic tests were included.

Results: 713 children were identified; nine were excluded because of insufficient information, leaving a cohort of 704 (220 f, 484 m). 142 had no additional features, 562 had additional features. 80 participants had no investigations. 85/624 (13.6%) achieved a diagnosis. Participants with additional features were twice as likely as those without to achieve a diagnosis, but this was not statistically significant (2.190, p=0.17).

Microarray was diagnostic in 51/441 (11.6%). 84/263 who had no microarray underwent karyotype: 1 (1.2%) was abnormal. Fragile-X Syndrome testing was diagnostic in 1/108 (0.93%); TFT in 3/473 (0.63%); plasma amino acids in 4/416 (9.6%) one of whom also had a contributing genetic diagnosis; urine organic acids 2/321 (0.62%): all had additional features. FBC, U&E, LFT, bone profile, biotinidase, urine GAGs, CK, lead levels were not diagnostic in any participant.

The proportion of participants who achieved a diagnosis differed between the additional feature groups, with over 20% of participants with immune system, antenatal cardiac airway, facial movement, skeletal and urological abnormalities achieving diagnoses.
Conclusions: The majority of our aetiological investigations for EDI are negative. Clinical phenotype affects the likelihood of a diagnosis being reached. We propose a more streamlined and cost-efficient diagnostic pathway for EDI investigation.

Globus pallidus neuronal firing properties correlate with dystonia aetiology and phenotype in children

VM Mcclelland1, A Valentin1, HG Rey2, DE Lumsden3, ME Elze4, A Selway5, GA Alarcon1, JP Lin4

1Basic and Clinical Neuroscience, King’s College London, UK; 2Centre for Systems Neuroscience, University of Leicester, UK; 3Complex Motor Disorders Service, Evelina Children’s Hospital, Guys and St. Thomas’ NHS Foundation Trust, London, UK; 4Department of Statistics, University of Warwick, Coventry, UK; 5Department of Functional Neurosurgery, King’s College Hospital NHS Foundation Trust, London, UK

Objective: To report microelectrode data from the Globus Pallidus interna (GPI) and externa (GPe) in children undergoing Deep Brain Stimulation (DBS) for dystonia and to investigate whether pallidal firing rates differ between dystonia types.

Methods: Microelectrode data were obtained under anaesthesia to guide DBS electrode position in 44 children with dystonia (14 Primary, 22 Secondary Static and 8 Progressive secondary forms) undergoing multidisciplinary assessment for possible DBS. Outcome from DBS was assessed as the percentage improvement in Burke-Fahn-Marsden Dystonia Rating Scale motor score (BFMDRS-m).

Results: Both GPI and GPe firing frequencies differed significantly with dystonia aetiology. Median GPI firing frequency was higher in the Primary than the Secondary Static Group (13.5 Hz vs 9.6 Hz; p=0.002) and higher in the NBIA group than either the Primary (25 Hz vs 13.5 Hz; p=0.006) or Secondary Static group (25 Hz vs 9.6 Hz; p=0.00004). Median GPe firing frequency was higher in the NBIA than the Secondary Static Group (15.9 Hz vs 7 Hz; p=0.013). The NBIA group also showed a higher proportion of regularly firing GPI cells compared with the other groups (p < 0.001). A higher proportion of regular GPI cells was also seen in patients with fixed/tonic dystonia compared with a phasic/dynamic dystonia phenotype (p < 0.001). GPI firing frequency showed a positive correlation with 1-year outcome from DBS measured by improvement in Burke-Fahn-Marsden Dystonia Rating Scale motor score (p=0.030). This association was stronger for the non-progressing patients (p=0.006).

Conclusions: Pallidal firing rates and patterns correlate with dystonia aetiology and phenotype in children. Identification of specific firing patterns may help determine targets and patient-specific protocols for neuromodulation.

Abnormal Somatosensory Evoked Potentials in Children with dystonia - a potential predictive marker for outcome from Deep Brain Stimulation?

VM Mcclelland1, D Fialho2, D Flexney-briscoe3, GE Holder3, JP Lin4

1Department of Basic and Clinical Neuroscience, King’s College London, UK; 2Department of Clinical Neurophysiology, King’s College Hospital NHS Foundation Trust, London, UK; 3Moorfields Eye Hospital NHS Foundation Trust, London, UK; 4Complex Movement Disorders Service, Evelina Children’s Hospital, Guys and St. Thomas’ NHS Foundation Trust, London, UK

Objective: To report Somatosensory Evoked Potentials (SEPs) from children with primary and secondary dystonia and investigate the potential role of SEPs as a predictive marker for outcome from Deep Brain Stimulation (DBS).

Methods: Data were obtained in 102 children with dystonia undergoing multidisciplinary assessment for possible DBS. Mean age was 10 (range 2.5–19) years. Median nerve SEPs were recorded over ipsilateral Erb’s point, the 7th and 2nd cervical vertebrae and contralateral centro-parietal scalp. Posterior tibial nerve SEPs were recorded over ipsilateral popliteal fossa and midline centro-parietal scalp. A mid-frontal tibial nerve SEPs were recorded over ipsilateral popliteal fossa and midline centro-parietal scalp. A mid-frontal waveform. Technically unsatisfactory recordings were excluded. Outcome from DBS at 1 year was assessed as the percentage improvement in Burke-Fahn-Marsden Dystonia Rating Scale motor score (BFMDRS-m).

Results: Technically satisfactory cortical SEPs were obtained from 368 limbs (99 children). Half of all patients (50.5%) showed at least one abnormal cortical potential. Abnormal SEPs were seen in a higher proportion of patients with secondary dystonia (55.1%) than primary dystonia (28.6%) (Chi square 0.031). Abnormal SEPs were identified in 8 of 25 patients (32%) with normal cranial MRI. Of the 51 children who proceeded to DBS, outcome was better in those with normal SEPs (n=33) than those with abnormal SEPs (n=18) (Mann Whitney test p=0.005). In a sub-group with normal imaging (n=14), outcome was again better in those with normal SEPs (n=10) than those with abnormal SEPs (n=4) (MW p=0.034).

Conclusions: SEPs can provide objective evidence of sensory pathway disruption in children with dystonia, even when cranial imaging is normal. The data also suggest that SEP findings could contribute to the patient selection process and counselling of families about potential outcome from DBS.

Altered functional brain connectivity in children and young people with Opsoclonus- myoclonus syndrome

G Anand1, AM Chekroud2, S Thomas1, M Pike1, H Bridge2

1Paediatric Neurology, Oxford Children’s Hospital, Oxford; 2Nuffield Department of Clinical Neurosciences, Oxford University Hospitals, Oxford

Aim: Opsoclonus-myoclonus syndrome (OMS) is a rare, poorly understood condition that can result in long-term cognitive,
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The expanding spectrum of movement disorders in genetic epilepsies

A PAPANDREOU1,2, A MCTAGUE1, FR DANTI1, J NG1, A NGOH1, LJ CARR2, S JAYAWANT3, J POULTON4, JH CROSS2,5, MA KURIAN1,2
1Developmental Neurosciences Programme, UCL-GOS Institute of Child Health, London, UK; 2Neurology Department, Great Ormond Street Hospital, London, UK; 3Paediatric Neurology Department, John Radcliffe Hospital, UK; 4Nuffield Department of Obstetrics and Gynaecology, University of Oxford, The Women’s Centre, Oxford, UK; 5Clinical Neurosciences Programme, UCL-GOS Institute of Child Health, London, UK

Objective: The co-occurrence of non-epileptic movement disorders in genetic forms of epilepsy is increasingly recognised. We report the clinical spectrum of movement disorders associated with early-onset infantile epileptic encephalopathy (EOEE) and childhood-onset epilepsies.

Methods: We reviewed a cohort of patients presenting in specialist neurogenetic, movement disorder and epilepsy clinics throughout the UK with EOEE or childhood-onset epilepsy and associated abnormal involuntary movements. In order to characterise the movement disorder semiology, we performed detailed clinical examination and reviewed available video footage and patient case notes.

Results: Movement disorders were detected in a wide range of patients with genetically confirmed early-onset epilepsy. Most patients had hyperkinetic movement disorders, namely dystonia, choreoathetosis and myoclonus, while stereotypies were also commonly seen. Hypokinetic/ parkinsonian features were more rarely reported, often presenting later in the disease course. Abnormal movements were often difficult to control, and specific anti-epileptic treatments sometimes led to exacerbation of the movement disorder. Causative genes encoded for diversely-functioning proteins including: ion channels (SCN2A, SCN8A, KCNQ2, KCNT1), transporters (SLC16A2, SLC2A1, SLC6A1, SLC9A6), Sodium/Potassium pumps (ATP1A3), receptors (GRIN1, GRIN2B), transcription factors (MECP2, FOXG1, ARX), autophagy-related proteins (WDR45, EPG5, SNX14) and proteins involved in ubiquitin-mediated proteolysis (UBE3A); proteins involved in the synaptic vesicle cycle (PRRT2, STXBP1, DN1M, TBC1D24, DNAJC6), transcription regulation (CDKL5), post-translational protein modification (AARS, ALG13), axonal myelination (SPTAN1) and G-protein-coupled signal transduction (GNAO1). Mutations in genes leading to inborn errors of metabolism (such as lysosomal storage disorders and mitochondrial cytopathies) were also identified.

Conclusions: A number of genetic epilepsies are associated with movement disorders, which can be debilitating and associated with significant morbidity. Our findings implicate a role for these genes in the control of voluntary movement, though underlying disease processes remain unclear. Further research is necessary to elucidate pathophysiological mechanisms and develop targeted therapies for these early onset genetic disorders.

Stiff face syndrome associated with glycine receptor antibodies

J GADIAN, K LASCELLES, M LIM
Children’s Neurosciences Centre, St Thomas’ Hospital, London, UK

Objective: We present the case and videos of a boy with severe stimulus sensitive spasms primarily affecting the face, and associated with glycine receptor antibodies (GlyR-Ab) tested at the Nuffield neuroimmunology laboratory, Oxford using immunofluorescence cell-based assay.

Case report: A 4 year old boy presented with facial asymmetry, confusion, arm and leg rigidity, and intermittent severe stimulus sensitive dystonic spasms of the limbs and mouth initially diagnosed as trismus; predated by 3 weeks of mandibular spasms whilst eating (Video 1). Clinical examination revealed hyperekplexia (Video 2).

Initial CSF analysis and neuroimaging were normal. The dystonic episodes worsened despite clonidine and benzodiazepines, and he required PICU admission due to severe facial spasms. EEG showed encephalopathy, repeat neuroimaging was unremarkable and an ultrasound excluded neoplasia. He was treated with intravenous immunoglobulin (IVIG;2 g/kg), and after infective aetiology was excluded, antibiotics were discontinued and he received high dose methylprednisolone (30 mg/kg/day for 5 days) followed by oral prednisolone. He dramatically improved (Video 3) over the following 2 weeks, and was discharged on maintenance oral steroids (2 mg/kg/ day). GlyR-Ab were detected in the serum and oligoclonal bands in the CSF.

Discussion: Stiff person syndrome is a spectrum of disorders characterised by spinal cord hyperexcitability, with rigidity primarily of the lower limbs and trunk, stimulus-sensitive
Delineation of the movement disorder spectrum in FOXG1-related disease

A PAPANDREOU1,2, RB SCHneider3, EF AUGUSTINE4, J NG5, K MANKAD5, E MEYER1, A MCTAGUE1, A NGOH1, C HEMINGWAY5, R ROBINSON5, SM VARADKAR2, M KINALI6, V SALPIETRO6, MC O'DRISCOLL7, N BASHEER8, W WEBSTER9, SS MOHAMMAD1,9, S PULA10, M MCGOWAN10, N TRUMP11, L JENKINS11, F ELMSLIE12, RH SCOTT13, B PEREZ-DUENAS14, AR PACIORKOWSKI13,16, MA KURIAN1,2
1Developmental Neurosciences Programme, UCL-GOS Institute of Child Health, London, UK; 2Neurology Department, Great Ormond Street Hospital, London, UK; 3Department of Neurology, University of Rochester Medical Center, Rochester, NY, USA; 4Center for Human Experimental Therapeutics, University of Rochester Medical Center, Rochester, NY, USA; 5Radiology Department, Great Ormond Street Hospital, London, UK; 6Department of Paediatric Neurology, Chelsea and Westminster NHS Foundation Trust, London, UK; 7Department of Paediatrics, Chelsea and Westminster NHS Foundation Trust, London, UK; 8Department of Perinatal Neurology, Hammersmith Hospital, London, UK; 9Neurology Department, The Children’s Hospital at Westmead, Sydney, AU, USA; 10Child Development Centre, St. George’s Healthcare NHS Trust, London, UK; 11Molecular Genetics Department, North East Thames Regional Genetics Services, Great Ormond Street Hospital, London, UK; 12South West Thames Regional Genetics Service, St. George’s Healthcare NHS Trust, London, UK; 13Department of Clinical Genetics, Great Ormond Street Hospital, London, UK; 14Department of Neurology, Hospital Sant Joan de Déu, Universitat de Barcelona, Spain; 15Departments of Pediatrics and Biomedical Genetics, University of Rochester Medical Center, Rochester, NY, USA

Objective: Patients with FOXG1 mutations typically present with acquired microcephaly, severe neurodevelopmental delay and epilepsy. Abnormal involuntary movements are also reported but not well delineated. Our objective was to better characterise the movement disorder associated with FOXG1-related disease.

Methods: We identified patients with FOXG1 mutations from tertiary movement disorder, epilepsy and genetics clinics in the UK and USA. Characterisation of movement semiology was undertaken by direct clinical examination, review of available video footage and retrospective review of medical records.

Results: Twenty-eight patients with FOXG1 mutations were identified. Full characterisation of motor phenotypes was possible in 25 cases. Patients presented with a wide variety of movement disorders with onset in infancy. Choreoathetosis (22/25), orofacial dyskinesias (20/25) and dystonia (19/25) were most commonly present. Stereotypies were also seen in 13/25 patients. Abnormal involuntary movements were severe, disabling and progressive in many cases, though status dystonicus was not reported in any patients. Four patients with mis-sense FOXG1 mutations presented atypically, with a significantly milder phenotype than that previously reported in patients with classical FOXG1-related disease. These patients achieved independent ambulation, spoken language and were normocephalic. Hyperkinetic involuntary movements (dystonia, choreoathetosis, myoclonus) were major clinical features in all 4 patients. A number of different therapeutic agents were trialled in the cohort and although most had no significant effect, levodopa and tetrabenazine led to clinical improvement in 4/9 and 2/3 cases, respectively.

Conclusions: Abnormal involuntary movements are a major defining feature of FOXG1-related disease, though underlying disease mechanisms remain yet to be fully elucidated. We propose that symptomatic treatment should be considered for severe or disabling movements.

Heterogeneity of movement disorders in hypomyelination with atrophy of the basal ganglia (H-ABC) syndrome and their management with Deep Brain Stimulation (DBS) or Intrathecal Baclofen Pump (ITB)

V NAKOU1, S PERIDES2, C LUNDY3, G MACKIN3, T TUSTIN1, H GIMENO1, L BAKER1, DE LUMSDEN1, R SELWAY4, K ASHKAN4, S BASSI4, J-P LIN4, M KAMINSKA1
1Complex Motor Disorders Service, Evelina Children’s Hospital, Guy’s & St Thomas’ NHS Foundation Trust, London, UK; 2Paediatric Neurology Service, Royal Belfast Hospital for Sick Children, Belfast Health and Social Care Trust, Belfast, UK; 3Paediatric Service, South West Acute Hospital, Western Health and Social Care Trust, Enniskillen, UK; 4Department of Neurosurgery, Kings College Hospital NHS Foundation Trust, London, UK

Objective: H-ABC syndrome is a rare neurodegenerative disorder, initially identified by MRI pathognomonic finding. We present videos of 3 cases with H-ABC syndrome- confirmed TUBB4A mutation- with differing movement disorders, managed with Deep Brain Stimulation (DBS) or intrathecal baclofen pump (ITB).

Case 1: A 12-year old girl was born at term, in good condition, small-for-date. Two elder brothers had developmental difficulties. She presented with profound early developmental delay, visual impairment, total body dystonia with spasticity in lower limbs and seizures from 1 to 5 years of age. A brain MRI confirmed H-ABC. An ITB pump was implanted at 7 years resulting in improved dystonia and daily care.

Case 2: An 18-year old girl of unrelated parents, born at term in good condition with normal early development but toe-walked independently at 21 months. Diagnosed with spastic diplegia at 3 years. Brain MRIs showed a hypomyelinating leucodystrophy. She deteriorated at the age of 11 years and lost ambulation at 14 years. She has learning and behavioural difficulties with slurred speech. An ITB pump was implanted at 16 years with improvement of tone and comfort.
Case 3: This girl died at the age of 5. She was born at term in good condition, following IVF conception. After normal early development she developed a progressive severe total body dystonia/dyskinesia initially in the left foot at 19 months. Cognition was preserved. Brain MRI confirmed H-ABC syndrome. DBS was implanted at the age of 7 years, with positive effects but required removal due to infection at 8.5 months. She died 8 months later due to complicated pneumonia aged 8.5 years.

**Conclusion:** As recently reported H-ABC syndrome can present with different movement disorders phenotypes and severity and atypical MRI patterns. DBS and ITB implantation can be considered in the management of movement disorders of patients with this condition.

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Infantile tremor syndrome in a malnourished child

**DR KRUPA TORNE**
Sir J.J. Group of Hospital & Grant Government Medical College

**Background:** Infantile Tremor Syndrome (A rare presentation).

**Case Report:** 10 month old girl admitted in with abnormal movement of left side of the body with 8 days of duration disappearing in sleep with disinterest in surroundings. Birth history was unremarkable. Exclusively breast fed baby. Mother vegetarian. There was gross motor delay in the form of not able to sit without support. Neuroregression was noticed in the form of loss of head control & social smile after starting of the abnormal movements. She was malnourished with weight of 6.5 kilograms. Noticed pallor, thin sparse hair with knuckle hyperpigmentation. Neurology revealed hypotonia with unilateral tremors of the left side of the body with twitching of the left side of face.

**Interventions:** Complete blood work up including metabolic, vitamin B12 and folic acid assay was negative except urine homocysteine was positive. MRI Brain showed Generalised atrophy. Child was started on injection Vitamin B12 in high doses. Tremors gradually reduced and completely stopped after 3 weeks. Child regained social smile, head control and started to sit with support.

**Discussion:** Infantile tremor syndrome is a rare syndrome can be presented from 6 months to 18 months of age with neuroregression, malnutrition and acute tremor which attributed to structural and functional alteration of extrapyramidal system. Though Vitamin B12 blood levels were normal, there is deficiency at tissue level She was treated successfully with Vitamin B12 in high doses.

**Message:** Infantile Tremor Syndrome needs to be considered in a young child with tremors, malnutrition, developmental delay and neuroregression.

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**Movements in Menkes**

MT ONG, S BARFIELD, SR MORDEKAR
Paediatric Neurology, Sheffield Children’s Hospital, Sheffield, UK

**Objective:** Epilepsy is common and often difficult to treat in Menkes disease. We report 2 cases of Menkes disease with significant non-epileptic spasms and a movement disorder occurring alongside epileptic seizures making it difficult to differentiate.

**Case 1:** A 7 month old white British boy with Menkes disease (genetically confirmed) presented with central hypotonia and global developmental impairment and spasms. EEG showed pseudoperiodic burst suppression. West syndrome was diagnosed. Tetracosactide and Vigabatrin were commenced but unfortunately the spasms did not remit and he required midazolam infusion to control them. Repeat EEG captured clusters of asymmetric flexion and symmetric extension of trunks and limbs with no EEG correlates. Clonazepam was tried successfully. At 11 months, spasms recurred with pseudoperiodic burst suppression pattern and were treated with prednisolone successfully. Between 15 to 17 months he developed further abnormal movements (shuddering, lateral head and eye movements, chewing movements, athetoid movements) without EEG changes alongside episodes of epileptic seizures. He died at 4.5 years from pneumonia.

**Case 2:** A 3 month old white British term baby with Menkes disease (confirmed genetically) developed right temporal focal seizures at 3 months of age and was treated with Levetiracetam. He then developed clusters of repeated outstretching of his arms for 10 minutes, unfortunately not captured on EEG. Background EEG remained unchanged. Vigabatrin was added. Between 6–8 months he developed episodes of head turn to left, eye deviation to the right, flexor spasms of arms and trunk but no EEG correlates were recorded. He was treated with Nitrazem but continued to have non-epileptic movements and epileptic seizures and died at 13 months from pneumonia.

**Conclusions:** Non-epileptic movements can occur alongside epileptic seizures in Menkes disease. Neurophysiology is helpful in differentiating between the two to aid management.

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**Epidemiology of paediatric acquired brain injury requiring early rehabilitation in the UK**

L HAYES, MS PEARCE, RJ FORSYTH
Newcastle University

The health impact of paediatric Acquired Brain Injury (ABI) is increasingly recognised. Secular trends have seen falls in the incidence of TBI associated with road traffic accidents although improvements in intensive care management have increased survival after severe illness, sometimes at the expense of brain insult. Although data on incidence of conditions potentially causing ABI and disability are available there is little data on rates of survival with significant disability and thus population needs for rehabilitation.

**Methods:** We used anonymised, individual patient-level Hospital Episode Statistic (HES) data from the NHS Information Centre (HSCIC) to infer “probable severe ABI needing early
Severe ventriculomegaly diagnosed at late gestation: etiology, prognosis and implications for counseling

A DALL’ASTA1,2, N VAN OOSTRUM3, N BASHEER2,4, G PARAMASIVAM2, T GHI1, L GALLI1, I GROENENBERG3, T FRUSCA1, A GO3, C LEES2,5,6
1University of Parma, Parma, Italy; 2Centre for Fetal Care, Queen Charlotte’s and Chelsea Hospital, Imperial College Healthcare NHS Trust, London, UK; 3Department of Obstetrics, Gynaecology and Prenatal Diagnosis, Erasmus Medical Centre, Rotterdam, Netherlands; 4Department of Paediatric Neurology and Neonatal Medicine, Hammersmith Hospital, London, UK; 5Imperial College London, London, UK; 6Department of Development and Regeneration, KU Leuven, Leuven, Belgium

Objectives: Severe Ventriculomegaly (VM), defined by ventricular width 15 mm or above may be isolated or associated with additional pathologies. Severe VM presenting at 20 weeks is usually associated with a poor prognosis. This study was designed to assess causes and prognosis of severe VM diagnosed after 24 weeks gestation.

Methods: Multicentre retrospective study involving three European teaching hospitals. Inclusion criteria were normal brain anatomy at 20 week anomaly scan, uni/bilateral finding of posterior ventricle measuring >15 mm and available information about neonatal and postnatal assessment by Paediatric/Neurology services.

Results: Thirty cases were enrolled at a median gestation of 33 ± 5 weeks (25–40) weeks. VM was unilateral in 6 cases, bilateral in 24. Agenesis of the corpus callosum (ACC) and intraventricular haemorrhage (IVH) accounted for 9 and 8 cases respectively. ACC was isolated in 7 fetuses and associated with interhemispheric and porencephalic cyst in two. Grade 3 and 4 IVH were reported in 5 and 3 cases respectively. Obstructive abnormalities included 2 arachnoid cysts, 1 cavum velum interpositum cyst and 1 aqueduct stenosis. Five fetuses had an associated genetic syndrome, and there was one case of Toxoplasmosis. One neonatal death and 3 terminations of pregnancy were recorded. Twenty-six fetuses had postnatal neurological assessment up to a median age of 13 months (1–84); 12/26 babies had normal neurodevelopmental outcome (4 ACC, 3 Grade 3 IVH). All cases of genetic syndromes were associated with delayed neurodevelopment.

Conclusions: One half of babies with severe VM diagnosed after 24 weeks have normal infant outcome with ACC and IVH representing the most common causes. Etiology appears to be the most important factor affecting the prognosis of fetuses with severe VM diagnosed at late gestation.

Course and outcome of post-neonatal presentations of vein of Galen malformation

V GOPALAN1, V GANESAN2,3, A RENNIE4, F ROBERSTON5, C TOOLIS3
1University College London Medical School, London, UK; 2Developmental Neuroscience, UCL Institute of Child Health, 3Neurology, Great Ormond Street Hospital, London, UK; 4Radiology, Great Ormond Street Hospital, London, UK

Objective: To describe presentation, clinical course and outcome in children with post-neonatal presentation of vein of Galen malformation (VGM).

Methods: Children presenting to GOSH >28 days of age with a diagnosis of VGM after 01/01/2006 were included. Case notes/scans were reviewed. Outcome was assessed using the Recurrence and Recovery Questionnaire (RRQ), with subsequent dichotomisation into ‘good’ or ‘poor’ outcomes. Univariable logistic regression was performed to explore the relationship between clinico-radiological features (presence of brain injury, presence of abnormal venous outflow and presence of hydrocephalus) and outcome, with the intention of entering significant predictors into a multi-variable model.

Results: 30 children were identified; median age of presentation was 9.6 months (range=1.2 months-7.0 years). The most common presenting features were macrocrania (n=23) and prominence of facial veins (n=9). Seven children had evidence of cardiac failure and VGM morphology was choroidal in 18. Hydrocephalus (n=23) and venous congestion (n=19) were the most prevalent radiological features, and white matter volume loss (n=14) was the most common pattern of brain injury. 29 patients were treated with trans-arterial glue embolisation; the remaining one patient had spontaneous VGM closure. All patients required recurrent treatments (median=2 per child). Angiographic exclusion was achieved in 21 of 27 survivors.
Three children died of catastrophic spontaneous intracranial haemorrhage (1, 30 and 363 days post-embolisation). Ten patients underwent neurosurgical procedures; to treat haemorrhage in four and hydrocephalus in the rest. On the RRQ, outcome was categorised as good in 20 of 27 survivors, but this was not predictable based on the variables listed above. **Conclusions:** VGM has distinctive clinical and radiological features when it presents beyond the neonatal period. This is attributable to venous hypertension rather than circulatory overload or arterial ischaemia in the brain. Endovascular treatment is generally associated with good outcomes, but more specific prognostic prediction is not yet possible.

**Frontal lobe white matter abnormalities in children and young adults with sickle cell anaemia: relationship with overnight oxygen saturation and size of silent cerebral infarction**

J M KAWADLER¹, H STOTESBURY¹, F J KIRKHAM²
¹Developmental Imaging & Biophysics Section, UCL Great Ormond Street Institute of Child Health; ²Clinical Neurosciences, UCL Great Ormond Street Institute of Child Health

**Background:** Sickle cell anaemia (SCA) is associated silent cerebral infarction (SCI), typically in frontal deep white matter. The study investigates frontal lobe white matter tracts in patients undergoing overnight oximetry for the Phase II Prevention of Morbidity in Sickle Cell Anaemia (POMS) trial of auto-adjusting CPAP.

**Methods:** Forty-two patients with SCA (23 male, 8-25 years) and sixteen sibling controls (3 male, 8-26 years) underwent MRI at Great Ormond Street Hospital on a 3T Siemens Prisma with T2-weighted turbo spin echo, FLAIR, T1-weighted MPRAGE and multishell diffusion-weighted sequences. TRACULA was applied, which uses a global ball-and-stick probabilistic tractography algorithm, to segment the genu and splenium of the corpus callosum, and left- and right- anterior thalamic radiations, cingulum, superior longitudinal fasciculus and uncinate fasciculus.

**Results:** After correcting for age, gender and their interaction, patients showed significantly lower fractional anisotropy (FA) in left/right anterior thalamic radiations, higher mean diffusivity (MD) in left/right anterior thalamic radiations, left cingulum and left superior longitudinal fasciculus, and higher radial diffusivity (RD) in left/right anterior thalamic radiations and left/right uncinate fasciculus (all p < 0.05). Mean overnight oxygen saturation (SpO₂) significantly correlated with FA (r=0.380, p=0.022), MD (r=−0.331, p=0.049) and RD (r=−0.409, p=0.013) in the splenium, and significantly correlated with FA in the left anterior thalamic radiation (r=0.406, p=0.014). Similar correlations were seen with minimum overnight SpO₂ and FA (r=0.391, p=0.018) and RD (r=−0.339, p=0.043) in the splenium. Furthermore, in 16 patients with SCI in the frontal lobes, manual volumetric tracing of SCI revealed a negative trend between lesion size and FA (r=−0.437, p=0.09) and a positive trend between lesion size and RD (r=0.444, p=0.086) in the genu of the corpus callosum.

**Discussion:** These results confirm the association between SpO₂ and interhemispheric white matter in SCA. Improving overnight SpO₂ may improve DTI metrics.

**Incidence of primary stroke in a cohort of Nigerian children with sickle cell disease and elevated TCD velocities treated with hydroxyurea**

IA LAGUNJU, BJ BROWN, OO SODEINDE
Department of Paediatrics, University College Hospital, Ibadan, Nigeria

**Background:** Elevated transcranial Doppler (TCD) velocities accurately predict stroke risk in children with sickle cell disease (SCD). Chronic blood transfusion, the gold standard for primary stroke prevention is faced with numerous challenges in resource-poor countries. Hydroxyurea (HU) has been shown to reduce elevated TCD velocities in children with SCD.

**Aim:** To determine the effectiveness of HU in reducing the risk of primary stroke in a cohort of Nigerian children with SCD and elevated velocities treated with HU.

**Methods:** Prospective, observational study. Children with SCD and elevated TCD velocities > 170 cm/sec treated with HU were prospectively followed for a minimum period of 12 months to determine annual incidence of primary stroke in the cohort.

**Results:** Eighty-six children, 46 males and 40 females were enrolled into the study. Their ages ranged from 2 to 16 years with a mean of 7.1 years. At first TCD examination, velocities ranged from 175 to 245 cm/sec, mean (SD) 196.0 (13.3) cm/sec. TCD velocities were in the conditional risk (CR) and abnormal risk (AR) range in 26 (30.2%) and 60 (69.8%) children respectively. Duration of follow up ranged from 1 to 7 years with a mean of 3 years. Mean TCD velocities showed a significant decline to 174.7 (SD=21.9) cm/sec (p < 0.001). One stroke event occurred in the cohort, giving a stroke incidence of 0.7/100 person years. None of the children with CR velocities progressed to AR.

**Conclusion:** Hydroxyurea significantly reduces TCD velocities in Nigerian children with SCD and elevated TCD velocities. This is accompanied by a corresponding reduction in the incidence of primary stroke. Hydroxyurea may represent a potential alternative for primary stroke prevention in resource-poor countries where chronic transfusions are faced with a myriad of challenges and the burden of SCD resides.

**International study of the natural history, associated comorbidities and treatment of CDKL5-disorder**

S AMIN¹, J PATEL¹, A MAJUMDAR³, AA MALICK¹, A LUX², C PARTRIDGE²
¹University Hospitals Bristol; ²CDKL5 UK

**Introduction:** CDKL5 is a genetic condition associated with drug-resistant epilepsy and intellectual disability. The function of the CDKL5 gene is not well understood and there is limited information on its natural history. We investigated the
natural history, complications, and the effectiveness of current treatment strategies.

Methods: This study was conducted in conjunction with the charity CDKL5 UK, with patients recruited from the USA and Europe. Online questionnaires were completed by parents/carers and included information relating to demographics, growth, development, epilepsy, comorbid conditions, and efficacy and side effects of antiepileptic treatments. The assessment of AED response was qualitative.

Results: Thirty-nine of the 44 patients were female. Median age was 5 years (range 5 months to 31 years) and all had a history of epilepsy.

All patients had developmental delay, with 15% able to run and 10% climb. Cardiovascular and gastrointestinal problems were reported in 29% and 72% respectively. Arrhythmia was seen in 40%.

The first five most commonly used AEDs were levetiracetam, which was reportedly the most effective AED in 3/34 (9%) cases; sodium valproate [most effective in 3/27 (11%)]; topiramate [most effective in 0/22 (0%)]; phenobarbitone [most effective in 0/19 (0%)]; and Vigabatrin [most effective in 13/19 (68%)].

VNS was reported to be effective in 9/12 (75%). 1 year after insertion 75% reported improved QoL, and mood, school achievement and concentration in 80%. Ketogenic diet was effective and improved QoL in 53%.

Conclusion: Vigabatrin appears to be more effective than other AEDs. VNS and ketogenic diet are also relatively effective. Gastrointestinal and cardiovascular system complications are common. All patients had developmental delay of varying severity. The results may help guide management of epilepsy in CDKL5 and potentially treatable life threatening complications such as arrhythmia.

Session 6 13th January 2017

Growth patterns and fractures in boys with Duchenne muscular dystrophy: insights from over 800 boys in the UK North star cohort (Presented on behalf of The North Star Clinical Network)

S JOSEPH1,2, K BUSHBY3, M GUGLIERI3, SF AHMED2, SC WONG2, I HORROCKS1, NORTH STAR CONSORTIUM*

1Paediatric Neurosciences Research Group Department of Paediatric Neurology, The Royal Hospital for Children, Glasgow, UK; 2Developmental Endocrinology Research Group The Royal Hospital for Children & School of Medicine, University of Glasgow, Glasgow, UK; 3Institute of Human Genetics, International Centre for Life, Newcastle University, Newcastle, UK; *North Star Clinical Network

Background: There is little information on growth and fractures in boys with Duchenne Muscular Dystrophy (DMD).

Objective & Hypothes: To determine the extent of growth & skeletal morbidity in a contemporary cohort of DMD in the UK.

Method: Clinical details of 832 boys with DMD in the North Star database (2006–2015) from 23 centres were analysed the following categorisation into five age groups: A:<5 years (n,113), B:5–7.9 years (384), C:8–10.9 years (421), D:11–13.9 years (299) and E:<14 years (160).

Results: Proportion of boys on glucocorticoids (GC) ranged from 36% in GroupA to 88% in GroupC. The proportion of non-ambulant boys was 26% in GroupD and 56% in GroupE. Of the 46 GC-naive boys in GroupA, 10/46 (22%) had height standard deviation score (HtSDS)< -2.0. Median HtSDS in GroupE was –1.8 (~4.9, 1.0) with 48% <-2.0SD. The difference between the HtSDS of boys on GC and not on GC was only significant in Group B, D and E (p < 0.05). The number of boys with new reports of all fractures in the five groups were 7(6%), 23(7%), 51(12%), 52(17%), 31(19%), respectively. New symptomatic vertebral fractures (VF) were reported in Groups B-E: 2/384 (0.5%), 7/421 (1.7%), 6/299 (2.0%) and 8/160 (5%), respectively.

Conclusion: In the largest cohort of boys with DMD to date with height and fracture data, short stature was already evident in 22% of young GC-naive boys and its pathophysiology need further investigation.

VF are present across the age spectrum and the relationship between back pain and VF in this age group requires further exploration.

Proof-of-mechanism in humans of oral selective SMN2 splicing modifiers for the treatment of Spinal Muscular Atrophy

AM MARQUET, S STURM, H KLETZL, C CZECH, A POIRIER, T SEABROOK, L MUELLER, R KINCH, H RATNI, F METZGER, OS KHWAJA
Roche Pharmaceutical Research and Early Development, Basel, Switzerland

Objective: SMA is one of the leading genetic causes of death and disability in children and is caused by loss-of-function of the SMN1 gene. We have developed selective orally-available small molecules that modify splicing of the SMN2 pre-mRNA to promote inclusion of exon 7 and thereby increase levels of SMN protein. We aimed to demonstrate proof-of-mechanism of novel SMN2 splicing modifiers in healthy volunteers and patients with SMA.

Methods: We studied two molecules RG7800 and RG7916 in two First-in-Human studies in healthy volunteer subjects. In addition RG7800 was assessed in a 12 week multiple dose study in patients with type 2 and type 3 SMA (Moonfish Study).

Results: RG7800 and RG7916 were safe and well-tolerated at all dose levels tested. In both First-in-Human studies, we demonstrated human proof-of-mechanism by dose-dependent modulation of SMN2 splicing towards full-length mRNA. In the Moonfish SNA patient study of RG7800 we were also able to demonstrate exposure-dependent increase in SMN protein to levels that we predict to be efficacious in the clinic.
**Conclusions:** We have demonstrated human proof-of-mechanism of two novel oral and selective small molecule SMN2 splicing modifiers for the treatment of SMA. RG7916 is moving forward in clinical development and will enter clinical trials of safety and efficacy in patients with SMA.

**Skeletal muscle channelopathies: rare group of disorders but with common paediatric presentation**

*Objective:* Skeletal muscle channelopathies (SMC) are rare inherited childhood onset disorders. Average time to diagnosis from first symptom is 19 years which indicates a missed opportunity to treat them in childhood.

**Methods:** Retrospective case-note review of 40 genetically confirmed patients with SMC at a tertiary centre in the UK.

**Results:** 19 children were identified with sodium channel myotonia/paramyotonia congenita, 10 with myotonia congenita (chloride channel); Periodic paralysis in 7 (4 hyperkalaemic, 2 hypokalaemic and 1 normokalaemic); Andersen-Tawil syndrome in 2 and congenital myopathy with periodic myotonia/paramyotonia congenita, 10 with myotonia congenita. Time to genetic diagnosis ranged from 1–15 years. Age of symptom onset was from birth to 15 years; 10 children presenting in infancy with blepharospasm on crying, keeping fist / feet clenched, gasping in cold air or hypotonia and weakness.

The commonest presentation was with gait disorder in the myotonia group (10/10 chloride channel and 9/19 sodium channel mutation). Strabismus and diplopia occurred mainly in the sodium myotonia (10/19) and respiratory and/or bulbar symptoms occurred in 16/40. Contractures/seclerosis (3 myotonia congenita and 2 congenital myopathy) was also reported.

22 children had clinical myotonia. 14 (of the 17 done) had myotonic discharges on neurophysiology of which 3 had no clinical myotonia. 28 children were treated with good response (17 with Mexiletine and 11 with acetazolamide) and a majority needed school modifications (28/40; 70%).

**Conclusions:** There is a significant delay to diagnosis of channelopathies. They are an important differential for undiagnosed congenital myopathies. Myotonia is an important clue to diagnosis. Early recognition and treatment can prevent morbidity and aid in provision of timely support.

**Session 7 13th January 2017**

**Delineating the neurodevelopmental and electrophysiological phenotype associated with SYT1 mutation**

*K BAKER1, SL GORDON2, MA COUSIN3, S BOYD4, MA KURIAN4, FL RAYMOND1*

1Department of Medical Genetics, Cambridge Institute for Medical Research, University of Cambridge, Cambridge, UK; 2The Florey Institute, Melbourne, Vic., Australia; 3Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK; 4Great Ormond Street Hospital for Children NHS Trust and UCL Institute of Child Health, London, UK

**Objectives:** Synaptotagmin-1 (SYT1) is a calcium-binding synaptic vesicle protein required for both exocytosis and endocytosis. We recently reported the first human disorder associated with a rare variant in SYT1. We now present clinical and genetic data for the first seven identified cases, to delineate the neurodevelopmental and electrophysiological phenotype associated with de novo mutation in SYT1.

**Methods:** We collected molecular, clinical, imaging and electrophysiological data from patients with de novo heterozygous missense mutations in SYT1 identified within international diagnostic and research cohorts.

**Results:** The phenotypic spectrum associated with SYT1 mutations includes early-onset progressive hyperkinetic movement disorders, ophthalmic problems and central visual impairment, motor delay and intellectual disability of variable severity. Behavioural features include sleep disturbance, episodic agitation and hand-to-mouth stereotypy. Severe EEG disturbance characterised by low frequency high amplitude oscillations is a universal feature, although overt seizures have not been reported for any case and anti-epileptic medications are ineffective. All mutations altered highly conserved residues absent from control databases. Mutations cluster in a small region of the C2B domain, altering amino acids involved in calcium binding and predicted to regulate fast synchronous transmitter release.

**Conclusions:** SYT1 mutation is a recurrent neurodevelopmental disorder, with clinical features in keeping with a functional disorder of synaptic transmission. Characteristic EEG disturbance is a discriminating phenotype. Dominant negative disturbance to the calcium-dependent kinetics of synaptic vesicle cycling is proposed as the pathogenic mechanism and may offer novel treatment options.

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Landau Kleffner syndrome: clinical features and molecular genetic findings in a cohort of 50 patients

A NgoH1,2, M Clark2, R Greenaway2, R Thornton2, B Neville1,2, JH Cross1,2, D Kullmann2, R Harvey2, MA KuriAn1,2, R Thornton2, B Neville1,2, JH Cross1,2

1Developmental Neurosciences Unit, UCL-Institute of Child Health, London, UK; 2Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; 3National Hospital for Neurology and Neurosurgery, UCL Institute of Neurology, London, UK; 4Department of Pharmacology, UCL School of Pharmacy, London, UK

Introduction: Landau Kleffner syndrome (LKS) is a rare epileptic encephalopathy, with an estimated incidence of 1 in 978,000. It presents in the 3–10 year age range with language regression and characteristic abnormalities on electroencephalogram. Recently, mutations in the gene encoding subunit 2A (GRIN2A), have been reported in 8–20% of individuals with LKS and related focal epilepsies with aphasia3,4,5.

Methods: In this study, we (i) delineate the clinical features of our cohort (including response to treatment and long-term outcome) through retrospective case note review and (ii) determine the frequency of GRIN2A mutations using direct Sanger Sequencing and multiplex ligation probe amplification (MLPA) techniques.

Results: Fifty patients were identified. 82% had clinical seizures. The mean age of regression was 4.8 years (S.D. 2.1 years). 50% are now adults. In adulthood, approximately 28% remain dependent (unable to gain employment/in residential care), 44% are fully independent with no/minimal difficulties, and 28% are independent but have significant residual impairment of speech and language or continue to have seizures or neuropsychiatric symptoms. Age at onset of speech regression and below average non-verbal IQ showed statistically significant correlation with worse language outcomes. 12% of the cohort were positive for GRIN2A mutations. Mutations include frameshift, missense, and nonsense mutations. When compared to GRIN2A negative individuals, mutation-positive patients tended to manifest signs of regression at an older age and also had prominent symptoms of dyspraxia.

Conclusion: This is one of the largest reported cohorts of children with LKS with long-term follow up data, providing valuable information for prognostication. The frequency of GRIN2A mutations in this cohort is in keeping with previous studies confirming that LKS is likely to be genetically heterogeneous.

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Cannabidiol as add on therapy in children with complex epilepsy

K Vezyroglou1, C Eltze1, S Varadkar1, L Carr1, C O'Sullivan1, E Nininis1, JH Cross1,2

1Neurology, Great Ormond Street Hospital for Children, London, UK; 2Clinical Neurosciences, UCL Institute of Child Health, London, UK

Objective: To assess the efficacy and tolerability of cannabidiol (CBD) as an adjunctive treatment in children with drug resistant epilepsy.

Methods: An open label add-on compassionate use programme in children with drug resistant epilepsy. Oral CBD (Epidiolex®, GW Pharma) was initiated at 2 mg/kg/day in two divided doses and titrated up to an end dose of 16 mg/kg/day after 8 weeks, further up-titrated as tolerated. FBC, U+E, and LFTs were monitored every two weeks. Seizure frequency (via seizure diaries) and adverse effects were continuously assessed in weekly telephone calls.

Results: 24 children aged 2 to 19 (mean age 10) years were enrolled, with epilepsy of underlying structural (7), genetic (5), metabolic (1), inflammatory (3) and unknown (8) cause, December 2014 to June 2016. Patients had previously failed 3–11 antiepileptic drugs. Three continue in up titration with < 3 months of treatment. One received only 5 days of CBD treatment as part of acute treatment for ultimately fatal status epilepticus (presumed FIRES) and was excluded. In the remaining 20 doses reached 6–45 (mean 19.95) mg/kg/d. Eight (40%) reported >50% seizure reduction, while 12 (60%) showed little change. Adverse events were diarrhea (n=4, 20%), somnolence (n=2, 10%), loss of appetite (n=2, 10%), weight loss (n=1, 5%) and respiratory depression due to increased clozapam levels (n=1, 5%). In 4 patients (20%) transaminases increased, transient in three, but leading to CBD dose reduction in one. One patient died of pneumonia during the trial unrelated to CBD. After 1–19 months 7 discontinued treatment; Four due to lack of efficacy, and 3 lack of efficacy and side effects. All patients reporting benefit (n=8) continue treatment.

Conclusions: CBD was reasonably well tolerated in this challenging cohort of patients with very severe drug-resistant epilepsy with >50% seizure reduction in 40%. Randomized controlled trials are needed and are under way.

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Identifying and treating mental health disorders in children and young people with epilepsy: a screening and brief intervention study

S Bennett1, I Heyman1, A Coughtrey1, J Simmonds2, S Varadkar3, T Stephenson1, M Dejong2, R ShafraN1

1University College London, Great Ormond Street Hospital Institute of Child Health; 2Psychiatry, Great Ormond Street Hospital, London, UK

Objective: Children and young people with chronic neurological conditions have significantly higher rates of mental health disorders than those without a chronic health condition, or those with chronic illnesses that do not involve the CNS. Mental health problems can impact on quality of life as well
as on the management and medical consequences of the physical illness yet may be relatively easy to treat. However, such mental health disorders often go unrecognised and therefore untreated. The aim of the current study was to establish the feasibility of routine screening and brief telephone intervention for mental health disorders in paediatric neurology clinics.

Methods: Parents of children and young people aged 7–18 attending specialist paediatric neurology clinics were asked to complete an online screening questionnaire (the Strengths and Difficulties Questionnaire; SDQ) on a tablet computer in clinic. Those who had symptoms of a mental health disorder were invited to complete a longer online diagnostic questionnaire, the Development and Wellbeing Assessment (DAWBA), at home. Those with impairing symptoms were offered a 10-session guided self-help intervention delivered over the telephone. Standardised measures were completed before, during and after the intervention.

Results: The method of identification proved feasible in terms of numbers completing the SDQ (n=319, of which n=224 had significant symptoms of a mental health disorder) and DAWBA (n=121). 71% of those completing the DAWBA met DSM-V diagnostic criteria for a mental health disorder. 40 families took part in the brief intervention and results so far are promising, with progress made towards families chosen goals and high levels of satisfaction reported by families and clinicians.

Conclusions: Children and young people with chronic neurological conditions have high rates of mental health disorders. These disorders can be detected and treated through a simple online diagnostic tool and telephone intervention and this method is acceptable to families.