Catastrophic disruption of the blood-brain barrier in paediatric traumatic brain injury
– Dr Josie Fullerton

Background:

Traumatic brain injury (TBI) represents the leading cause of death in children and adolescents in the developed world. This age group appear uniquely vulnerable to catastrophic diffuse brain swelling (DBS) following TBI; however, the pathological mechanisms causing DBS in the paediatric patients remain unknown. In particular, although widespread disruption of the blood-brain barrier (BBB) in association with brain swelling has been well characterized in adults post-TBI, little is known of how this pathological change may contribute to DBS in paediatric TBI.

Methods:

From the Glasgow TBI Archive, paediatric cases were selected with acute survival from moderate to severe TBI (n=81; aged 3-18y) and compared with adult acute TBI (n=62; aged 19-60y). Multiple cortical regions were examined using immunohistochemistry markers of BBB integrity, fibrinogen (FBG) and immunoglobulin-G (IgG), and the extent, pattern and distribution of BBB disruption were assessed, together with the diameters of cortical vessels. Results: Widespread disruption in BBB, manifesting as multifocal, abnormal, perivascular FBG and IgG was present in adult (91.9%) and paediatric (80.2%) acute TBI cases. Whilst vessel diameters overall in paediatric and adult material were similar, an overwhelming majority (80.5%) of vessels showing evidence of BBB disruption in paediatric TBI cases were of capillary diameter (<10µm), compared to just 30.9% at this diameter in adults (p<0.001; Fisher’s exact test).

Conclusion:

These data suggest that, similar to adults, BBB disruption post-TBI is common in paediatric patients dying in the acute phase after injury. However, while the disrupted vessels in adult TBI where typically arteriolar or small artery in diameter, paediatric TBI BBB disruption preferentially involved capillary level vessels. These findings warrant investigation into the potential role of more subtle capillary damage from an initial TBI in predisposing the paediatric population to DBS/SIS. Supported by GCHC grant GCHC/SPG/2017/01.
Objectives:

We report the first study establishing normative developmental data on cognitive empathy with a large cohort, using a standardised measure of cognitive empathy ability.

Design: Participants (n=4545, aged <5 years to >75 years, 60% female) were visitors to the "Mindworks" exhibition at the Glasgow Science Centre over a sixteen-month period. Participation was voluntary; no identifying information was recorded other than age, sex and occupation.

Methods:

Participants completed a computerised version of the ‘Reading the Mind in the Eyes Test’. This standardised test of cognitive empathy involves viewing the eye region of the human face and selecting a mental state term describing what the person was ‘thinking or feeling’.

Results:

Cognitive empathy abilities showed three critical periods of development in childhood and early-adulthood where performance was significantly greater than previous age bands; 6-7yrs (p=0.048), 10-12yrs (p=0.042), and 19-25yrs (p=0.001), after which performance remained stable across adulthood before substantially declining in people aged >75yrs (p=0.001). The most significant difference was between the 13-18yrs and 19-25yrs age groups, suggesting that late adolescence/early adulthood is a critical point at which cognitive empathy skills reach maturity. Females performed better than males at all ages (p<0.001); however, these differences were more prominent at several points across the lifespan.

Conclusions:

These findings provide significant value in understanding the influence of age and sex on the development of cognitive empathy ability, and have clinical utility in identifying social-cognitive deficits using standardised tests. Our findings are discussed in relation to a range of clinical disorders across the lifespan where the use of cognitive empathy tests could support early diagnosis/detection. Understanding developmental issues in cognitive empathy could also influence approaches to moral and social education.
Comprehensive Phenotyping and genotyping in a Scottish population-based cohort of children presenting with epilepsy < 3 years  -  Dr Joseph D Symonds

Background:

Early childhood is associated with a high age-specific incidence of epilepsy. Epilepsy is aetiologically heterogenous, though genetic factors play a major role. Genetic testing now allows a significant proportion of early-onset epilepsies cases to be aetiologically resolved.

Aims:

To calculate the difference that genetic testing has made to aetiological yield in early-onset epilepsy, and to investigate clinical associations with genetic aetiology.

Methods:

Early-onset epilepsy cases in the West of Scotland (population 2.65 million; 27,000 births per year) were identified from two independent sources: a prospective case identification study, and retrospective case note review of all children who had EEG investigation. Inclusion criteria were: 1. Diagnosis before third birthday and 2. Diagnosis between May 8th 2014 and May 7th 2017 All cases without identified aetiology after neuroimaging and metabolic tests were tested on a 104 gene epilepsy panel. Capture-recapture analysis was used to estimate missing cases. Follow-up was for a minimum of 12 months. Associations between clinical features of presentation, aetiology, and the development of drug-resistance and/or global developmental delay (GDD) were investigated using multivariate regression analysis.

Results:

The estimated total was 218 cases, making the incidence of epilepsy under three years 1 per 380 live births. 34% developed drug-resistance and 50% had GDD. 51% had an aetiology identified. Aetiologies were: 27% genetic; 20% structural; 3% metabolic; and 1% immune. Without genetic testing, only 24% of cases would have been resolved. Genetic testing increased diagnostic yield by 113% (p < 0.001). Identification of genetic aetiology was associated with drug-resistance (Odds ratio [OR] 4.34; 95% Confidence Intervals [CI] 2.34-8.07) and GDD (Odds ratio 2.54; 95% CI 1.40-4.63).

Discussion/conclusions:

One in 380 children will develop epilepsy before their third birthday, of whom one third develop drug resistance and half have GDD. Identifying a genetic aetiology is predictive of drug-resistance and developmental impairment.
Exomic sequencing uncovers novel genetic associations in children with hypospadias and neurodevelopmental abnormalities – Dr Gabriella Gazdagh

**Background:**

At the present time a molecular diagnosis is not reached in the majority of cases of hypospadias. Cohorts such as the Deciphering Developmental Disorders (DDD) Study represent a useful resource of large molecular and phenotypic datasets obtained from individuals with undiagnosed conditions including hypospadias.

**Objective:**

To review associated features and identify likely pathogenic variants in previously undiagnosed DDD participants with hypospadias and neurodevelopmental disorders.

**Method:**

Retrospective review of anonymised phenotype data and bioinformatic re-analysis of variant call format (VCF) files of 33 DDD participants (22 family trios and 11 singleton cases) manifesting hypospadias and neurodevelopmental abnormalities. A customised filter chain (using GoldenHelix, Varseq 1.4.4) specific to each inheritance pattern was created and searches were performed in genetic databases (Online Mendelian Inheritance in Man, PubMed and the Jackson Laboratory).

**Results:**

Analysis was undertaken in 238 and 155 phenotype entries, recorded in 22 family trios and 11 singleton cases, respectively. Additional features included ophthalmic (34/393, 7%), skull (19/393, 5%), skeletal (18/393, 5%) and hand (17/393, 4%) abnormalities. 3 previously unidentified, de novo variants in 3 genes, including CTNND1 and TRIO are described in the family trios. The CTNND1 gene encodes a protein which has a role in cell-cell adhesion and signal transduction and the TRIO protein is involved in actin remodelling, necessary for cell migration and growth. Variants in CTNND1 and TRIO are linked to blepharocheilodontic syndrome 2 and intellectual disability, respectively. Variant analysis of singleton cases revealed an additional variant in HIST1H1E gene, encoding a histone H1 protein. Mutations in HIST1H1E are linked to overgrowth and intellectual disability.

**Conclusion:**

Not only has exome sequencing proven a powerful tool for the investigation of conditions associated with hypospadias but it has also extended our understanding of the level of genetic heterogeneity that may be associated with disorders of sex development.
Acute Neurotoxicity during ALL therapy is associated with treatment intensity, age and female sex – An analysis of SAE reports from the UKALL 2003 Trial – Dr Qurat-ul-Ain Wahid

Background:

Chemotherapy for childhood acute lymphoblastic leukaemia (ALL) can cause acute and sub-acute central neurotoxicity, as well as potential long-term neurocognitive dysfunction. Currently little is known about risk factors for developing neurotoxicity, with most information coming from case-reports and small case-series.

Aims:

To investigate a large cohort of children undergoing ALL therapy to identify predictors of susceptibility to neurotoxicity and any impact on disease outcomes. Methods: From Oct 2003-June 2011, patients (1-24 years) enrolled in the UKALL2003 trial (n=3113) were included. Serious adverse event reports (SAE’s) were interrogated for neurotoxic events (seizures, encephalopathy, and arachnoiditis). Survival rates were analysed with Kaplan Meier methods, and log-rank tests and risk factors for neurotoxicity were investigated using the χ² test, univariate and multivariate logistic regression analysis.

Results:

There were 276 incidents of neurotoxicity in 254 patients (8.2% of all patients), 159 with encephalopathy, 86 with seizures and 9 others. The 254 patients were compared with 2837 controls without neurotoxicity. There was no significant difference in 5-year event-free survival, overall survival or relapse rate. Age (p=<.001), female sex (p= 0.008), treatment intensity (regimen B/C v A, (p= <.001), CNS status (CNS2/3/TLP v CNS1, p= <.001), showed a significant association with neurotoxicity and remained significant independent predictors on multivariate analysis.

Discussion/Conclusions:

Treatment intensity appears to be the main risk factor for developing acute neurotoxicity, with female sex, age and CNS status having a significant modifying effect. CNS status may reflect increased intrathecal therapy given to non-CNS-1 patients. This is the first report of female sex as a risk factor for patients on contemporary protocols. Though neurotoxicity events did not influence survival rates, these add to the burden of acute and chronic illness. These data provide a benchmark for ongoing international deep phenotyping studies of chemotherapy-associated neurotoxicity.