Rochester Minnesota was 1 per 614. One third of these children develops DRE and half have GDD. Aetiology can be identified in 54%. Identification of aetiology is associated with DRE and GDD.

Plenary

P07 ONASEMNOGENE ABEPARVOVEC GENE-REPLACEMENT THERAPY (GRT) FOR SPINAL MUSCULAR ATROPHY (SMA): FROM BENCH TO BEDSIDE

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Aims Report onasemnogene abeparvovec (formerly AVXS-101) GRT development for SMA. Onasemnogene abeparvovec is a one-time, intravenous GRT that addresses the genetic root cause of SMA, a progressive neurological disease. Onasemnogene abeparvovec delivers the survival motor neuron gene (SMN) via a self-complementary adeno-associated serotype 9 viral vector (scAAV9) that crosses the blood-brain barrier. Onasemnogene abeparvovec is designed for immediate and sustained expression of SMN protein in non-dividing neurons, allowing for rapid onset and durable therapeutic effect.

Methods SMA mice (SMN2^{+/+}; SMNΔ7^{+/+}; *Smn*^{-/-}) received intravenous scAAV9-SMN or scAAV9-GFP at post-natal day 1; survival and motor function were assessed. Non-human primates (NHPs) received intravenous scAAV9-GFP; transduced cell types were assessed. A phase 1/2a study (START; NCT02122952) evaluated onasemnogene abeparvovec infused at low (Cohort 1, n=3) or high (Cohort 2, n=12) doses in symptomatic SMA type 1 (SMA1) infants; patients were followed for 2 years for safety/tolerability and efficacy and could enroll in a long-term follow-up (LTFU) study to assess long-term safety.

Results In SMA mice, scAAV9-SMN improved survival (>200 versus 15 days in controls), and increased motor function. In NHPs, scAAV9-GFP efficiently targeted motor neurons throughout the central nervous system. In the phase 1/2a START trial, all patients survived free of permanent ventilation at 24 months. In the high-dose cohort, 11/12 patients reached CHOP INTEND >40; 11 sat unassisted ≥5s, 10 for ≥10s, 9 for ≥30s. Two patients crawled, stood, and walked. No patient received nusinersen during the 24-month study period. In the LTFU study, 2 more patients in Cohort 2 have gained the motor milestone of standing with assistance (as of 31 Dec 2019); neither patient has ever received nusinersen. No new treatment-related serious adverse events or adverse events of special interest have occurred in LTFU (as of 31 Dec 2019). The oldest patient in Cohort 2 is aged 5.6 years, with 5.2 years of follow-up since onasemnogene abeparvovec dosing.

Conclusion Onasemnogene abeparvovec has demonstrated unprecedented outcomes in patients with SMA compared with untreated natural history. Phase 3 trials of onasemnogene abeparvovec in SMA1 are ongoing (US, EU, Asia-Pacific); additional trials are investigating presymptomatic SMA and intrathecal administration in older patients.

G32 IMPROVING SURVIVAL OF THOSE WITH CEREBRAL PALSY IN ENGLAND AND WALES OVER THE LAST 18 YEARS

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Aims To assess the rate of change in median age of death over time, where cerebral palsy (CP) is documented as a cause of death, with reference to all-cause mortality in England and Wales.

Methods Published death registration statistics for England and Wales for all-cause mortality as well as ICD 10 code 'G80 – Cerebral Palsy' were extracted from the WHO Causes of Death Query online for 2001–2016 and the Office for National Statistics for 2013–2018. This captures those who died, where cerebral palsy was documented in part 1 of the death certificate. Linear interpolation was used to calculate the median age of death for the different groups. Data was imported into SPSS and linear regression was used to assess trends.

Results Median age of death was significantly lower in the CP group compared to the general population, with the median age of death increasing from 22.5 in 2001 to 49.6 in 2018. The trends in median age of death from 2001–2018 in England and Wales are highlighted in table 1.

Abstract G32 Table 1 Change in median age of death (in life years per year) from 2001–2018 in England and Wales

	Cerebral Palsy	All Causes
Combined	+1.59 (95%CI 1.19 to 1.99)	+0.15 (95%CI 0.11 to 0.18)
Male	+1.61 (95%CI 1.23 to 1.99)	+0.14 (95%CI 0.13 to 0.15)
Female	+1.46 (95%CI 0.88 to 2.04)	+0.11 (95%CI 0.10 to 0.12)

Conclusion The increasing median age of deaths due to CP hints at improved survival due to improvements in care. The rate of this improvement is significantly greater than that of the general population.

These death registration data cannot directly report improved survival. However, this finding is supported by the absolute numbers for registration of deaths due to CP remaining constant. Prolonged survival may therefore be inferred by the increasing median age of death.

G33 EACH AND EVERY NEED – A COMPLETED AUDIT CYCLE OF ACUTE CARE RECEIVED BY CHILDREN WITH CHRONIC NEURODISABILITY

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Aims In 2018 the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) launched 'Each and Every Need: a review of the quality of care provided to patients 0–25 with chronic neurodisability' detailing the standards of care relating to both acute and community care. Our experience was that these were not being met when our complex

community patients were admitted to the acute inpatient setting. We therefore audited the standards relating to inpatient care which included the need to record the cause of neurodisability on admission, on daily ward rounds and at discharge, recording of a child's mobility, communication and if a child had a handheld patient record (or if one was recommended).

Methods We retrospectively audited 30 children admitted over a 1 year period, randomly selecting 10 elective admissions, 10 emergency admissions with short stay spells (<24 hours) and 10 longer term emergency admissions (>24 hours). Baseline data is shown in the table 1. Our short-term interventions following baseline data collection included delivering teaching to all ward doctors about the children with neurodisability & why these aspects of care were important to record and attaching a prompt sheet to notes trolleys. A re-audit of 10 patients over the next 2 months (limited numbers due to reduced summer admissions) showed improvement in all areas.

Results

Abstract G33 Table 1

	Baseline (30 patients)	After Intervention (10 patients)
Cause of neurodisability recorded:		
On Admission	87%	100%
Daily Summary	60%	90%
In discharge documentation	67%	100%
Mobility Recorded	3.3%	60%
Mode of Communication recorded	6.6%	50%
Patient Held Record (had or offered)	10%	60%

Conclusions Our short term intervention, which did not require any hospital committee approval or funding, showed significant improvement in our documentation towards the NCEPOD standards allowing us to better support these families. We have also designed a proforma for medical notes which is in the process of going through health records approval and will be re-audited once introduced.

G34 UK CHILDREN WITH PROGRESSIVE NEUROLOGICAL DISEASE: DIFFERENTIAL DIAGNOSES BY AGE

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Aims To review the cases referred to this UK-wide study of children with progressive intellectual and neurological deterioration (PIND) and analyse the differential diagnoses in these children by age at presentation.

Methods Children meeting the case definition for PIND were identified via the British Paediatric Surveillance Unit. Data were obtained by standard questionnaire, with additional information from hospital records and laboratory reports, allowing validation of diagnoses and estimation of the age of presentation to clinicians.

Results Between April 1997 and October 2019, 4612 children had been notified to the study. 2072 were found not to meet the PIND case definition. 2009 had an underlying diagnosis to explain their deterioration; of these the numbers presenting by age were: <1 year 805 (40%), 1–4 years: 825 (41%), 5–9

years 265 (13%), 10–15 years 114 (6%), with over 220 different disorders including 6 cases of variant Creutzfeldt-Jakob disease (vCJD) (the last identified in 2000). The children who presented aged 10–15 years included the 6 vCJD cases. Of the other disorders in this age group the commonest were: mitochondrial cytopathy (mito) 17, adrenoleukodystrophy (ALD) 9, Lafora body disease 8, Niemann-Pick type C 8, Huntington's disease 7, neuronal-ceroid lipofuscinoses (NCL) 7, SSPE 5, metachromatic leukodystrophy 4, Wilson's disease 4. The distribution of disorders varied with age e.g. the 3 commonest disorders in the other age groups were - 5–9 years: NCL, ALD, mito; 1–4 years: NCL, mucopolysaccharidosis III, mito; < 1 year: mito, GM2-gangliosidosis, Krabbe's disease.

Conclusion Since 1997 the PIND Study has provided unique epidemiological data about neurodegenerative diseases in UK children. It shows that children meeting the criteria for PIND tend to present early in life (over 80% before the age of 5 years) – not surprising because of the inherited basis for so many of these disorders. The study provides a differential diagnosis for PIND children by age and remains the only means of performing systematic surveillance of the neurodegenerative diseases that make up the differential diagnosis of vCJD.

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G35 NATIONAL SURVEILLANCE OF SEVERE MICROCEPHALY DIAGNOSED IN INFANTS IN THE UNITED KINGDOM AND IRELAND

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Background Severe microcephaly is defined by WHO as a head circumference (HC) more than 3 standard deviations below mean (<-3SD) for age and sex. Although UK congenital anomaly registrations suggest microcephaly is uncommon, there is uncertainty about the number of babies affected each year. To monitor emerging infections, such as Zika Virus, and understand the impact on health and neurodevelopment, it is essential to characterise the current burden of disease.

Aim To report the incidence, characteristics and causes of severe microcephaly diagnosed in children aged under one year in the UK and Ireland.

Methods Active surveillance through the British Paediatric Surveillance Unit for 13 months from October 2017 to ascertain all live born children aged under 1 year who were diagnosed during this period with microcephaly or noted to have a HC <-3SD or <0.4th percentile for age and sex, excluding babies with anencephaly. Clinicians who reported a child completed a clinical questionnaire.

The annual incidence of severe microcephaly was calculated for infants with HC <-3SD for age and sex. For all other analyses, children with HC <0.4th percentile were also included. All reported findings are based on confirmed cases to date.

Results The annual incidence of severe microcephaly (HC <-3SD) between November 2017 and October 2018 was 5.6