follows: impaired glucose tolerance (19%) and CF-associated diabetes mellitus (43%). Calculated indices of insulin resistance (Homa and Caro) showed that 71% of patients with carbohydrate metabolism disorders had a decrease in Caro (<0.332) on the 120th minute of the oral glucose tolerance test, which indicated insulin resistance.

The average HbA1c levels in children with CF-associated diabetes mellitus were $7.3 \pm 3.4\%$, children with glucose tolerance – $6.3 \pm 0.4\%$ and in children with normal carbohydrate metabolism – $5.8 \pm 0.3\%$.

The CGMS assessment detected hyperglycemia in 81% patients, while carbohydrate metabolism disorders were diagnosed only in 28% of the cases. Stable postprandial hyperglycemia was detected with CGMS in 91% children aged ≥ 11 and 64% in group 3–11.

The 74.4% patients had delF508 mutations (homozygous–32%). All the cases of CF-associated diabetes mellitus were diagnosed in these patients.

Conclusions The incidence of carbohydrate metabolism disorders in CF-children was reliably higher than in overall population (28%). Carbohydrate metabolism disorders and CF-associated diabetes were reliably more frequent in children over 11 years of age.

Insulin resistance must be the most likely cause of carbohydrate metabolism disorders.

CGMS in patients with cystic fibrosis helps to detect hidden hyperglycemia that cannot be detected with the help of standard methods.

Carbohydrate metabolism disorders and CF-associated diabetes mellitus are more frequent in patients with delF508 mutation.

OC45 POLYCYSTIC OVARIAN SYNDROME IN ADOLESCENTS: UTILISING DISCOVERY PROTEOMICS TO IDENTIFY NOVEL NON-INVASIVE BIOMARKERS

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10.1136/archdischild-2019-epa.43

Background Polycystic ovarian syndrome (PCOS) is the most common hormone disorder in females, affecting 4–20% of the population. PCOS is associated with metabolic dysfunction, pro-inflammation and mood disorders. Despite this, it is poorly understood, and diagnosis and management remain challenging in adolescents. Proteomics enables a better understanding of disease mechanisms and facilitates the identification of novel biomarkers.

Aims

1. To better understand the clinical phenotype of PCOS in adolescents.

2. To undertake discovery proteomic urine profiling using ultra-performance liquid chromatography-mass spectrometry (UPLC-MS/MS) to identify novel non-invasive biomarkers of PCOS.

Method In this prospective longitudinal study, females aged 12–19 years meeting NIH diagnostic criteria for PCOS were recruited from adolescent endocrine and gynaecology clinics. At baseline and annual follow-up, the following were measured: pituitary, adrenal and ovarian hormones, anti-Müllerian

hormone, inflammatory and metabolic markers including an oral glucose tolerance test, psychometric questionnaires, menstrual records, pubertal assessment, anthropometric parameters and pelvic ultrasounds. We have undertaken UPLC-MS/MS and developed new methods for discovery proteomic profiling of urine samples in an attempt to identify new disease mechanisms, drug targets and potential biomarkers.

Results To date, 37 participants have been recruited (median age 15.0 years, range 12.6–18.3), and 22 have completed annual follow-up. Clinical signs at presentation included acne (89%), hirsutism (78%), acanthosis nigricans (49%) and overweight/obesity (81%). Two-thirds of participants had depressive or anxiety symptoms. Only one-third were known to mental health services. Metabolic dysfunction was common; elevated body fat (88%), dyslipidaemia (24%), insulin resistance (62%), and impaired fasting glucose, impaired glucose tolerance or type 2 diabetes (40%). AMH was elevated in one-third of participants and three-quarters had an elevated free androgen index. Elevated inflammatory markers (CRP/ESR) were present in 40% participants. Only three participants had definitive ultrasonographic evidence of PCOS. Interventions included lifestyle advice only (27%), combined oral contraceptive pill (COCP) $\pm$ anti-androgen (16%), metformin (30%) or metformin + COCP $\pm$ anti-androgen (27%).

Conclusion and Future Directions Diagnosing PCOS in adolescents remains challenging; acne and irregular menstrual cycles are common and ultrasonographic diagnosis of PCOS is sub-optimal. Given the high prevalence of metabolic and mental health disorders, early diagnosis and intervention are imperative. We describe the use of urinary proteomics to study metabolic pathways affected in PCOS and the potential identification of novel non-invasive biomarkers. Subsequently, we will use this hypothesis-generating data-set to create a non-invasive and clinically translatable assay to aid diagnosis and stratify management of this common adolescent condition.

OC46 THE POPULATION INCIDENCE OF CHILDHOOD GONADOBLASTOMA OVER 20 YEARS IN THE REPUBLIC OF IRELAND

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10.1136/archdischild-2019-epa.44

Background Gonadoblastoma (GB) is a rare tumour of the gonads presenting in childhood or adolescence. It is a lesion composed of a mixture of germ cells at different stages of maturation, with low malignant potential. It is associated with disorders of sex development, most commonly Turner mosaic syndrome with Y chromosome material (TMSY), and 46XY gonadal dysgenesis (GD). Little is known about the natural history and incidence, however prophylactic gonadectomy is recommended.

Objectives To determine the incidence and clinical features of GB presenting in childhood in the Irish Republic (RoI) from 1999–2018 inclusive.

Methods A retrospective review of children and adolescents with a diagnosis of GB was undertaken using the records of the National Cancer Registry Ireland (NCRI) and the

Departments of Endocrinology, Pathology and Surgery at the main children's hospitals.

Results Fifteen cases of gonadoblastoma were identified, all except one phenotypically female. Fourteen patients had prophylactic gonadectomy and one presented with an ovarian mass and raised tumour markers. Eight had TMSY (age at gonadectomy 2 weeks – 14 years). Seven were phenotypically female and one was male. Seven cases of 46 XY GD (all female phenotype) were diagnosed with gonadoblastoma with an age range of 4 months – 15 years at time of surgery. Four of these were unilateral. In the remaining three cases, one patient had bilateral gonadoblastoma, one had unilateral dysgerminoma and contralateral gonadoblastoma and the third had bilateral dysgerminoma with features of gonadoblastoma.

Conclusions This is the first reported population incidence rate of GB in children with a 20 year incidence of gonadoblastoma in the Republic of Ireland of 1/100,000 live births. The data supports the recommendation for elective gonadectomy in high risk conditions. Due to the wide age range in presentations, however, the timing of gonadectomy should be individualised, based on underlying diagnosis and following multidisciplinary team discussion. The true rate of malignant transformation in early onset GB remains to be studied.

OC48

RE-INTERROGATION OF WHOLE EXOME SEQUENCING DATA IN DEVELOPMENTAL EPILEPTIC ENCEPHALOPATHIES

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10.1136/archdischild-2019-epa.45

Introduction The severe epilepsies of infancy and childhood are a heterogeneous group of severe epilepsies characterised by several seizure types, where the epileptic activity in addition to the seizures contributes to cognitive impairment or regression. They account for a significant proportion of the refractory epilepsies and are usually associated with poor outcome.¹ The term developmental epileptic encephalopathies (DEE) is now the preferred term for this group of children. It may be the result of a specific congenital or acquired structural brain lesions, metabolic disorders, chromosomal abnormalities, copy number variants or single-gene defects.

Next-generation sequencing (NGS) includes gene panels, whole-exome sequencing (WES) and whole-genome sequencing. The reported rates of diagnosis in DEE using NGS technology ranges from 10–100%. We previously reported a cohort of 50 patients who underwent single research WES for investigations of DEE. The yield at the time of publication was 22% (11 known epilepsy gene, 1 candidate gene).² 38 patients remained undiagnosed. Since then, the number of new genes reported with DEE continues to expand and the technology improved to aid interpretation of variants. Therefore, we reanalysed WES data, with the addition of parental samples for trio analysis, to enable data interpretation and identification of pathogenic disease-causing variants.

Methods Re-analysis of WES data, single (proband only) or trio (proband and parents)WES, if parental samples were available.

Results We identified a genetic cause in 25 individuals in the cohort; 22 pathogenic variants in DEE genes, 3 candidate genes, increasing the diagnostic yield to 50%. With re-analysis, we identified 10 pathogenic variants (*CDKL5*, *KCNA2*, *NRXN1*, *PRODH*, *RELN*, *RHOBTB2*, *SCN1A*, *SLC1A4*, *SMC1A*), 1 candidate gene (*NAPB*) and 1 variant of uncertain significance (*GRIN2A*). A number of genes had not been identified at the time of initial analysis, including *RHOBTB2*, *SLC1A4*, *SMC1A*. Two mosaic variants in *CDKL5* and *SCN1A* were identified with trio WES analysis and reducing read depth filter to 15, previously set at 20.

Discussion This study highlights the importance of the re-interrogation of WES data for newly discovered genes. Trio WES had a higher diagnostic yield (50% compared to 22%) in keeping with previous studies. Trio WES is effective for the identification of *de novo* variants and aids in the interpretation of variants. Reducing read depth filter can aid the identification of mosaic variants, increasing reported to be important in DEE.

OC49

NON-ALCOHOLIC FATTY LIVER DISEASE IN OBESE AND OVERWEIGHT IRANIAN CHILDREN: A CROSS SECTIONAL STUDY

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10.1136/archdischild-2019-epa.46

Background Non-Alcoholic Fatty Liver Disease (NAFLD), the main cause of childhood liver abnormalities, is rising with the increase of pediatric obesity and overweight. This study aimed to investigate the prevalence of NAFLD and its predisposing factors in children of Urmia province, northwest of Iran.

Methods In this cross-sectional study, 508 overweight and obese children (251 boys) aged 6–19 years were recruited by convenience sample from the Shahid Motahari Hospital during 2016–2017. The anthropometric and laboratory measurement and abdominal ultrasonography for liver echogenicity and size were conducted. A questionnaire was also used to obtain information on demographical characteristic and alcohol consumption. Eligibility criteria were: (1) 6 ≤ age ≤ 19 years; (2) BMI > 85th percentile for gender and age (3) absence of any drug toxicity; (5) abstinence from alcohol; (6) absence of hepatitis B, C and Wilson's disease. Fatty liver was diagnosed by ultrasonography using standard criteria. Serum Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline Phosphate (ALK), Triglyceride (TG), Cholesterol (Chol), Low density lipoprotein (LDL) -cholesterol, High density lipoprotein (HDL)-cholesterol, Thyroid stimulating hormone (TSH) and glucose, were measured in children blood samples using standard laboratory methods. Insulin resistance was estimated using the homeostasis model assessment of the insulin resistance (HOMA-IR). Univariable and multivariable logistic regression and 95% confidence interval was used to evaluate predictors of NAFLD.