Results Primarily we compared thickness of subcutaneous adipose tissue in girls-carriers of different genotypes in both groups. Girls with android obesity - carriers of AA genotype, thickness of subcutaneous adipose tissue in breast was 1.1 ± 0.2 cm; AG genotype - 0.94 ± 0.2 cm; GG-genotype - 0.93 ± 0.2 cm ($p^{AA-AG} = 0.04$). Metabolism parameters: insulin in carriers of AA genotype was 25.2 ± 13.6 ; AG genotype - 15.5 ± 8.3 ; GG genotype - 18.1 ± 11.4 ($p^{AA-AG} = 0.01$); HOMA-IR, 6.1 ± 3.6 ; 3.4 ± 2.0 ; 4.4 ± 3.3 ($p^{AA-AG} = 0.01$), respectively. Leptin without statistically significant differences was elevated in AA genotype carriers 67.1 ± 25.1 , in contrast to carriers of AG and GG genotypes: 54 ± 26.6 ; 50.8 ± 26.5 , respectively. In girls with a gynoid obesity - carriers of AA genotype, thickness of subcutaneous adipose tissue in thighs was 2.0 ± 0.2 cm; AG genotype - 2.1 ± 0.3 cm; GG-genotype - 2.5 ± 0.8 cm ($p^{AA-GG} = 0.03$). Metabolism parameters: insulin in AA genotype carriers was 13.4 ± 5.1 ; AG genotype - 11.8 ± 6.3 ; GG genotype - 21 ± 14.2 ($p^{AA-GG} = 0.04$; $p^{AG-GG} = 0.02$). Leptin 34.5 ± 15.7 ; 32.2 ± 16.3 ; 55.8 ± 19.7 ($p^{AA-GG} = 0.005$; $p^{AG-GG} = 0.003$) respectively. HOMA-IR in carriers of AA genotype was 3.0 ± 1.6 ; AG genotype - 2.6 ± 1.4 ; GG-genotype - 4.5 ± 3.2 ($p^{AG-GG} = 0.04$).

Conclusions In girls of android morphotype, the carriage of A-allele is associated with carbohydrate and energy metabolism disorders, and is a risk marker of excess fat deposition in chest area. For a gynoid morphotype, G-allele is a risk marker and is associated with excessive fat deposition in the thighs, as well as with carbohydrate and energy metabolism disorders.

GP223 CREATINE DEFICIENCY DISORDERS THE ALL-IRELAND EXPERIENCE

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Background Cerebral creatine deficiency is caused by rare inherited disorders of either creatine biosynthesis (i.e. guanidinoacetate methyltransferase (GAMT) and arginine:glycine amidinotransferase (AGAT) deficiency), or creatine transport (i.e. creatine transporter deficiency, CRTR). Clinical features include variable hypotonia, speech delay (often the dominant feature), seizures, extrapyramidal signs and behavioural issues. Patients may have feeding issues and low weight. There is some evidence that early treatment of these disorders is successful, particularly in GAMT and AGAT deficiency.

Method A retrospective chart review was undertaken of all patients who have attended the national metabolic referral centres at Dublin and Belfast with creatine deficiency. Details recorded included history, clinical findings, treatments and results of laboratory, genetic and radiological investigations.

Results Six patients with current ages between 5 and 29 years were identified with a confirmed disorder of creatine metabolism – four male patients with X-linked CRTR and two female siblings with autosomal recessive GAMT deficiency. Initial diagnosis was made on urine biochemistry (analysis of creatine/creatinine and guanidinoacetate) in two patients, on MR spectroscopy in three patients (creatine peak significantly reduced) and via exome sequencing in one patient. All cases were confirmed biochemically and genetically. Despite onset of symptoms before the age of 2 years, mean age at diagnosis was 7.5 years, with range from 20 months to 17 years.

Six patients had significant developmental delay, particularly in the domains of speech and behaviour. Three of the patients have weights <9th centile. Five of the patients had documented head circumferences, and all were normocephalic proportional to height and weight. Both patients with GAMT deficiency had epilepsy which responded to treatment with creatine and ornithine. Three patients with CRTR also had epilepsy. Two patients with CRTR have been treated with creatine and creatine/arginine/glycine/S-adenosylmethionine in combination, without notable effect on clinical symptoms or MR spectroscopy findings, which is in keeping with expectations for this condition.

The four patients with CRTR are hemizygous for pathogenic mutations in the *SLC6A8* gene, *de novo* in two patients and maternally inherited in another, one has not had parental testing. The siblings with GAMT deficiency are compound heterozygous for mutations in the *GAMT* gene.

Conclusion Although rare in Ireland, these treatable disorders are likely under-diagnosed. In a patient with developmental delay (particularly speech impairment) and behavioural difficulties, consideration should be given to sending a urine sample for analysis of creatine/creatinine ratio and guanidinoacetate, particularly if there is comorbid epilepsy.

GP224 MULTISYSTEM MITOCHONDRIAL DISEASES IN CHILDREN WITH MATERNALLY INHERITED COMPLEX I DEFICIENCY

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Mitochondrial disorders (MD) in childhood represent a heterogeneous group of disease. The most common cause of MD is respiratory chain complex I (CI) deficiency, which may be caused by mutations in either nuclear or the mitochondrial DNA (mtDNA). In the cohort of 106 unrelated families with mtDNA mutations from our region with 10,5 million of inhabitants, the multisystem MD due mtDNA mutations in *MT-ND* genes for structural subunits of CI were recognized in 12 families with 13 affected children.

Results In the group of 13 patients, altogether 8 different heteroplasmic mtDNA mutations in *MT-ND* genes were found. Mutations in *MT-ND5* gene were most frequent including one novel mutation m.13091T>C. Six children with the mutation heteroplasmy >60% had Leigh syndrome and significantly worse prognosis than five patients with heteroplasmy <60%, who developed MELAS syndrome with stroke-like episodes. In last two children, the diseases started with optic neuropathy but both children transitioned later to multisystem diseases compatible with MELAS syndrome. The activities of CI in isolated muscle mitochondria were decreased in most patients and analyses with [$1-^{14}$ C]pyruvate, [U- 14 C]malate and [1,4- 14 C]succinate substrates revealed decreased CO₂ production in some patients.

Conclusions Children with the multisystem MD due to CI deficiency and heteroplasmic mtDNA mutations usually develop Leigh or MELAS syndromes and represent approximately 11% of families with maternally inherited MD diagnosed in our region. Early onset of the disease and higher level of heteroplasmy of mtDNA mutations resulted in Leigh

phenotype with worse prognosis. *Supported by projects AZV 17-30965A and RVO VFN 61514.*

GP225 BETTER OUTCOMES OF 'HIGH-RISK' SCREENED GLUTARIC ACIDURIA TYPE 1 PATIENTS GIVE OPTIMISM TO FUTURE CASES DIAGNOSED THROUGH NEWBORN SCREENING IN IRELAND

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Introduction Glutaric aciduria Type 1 (GA1), first described in 1975, has an incidence of approximately 1:56,000 in Ireland. GA1 usually presents clinically during an intercurrent illness at 3–18 months' age with encephalopathy and dystonia, resulting in dyskinetic/spastic cerebral palsy and sometimes intellectual disability.

Management of GA1 involves a low-protein diet with synthetic lysine-free/low-tryptophan protein supplement and L-carnitine treatment, with aggressive management of inter-current illnesses to prevent catabolic crisis and encephalopathy. This review assessed outcomes of high-risk (familial) screened Irish patients versus non-screened patients who presented clinically, prior to the very recent introduction of newborn screening (NBS) for GA1 in Ireland.

Method Retrospective chart review of GA1 patients attending the National Centre for Inherited Metabolic Disorders (1981 – 2018). Data was collected to determine patient clinical and neurological status at diagnosis and at school age.

Results 29 patients were diagnosed with and treated for GA1 during the review period (352 patient treatment years). Thirteen (45%) presented clinically and 16 (55%) were diagnosed early by 'high-risk screen' due to family history. Median age at diagnosis was 365 days (IQR 206–626) for those presenting clinically and 4.5 days (IQR 3–29) for those screened ($p < 0.001$ Mann-Whitney). Six of twelve (50%) patients who presented clinically (one was lost to follow-up) are deceased compared to one patient (6.3%) in the screened group ($p = 0.008$, Chi-squared).

Eighteen (62%) patients were from the Irish Travelling Community of which 12 (66.7%) were diagnosed by high-risk screen compared to four of 11 (36.4%) from the non-Traveller population ($P = 0.111$, Chi-squared).

Nine of 15 patients (60%) diagnosed by high-risk screen had either radiological only or no features of GA1 at diagnosis, compared to one patient (7.7%) in the clinically presenting group ($p = 0.004$, Chi-squared).

Two of the eight patients (25%) presenting clinically who survived to school-age attended mainstream school without significant impairment versus 10 of 14 (71.4%) screened patients ($p = 0.035$ Chi-squared). Three of eight (37.5%) clinical presenters at 5–7 years had either full motor function or a Gross Motor Function Classification System score of 1, compared with all fourteen diagnosed by high-risk screen ($p = 0.001$, Chi-squared).

Conclusion Our data supports the necessity to diagnose infants with GA1 in the newborn period and we expect that future outcomes in the Irish NBS population will be similar to this historical high-risk screening group.

GP226 TETRAHYDROBIOPTERIN DISORDERS IN IRELAND: A CASE SERIES OF 7 PATIENTS

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Background Classical Phenylketonuria (PKU) is an autosomal recessively inherited disorder in phenylalanine metabolism caused by profound deficiency of the enzyme phenylalanine hydroxylase (PAH). Newborn screening for PKU was introduced in Ireland in 1966. A low phenylalanine diet is the well-established standard treatment for patients with Classical PKU. However, approximately 1% of all cases in Ireland are caused by an inborn metabolic defect of the cofactor of PAH, tetrahydrobiopterin (BH4). BH4 is an essential cofactor for various metabolic pathways, including phenylalanine, Dopa and 5-OH-Tryptophan metabolism. This subgroup of ultra-rare neurometabolic diseases is referred to as 'Malignant/Atypical Phenylketonuria', as most of these patients have raised phenylalanine blood levels and develop profound neurological symptoms despite adequate dietary restriction of phenylalanine, if not treated with additional medications to prevent neurotransmitter deficiencies.

Methods We describe diagnostic approaches, biochemical findings and mutational spectrum, clinical presentation, treatment and outcomes in a case series of 7 patients diagnosed with either 6-pyruvoyl-tetrahydrobiopterin synthase (PTPS) deficiency ($n = 2$), a defect in BH4 biosynthesis, or dihydropteridine reductase (DHPR) deficiency ($n = 5$), a defect in BH4 regeneration.

Results Seven patients aged 2 to 33 years were included in this study after ethics approval was obtained. Six patients were diagnosed in the newborn period; all five patients with DHPR deficiency were diagnosed following detection of an elevated phenylalanine on newborn screening. Four patients had developmental delay and one patient with DHPR deficiency had epilepsy. All five patients with DHPR deficiency were homozygous for c.353C>T mutation in the *QDPR* gene. One patient with PTPS deficiency was diagnosed at age 3 years and 9 months when he presented with developmental delay and oculogyric crises, his sibling was subsequently diagnosed as a newborn and is neurologically normal at age 2 years, neither required dietary therapy as their hyperphenylalaninaemia is mild. Both patients with PTPS deficiency are homozygous for c.84–3C>G mutation in the *PTS* gene. All patients have been treated with neurotransmitter replacement.

Conclusion Some disorders of BH4 metabolism such as DHPR deficiency may mimic Classical Phenylketonuria biochemically with a raised blood phenylalanine level, in others, such as PTPS deficiency, the hyperphenylalaninaemia may be mild. However, early differential diagnosis is crucial to commence appropriate treatment in a timely manner to improve outcomes in patients with a rare 'Atypical PKU'. These cases demonstrate the importance of BH4 measurement in patients with a positive PKU newborn screening result and also when evaluating children with unexplained neurological deterioration such as oculogyric crises.