MULTIPLE ACYL-COA DEHYDROGENASE DEFICIENCY (MADD) – ADULT AND NEONATAL PRESENTATION

Beena Devanapalli[1], Michel Tchan[2], Carolyn Ellaway[3], Adviye Ayper Tolun[1]
[1]*NSW Biochemical Genetics Service, The Children's Hospital at Westmead, Westmead, NSW, Australia;* [2]*Genetic Medicine, Westmead Hospital, Westmead, NSW, Australia;* [3]*Genetic Metabolic Disorders Service, The Children's Hospital at Westmead, Westmead, NSW, Australia*

Multiple acyl-CoA dehydrogenase deficiency (MADD), or glutaric acidemia type II, is an autosomal recessive disorder of oxidative metabolism. MADD has a wide clinical spectrum with clinical presentation in the neonatal period with or without congenital malformations, through to later onset. Episodes of clinical decompensation may be triggered by catabolic stressors such as intercurrent illnesses and prolonged fasting. The diagnosis of MADD is made according to the profiles of urine organic acids and plasma or dried blood spot (DBS) acylcarnitines. The infant was identified by the NSW newborn screening program and biochemically confirmed by the characteristic plasma and urine diagnostic profile. He was asymptomatic in the neonatal period and has not had any metabolic decompensation. He is growing and developing normally. However, diagnosis in the adult was challenging as the initial urine organic acid profile was normal at the time of severe metabolic decompensation and the biochemical markers of MADD were only detected after carnitine supplementation. He has shown clinical improvement after treatment with carnitine, 3-hydroxybutyrate, CoQ, riboflavin and glycine. This report highlights the need for early diagnosis as patients including those with late onset forms can have a favourable response with intervention.

DISORDERS IN STEROL METABOLISM: A CASE SERIES

Joy Lee[1,2,3], Sharmila Kiss[3], David J. Amor[1,4], Natasha J. Brown[1,2], Winita Hardikar[1,4,5], Kai M. Hong[2], Duncan MacGregor[6], Melanie Marty[2], Justine Marum[2], Gautham Pai[5], Jane Wallace[2], James Pitt[1,2]
[1]*Department of Paediatrics, University of Melbourne, Vic, Australia;* [2]*Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Vic, Australia;* [3]*Department of Metabolic Medicine, The Royal Children's Hospital, Melbourne, Vic, Australia;* [4]*Murdoch Children's Research Institute, University of Melbourne, Vic, Australia;* [5]*Department of Gastroenterology and Clinical Nutrition, The Royal Children's Hospital, Melbourne, Vic, Australia;* [6]*Department of Anatomical Pathology, The Royal Children's Hospital, Melbourne, Vic, Australia*

Disorders of sterol metabolism are rare genetic conditions with phenotypic heterogeneity. Early diagnosis is crucial for precise management and genetic counselling.
Patient 1 presented with intellectual disability, facial dysmorphism, limb anomalies, bilateral cataracts, elevated liver transaminases and severe liver fibrosis. Exome sequencing identified two likely pathogenic variants in exon 3 of the *SC5D* gene. Plasma lathosterol was 54 µmol/L (RR<10) confirming the diagnosis of lathosterolosis. Simvastatin treatment resulted in lowering of lathosterol, improvement in liver transaminases and fibrosis.
Patient 2 had multiple xanthomas since 5.5 years of age. Initial diagnosis of juvenile
xanthogranuloma was made based on histology and clinical presentation. Total cholesterol 12.8 mmol/L (RR 2.5–4.9) and LDL 10.3 mmol/L (RR <3.5) were noted at 8 years of age. Despite a low cholesterol diet and simvastatin up to 40 mg daily, there was minimal biochemical response. Exome sequencing identified two pathogenic variants in the *ABCG8* gene. Plasma sitosterol was 736 mmol/L (RR <20) confirming the diagnosis of sitosterolaemia. A diet low in cholesterol and plant sterols and Ezetimibe at 10 mg resulted in reduction of xanthomas and improvement in lipid profile.
These two patients highlight the importance of an accurate diagnosis, targeted treatment, the clinical benefits of a full sterol profile analysis and genomic sequencing.

CLEFTING AND CANCER: A COMPLEX *CDH1* CASE

Jennifer Phan[1,2], Abhijit Kulkarni[3], Andrew Dubowsky[1], Lesley Rawlings[1], Kathryn Friend[1], Tristan Hardy[1,4], Sui Yu[1]
[1]*Genetics and Molecular Pathology, SA Pathology, Adelaide, SA, Australia;* [2]*Associate Lecturer, College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia;* [3]*Genomic Diagnostics, Heidelberg, Vic, Australia;* [4]*Repromed, Dulwich, Adelaide, SA, Australia*

The *CDH1* gene plays an important role in normal craniofacial development and acts as a tumour suppressor protein. *CDH1* is a pleiotropic gene; pathogenic variants in *CDH1* have been associated with autosomal dominant hereditary diffuse gastric cancer (HDGC), with or without cleft lip and/or palate, as well as autosomal dominant blepharocheilodontic syndrome 1 (BCDS1). We report a case of a family with two phenotypes: a mother and daughter with bilateral cleft lip and palate, and a maternal grandfather with diffuse gastric cancer (deceased). A previously undescribed heterozygous missense *CDH1* variant of uncertain significance (VUS) was detected in the daughter using next generation sequencing. This same *CDH1* VUS was detected in her mother. Segregation studies on the maternal grandfather using DNA extracted from an archival gastrectomy tumour specimen demonstrated that this *CDH1* VUS is *de novo* in the mother. This provided sufficient evidence to reclassify this variant to Likely Pathogenic for BCDS1 and the option for prenatal and/or pre-implantation genetic testing.

MAKING SENSE OF EXPRESSION STUDIES: LESSONS LEARNED IN THE ZERO CHILDHOOD CANCER PRECISION MEDICINE PROGRAM

Chelsea Mayoh[1,2,3]
[1]*Children's Cancer Institute, Lowy Cancer Centre, UNSW Sydney, Kensington, NSW, Australia;* [2]*School of Women's and Children's Health, UNSW Sydney, Kensington, NSW, Australia;* [3]*University of New South Wales Centre for Childhood Cancer Research, UNSW Sydney, Sydney, NSW, Australia*

The Zero Childhood Cancer Precision Medicine Program (ZERO), a joint initiative of Children's Cancer Institute, and Kids Cancer Centre, Sydney Children's Hospital, Randwick,