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Biochemical and Metabolic Genetics Abstracts (poster)

eP001

Newborn screening experience for very long chain Acyl-CoA Dehydrogenase (VLCAD) deficiency in Kuwait

Fatima Alabdulrazzaq[1], Hind AlSharhan[2], Amir Ahmed[3], Makia Marafie[3], Ibrahim Sulaiman[3], Reem Alshafie[3], Ahmad AlAhmad[3], Buthaina AlBash[3], Naser Ali[3], Parakkal Cyril[4], Usama Alkazzaz[5], Samia Ibrahim[6], Yasser Elfeky[7], Ayman Salloum[8], Asma Alshammari[3], Rehab Abdelrahman[3], Rasha Alsafi[9], Dina Ramadan[9], May Al-Rushood[3], Laila Bastaki[3]

[1]The Ministry of Health in Kuwait; [2]Faculty of Medicine, Kuwait University, Farwaniya Hospital, Ghanima Alghanim Genetic Center; [3]Kuwait Medical Genetics Center; [4]Newborn Screening Office, Al-Adan Hospital; [5]Newborn Screening Office, Al-Farwaniya Hospital; [6]Newborn Screening Office, Al-Sabah Hospital; [7]Newborn Screening Office, Al-Jahra Hospital; [8]Biochemistry Lab, Al-Sabah Hospital; [9]Department of Pediatrics, Al-Adan Hospital

Introduction: Among the various inborn errors of fatty acid oxidation disorders, very long chain acyl-CoA dehydrogenase (VLCAD) deficiency is the most common disorder in Kuwaiti population, which has been noticed especially following the launch of the expanded newborn screening program in Kuwait in October 2014. VLCAD deficiency is a rare autosomal recessive disorder with a worldwide incidence of 1:30,000 to 1:100,000 births. It is caused by deficiency of VLCAD coenzyme, encoded by *ACADVL* gene which converts very-long-chain fatty acids into energy. In October 2014, the Kuwait Ministry of Health has started a publicly funded expanded newborn screening program meeting the highest international standards to screen for a wide range of metabolic and endocrine disorders including a total of 22 disorders via testing dried blood spots and thus replacing the old, limited newborn screening for congenital hypothyroidism and phenylketonuria that was introduced in 2005.

Methods: A retrospective analysis of the data registry for the newborn screening over the 6-year period between January 2015 and December 2020 in Kuwait has been conducted after obtaining consent from the newborn screening program. This data included newborns delivered in hospitals all over Kuwait. Data on metabolite concentrations in dried blood spots at the time of screening obtained from all newborns were reviewed and only dried blood spots detecting elevated blood C14:1 (cutoff 0.29 mmol/L) and C14:1/C2 ratio (cutoff 0.03) via tandem mass spectrometry (MS/MS) were included in this study. The positive initial screening is followed by a confirmatory plasma or dried blood acylcarnitine analysis (cutoff $\geq$ 1 mmol/L) with or without a follow-up genetic analysis of *ACADVL* gene, either targeted variant testing using PCR amplification followed by Sanger sequencing, or through next generation sequencing technology.

Results: Total of 36 cases (19 male/17 female) out of 304,086 screened newborns have been identified and confirmed to have VLCAD deficiency with an incidence of ~1:8300. The diagnosis was based on the detection of elevated blood C14:1 and C14:1/C2 ratio in the initial dried blood spots in the newborn screening, followed by a confirmatory plasma or dried blood acylcarnitines profile for VLCAD deficiency with or without a follow-up genetic analysis, except for three babies who had positive initial screen but have died before obtaining confirmatory acylcarnitine or genetic analyses. Out of the 36 individuals, there were 3 cases from Kingdom of Saudi Arabia, 2 cases from India and the rest were Kuwaiti. Molecular testing of 24 of them has revealed a founder truncating pathogenic variant in exon 2 of the *ACADVL* gene, * c.65C>A; p.(Ser22Ter); the reference transcript is NM_001178008.2(hg19/GRCh3). We have identified three genetically confirmed cases with VLCAD deficiency following a positive initial screen but negative confirmatory acylcarnitine analysis. Furthermore, we identified four heterozygous individuals for VLCAD deficiency via molecular testing, after a positive initial newborn screening and normal confirmatory acylcarnitine profile.

Conclusion: This is the first study to review the Kuwaiti newborn screening experience of VLCAD deficiency since its launch in October 2014. We recommend including molecular genetic testing for *ACADVL* gene as part of the newborn screening for VLCAD deficiency particularly for the cases with negative confirmatory acylcarnitine profile. Our study provides evidence that the expanded newborn screening in Kuwait has led to the early detection of VLCAD deficiency cases and thus the initiation of the adequate management plan for these individuals aiming to prevent death and disability.

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eP002

Pilot study of insulin-like growth factor 1 on differing metabolic responders with Phelan-McDermid syndrome: Preliminary results

Bridgette Allen[1], Luigi Boccuto[1], Diana Ivankovic[2], Sara Sarasua[1]

[1]Clemson University; [2]Clemson University, Anderson University

Introduction: Phelan-McDermid Syndrome (PMS) is a rare genetic neurodevelopmental disorder with variable clinical manifestations. These features can include intellectual disability, autism, developmental delays, and seizures. PMS can be caused by deletions within the 22q13 region or pathogenic variants of the *SH3 and multiple ankyrin repeat domains 3* (*SHANK3*) gene, which plays an important role in the development, function, and maintenance of excitatory synapses. While there are currently no approved treatments for PMS, one potential therapy is insulin-like growth factor-1 (IGF-1). IGF-1 is a protein that