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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

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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

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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

supports the development of mature synapses and regulates cellular function via several regulatory pathways. IGF-1 has been used to promote growth in children with short stature due to IGF-1 deficiency or growth hormone (GH) deficiency, but only for a limited amount of time. Animal models of PMS have shown the rescue of neurological and behavioral functions following treatment with IGF-1. We aim to explore the impact of IGF-1 treatment on the metabolic response to a large panel of metabolites and effectors to determine if IGF-1 can rescue the abnormal metabolic pathways present in individuals with PMS.
Methods: Previous experiments employing the Biolog Phenotype Mammalian Microarrays (PM-Ms) assessed the metabolic profile of lymphoblastoid cell lines (LCLs) from individuals with PMS: results from these experiments were analyzed to identify five subjects who were high metabolizers of IGF-1 and five that were low metabolizers. The Biolog data for those ten people were evaluated across all eight PM-M Biolog plates to determine which plates had the greatest differences when compared to a group of 50 controls.
Results: Ten abnormal metabolic responders were identified from a PMS cohort of 54 individuals. Five controls were randomly selected from a cohort of 50 people. Four Biolog PM-M plates were identified as plates of interest with the effectors being carbon energy sources, hormones, growth factors and cytokines (PM-M1, and PM-M6 to M8). The LCLs of these ten subjects with PMS showing abnormal metabolic response to IGF-1 will be utilized in our pilot study aimed at addressing the efficacy of IGF-1 treatment with the potential to identify ideal candidates for the treatment.
Conclusion: The 15 selected LCLs will be used to determine the effect IGF-1 has on the differing metabolic profile of the high, low, and average responders.

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eP003

Novel use of IL-1 inhibition via canakinumab in two patients with lysinuric protein intolerance and immune dysregulation

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Background: Lysinuric protein intolerance (LPI) is an autosomal recessive condition caused by the deficiency of the light subunit of the y^+ LAT1 transporter and biallelic pathogenic variants in the *SLC7A7* gene. The y^+ LAT1 transporter is most heavily expressed by renal epithelial cells and the intestinal basolateral membrane. Deficiency of this transporter in these tissues results in decreased absorption and reuptake of the cationic amino acids: lysine, ornithine, and arginine. Decreased arginine and ornithine results in secondary urea cycle dysfunction that is associated with some of the clinical features associated with LPI including hyperammonemia, protein avoidance, and poor growth. However, LPI has multiple clinical features not commonly seen in primary urea cycle disorders including osteoporosis, renal disease, interstitial lung disease, and immune dysfunction including hemophagocytic lymphohistiocytosis (HLH). In vitro studies of *SLC7A7*-deficient monocyte and macrophage cell lines suggest that some of the immune phenotype is driven by high levels of pro-inflammatory cytokines TNF-alpha and IL-1beta.
Case presentation: The proband is an 11-year-old female who was seen in general genetics clinic for evaluation of recurrent fractures and concern for osteogenesis imperfecta. She had a history of 5 lifetime fractures that were notable for prolonged healing requiring casts/braces for longer than expected. On physical exam, she had short stature and hepatomegaly. A skeletal survey was obtained that showed significant demineralization, healed/healing prior fractures, multiple compression fractures of the thoracic spine, and interstitial lung disease. The combination of demineralization and interstitial lung disease raised the question of LPI. Subsequent screening labs were performed and notable for elevated transaminases, LDH, ferritin, and zinc. Hematologic labs were notable for mild neutropenia (absolute neutrophil count 1000 cells/microliter), but normal platelets, hemoglobin, and fibrinogen. LPI was biochemically confirmed with plasma amino acids (elevated glutamine, decreased ornithine and lysine), urine amino acids (elevated lysine, arginine, and ornithine), and urine organic acids (orotic acid present). Molecular testing identified two pathogenic variants in *SLC7A7* (NM_001126106.2:c.426_434del, p.Tyr142* and c.1263_1269del, p.Ile422Serfs*95), confirming the diagnosis of LPI. After diagnosis, the proband was referred to several specialists including Immunohematology, Endocrinology, Nephrology, Pulmonology, and Hepatology for further evaluation. Additional labs ordered by Immunohematology were consistent with a smoldering HLH picture, where the patient was asymptomatic but had laboratory findings consistent with severe immune dysregulation: elevated ferritin, slightly reduced CD107a, elevated sCD163 and elevations in various cytokines, including sIL2R. Interestingly, ESR and CRP were normal.
The proband's 12-year-old full sister was noted to have similar features (short stature, multiple fractures, and protein intolerance). Initial labs obtained as part of screening for LPI when she was asymptomatic were notable for an elevated ferritin of 1447 mg/mL (normal 6-155), elevated triglycerides (450 mg/dL, normal < 90), elevated transaminases (AST 247 IU/L, ALT 149 IU/L), CBCD with mild thrombocytopenia (126,000 cells/microliter), mild neutropenia (ANC 1100 cells/μL) and normal hemoglobin and fibrinogen. Subsequent molecular testing confirmed the diagnosis of LPI in this patient as well. Her imaging was notable for hepatic steatosis and splenomegaly. A chest CT showed mild interlobular septal thickening bilaterally, likely representing early manifestation of interstitial lung disease. During her evaluation with Immunohematology, she also had evidence of smoldering chronic inflammation with laboratory features of HLH (elevated ferritin, increased S100A proteins, reduced CD107a, elevated sCD163, cytopenias and increased cytokines).
Following the LPI diagnosis, both sisters were started on a protein-restricted diet (although this was similar to their protein intake prior to diagnosis). They were also started on glycerol phenylbutyrate and supplementation of lysine, citrulline, and carnitine. Due to numerous fractures, both children were started on zoledronic acid infusions every 6 months. Based on concerns for smoldering HLH and rapidly progressive lung disease, they were started on IL-1 inhibition via canakinumab 2 mg/kg every 4 weeks. In the 6 months since canakinumab initiation, both sisters have had reductions in their ferritin levels. The older sister with higher ferritin at diagnosis, also had more dramatic decreases in her transaminases. Both sisters continue to have stable, mild neutropenia and remain asymptomatic from a HLH perspective.
Conclusion: We present two patients with LPI to highlight a new treatment modality for this condition using the IL-1 antagonist canakinumab. In the 6 months since starting this treatment, their inflammatory markers have improved. How this may alter the overall trajectory of LPI including the insidious progression of lung disease is unknown but warrants further consideration.

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