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Introduction:
Limited data exist regarding physical and cognitive functioning of adults with hypophosphatasia (HPP), and there are no guidelines for evaluation by physical therapists (PT), occupational therapists (OT), or speech-language pathologists (SLP). We evaluated physical and cognitive functioning among adults with HPP through comprehensive assessments and patient reported outcome tools.
Methods:
Sixteen participants with HPP (median age 42 (32.5–50.5) yrs, 73% female, 100% Caucasian, 50% on enzyme replacement therapy) completed standardized assessments of mobility, balance, fine motor control, activities of daily living and cognition, as well as self-reported measures of health-related quality of life, fatigue, depression and anxiety.
Results:
Compared with normative data from community dwelling adults, participants traveled less distance on a Six-Minute Walk Test (1,376 ± 431** ft vs 1873±299) and had slower gait on a 10-Meter Walk Test (1.04±0.21 vs 1.39–1.46 m/s). Participants were slower to respond on the Nine Hole Peg Test (20.6±2.4s** for right & 21.7±2.4s** for left hand vs 16.5s to18.5s), and 2 had an abnormally slow reaction time via Dynavision (0.9s* [0.85,0.96], functional speed is <1.15s). 20% scored in the low average/borderline range of performance on the Repeatable Battery for the Assessment of Neuropsychological Status, suggesting potential cognitive impairment. On the Short Form-36, 75% reported limitations in their ability to fulfill life roles due to physical problems (25%±39%ile**), 75% reported below average energy (30%±23ile**), and 100% rated their health as unlikely to improve (32%±15%ile**). Fatigue Severity Scale scores were well above the median for a healthy population (47 [34,60.5]* vs 2.3). Median scores for Depression, Anxiety, and Stress were within the normal range, but moderately severe depression was reported by 4 participants. Participants reported moderate (4), severe (1), or extremely severe (1) anxiety; and 4 reported severe (2) or extremely severe (2) stress.
Conclusions:
Objective functional assessments indicate mild deficits, but participants self-reported significant limitations due to physical dysfunction, indicating that current objective testing may not be sufficient in the HPP population. Impaired reaction time may indicate potential safety concerns with driving or certain occupations, and screening may be indicated. A subgroup of participants was significantly affected by depression, stress, and/ or anxiety. Guidelines and additional assessment tools should be created to further evaluate physical and cognitive functioning among adults with HPP. The use of PT, OT, and SLP specialists can aid in establishing baseline assessment of impairment and developing treatment plans with objective metrics for assessing efficacy of treatment.
*median
**mean

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

MDC1 Is a Novel Estrogen Receptor Co-Regulator in Invasive Lobular Carcinoma of the Breast

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Invasive Lobular Carcinoma (ILC) is the 2nd most common histotype of breast cancer, but is critically understudied. ~95% of ILC are estrogen receptor (ER) positive, and previous studies demonstrate the importance of estrogen in ILC etiology. However, retrospective studies show that anti-estrogens are substantially less effective in ILC than in ER+ Invasive Ductal Carcinoma (IDC). This strongly suggests that regulation of ER function is unique in ILC, and we hypothesize that this is due to an ILC-specific cohort of ER co-regulators. We performed Rapid Immunoprecipitation Mass Spectrometry of Endogenous Proteins (RIME) to determine ILC-specific ER-interacting proteins, and identified Mediator of DNA Damage Checkpoint 1 (MDC1) as a novel ER co-regulator in ILC cells. We confirmed ER:MDC1 interaction by co-immunoprecipitation and proximity ligation assays (PLA); interaction was specifically observed in ILC cell lines but not IDC cell lines. Consistent with co-regulator function, we found MDC1 is essential for ER-driven proliferation of ILC cells. MDC1 knockdown dysregulates transcription of ER target genes in ILC cells (e.g. *IGFBP4*, *WNT4*). Moreover, RNA-seq analysis showed that in ILC cell line MDA MB 134VI, >50% of ER target genes require MDC1 for their regulation. To understand how MDC1 controls ER transcriptional activity, we performed ChIP-qPCR and found that MDC1 controls ER binding to DNA in ILC cells. Further, MDC1 controls binding of the pioneer factor FOXA1 to DNA, and Dual PLA studies of ER:MDC1 and ER:FOXA1 interaction revealed that MDC1 knockdown decreased ER:FOXA1 interaction. MDC1 canonically functions in DNA damage response, but our preliminary data suggest MDC1 is decoupled from its canonical role in DDR in the context of ER co-regulator activity in ILC cells. Together, these data suggest MDC1, independent of its role in DDR, acts as a novel ER co-regulator in ILC and regulates ER:DNA binding and ER transcriptional function to drive ILC cell proliferation and survival.

Reproductive Endocrinology

CLINICAL STUDIES IN FEMALE REPRODUCTION I

Insulin Treatment in Human Pregnancy Mitigates an Increased Risk of Postpartum Psychological Distress with Maternal Obesity in the Absence of a Pre-Existing Mood and Anxiety Disorder

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