targeting co-morbidities in people living with HIV to account for both inflammation and dysbiosis.

4472

Plasma Neurofilament Light as a Biomarker for Pediatric Patients with Huntington's Disease

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OBJECTIVES/GOALS: The goal of this study is to compare plasma neurofilament light (NfL) concentrations in asymptomatic children and young adults that carry the gene expansion (GE group) that causes Huntington's Disease to similar subjects that do not carry this genetic mutation (GNE group). METHODS/STUDY POPULATION: Subjects from the Kids-HD study in the GE group were divided into groups based on their estimated years to motor onset. Each subgroup was compared to the subjects from the GNE group. Additionally, a group of participants with juvenile HD were compared to the GNE group. These comparisons were made by utilizing linear mixed effects regression models that included a random effect per subject and family and also included the covariates of age and parental socioeconomic status. A post-hoc analysis of subjects in the GE group who were within 20 years from their predicted motor onset was conducted to assess the relationship between striatal volume and plasma NfL concentrations. RESULTS/ANTICIPATED RESULTS: GE participants more than 20 years from their predicted motor onset did not have elevated plasma NfL concentrations relative to the GNE group. However, participants who were 15-20 years from their predicted motor onset had a mean NfL concentration of 1.61 pg/uL compared to 1.31 pg/uL in the GNE group ($p = 0.036$). Participants who were within 15 years from their predicted motor onset had a mean NfL concentration of 2.08 pg/uL, which was also significantly elevated relative to the GNE group ($t = 3.03$, $p = 0.003$). Additionally, the participants with juvenile HD had a mean NfL level of 3.22 pg/uL, which was significantly elevated compared to the GNE group ($p<0.0001$). NfL concentrations were significantly correlated with striatal volume amongst participants who were within 20 years of onset ($p = 0.017$). DISCUSSION/SIGNIFICANCE OF IMPACT: The huntingtin protein is essential to neurodevelopment but current gene therapies for HD focus on blocking production of this gene. These results will provide guidance on the optimal timing of administration of gene therapies by identifying neurodegeneration decades prior to motor onset of HD.

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Potential Sudden Unexpected Death in Epilepsy (SUDEP) Biomarkers in Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes with DEPDC5 Loss-of-Function

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OBJECTIVES/GOALS: Sudden Unexpected Death in Epilepsy (SUDEP) is a leading cause of death in epilepsy patients. This study aims to determine whether cardiac mechanisms contribute to SUDEP in epilepsy patients with variants in *DEPDC5*, a gene encoding a member of the mTOR GATOR complex, to identify SUDEP biomarkers. METHODS/STUDY POPULATION: SUDEP has been reported in 10% of epilepsy patients with *DEPDC5* loss-of-function variants. We used human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) to measure changes in cellular excitability that are known to be substrates for cardiac arrhythmias. CRISPR-derived isogenic *DEPDC5* iPSC-CMs and *DEPDC5* patient-derived iPSC-CMs were used in this study. Whole-cell patch-clamp was used to measure voltage-gated sodium current (I_{Na}) and calcium current ($I>_{Ca}$) in single iPSC-CMs in voltage-clamp mode; and to measure action potentials (APs) in 3-dimentional iPSC-CM-derived micro-tissues in current-clamp mode. RESULTS/ANTICIPATED RESULTS: CRISPR generated heterozygous deletion of 1 base-pair in the first coding exon of *DEPDC5* gene, resulting in a premature stop codon, simulated the variants identified in *DEPDC5* epilepsy patients. In CRISPR generated heterozygous*DEPDC5* iPSC-CMs, whole-cell voltage-clamp recordings revealed that I_{Na} was increased and I_{Ca} was reduced compared with isogenic control iPSC-CMs. Whole-cell current-clamp recordings revealed that AP duration at 80% and 90% of repolarization, APD_{80} and APD_{90}, respectively, were prolonged compared to isogenic control iPSC-CMs. Similar measurements will be performed for iPSC-CMs derived from *DEPDC5* patients. DISCUSSION/SIGNIFICANCE OF IMPACT: This study shows that epilepsy patients with non-ion channel gene variants in *DEPDC5* have altered CM excitability, which may serve as a substrate for cardiac arrhythmias in *DEPDC5* patients. Importantly, this work may allow us to identify biomarkers for SUDEP risk in these patients in the future. CONFLICT OF INTEREST DESCRIPTION: L.L.I. is the recipient of a collaborative research grant from Stoke Therapeutics.

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Quantifying the art of surgical decision-making in total knee arthroplasty

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OBJECTIVES/GOALS: To quantify clinical exam in total knee arthroplasty by answering the following questions: (1) What are the magnitudes of forces applied by surgeons during the varus-valgus exam? (2) Is the choice of tibial insert thickness related to the magnitude of the applied forces? (3) How accurately does a surgeon estimate the gaps in the varus-valgus exam? METHODS/STUDY POPULATION: Three cadaveric knees were implanted with standard TKA trial implants. Four pliable force sensors were wrapped around the foot and ankle of each cadaver to measure the push-pull forces applied during the varus-valgus exam. Six surgeons with varying experience independently conducted a varus-valgus exam in extension and flexion and reported the gaps that they observed. Motion capture was used to measure the gaps between femur and tibia by placing cluster of reflective markers on femur and tibia. Subsequently, each surgeon chose the tibial insert that they thought best fit each knee. The measured peak applied forces were related to the insert thickness and the measured gaps were compared to the observed gaps by surgeons. Since insert thickness was in 1 mm increments, 1 mm gap error was considered a meaningful difference. RESULTS/ANTICIPATED RESULTS: The peak forces varied among surgeons for each cadaver. In cadaver one, the peak forces in varus and valgus in extension were 48±20 and 20±12 N, and in flexion were 27±14 and 8±11 N. Peak forces in cadavers two and three were similar; in varus and valgus in extension, 24±14 and 35 ±10 N, and in flexion, 23±12 and 20±10 N, respectively. It was observed that the larger the valgus force in extension, the thinner

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