84084

Team Science to maximize rapid collection and analyses of biosamples from patients with Covid-19

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ABSTRACT IMPACT: Indiana CTSI Team Science to maximize rapid collection, analyses and dissemination of biosamples collected from patients with Covid-19 to provide preliminary data for grant applications on the pathogenesis and outcomes of patients with Covid-19. OBJECTIVES/GOALS: When Covid-19 hit Indiana in April, there was an immediate need to respond rapidly to coordinate research across our healthcare systems. The CTSI became a point of contact for coordinating research endeavors including activation of clinical trials and use of precious samples from patients with Covid-19 to maximize preliminary data for grants. METHODS/STUDY POPULATION: The Indiana CTSI coordinated collection of biospecimens at multiple hospitals using in person and remote consenting via telephone or on a smartphone utilizing a QR code. We also retrieved existing samples from the Indiana Biobank previously collected for future research and from subject positive for Covid-19 by search of the linked electronic health record (EHR). A total of 224 subject samples (7 children, 36 previously collected, and 6 with both acute and recovered specimens) were obtained over a four month period. Our CTSI cores ran varied analyses collated to a single database, linked to the EMR for use as preliminary data for grant applications to avoid redundancy of measures on limited samples. RESULTS/ANTICIPATED RESULTS: The 224 subject samples were used for whole exome DNA sequencing, RNA seq, analyses of 48 plasma cytokine/chemokines by multiplex analyses, and PBMC isolated for culture and assessment of secreted cytokines. The clinical data were linked and included demographics, hospitalization length of stay and need for mechanical ventilation, max and min oxygen levels, liver function tests, IL-6, D-dimer, CRP, LDH, and ferritin, need for dialysis, and echocardiography. Additional clinical data were available upon request. A survey was sent to our CTSI email to query for potential interest in the data with 87 inquiries, and to date 46 investigators have requested data and/or additional samples. DISCUSSION/SIGNIFICANCE OF FINDINGS: During the first surge of Covid-19, the CTSI coordinated analyses for the dissemination of results for use by CTSI investigators to minimize duplication of assays and increase availability. The collaboration of research coordinators, biobank, research cores, and informatics demonstrates the power and agility of team science in the Indiana CTSI.

86583

The role of creatine in developmental myelination and remyelination*

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ABSTRACT IMPACT: This study highlights the importance of creatine in developmental myelination and remyelination to investigate whether creatine provides a therapeutic value during a central nervous system (CNS) demyelinating insult with a potential value in patients with Multiple Sclerosis. OBJECTIVES/GOALS: Creatine is vital for ATP buffering in the brain. Interestingly, the cells that generate myelin express the main enzyme for creatine synthesis, Gamt. Patients with Gamt mutations display intellectual delays and impaired myelination. Therefore, we hypothesize that creatine is essential for developmental myelination and improves remyelination. METHODS/STUDY POPULATION: To investigate these hypotheses, we developed a new transgenic mouse model with LoxP sites flanking exons 2-6 of the guanidinoacetate methyltransferase (Gamt) gene where excision leads to expression of a green fluorescent tag allowing us to track the cells normally expressing Gamt. We used immunohistochemistry techniques to look at the corpus callosum, the main white matter tract in the brain, and evaluate the number of oligodendrocytes (OL), glial cells responsible for generating myelin. We also used the cuprizone model of toxic demyelination to investigate whether dietary creatine and cyclocreatine, a planar analog of creatine that more efficiently crosses the blood-brain barrier, can enhance remyelination. RESULTS/ANTICIPATED RESULTS: In this mouse model, we show a 95% (+/-0.47%, n=3) co-localization of Gamt within mature OL during postnatal (P) day P14 with no co-localization in neurons or other glial cells. This suggests that mature OL are the main cells making creatine in the CNS. Next, we show that knocking out Gamt leads to a significant reduction in OL in the developing corpus callosum, at P14 and P21 (P14: 0.007, n=3; P21: 0.04, n=3). We also show that creatine supplementation causes a trending increase in mature OL density in the corpus callosum following cuprizone demyelination (2% creatine; p=0.052; n=4). Interestingly, cyclocreatine supplementation significantly increased mature OL density in the corpus callosum following cuprizone demyelination (0.1% cyclocreatine; p=0.034; n=4). DISCUSSION/SIGNIFICANCE OF FINDINGS: These studies highlight the important role creatine plays in developmental myelination and remyelination to investigate whether creatine and cyclocreatine provide a therapeutic value during a CNS demyelinating insult. This work investigates a potential therapeutic value of creatine to patients with Multiple Sclerosis.

Precision Medicine

Basic Science

48352

Mechanisms Underlying Lipidomic Changes in Major Depressive Disorder

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ABSTRACT IMPACT: Lipidomics is emerging as a powerful strategy to identify biomarkers for Major Depressive Disorder, as well as therapeutic targets in lipid metabolic pathways. OBJECTIVES/GOALS: Lipidomics is increasingly recognized in precision psychiatry for global lipid perturbations in patients suffering from Major Depressive Disorder (MDD). We will test the hypothesis that lipid metabolism dysregulation is associated with familial risk of depression. METHODS/STUDY POPULATION: Patients with MDD (G1), children (G2), and grandchildren (G3) have been part of a longitudinal study since 1982. If a parent G2 and grandparent G1 have MDD, G3 is considered a high risk of depression. Biospecimens (saliva and serum) were collected for full exome sequencing and RNA analysis. Samples will also be extracted for lipid content and lipids will be identified by mass spectrometry. A panel of nearly 600 lipid species can reliably be identified and quantified using liquid chromatography paired with tandem mass spectrometry

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