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Cancer-related fatigue during combined treatment of androgen deprivation therapy and radiotherapy is associated with mitochondrial dysfunction

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OBJECTIVES/GOALS: Combined androgen deprivation therapy (ADT) and radiation therapy (RT) is the standard of care treatment for non-metastatic prostate cancer (NMPC). Despite the efficacy, treatment-related symptoms including fatigue greatly reduce the quality of life of cancer patients. The goal of the study is to examine the influence of combined ADT/RT on fatigue and understand its underlying mechanisms. METHODS/STUDY POPULATION: Sixty-four participants with NMPC were enrolled. Fatigue was assessed using the Functional Assessment of Cancer Therapy–Fatigue. Mitochondrial function parameters were measured as oxygen consumption from peripheral blood mononuclear cells (PBMCs) extracted from participants' whole blood. An ADT/RT-induced fatigue mouse model was developed with fatigue measured as a reduction in voluntary wheel-running activity (VWRA) in 54 mice. Mitochondrial function was assessed in the ADT/RT mouse brains using Western blot analysis of Glucose transporter 4 (GLUT4) and transcription factor A, mitochondrial (TFAM). RESULTS/ANTICIPATED RESULTS: Fatigue in the ADT group was exacerbated during RT compared to the non-ADT group. This effect was specific to fatigue, as depressive symptoms were unaffected. PBMCs of fatigued subjects exhibited decreased ATP coupling efficiency compared to non-fatigued subjects, indicative of mitochondrial dysfunction. The ADT/RT mice demonstrated a synergistic effect of ADT and RT in decreasing VWRA. Brain tissues of ADT/RT mice exhibited decreased levels of GLUT4 and TFAM suggesting that impaired neuronal metabolic homeostasis may contribute to fatigue pathogenesis. DISCUSSION/SIGNIFICANCE OF IMPACT: These findings suggest that fatigue induced by ADT/RT may be attributable to mitochondrial dysfunction both peripherally and in the central nervous system (CNS). The synergistic effect of ADT/RT is behaviorally reproducible in a mouse model, and its mechanism may be related to bioenergetics in the CNS.

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Characterization of Physical Restraint and Sedative Use for Treatment of Agitation in the Emergency Department

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OBJECTIVES/GOALS: Agitation has high prevalence in the emergency department (ED), but limited evidence exists regarding clinical decisions to use sedatives and physical restraint. We examined clinical factors and agitation attributes impacting thresholds for sedative and restraint use in the emergency setting. METHODS/STUDY POPULATION: We conducted a prospective cohort study of adult patients (^{3}18 yo) with acute or escalating agitation during their ED visit at an urban tertiary care referral center. Consecutive patients requiring security presence or scoring >1 on an agitation scale were enrolled during randomized 8-h blocks. We recorded patient characteristics, staff/team factors, and environmental/systems data as well as scores on 3 validated agitation scales: Agitated Behavior Scale, Overt Aggression Scale, and Severity Scale. We performed descriptive analyses, bivariable analyses, and logistic regression modeling of factors with relation to sedative/restraint use. We observed 95 agitation events on unique patients over 2 months. RESULTS/ANTICIPATED RESULTS: Median age was 42, and 62.1% were male. Most frequent chief complaints were alcohol/drug use (37.9%) and psychiatric (23.2%). Majority of events (73.7%) were associated with sedative/restraint use. Factors related to treatment course or staff interactions were the primary reasons for agitation in 56.8% of events. A logistic regression model found no association between demographics and odds of sedative/restraint use. Overt Aggression Scale scores were associated with significantly higher odds of sedative use (AOR 1.62 [1.13–2.32]), while Severity Scale scores had significantly higher odds of restraint use (AOR 1.39 [1.12–1.73]) but significantly lower odds of sedative use (AOR 0.79 [0.64–0.98]). DISCUSSION/SIGNIFICANCE OF IMPACT: External factors may be important targets for behavioral techniques in ED agitation management. Further study of the Severity Scale may allow for earlier detection of agitation and identify causal links between agitation severity and use of sedatives and restraints.

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Characterization of vascular disease in an Acta2 mutant mouse model

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OBJECTIVES/GOALS: *ACTA2* R179 carriers present with early-onset stroke; occlusive lesions of the distal internal carotid artery and branches are filled with cells staining positive for smooth muscle cell (SMC) markers. We will identify pathways leading to increased SMC proliferation and migration and thus occlusion. METHODS/STUDY POPULATION: We generated an $Acta2^{SMC\text{-}R179C/+}$ mouse model, which expresses the *Acta2* R179C mutation in SMCs via the SM22a-Cre-Lox system. rt-PCR performed in aortic tissue confirms the presence of the mutation in the mutant mice and absence in mice with only the floxed allele (WT). We will determine phenotypic differences between mutant and WT brains using micro CT, vascular casting, histology, and immunostaining. We will characterize mutant SMC phenotype in culture by assessing expression of contractile genes and stem cell markers, proliferation, and migration. Single cell RNA (scRNA) sequencing of the brain will assess differential gene expression and cell populations between mutant and WT mice. RESULTS/ANTICIPATED RESULTS: Mutant mice have decreased blood pressure compared to WT mice from 8-24 weeks old, consistent with the phenotype seen in *ACTA2* R179 patients. We expect to see occluded and straighter cerebrovascular arteries and white matter changes in the $Acta2^{SMC\text{-}R179C/+}$ mice. iPSC-derived SMCs from patients show de-differentiation, continued expression of stem cell markers, and increased proliferation and migration. We expect to see a similar phenotype in $Acta2^{SMC\text{-}R179C/+}$ mouse SMCs in culture. Via scRNA sequencing, we expect to see altered transcriptional profiles in mutant mice brains including upregulated proliferative pathways in SMCs, glial cell activation, and gene expression changes in neurons. DISCUSSION/SIGNIFICANCE OF IMPACT: These

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