

recruited from the brain metastases and lung clinics at the Princess Margaret Cancer Centre. Participants completed standardized tests (WTAR, HVLt-R, BVMT-R, COWAT, Trailmaking test, WAIS-IV Digit Span) and questionnaires (FACT-Cog v3, EORTC-QLQ C30 and BN20, PROMIS Depression(8a) and Anxiety(6a)) prior to cranial radiotherapy for those who required it. Test scores were converted to z-scores based on published normative data and averaged to create a composite neurocognitive performance score and domain scores for memory, attention/working memory, processing speed and executive function. Neurocognitive impairment was defined according to International Cancer and Cognition Task Force criteria. Univariate and multivariate regressions were used to identify individual, disease and treatment variables that predict cognitive performance.

Results: 76 patients (mean (SD) age: 63.2 (11.7) years; 53% male) with BrMets were included. 61% experienced neurocognitive impairment overall; impairment rates varied across domains (38% memory, 39% executive functioning, 13% attention/working memory, 8% processing speed). BrMets quantity, volume, and location were not associated with neurocognitive performance. Better performance status (ECOG; β [95%CI]:-0.38[-0.70,-0.05], $p=0.021$), higher premorbid IQ (0.34[0.10,0.58], $p=0.005$) and greater cognitive concerns (0.02[-3.9e-04,0.04], $p=0.051$) were associated with better neurocognitive performance in univariate analyses. Only premorbid IQ (0.37[0.14,0.60], $p=0.003$) and cognitive concerns (0.02[0.0004,0.03], $p=0.05$) remained significant in multivariate analysis. We also recruited 31 patients with metastatic non-small cell lung cancer (mNSCLC) with no known BrMets (age: 67.5 (8.3); 32% male) and compared them to the subgroup of BrMets patients in our sample with mNSCLC (N=32; age: 67.8 (11.7); 53% male). We found no differences in impairment rates (BrMets/non-BrMets: Cognitive Composite, 59%/55%; Memory, 31%/32%; Executive Functioning, 35%/29%; Attention/working memory, 16%/13%; Processing speed, 7%/6%; Wilcoxon rank-sum test, all p-value's > 0.5). The presence or absence of BrMets did not predict neurocognitive performance. Among patients with mNSCLC, higher education (0.11[0.03,0.18], $p=0.004$) and premorbid IQ (0.36[0.12,0.61], $p=0.003$), fewer days since primary diagnosis (0.00290[-0.0052,-0.0005],

$p=0.015$) fewer pack-years smoking history (0.01[0.02,-0.001], $p=0.027$) and greater cognitive concerns (0.02[7e-5,0.04], $p=0.045$) were associated with better neurocognitive performance in univariate analyses; only premorbid IQ (0.26[0.02,0.51], $p=0.04$) and cognitive concerns (0.02[0.01,0.04], $p=0.02$) remained significant in multivariate analysis.

Conclusions: Cognitive impairment is prevalent in patients with advanced metastatic cancers, particularly affecting memory and executive functioning. However, 39% of patients in our sample were not impaired in any domain. We found no associations between the presence of BrMets and neurocognitive function in patients with advanced cancers prior to cranial radiation. Premorbid IQ, a proxy for cognitive reserve, was associated with cognitive outcomes in our sample. Our longitudinal study will allow us to identify risk and resilience factors associated with neurocognitive changes in patients with metastatic cancers to better inform therapeutic interventions in this population.

Categories: Cancer

Keyword 1: brain tumor

Keyword 2: neurocognition

Keyword 3: neuro-oncology

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3 The Relationship Between Apolipoprotein-E4 Genotype, Memory, and the Medial Temporal Lobe and How These Relationships Vary by Race in Middle-Aged Persons with HIV

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Objective: Many people with HIV (PWH) are at risk for age-related neurodegenerative disorders such as Alzheimer's disease (AD). Studies on the association between cognition, neuroimaging outcomes, and the Apolipoprotein E4 (APOE4) genotype, which is associated with greater risk of AD, have yielded mixed results in PWH; however, many of these studies have examined a wide age range of PWH and have not examined APOE by race interactions that are observed in HIV-negative older adults. Thus, we examined how APOE status relates to cognition and medial temporal lobe (MTL) structures (implicated in AD pathogenesis) in mid- to older-aged PWH. In exploratory analyses, we also examined race (African American (AA)/Black and non-Hispanic (NH) White) by APOE status interactions on cognition and MTL structures.

Participants and Methods: The analysis included 88 PWH between the ages of 45 and 68 (mean age=51±5.9 years; 86% male; 51% AA/Black, 38% NH-White, 9% Hispanic/Latinx, 2% other) from the CNS HIV Antiretroviral Therapy Effects Research multi-site study. Participants underwent APOE genotyping, neuropsychological testing, and structural MRI; APOE groups were defined as APOE4+ (at least one APOE4 allele) and APOE4- (no APOE4 alleles). Eighty-nine percent of participants were on antiretroviral therapy, 74% had undetectable plasma HIV RNA (<50 copies/ml), and 25% were APOE4+ (32% AA/Black/15% NH-White). Neuropsychological testing assessed seven domains, and demographically-corrected T-scores were calculated. FreeSurfer 7.1.1 was used to measure MTL structures (hippocampal volume, entorhinal cortex thickness, and parahippocampal thickness) and the effect of scanner was regressed out prior to analyses. Multivariable linear regressions tested the association between APOE status and cognitive and imaging outcomes. Models examining cognition covaried for comorbid conditions and HIV disease characteristics related to global cognition (i.e., AIDS status, lifetime methamphetamine use disorder). Models examining the MTL covaried for age, sex, and

relevant imaging covariates (i.e., intracranial volume or mean cortical thickness).

Results: APOE4+ carriers had worse learning ($\beta=-0.27$, $p=.01$) and delayed recall ($\beta=-0.25$, $p=.02$) compared to the APOE4- group, but APOE status was not significantly associated with any other domain ($ps>0.24$). APOE4+ status was also associated with thinner entorhinal cortex ($\beta=-0.24$, $p=.02$). APOE status was not significantly associated with hippocampal volume ($\beta=-0.08$, $p=0.32$) or parahippocampal thickness ($\beta=-0.18$, $p=.08$). Lastly, race interacted with APOE status such that the negative association between APOE4+ status and cognition was stronger in NH-White PWH as compared to AA/Black PWH in learning, delayed recall, and verbal fluency ($ps<0.05$). There were no APOE by race interactions for any MTL structures ($ps>0.10$).

Conclusions: Findings suggest that APOE4 carrier status is associated with worse episodic memory and thinner entorhinal cortex in mid- to older-aged PWH. While APOE4+ groups were small, we found that APOE4 carrier status had a larger association with cognition in NH-White PWH as compared to AA/Black PWH, consistent with studies demonstrating an attenuated effect of APOE4 in older AA/Black HIV-negative older adults. These findings further highlight the importance of recruiting diverse samples and suggest exploring other genetic markers (e.g., ABCA7) that may be more predictive of AD in some races to better understand AD risk in diverse groups of PWH.

Categories: Infectious Disease (HIV/COVID/Hepatitis/Viruses)

Keyword 1: genetics

Keyword 2: memory disorders

Keyword 3: neuroimaging: structural

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4 HIV Status and Cannabis Use: A Rigorous Examination of Between Group Differences in Neurocognitive Functioning

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