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Commentary

COVID-19 as a risk factor for Alzheimer's disease and related dementia: A perspective from Detroit, MI

Dear Editor

Risk for Alzheimer's disease and related dementia (ADRD) stems from health and lifestyle factors that accumulate over the life course. Models of risk for cognitive decline typically do not include acute disease incidence. Future gerontology research and clinical care need to consider contraction of the SARS-CoV-2 virus (COVID-19) as a long-term risk factor for ADRD. We illustrate this with data from Detroit, MI where the majority of COVID-19 confirmed cases within the state have presented and there is a confluence of risk factors for cognitive decline in the population.

Risk factors for COVID-19 contraction and complications are similar to those for ADRD: advanced age, chronic cardiovascular and metabolic diseases (Zhou et al., 2020). According to the Detroit Health Department, there are 15,280 confirmed cases and 1,552 related deaths in the city as of October 24, 2020. While older adults are at greater risk for COVID-19 mortality, only 12% of Detroit cases are adults age 60 years or older. A small proportion of Detroit COVID-19 cases are self-reported by nursing homes (~10%); efforts are underway to obtain additional information about this vulnerable population. Preliminary clinical observations are consistent with an increased prevalence of chronic health conditions that are associated with ADRD among COVID-19-related infections and deaths (e.g., hypertension, diabetes and cardiopulmonary disorder). Therefore, a large number of confirmed COVID-19 cases in Detroit are middle-aged and older adults who will recover from the virus and have pre-existing health conditions that increase their risk for future ADRD.

The risk for contraction and complications appears to be differentially higher among Black adults. In Detroit, a predominantly Black or African American city, Black residents are under-represented among confirmed COVID-19 cases (61.5%), yet they are over-represented among related deaths (82.8%), compared to 2019 US Census Bureau general population estimates for Detroit (78.6%). This may stem from social and behavioral determinants of health, including higher incidence of hypertension and diabetes among Black adults as compared to White counterparts. A similar hypothesis is made for the higher prevalence of ADRD among older Black adults as compared to White adults. We must consider the disproportionate risk for neural and cognitive decline that COVID-19 presents for vulnerable populations following acute recovery.

Although the risk for COVID-19 contraction and mortality related to dementia has been documented (Bianchetti et al., 2020), the long-term risk that COVID-19 symptom severity may pose for future dementia, including among middle-aged adults, has not been widely considered. We review three pathways for COVID-19 infection and symptom severity to act as risk factors for future ADRD, including effects that are initiated in mid-life and may be modifiable with targeted clinical intervention.

First, disrupted cardiorespiratory function causes cellular senescence and metabolic dysfunction that may contribute to neurological symptoms in COVID-19 patients and will drive subsequent age-related neurodegeneration. Typically cerebrovascular risk for cognitive decline is associated with chronic disease, but acute respiratory failure also increase risk for future ADRD. COVID-19 patients with white matter damage are vulnerable to executive dysfunction that is a pre-clinical indicator of ADRD, especially among older Black adults (Gamaldo et al., 2010).

Second, neurological symptoms in COVID-19 patients may also follow from the extreme inflammatory response to the infection. Increased levels of interleukin-6 (IL-6), IL-1β, and tumor necrosis factor alpha (TNF-α) are reported in novel coronavirus infections, as well as in aging and ADRD. Pro-inflammatory cytokine expression promotes oxidative stress, which if unchecked, degrades mitochondria, causes DNA mutations, and accelerates apoptosis (Raz and Daugherty, 2018). The cumulative effect is fundamental energetic failure and cell death that causes neural dysfunction and, eventually, neurodegeneration (Raz and Daugherty, 2018). The action between inflammation and oxidative stress is reciprocal and a severe, acute disease reaction may initiate a self-propagating cascade that drives subsequent age-related decline. Even after successful acute recovery, the middle-aged or older COVID-19 patient may be set on an accelerated decline trajectory with consequences that take years to detect.

Third, COVID-19 not only exacerbates risk, but also removes protective factors; two, in particular, bear mention. First, frequent aerobic exercise mitigates the risk associated with cardiovascular disease, and promotes physiological and cognitive resiliency. During patient recovery from COVID-19, cardiopulmonary symptoms and muscle damage will interfere with exercise. For middle-aged and older adults with chronic health conditions there is additional risk for frailty that often precedes ADRD and disproportionately affects Black adults as compared to White counterparts (Hirsch et al., 2006). Second, the public health response to COVID-19 has limited socialization and access to community resources, which can be detrimental to mental health and increases the risk for worse control of chronic health conditions. Thus, COVID-19 may shift the multivariate risk profile for ADRD.

Prospective longitudinal study, beginning in acute recovery and extending for several years, is necessary to determine the effect of COVID-19 on the progression of dementia-related pathology. On-going longitudinal studies of dementia risk uniquely can follow individuals with a pre- and post-infection comparison. Studies of long-term COVID-19 recovery that integrate cognitive assessments with blood and neuroimaging biomarkers of metabolic function, inflammation and oxidative damage will be integral to evaluate the pathways for risk we outlined. In all study designs, dementia risk related to COVID-19 is not

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only a history of infection but also symptom type, severity and chronicity.

The rapid spread of COVID-19 across the globe has required an immediate response that prioritizes acute patient recovery and public health. When the dust settles, we must look beyond the next few years to consider the long-term risk COVID-19 will present to the world's aging population, especially among persons vulnerable to ADRD.

Declaration of Competing Interest

The authors have no conflicts of interest to disclose.

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