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Slaying Dementia Dragons with Blood, Lungs and Guts

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Ancient mapmakers used to ink on maps the phrase “here be dragons” at the limits of their known world. These mapmakers would place at their edges of their maps, beyond the boundaries of charted territories, mythic creatures such as unicorns, sea serpents, basilisks, and yes, dragons. Four new studies in this issue of the journal attempt to fill in gaps and discover uncharted territories on the dementia map.^{1–4} There has been much scientific focus on Beta amyloid and tau pathways in the context of dementia, especially Alzheimer's disease. However, there has been a slow but growing recognition that other biological pathways and clinical variables may also play an important role in increasing the risk of developing various dementia syndromes as well as in accelerating the rate of cognitive decline in normal aging.

Vascular and other emerging risk factors may influence transitions between various cognitive stages in older adults, from cognitive normalcy to intermediate cognitive risk states such as the Mild Cognitive Impairment syndrome (MCI), or from MCI to dementia.^{5,6} It is also possible that some individuals may appear to transition directly to dementia from the stage of cognitive normalcy due to the transitory nature of intermediate cognitive stages, rapidity of progression of dementia pathology, or long intervals between assessments. Goldstein and colleagues report that in 1385 participants diagnosed with MCI, presence of elevated systolic or diastolic blood pressure assessed over multiple time points was associated with a faster rate of cognitive decline in these high-risk individuals.¹ The role of mid-life hypertension as a risk factor for dementia in late life is well established.⁷ However, studies that have examined the role of late life hypertension as a risk factor for cognitive decline in older adults have had mixed results.⁸ It has been suggested that there is a U-shaped relationship between systolic blood pressure and dementia, suggesting that both high and low systolic blood pressure levels increase the risk of developing dementia.^{7,9} For diastolic blood pressure levels, lower values appear to be detrimental for cognitive health in aging.¹⁰ The current study in MCI participants was not designed to account for the effects of antihypertensive treatment or low (systolic or diastolic) blood pressure on cognitive decline; however, the results remained unchanged even after accounting for intervening strokes.¹

Size apparently does matter! Higher erythrocyte mean corpuscular volume (MCV) predicted accelerated rates of decline on tasks of global mental status, memory, and attention in 827 participants (mean age 67 years) enrolled in the Baltimore Longitudinal Study of Aging.²

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Conflict of Interest

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MCV may increase in many conditions such as low vitamin B12 or folic acid levels, liver disease, alcoholism, hypothyroidism, and reticulocytosis. The relationship between MCV and cognition in the Baltimore Longitudinal Study of Aging cohort did not appear to be explained by anemia or disappear after accounting for some measures of inflammation (erythrocyte sedimentation rate and white blood count blood), though more direct measures of inflammation such as interleukin-6 were not examined.²

Lower pulmonary function may be a marker of constitutional and early life environmental exposures or might have a more direct effect on cognition via decreased cerebral oxygenation, which in turn may lead to neurodegeneration, create a pro-inflammatory state, or increase the risk of cerebral ischemic damage.^{3,11} Vidal and colleagues report that lower pulmonary function measured in mid-life (mean age 52 years) in 3,665 subjects from the AGES-Reykjavik Study predicted lower memory, speed of processing, executive function, and higher likelihood of MCI and dementia 23 years later.³ However, longitudinal changes in pulmonary function were not associated with lower cognitive function or risk of dementia. In contrast, a previous large prospective cohort study involving 10,975 men and women aged 47 to 70 years enrolled in the Atherosclerosis Risk in Communities Study reported that reduced pulmonary function was associated with worse cognitive status at baseline and increased risk of being hospitalized with a diagnosis of dementia.¹¹ Lung function, however, in this study was not associated with change in cognitive scores over time.¹¹ Presence of a restrictive ventilatory pattern, but not an obstructive pattern, was associated with reduced cognitive scores and higher dementia risk in this large cohort.¹¹ Methodological differences in sample sizes, demographic characteristics, control for confounders, long intervals between assessments and outcome ascertainment, and racial composition, may also in part explain divergent results. Clearly this is not the final word on this issue.

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral, flagellated bacterium that colonizes the gastric mucosa of most humans worldwide, and is associated with various upper gastrointestinal diseases. Chronic *H. pylori* infection has also been implicated in a variety of extragastric diseases including vascular conditions such as ischemic heart disease and cerebrovascular disease.^{12,13} A high prevalence of *H. Pylori* seropositivity has also been reported in patients with Alzheimer's disease.¹³ Chronic *H. pylori* infection may increase dementia risk by potentiating cardiovascular risk in aging. In the population-based PAQUID Study based in the southwest of France, 391 of the 603 participants without dementia (mean age 73 years) were found to be seropositive for *H. pylori* at their baseline evaluation.⁴ These *H. pylori* seropositive individuals had a 46 percent higher risk of developing dementia over study follow-up even after controlling for multiple confounders including age, gender, educational level, apolipoprotein E4 status, cardiovascular risk factors and cognitive scores.⁴

These four new intriguing studies raise as many interesting questions as they answer.

- What is the optimal range to maintain blood pressure in order to reduce risk of cerebrovascular diseases and dementia? The collective knowledge gained thus far does not give clear directions for clinicians. This is an important future direction to pursue in the next generation of studies to develop blood pressure management guidelines in cognitively impaired as well as normal older patients.
- Hemorrheology, the scientific study of the deformation and flow properties of cellular and plasmatic components of blood, might provide new insights into cognitive decline mechanisms in aging. There is increasing evidence indicating that flow properties of blood are among the main determinants of proper tissue perfusion and alterations in these properties may play significant roles in disease processes.¹⁴ The investigators suggested that physiological changes in erythrocytes

on top of age-related changes in cerebral vasculature might explain the effect of higher MCV on cognitive risk in the Baltimore Longitudinal Study of Aging.²

- Is lower lung function an innocent bystander or an active participant in increasing risk for cognitive decline? Interestingly, proper management of chronic asthma in Alzheimer's disease patients has been reported to result in improvements in cognitive function and instrumental activities of daily living,¹⁵ suggesting a potential new avenue for treatment of cognitive decline.
- Could eradication of *H. pylori* infection improve cognitive function in older adults at risk for cognitive decline? In support, a small pilot study demonstrated that eradication of *H. pylori* infection in patients with Alzheimer's disease led to significant improvement of the clinical manifestations as measured on tests of global mental status.¹³
- How do these different risk factors interact with each other? For instance, a symbiotic relationship may exist between blood pressure levels, erythrocyte count and MCV, as exemplified by chronic obstructive lung disease in older adults and its sequel of polycythemia.^{16,17} At high erythrocyte levels, MCV may be down regulated, lowering blood viscosity and partially reduce diastolic blood pressure without compromising flow.¹⁷ A better understanding of the inter-relationships between potentially modifiable risk factors may help develop effective multifactorial interventions in dementia patients who also tend to carry a high comorbid disease burden.

While randomized controlled trials are considered the gold standard in testing new interventions and therapies, the four new studies in this issue of the journal highlight the value of carefully conducted observational studies in generating and validating new hypotheses. These large datasets are also a valuable resource for investigators to conduct secondary analyses as demonstrated in these studies. As is the nature with secondary analysis in established cohort studies, the assessments and cohort characteristics are dictated by the original design, and may limit the scope of analyses and caution needs to be exercised when interpreting any findings. To geriatricians, the multifactorial nature of cognitive decline and dementia in aging may not come as a surprise given the parallels in other major geriatric syndromes such as falls, heart disease, or delirium. These set of studies highlight an opportunity for geriatrics and related specialties to take the lead in devising and testing multimodal theory based interventions to ameliorate cognitive decline in aging; and finally driving out the dragons from the dementia maps.

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