EClinicalMedicine 11 (2019) 7–8

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: https://www.journals.elsevier.com/eclinicalmedicine

EClinicalMedicine
Published by THE LANCET

Commentary

Sickle cell trait: A sigh of relief?

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ARTICLE INFO

Article history:
Received 8 May 2019
Accepted 8 May 2019
Available online 29 May 2019

In this issue of *EClinicalMedicine*, Cahill and colleagues report an important substudy [1] from the REGARDS cohort [2], demonstrating that individuals with sickle cell trait (SCT) do not appear to be at increased risk for cognitive decline compared to the normal population [1]. At first blush, this might seem self-evident. Individuals with SCT are largely asymptomatic from the carrier state of sickle hemoglobin. Despite the high prevalence of cerebrovascular disease in patients with sickle cell disease, SCT has not been linked to increased ischemic stroke [3,4]. However, SCT is not completely benign. SCT is associated with increased risk of chronic renal disease [3] and atrial fibrillation [5]. SCT is also associated with increased red cell phosphotidylserine exposure, circulating D-dimers and increased thromboembolism [3,6]. Subjects with SCT have decreased capillary density and surface area in skeletal muscle [7] and are more prone to rhabdomyolysis under extreme stress [3]. Given the critical role of microvasculature health in kidney, muscle, and brain, it would not be surprising if SCT might be a risk factor for insidious small cerebral vessel disease and concomitant vascular cognitive impairment [8]. Small vessel disease certainly is a major problem in patients with sickle cell disease. Despite marked reductions in ischemic stroke, silent cerebral infarctions continue to plague patients with sickle cell disease, with a prevalence of 50% at 30 years of age [9].

The Reasons for Geographic and Racial Differences in Stroke (REGARDS) project was a longitudinal observational study of risk factors for stroke in 30,239 participants recruited from 2003 and 2007 [2]. Among the participants, 25.6% had sickle cell trait of which 63% were women. Neurocognitive function was tracked using several validated phone-based methods, including annual measurements of the Six-item Screener and biannual measures of word list learning, delayed word list recall, semantic fluency, and phonemic fluency. Median follow-up time was 7.1 years. Blood pressure, electrocardiograms, lipid profile, renal function, fasting glucose and hemoglobin A1c were measured in all participants. With these data, multivariate models of cognitive function were adjusted for age, sex, education, income, region of residence, estimated glomerular filtration rate, systolic blood pressure, alcohol use, smoking status, exercise frequency, coronary heart disease, left ventricular hypertrophy, atrial fibrillation, hyperlipidemia, statin use, diabetes, and hypertension.

The presence of SCT genotype yielded odds-ratio for incident cognitive impairment of 1.18 but the 95% confidence intervals were 0.93–1.51. Adjustment for other risk factors did not materially alter the results. While it is possible that a larger sample size might have been able to demonstrate a statistically significant difference, the calculated odds ratio was significantly smaller than other risk factors identified in the study, including male sex (OR 1.6), black race (OR 2.1), and low education (OR 2.2). It is also lower than reported for potentially modifiable risk factors such as cigarette smoking, diabetes, obesity, and alcohol consumption [10]. Thus, individuals with SCT should be comforted that any potential cognitive risks conveyed by their hemoglobin status are small compared with health modifiers under their control.

The study does have some intrinsic limitations. The phone-based neurocognitive screening tools used are not as sensitive as comprehensive neuropsychiatric batteries. Vascularly-mediated white matter disease often manifests as impaired processing speed, rather then verbal fluency or memory deficits, and subtle deficits might escape detection. Impaired processing speed can impact employability and quality of life in subtle ways, independent of neurocognitive testing. No brain imaging was performed, so it is impossible to speculate whether SCT subjects were at greater risk of preclinical cerebrovascular disease. With only an average of seven years of follow up, it is also impossible to comment on the impact of SCT on the rate of cognitive decline or the incidence of overt dementia.

Despite these caveats, the incidence of new cognitive impairment in the REGARDS study was sufficiently high (12.6%–14.6%) that clinically-meaningful differences in cerebrovascular health would likely have manifested themselves. While further research on the impact of SCT on the systemic and the cerebral vascular system is probably warranted, there is currently no indication for more aggressive neurocognitive screening of individuals with SCT as they age. This will likely come as good news to Americans of African descent who already suffer from increased hypertension, heart disease, and diabetes as well as greater barriers to comprehensive health care.

Author contribution

Dr. Wood interpreted the manuscript and wrote the commentary.

DOI of original article: https://doi.org/10.1016/j.eclinm.2019.05.003.
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https://doi.org/10.1016/j.eclinm.2019.05.004

Declaration of Competing Interest

Dr. Wood reports grants from National Heart Lung and Blood Institute (1RO1HL136484-A2, 1U01HL117718-05), during the conduct of the study; personal fees from Bluebirdbio, WorldCareClinical, Apopharma, Ionis Pharmaceuticals, BiomedInformatics, and Celgene, as well as non-financial support from Silence Therapeutics and Philips Healthcare outside the submitted work.

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