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113.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: BASIC AND TRANSLATIONAL

Associations between Epigenetic Age Acceleration and Psychoneurological Symptoms in Sickle Cell Disease

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Introduction:
Sickle cell disease (SCD) affects approximately 100,000 predominantly Black or African American individuals in the United States. The disease has several acute and chronic complications that lead to a reduced median lifespan of 42 years, which is significantly shorter than the general US population. In this shortened lifespan, people experience deleterious psychoneurological symptoms including pain, sleep disturbances, depressive symptoms, and cognitive impairment. The high occurrence of these symptoms has negative effects on quality of life and function, and contributes to health disparities in this population. Evidence suggests a person's epigenetic age may be associated with inter-individual variability in psychoneurological symptoms in SCD. Epigenetic age is a promising biomarker because it reflects the cumulative effects of exposures to stressors at the psychosocial, physical and environmental level, by capturing the molecular processes occurring with declining tissue function through globally assessing DNA methylation patterns that account for the pace of cellular aging.
Epigenetic age and age acceleration in relation to disease characteristics and symptom burden has been assessed in several chronic conditions such as cancer, obesity and Alzheimer's. None have assessed this association in SCD. To address this gap, our study aims to determine whether epigenetic age acceleration is associated with psychoneurological symptom burden (pain impact, emotional impact, sleep impact, and cognition) in SCD.
Methods:
Psychoneurological symptoms and DNA methylation were assessed in a subset of participants aged between 18 - 45 years enrolled in one of the Sickle Cell Disease Implementation Consortium sites. DNA methylation data were generated on the Infinium MethylationEPIC beadchip (Illumina) from the extracted DNA of blood specimens and used to calculate epigenetic age using five epigenetic clocks (Horvath, Hannum, PhenoAge, GrimAge, & DunedinPACE).
Psychoneurological symptoms were evaluated using validated instruments: the Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me), and Quality of Life in Neurological Disorders (NeuroQoL). Data were converted to T-scores and were used to determine associations with epigenetic age acceleration for each of the epigenetic clocks. Higher T-scores in ASCQ-Me and NeuroQoL indicate more desirable (better) outcomes.
Results:
Among participants (n=89) included in the analysis, the mean (SD) chronologic age was 30.6 (8.0) years. A majority identified as female (60.7%), non-Hispanic Black or African American (92%), never married (76.4%), had Hb SS genotype (68.5%), were taking hydroxyurea (60.5%), and had at least 4 pain events in past year (53.5%).
Two epigenetic clocks showed mean age acceleration (Horvath: 0.2 ±4.6 years; GrimAge: 12.6 ±4.0 years, whereas two clocks showed mean age deceleration (Hannum: -4.27 ±3.91 years; PhenoAge: -8.43 ±6.0 years). The DunedinPACE clock is on a different scale than other clocks, but also demonstrated evidence for accelerated aging whereby the epigenetic age increased 1.14 years for every chronologic year. Increased age acceleration was associated with worse pain impact scores (GrimAge β=-0.25, p= 0.02), worse emotional impact scores (GrimAge β=-0.24, p=0.03; Dunedin β= -0.30, p=0.01) greater sleep disturbance (Dunedin β=-0.22, p=0.04) and more depressive symptoms (Dunedin β=0.29, p=0.01) (Table 1).

Conclusion:
This was the first study, to our knowledge, that explored the relationship between epigenetic age and psychoneurological symptoms in SCD. Epigenetic age acceleration was associated with worse symptom scores. Our preliminary findings identified several variations in the associations between symptom outcomes and epigenetic age across the five clocks. These variations may be due to the differences in the models used to develop the clocks, as well as inherent differences in epigenetic loci used to calculate epigenetic age for each clock. Future assessment of those discrepancies is warranted to effectively characterize individuals at higher risk of age acceleration and higher symptom burden in SCD. Our findings also highlight the potential use of epigenetic age acceleration as a biological target for interventions aimed towards preventing age acceleration and symptom development, improving the quality of life of individuals with SCD.

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