To: ASNR
Characters: 2489 (limit 2500 across all sections)

Accelerated Brain Aging in Congenital Heart Disease and Relation to Neurodevelopmental Outcome

Authors: Ruhika Lankalapalli*, Sheng He*, James Ko. H. Arafat Hussain, Kiho Im, Ai Wern Chung, Patrick Johnston, Jane Newburger, Sarah U. Morton#, Ellen Grant#, Yangming Ou#

*,# equal contribution as co-first and co-senior

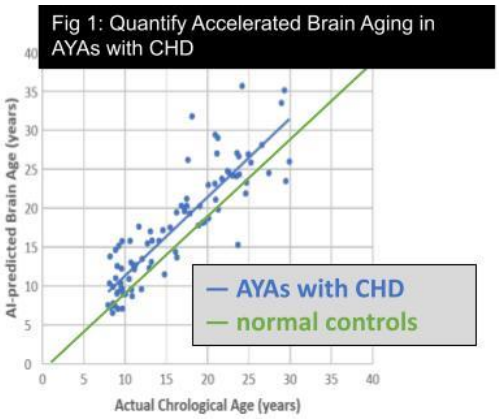
Purpose: Recent studies observed brain/behavior changes suggesting accelerated brain aging in adolescent and young adult survivors (AYAs) of congenital heart disease (CHD)[1–4]. We conducted the first study to quantify the severity of accelerated aging in AYAs with CHD, the contributing factors, and potential for accelerated aging to infer neurodevelopment outcome.

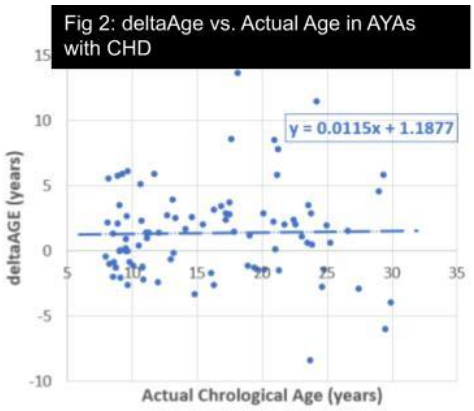
Materials and Methods: This IRB-approval study used a deep learning brain age estimator we trained on T1-weighted brain MRIs of 16,705 healthy brain MRIs[5], on 96 AYA survivors of CHD 8-30 years of age in the 8-site Pediatric Cardiac Genomics Consortium (PCGC). We computed the severity of brain aging by subtracting AI-estimated and the actual chronological ages (deltaAge), with a T-test with normal controls to confirm the existence and severity of accelerated brain aging (i.e., deltaAge>0 with $p<0.05$). We used ANCOVA to test whether deltaAge was significantly associated with contributing factors including demographics (sex, age at MRI, Body Mass Index (BMI)), genetics (High Brain Expression, Chromatin-modifying, Neurodevelopmental disorder, probability of loss of function intolerance, and ApoE genes), and Socioeconomic Status (SES: parental education, income). We used a general linear model to test the significance of associations between deltaAge and neurodevelopment scores (Wide Range Achievement Test-IV, Wechsler (version IV for adults and V for children), controlling for demographics, genetics and SES.

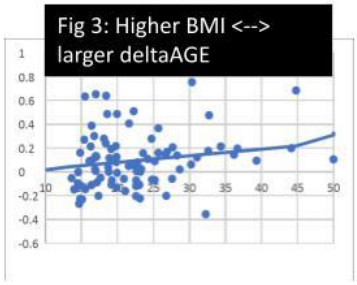
Results: AI-estimated deltaAge was 1.37 years ($p<0.01$) for AYAs with CHD (Fig 1), with 1.0115 years of brain aging for every year of chronological aging between 8 to 30 years age, after an initial brain aging of 1.18 yrs by age 8 years (Fig 2). ANOVA test showed that a higher BMI ($p=0.014$, Fig 3) and the e3/e4 alleles in the ApoE gene ($p=0.021$, Fig 4) were significantly associated with a greater deltaAGE. Among 22 neurodevelopmental scores, AI-estimated deltaAGE was significantly positively associated with Matrix Reasoning ($p=0.021$), Vocabulary($p=0.026$), Verbal Comprehension Index ($p=0.050$), and Fluid Reasoning Index (0.035), controlling for demographics, genetics, and SES.

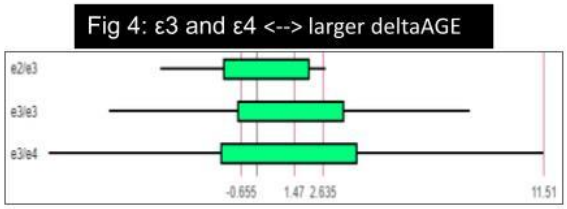
Conclusion: Survivors of CHD experience 1.37y of accelerated aging between 8 and 30 years, which may be alleviated by lowering BMI and the absence of ApoE gene. The severity of accelerated brain aging offers a new MRI metric to identify individuals at risk for some neurodevelopmental impairments. Next steps will be longitudinal studies in larger datasets.

Figure:









5 References: (AJNR style)

1. Kessler N, Feldmann M, Schlosser L, et al. Structural brain abnormalities in adults with congenital heart disease: Prevalence and association with estimated intelligence quotient. *Int J Cardiol*. 2020;306:61-66. doi:10.1016/j.ijcard.2020.02.061

2. Ehrler M, Latal B, Kretschmar O, von Rhein M, O'Gorman Tuura R. Altered frontal white matter microstructure is associated with working memory impairments in adolescents with congenital heart disease: A diffusion tensor imaging study. *Neuroimage Clin*. 2020;25:102123. doi:10.1016/j.nicl.2019.102123

3. Nattel SN, Adrianzen L, Kessler EC, et al. Congenital Heart Disease and Neurodevelopment: Clinical Manifestations, Genetics, Mechanisms, and Implications. *Can J Cardiol*. 2017;33(12):1543-1555. doi:10.1016/j.cjca.2017.09.020

4. Bagge CN, Henderson VW, Laursen HB, Adelborg K, Olsen M, Madsen NL. Risk of Dementia in Adults With Congenital Heart Disease: Population-Based Cohort Study. *Circulation*. 2018;137(18):1912-1920. doi:10.1161/CIRCULATIONAHA.117.029686

5. He S, Pereira D, David Perez J, et al. Multi-channel attention-fusion neural network for brain age estimation: Accuracy, generality, and interpretation with 16,705 healthy MRIs across lifespan. *Medical Image Analysis*. 2021;72:102091. doi:10.1016/j.media.2021.102091