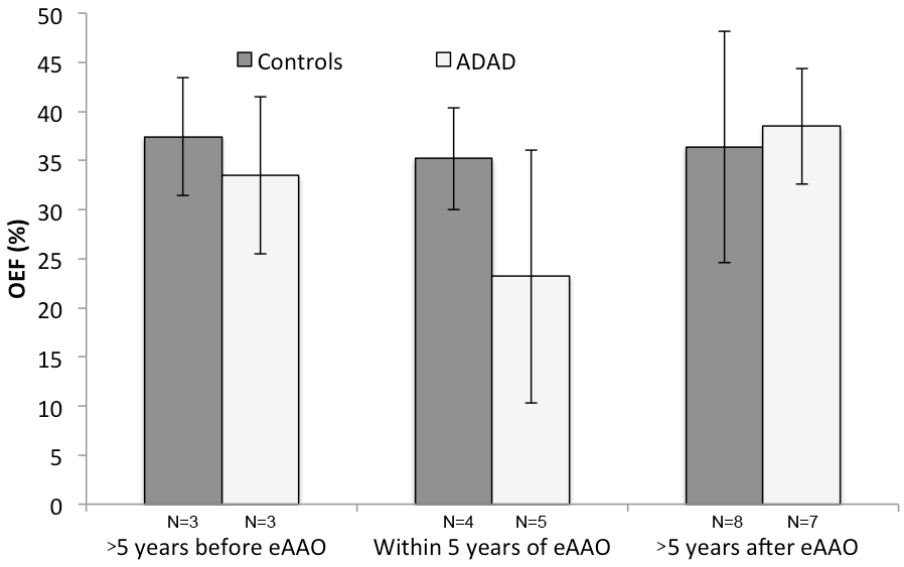
Early alterations in cerebral oxygen extraction in autosomal-dominant Alzheimer's Disease

Dustin Kenneth Ragan[1,2], Randall Bateman[3,4], Virginia D Buckles[3,4], Jose A Pineda[1,3], John C Morris[3,4], and Tammie LS Benzinger[2,4]

[1]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, United States, [2]Department of Radiology, Washington University School of Medicine, St. Louis, MO, United States, [3]Department of Neurology, Washington University School of Medicine, St. Louis, MO, United States, [4]Knight Alzheimer's Disease Research Center, Washington University School of Medicine, St. Louis, MO, United States

Background Alzheimer's Disease (AD) is a progressive neurological disease that ultimately produces severe dementia. Currently no disease modifying therapies are available. Ideally, candidate therapies could be delivered before substantial brain damage has occurred, which has motivated ongoing research to identify presymptomatic markers of disease. Autosomal Dominant Alzheimer's Disease (ADAD) is an inherited form of AD that has a 50% chance of being passed to children while maintaining a similar progression to other forms of AD. It is caused by mutations on one of three genes (APP, PSEN1, or PSEN2) with 100% penetrance. As a result, it is ideal for the study of preclinical AD [1]. We investigated defects in the cerebral oxygen extraction fraction (OEF) in ADAD patients using magnetic-susceptibility based oximetry. OEF represents the amount of oxygen taken up from the blood and, when combined with cerebral blood flow, provides a measure of cerebral metabolism.

Methods This project was part of the DIAN study of ADAD. The study population includes individuals with a parent with ADAD and who thus have a 50% chance of developing the disease themselves. Genetic testing divided the population into controls and patients with ADAD. Gradient-echo images were obtained of all subjects with acquisition parameters: TE/TR = 20/28 ms, field of view = 32 x 26 x 21 cm, nominal resolution = 0.7 x 0.7 x 2.4 mm. Phase images were reconstructed and background field effects were removed using low-pass filtering [2]. Deoxyhemoglobin concentration was determined by using a straight-cylinder approximation. A hematocrit of 0.42 was assumed. OEF was measured in the posterior portion of the superior sagittal sinus, which drains the majority of the cerebral cortex. Expected age of onset (eAAO) was determined by the difference between the patient's age and the parental age of onset. The correlation between OEF and the absolute value of the eAAO was determined. In ADAD, genetic factors lead to fairly consistent onset across generations [1], and the age difference is measure of time until the individual's onset.



Results For patients without ADAD, OEF and eAAO were uncorrelated (r^2<0.01; p=0.44). For subjects with ADAD, the average OEF was decreased near the age when parental symptoms appeared. OEF displays a significant Spearman correlation with the eAOO (r^2 = 0.23, p=0.03). Prior to and after the age of parental onset, OEF normalizes, as demonstrated in the figure.

Discussion We found defects in cerebral metabolism that occur prior to the estimated age of onset in our patient population. Although a few previous investigations have not found a decrease in OEF in AD patients, these studies were small and, more importantly, only included post-symptomatic patients [3]. Our data in patients later in the disease process is consistent with those findings. The normalization of OEF does not necessarily indicate a normalization of cerebral metabolism; it can be explained by a decrease in cerebral blood flow to compensate for a decrease in overall metabolism. This implies that defects in cerebral oxygen metabolism may be important early biomarkers of AD progression.

References

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