Longitudinal Accumulation of Cerebral Microhemorrhages in Dominantly Inherited Alzheimer Disease

Nelly Joseph-Mathurin, PhD, Guoqiao Wang, PhD, Kejal Kantarci, MD, MS, et al., on behalf of the Dominantly Inherited Alzheimer Network

Cite as: Neurology® 2021;96:e1632-e1645. doi:10.1212/WNL.0000000000011542

Study Question
What are the clinical risks associated with the presence of cerebral microhemorrhages (CMHs) in members of families affected by dominantly inherited Alzheimer disease (DIAD)?

What Is Known and What This Paper Adds
CMHs are common in older adults, especially those with dementia, but their clinical implications are unclear. This investigation in a young population affected by DIAD aims to elucidate the role of CMHs related to AD and show that presence of these CMHs is a risk factor for accumulation of additional CMHs and worsening dementia.

Methods
These cross-sectional and longitudinal analyses used observational data from 511 people with family histories of DIAD participating in the Dominantly Inherited Alzheimer Network (DIAN) study between 2009 and 2019. The investigators focused on 310 individuals carrying mutations in the APP, PSEN1, and PSEN2 genes and 201 individuals without such mutations as control. These participants underwent MRI assessments for CMH detection, cortical thickness, hippocampal volume, and white matter lesion volume. DIAN visits also included clinical assessments using the Clinical Dementia Rating and a comprehensive neuropsychological battery summarized with a composite cognitive measure. General linear mixed-effects models were used to investigate the longitudinal implications of the presence and severity of CMHs, including the relationships between the severity of prevalent CMHs and yearly increase in incident CMHs and between prevalent or incident CMHs and changes in clinical and cognitive metrics.

Results and Study Limitations
MRI scans revealed CMHs in 8% of mutation-carriers and 3% of noncarriers. In longitudinal analyses, prevalent or incident CMHs predicted faster change in clinical measures, but not faster changes in composite cognitive measures, cortical thicknesses, hippocampal volumes, or white matter lesion volumes. The presence of ≥2 CMHs predicted development of more CMHs. A limitation of the present study is that 23% of participants had no longitudinal data, but this group had similar clinical characteristics as those with longitudinal data. The use of data from multiple centers using 2 different sequences for CMH detection was another limitation but subsequent scanner sequence harmonization among sites and statistical accounting for the type of scanner sequence favor generalizability.

Study Funding and Competing Interests
This study was funded by the NIH. Some authors report receiving personal fees, committee appointments, and research support from healthcare companies, foundations, scholarly institutions and consortia, and US and UK government agencies; serving on journal editorial boards; holding various patents and equity in various companies; and serving as an investigator on industry-sponsored clinical trials. Go to Neurology.org/N for full disclosures.
Longitudinal Accumulation of Cerebral Microhemorrhages in Dominantly Inherited Alzheimer Disease

Nelly Joseph-Mathurin, Guoqiao Wang, Kejal Kantarci, et al.

*Neurology* 2021;96:e1632-e1645 Published Online before print January 25, 2021
DOI 10.1212/WNL.0000000000011542

This information is current as of January 25, 2021