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NEUROIMAGING

Progressive white matter injury in autosomal dominant Alzheimer's disease is strongly associated with cerebral microbleeds and neurodegeneration

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Abstract

Background: White matter (WM) injury visible on MRI is a common finding in Alzheimer's disease (AD) and is often attributed to small vessel ischemic changes secondary to increased systemic vascular risk. Increased WM injury has been associated with the progression of Autosomal Dominant AD (ADAD), though ADAD pathogenic variant carriers are relatively young and may not have elevated vascular risk factors. We hypothesized that WM injury in ADAD may reflect worsening of cerebral amyloid angiopathy (CAA) and neurodegeneration. Here we examine this hypothesis using cross-sectional and longitudinal data from the Dominantly Inherited Alzheimer Network observational study (DIAN).

Method: MRI data from ADAD pathogenic variant carriers (n=223) and non-carriers (n=136) were used in the present study (Table 1). We extracted FreeSurfer-based WM lesion (WML) volume from T1-weighted images (hypointensities). Cortical microbleed (CMB) burden was assessed visually on susceptibility weighted/T2*-weighted gradient echo images by experienced radiologists (blineded to the mutation status) at the Mayo Clinic in Rochester. Linear regression models compared WML volume at baseline in people with and without CMB. Linear mixed effect models assessed the relationships

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between longitudinal WML and both CMBs and FreeSurfer-based total gray matter (GM) volume. Models were corrected for age and estimated years to symptom onset (EYO).

Result: Greater baseline WML volume was seen in ADAD carriers vs. non-carriers, particularly close to the age of estimated symptom onset. Baseline WML volume was greater in carriers with CMBs compared to those without ($t=2.9$, $p=0.003$, Figure 1). Longitudinal increase in WML amongst ADAD pathogenic variant carriers with CMBs was estimated to be 214 mm^3/year greater than that amongst carriers without CMBs ($t=4.1$, $p<0.001$, Figure 2). Independent of this CMB effect, decreasing GM volume was strongly associated with increasing longitudinal WML volume ($t=-6.2$, $p<0.001$, Figure 3). Similar analyses in the non-carrier group yielded no significant findings.

Conclusion: Consistent with prior reports, WML volume was increased in ADAD pathogenic variant carriers. However, the results here suggest WML in ADAD may not solely be due to small vessel ischemic changes, but rather may be a result of worsening CAA and more rapid neurodegeneration.

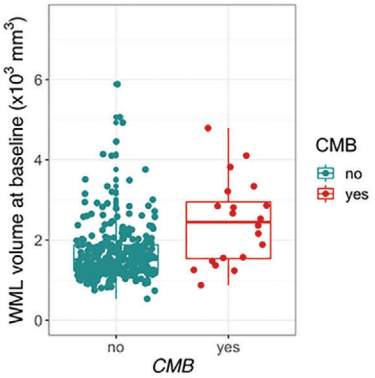

Figure 1: White matter lesion (WML) volume and cerebral microbleed (CMB) association in ADAD mutation carriers at baseline. WML was significantly greater in carriers with CMBs compared to those without (t=2.9, p=0.003) after correcting for significant effects of age (t=2.7, p=0.006) and estimated years to symptom onset (t=2.7, p=0.007).

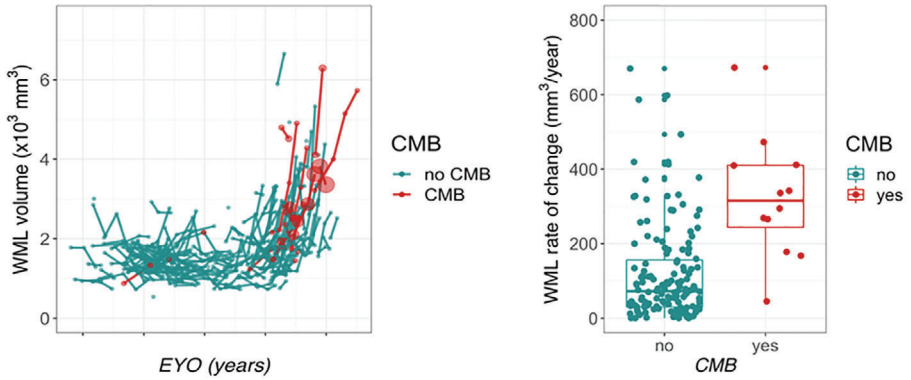

Figure 2: Longitudinal Change in white matter lesion (WML) volume in ADAD carriers with and without cerebral microbleeds (CMB). The size of the circles in the left panel is proportional to the number of CMB. The annual rate of change of WML volume was greater in carriers with CMB suggestive of CAA as opposed to those without CMB (t=4.1, p<0.001), even after correcting for age, estimated years to symptom onset (EYO), and total gray matter (GM) volume (shown in Figure 3).

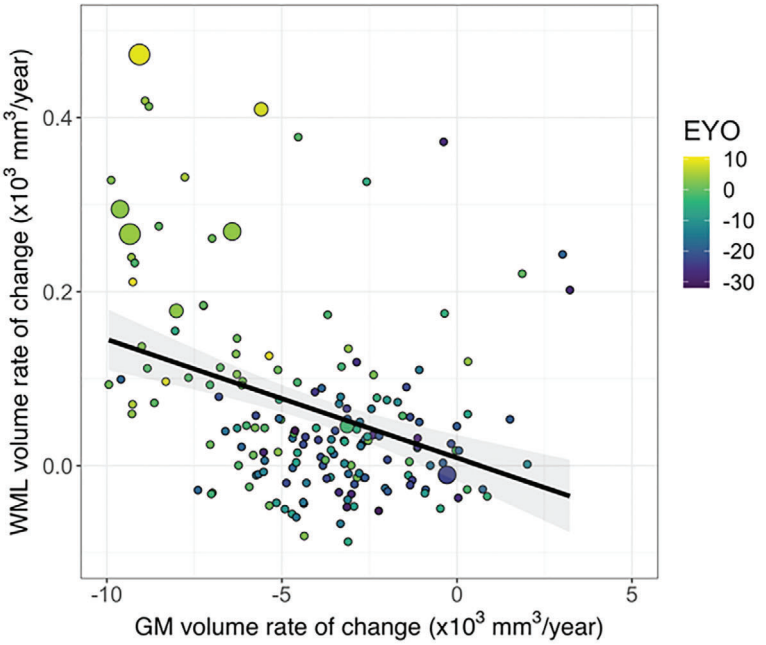

Figure 3: The rate of change of white matter lesion (WML) volume relates to the rate of change in gray matter (GM) volume (t=-6.2, p<0.001), even after adjusting for age, estimated years to symptom onset (EYO), and the presence of cerebral microbleeds (The size of the circles is proportional to the number of CMB). r = -0.51, p<0.001 uncorrected; r = -0.30, p<0.001 after adjusting for EYO and age.

Table 1: Participants' demographics and study information. Mean ± Standard deviation, or percentage are reported.

	ADAD carrier (n=223)	ADAD non-carrier (136)
Age at baseline (years)	38.5 ± 11.0	37.2 ± 10.9
Estimated years to symptom onset	-7.8 ± 11.0	-10.9 ± 11.1
APOE e4 (yes)	31%	29%
Sex (Female)	56%	61%
Education (years)	14.3 ± 3.0	14.9 ± 2.8
Definite CMB at baseline (yes)	8%	3%
Definite CMB at the last visit (yes)	11%	6%
CDR at baseline (0.5+)	43%	9%
CDR at last visit (0.5+)	47%	10%
Follow-up time (years)	3.6 ± 2.2	4.1 ± 2.2

APOE e4: Apolipoprotein E allele e4 status
CMB: cerebral microbleed
CDR: Clinical dementia rating (total)