MACHINE-LEARNING DERIVED MRI-BASED ATROPHY BIOMARKER PREDICTS LONG-TERM COGNITIVE DECLINE IN STROKE OR TRANSIENT ISCHEMIC ATTACK.

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Introduction

- Alzheimer's disease-resemblance atrophy index (AD-RAI) is a machine-learning derived MRI-based brain atrophy biomarker that is valid in predicting cognitive decline in subjects with AD. We investigated the performance of AD-RAI in predicting long-term cognitive decline in subjects with stroke or transient ischemic attack (TIA).

Methods and Materials

We recruited consecutive dementia-free stroke/TIA subjects who had brain MRI at baseline (i.e., within 3-6 months after the index event) and cognitive data at both baseline and 3 years. We defined cognitive decline as an increase in clinical dementia rating scale from 0 to 0.5 or above or from 0.5 to 1 or above at 3 years when compared with baseline. We investigated the association between AD-RAI, traditional brain atrophy biomarkers (hippocampus volume [HV], hippocampal fraction [HF], total brain volume [TBV], TBV/intracranial volume [ICV] ratio, ventricular-brain-ratio, presence of medial temporal lobe atrophy [MTLA]), and cerebral small vessel disease biomarkers (white matter hyperintensity [WMH]) volume, WMHV/ICV ratio presence of confluent WMH, presence of >/=3 lacunes) with cognitive decline.

Results

Of 231 participants (mean age 66.0 ± 10.9, 124 [53.7] male), 55(23.8) had cognitive decline at 3 years. Among all the imaging biomarkers, AD-RAI and HV were associated with cognitive decline in univariate regression. Such a relationship was still significant with AD-RAI after adjusted for age, gender, and education (aOR [95%CI] 3.900 [1.221-12.458]). Among all imaging biomarkers, only AD-RAI was associated with slope of Montreal cognitive assessment (MoCA) after adjusted to age, gender, education (β(SE) −0.742[0.242], p=0.002).

Discussion

- AD-RAI was independent predictors of long-term cognition decline after stroke and/or TIA, which outperformed all the other traditional brain atrophy biomarkers. Consistent with our previous finding in AD, which AD-RAI also outperformed HV and HF
- Although confluent white matter changes (ARWMC global score of 3) or multiple lacunes were not associated with the presence of CDR change, but both biomarkers are strong predicters of MOCA slope.

Conclusions

AD-RAI predicted long term cognitive decline in subjects with stroke/TIA.

Table 1. Cohort Characteristics

Characteristics	CDR stable (n=176)	CDR Declined (n=55)	P
Age (years)	65.0 ± 11.0	69.3 ± 10.0	0.012
Male	99(56.3)	25(45.4)	0.167
Education (years)	7.0 ± 4.5	5.0 ± 4.9	0.008
BMI	24.3 ± 3.8	24.8 ±3.4	0.280
APOE ε4 carriers*	24(17.1)	5(12.8)	0.628
Baseline NIHSS	3.3 ± 3.5	4.2 ±3.8	0.070
Baseline MMSE	26.7 ± 3.6	25.1 ± 5.1	0.016
Stroke subtype			0.202
Large-artery atherosclerosis	64(36.4)	21(38.2)	
Small-artery occlusion	53(30.1)	18(32.7)	
Cardio embolism	14(8.0)	1(1.8)	
Intracerebral hemorrhage	3(1.7)	1(1.8)	
TIA	33(18.8)	7(12.7)	
Other stroke types	9(5.1)	7(12.7)	
Baseline brain changes			
ADRAI	0.2 ± 0.2	0.3 ± 0.3	0.002
ICV (ml)	1402.4 ± 126.7	1388.8 ± 140.6	0.432
HF	0.5 ± 0.1	0.4 ± 0.1	0.228
HV	6.4 ± 0.7	6.2 ± 0.7	0.046
VBR	29.0 ± 4.9	30.2 ± 3.0	0.002
TBV/ICV	0.9±0.1	0.8±0.1	0.180
TBV (ml)	1211.3±110.8	1186.6±142.0	0.135
Presence of MTLA	27(15.3)	8(14.5)	0.886
WMHV (ml)	6.5 ± 6.8	7.4 ± 8.4	0.335
WMH/ICV	0.5±0.5	0.5±0.6	0.299
Presence of severe ARWMC (=3)	33(18.8)	16(29.1)	0.130
Presence of multiple lacunes (>3)	26(14.8)	12(21.8)	0.297
Presence of Large old infarction	11(6.3)	4(7.3)	0.759
Baseline vascular risk factors			
Hypertension	119(67.6)	45(81.8)	0.060
Hyperlipidemia	117(66.5)	44(80.0)	0.065
Diabetes mellitus	55(31.3)	18(32.7)	0.869
Atrial fibrillation	16(9.1)	1(1.8)	0.081
Smoking	25(14.2)	4(7.3)	0.235
Alcohol consumption	14(8.0)	5(9.1)	0.385
3-year follow up			
Any stroke recurrence within 3 years	8(4.5)	5(9.1)	0.311
MMSE	26.1 ± 3.8	23.3 ± 5.6	<0.001
MOCA	21.7 ± 5.5	17.7 ± 6.7	<0.001

Values are mean ± standard deviation or numbers (%)

*Calculated among 179 subjects

Presence of MTLA defined as Scheltens scale ≥ 2 points

Abbreviations: BMI: Body mass index; APOE: Apolipoprotein E; NIHSS: The National Institutes of Health Stroke Scale MMSE: The Mini–Mental State Examination TIA: Transient ischemic attack; ADRAI: AD resemblance atrophy index; ICV: Intracranial volume; HF: Hippocampus fraction; HV: Hippocampus volume; VBR: ventricular-to-brain ratio; WMHV: White matter hyperintensity volume; ARWMC: Age-related white matter changes; MTLA: Medial temporal lobe atrophy

Table 2. Association between neuroimaging biomarkers, risk factor and 3-years CDR decline

	Crude OR (95%CI)	P value	aOR (95%CI) *	P value
BMI	1.037 (0.953-1.129)	.399	1.046 (0.958-1.143)	.316
Baseline NIHSS	1.068 (0.986-1.157)	.105	1.049 (0.964-1.142)	.266
Baseline MMSE	0.917 (0.855-0.983)	.014	0.963 (0.885-1.049)	.387
Baseline brain changes				
ADRAI	4.074(1.339-12.394)	.013	3.900 (1.221-12.458)	.022
ICV (ml)	0.999 (0.997-1.002)	.496	1.002 (0.998-1.005)	.348
HF	0.012 (0.000-5.760)	.161	0.016 (0.000-9.143)	.201
HV (ml)	0.655 (0.433-0.991)	.045	0.805 (0.497-1.304)	.377
VBR	1.057 (0.986-1.133)	.119	1.033 (0.964-1.106)	.358
TBV	0.998 (0.996-1.001)	.188	1.001 (0.997-1.004)	.703
TBV/ICV	0.086 (0.002 -4.390)	.222	0.068 (0.001-4.579)	.211
Presence of MTLA	0.939 (0.400-2.207)	.886	0.651 (0.263-1.611)	.353
WMHV (ml)	1.017 (0.975-1.060)	.439	1.009 (0.964-1.056)	.706
WMHV/ICV	1.282 (0.713-2.307)	.406	1.117 (0.590-2.116)	.734
Presence of severe ARWMC (=3)	1.778 (0.888-3.559)	.104	1.473 (0.715-3.036)	.294
Presence of multiple lacunes (>3)	1.610 (0.750-3.454)	.221	1.339 (0.606-2.961)	.471
Presence of Large old infarction	1.176 (0.359-3.854)	.788	1.142 (0.332-3.927)	.834
Baseline vascular risk factors				
Hypertension	2.155 (1.014-4.583)	.046	1.806 (0.831-3.927)	.136
Hyperlipidemia	2.017 (0.971-4.190)	.060	2.086 (0.980-4.441)	.056
Diabetes mellitus	1.070 (0.560-2.044)	.837	1.030 (0.531-1.999)	.930
Atrial fibrillation	0.185 (0.024-1.429)	.106	0.202 (0.026-1.592)	.129
Smoking	0.899 (0.579-1.393)	.633	1.049 (0.632-1.743)	.853
Alcohol consumption	0.855 (0.511-1.432)	.552	0.993 (0.571-1.728)	.981
Any stroke recurrence within 3 years	2.100 (0.658-6.706)	.210	2.036 (0.605-6.854)	.251

***Adjusted by age gender and education**

Table 3 Risk of MOCA decline for image biomarkers

	β (SE)	P value	aβ (SE)*	P value
AD-RAI (continues variable)	-.742(.242)	.002	-.742 (.242)	.002
AD-RAI (by cutoff 0.6)	-.620(.201)	.002	-.619(.201)	.002
HV	.138(0.084)	.099	.138(0.084)	.099
HF	2.035(1.24)	.102	2.022(1.24)	.104
VBR	-.022(.014)	.067	-.024(.013)	.066
TBV/ICV	1.152(.765)	.133	1.142(.765)	.136
Presence of MTLA	-.137(.168)	.419	-.137(.168)	.417
WMHV/ICV	-.340(.123)	.006	-.340(.122)	.006
Presence of severe ARWMC (=3)	-.388(.148)	.009	-.388(.148)	.009
Presence of multiple lacunes (>3)	-.399(.162)	.014	-.400(.162)	.014

The optimal cut-off of AD-RAI is 0.636 for predicting 3-year-conversion defined by CDR.

*We investigated the relationship between the different image biomarkers and MOCA over time using linear mixed models. We first used the image biomarker, time, and image biomarker * time as predictors. Next, we added age gender and education as covariates for adjusted β (SE)

REFERENCE

Zhao L, Luo Y, Lew D, et al. Risk estimation before progression to mild cognitive impairment and Alzheimer's disease: an AD resemblance atrophy index. Aging (Albany NY) 2019;11:6217-36.

Liu W, Au LWC, Abrigo J, et al. MRI-based Alzheimer's disease-resemblance atrophy index in the detection of preclinical and prodromal Alzheimer's disease. Aging (Albany NY) 2021;13:13496-514

Mok, V., et al. (2011). "Cortical and frontal atrophy are associated with cognitive impairment in age-related confluent white-matter lesion." J Neurol Neurosurg Psychiatry 82(1): 52-57.

Logue, M. W., et al. (2011). "Magnetic resonance imaging-measured atrophy and its relationship to cognitive functioning in vascular dementia and Alzheimer's disease patients." Alzheimer's & Dementia 7(5): 493-500.