Fewer Neurofibrillary Tangles and Slower Conversion to AD in MCI Patients Taking RAS Acting Antihypertensives

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Background

With the projected increase in Alzheimer's disease (AD) prevalence, repurposing existing medications generally recognized as safe, and that show promise in AD studies, shortens the time to provide urgently needed treatment options. Research suggests that antihypertensives that act via the renin angiotensin system (RAS) may decrease the risk of Alzheimer's disease (AD), possibly via Aβ or tau[1,2]. We previously reported that individuals taking RAS acting medications (ACE-Is or A2RBs), particularly those that are centrally acting, show slower cognitive decline and are less likely to progress from mild cognitive impairment (MCI) to AD over three years[3]. However, the potential mechanism was unclear, due to the absence of neuropathological findings in these individuals.

Participants

- We used data from the RUSH ADRC to test the hypothesis that individuals taking RAS acting antihypertensives may exhibit slower clinical disease progression and less AD related neuropathology than individuals taking non-RAS acting antihypertensives. Participants included 83 individuals with baseline MCI who were taking an antihypertensive medication at baseline and during at least two consecutive follow up visits. Neuropathological data was available in all participants. RAS users were more likely to be male (p=.02). Participants were older (M=83.1 yrs), well educated (M=15.7yrs) and 9.2% self-identified as Black. While there were no group differences in blood pressure or cholesterol, RAS users were more likely to be diabetic than non-RAS users (p=.01).

Disease Conversion by Antihypertensive Class

We analyzed whether there were differences in conversion rate from MCI to AD, for RAS acting vs. non-RAS acting users. 14 of 83 participants taking an antihypertensive medication converted to AD, which is consistent with reported conversion rates of 10% - 30% annually[4]. Adjusted conversion rate for RAS users was 3(7.9%) and non RAS non-users was 11(24.4%). Conversion rate to AD was slower for RAS users vs. non-users (p = 0.02).

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Results

Table 1: Baseline demographics for 38 RAS users and 45 RAS non-users

	RAS Users	RAS non-users
Age	82.6 ± 7.2	83.7 ± 5.9
Gender (% Male)	45%*	20%**
Education (yrs)	16.0± 3.6	15.4± 3.1
Race (% Black)	13.9%	4.4%
Systolic (mmHg)	138 ± 16.9	139 ± 21.4
Diastolic (mmHg)	72.7 ± 12.5	71.2 ± 10.7
BMI	27.0 ± 5.6	26.4 ± 4.9
Diabetes (%)	24%	0.4%**
ApoE4 positive (%)	22.9%	33.3%
Recent depression (%)	32%	33%
MMSE	26.9 ± 2.43	26.8 ± 2.24

Table 2: Neuropathological data by RAS medication group

Neuropathological Variable	RAS Medication (n=38)	Non-RAS Medication (n=45)	p value
Brain weight	1133.9 ± 148.0	1149.3 ± 127.8	0.62
High/intermediate probability of AD based on NIA Reagan score	23 (63.9)	32 (72.7)	0.40
Overall amyloid level	1.4 ± 1.3	1.7 ± 1.1	0.23
diffuse plaques	0.7 ± 0.6	1.0 ± 0.8	0.08
Arteriolosclerosis			
0	9 (23.7)	14 (31.1)	0.71
1	12 (31.6)	13 (28.9)	
2	12 (31.6)	15 (33.3)	
3	5 (13.2)	3 (6.7)	
Braak score			0.24
1	2	1	
2	2	0	
3	11	9	
4	14	19	
5	7	15	
NFT count total	0.55 ± 0.63	0.87 ± 0.68	0.0321
tangle count in hippocampus CA1	10 (5 - 27)	33 (18 – 55)	0.0010
tangle count in the entorhinal cortex	21 (9 – 35)	27 (15 – 49)	0.0405
average of tangles in angular gyrus, inferior temporal, mid-frontal cortex and superior frontal	1.6 ± 3.1	4.4 ± 7.8	0.0325
CERAD neuropathologic diagnosis of AD			
Four categories			0.75
Definite	12 (33.3)	19 (44.2)	
Probable	12 (33.3)	12 (27.9)	
Possible	2 (5.6)	3 (7.0)	
No AD	10 (27.8)	9 (20.9)	
Two categories			0.60
Yes	24 (66.7)	31 (72.1)	
No	12 (33.3)	12 (27.9)	

Neuropathological Results

Table 2 shows results comparing RAS-acting medication users vs. RAS non-users on postmortem neuropathological measures. Results revealed a beneficial effect of RAS use compared to non-RAS medication abnormal tau hyperphosphorylation measures. Specifically, RAS users had significantly fewer NFTs overall (p=0.03) and fewer tangles in all prespecified regions of interest including the hippocampal CA1 region (p<0.01), the entorhinal cortex (p=0.04) and the average number in brain regions including the angular gyrus, inferior temporal region, mid-frontal cortex, and superior frontal (p=0.03). RAS users and non-users did not differ on neuropathological indices of brain weight, amyloid burden, NIA Reagan, CERAD or Braak scores, diffuse plaques or arteriolosclerosis.

Conclusions

- Our main results are that individuals taking RAS acting antihypertensives for at least three years were less likely to convert from MCI to AD and showed fewer NFTs compared to individuals taking non-RAS acting antihypertensives.
- That the present study revealed a benefit of RAS medications on abnormal tau hyperphosphorylation may support the hypotheses that RAS - AD relationship is particularly important in prodromal disease states
- Further research, particularly clinical trials, investigating the influence RAS medications on AD biomarkers during prodromal disease stages is warranted.

References

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