Associations of Renin-angiotensin System Genetic Polymorphisms and Clinical Course After Aneurysmal Subarachnoid Hemorrhage

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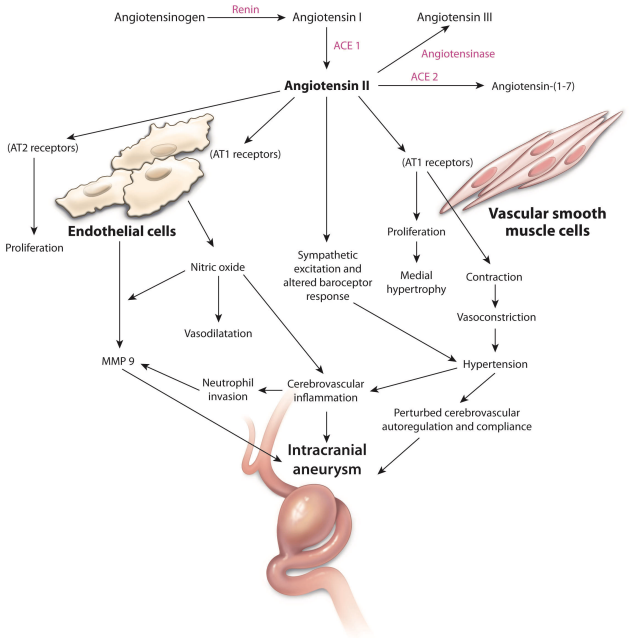
Introduction

Renin-angiotensin system (RAS) genetic polymorphisms are thought to play a role in cerebral aneurysm formation and rupture (Figure 1). The Cerebral Aneurysm Renin-Angiotensin System (CARAS) study prospectively evaluated associations of common RAS polymorphisms and their relation to aneurysmal subarachnoid hemorrhage (aSAH).

Figure 1.



Methods

The CARAS study prospectively enrolled aSAH patients and controls at two academic centers in the United States. A blood sample was obtained from all patients for genetic evaluation and measurement of plasma angiotensin converting enzyme (ACE) concentration. Common RAS polymorphisms were detected using 5'exonnuclease (Taqman) genotyping assays and pyrosequencing.

Results

Two hundred and forty eight patients were screened. One hundred and forty nine aSAH patients and 50 controls were available for analysis (Figure 2). There was a dominant effect of allele C of the angiotensin 2 receptor type 2 (AT2) A/C single nucleotide polymorphism (SNP) on aSAH in patients > 55 years of age (OR = 3.48, 95% CI = 1.23–9.84. p = 0.0192) as compared to controls. A recessive effect of allele I of the ACE I/D polymorphism was identified for Hunt & Hess grade in all patients (OR = 2.76, 95% CI 1.17–6.50, p = 0.0206) with subsequent poor functional outcome. There was a similar effect on delayed cerebral ischemia (DCI) in patients = 55 years of age (OR = 3.63, 95% CI 1.04–12.7, p = 0.0439). In patients > 55 years of age, there was a recessive effect of allele A of the AT2 A/C SNP on DCI (OR = 4.70, 95% CI 1.43–15.4, p = 0.0111) (Figure 3).

Conclusions

The allele I of the ACE I/D polymorphism was associated with higher Hunt & Hess grade and subsequent poor functional outcome. The ACE I/D polymorphism and the AT2 A/C showed age-dependent associations with aSAH and DCI.

Figure 2.

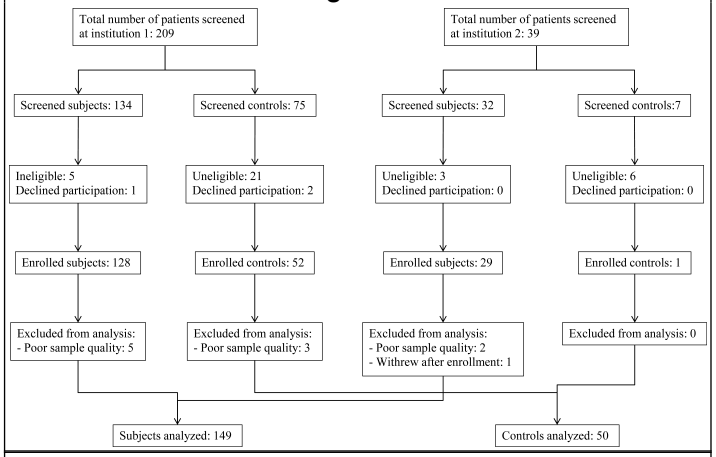


Figure 3.

TABLE 4. Dominant and recessive effects of RAS polymorphisms on neurological status at presentation and outcome measures in aSAH

Polymorphism	Outcome	Age	Effect	OR (95% CI)	p Value*
AGT G/A (rs699)	Aneurysm size <7 mm	All patients	Recessive effect of the C allele (CC vs CT + TT)	2.69 (1.86–3.91)†	0.0077
AGT G/A (rs699)	Clinical vasospasm	>55 yrs	Dominant effect of the T allele (TT + CT vs CC)	5.75 (1.21–27.4)‡	0.0278
AGT G/A (rs699)	DCI	>55 yrs	Dominant effect of the T allele (TT + CT vs CC)	10.1 (1.25–82.0)§	0.0300
ACE I/D (rs4340)	Hunt & Hess grade	All patients	Recessive effect of the I allele (II vs ID + DD)	2.76 (1.17–6.50)	0.0206
ACE I/D (rs4340)	mRS score at last follow-up	All patients	Recessive effect of the I allele (II vs ID + DD)	2.48 (1.01–6.10)¶	0.0475
ACE I/D (rs4340)	Hunt & Hess grade	>55 yrs	Recessive effect of the I allele (II vs ID + DD)	4.00 (1.25–12.8)	0.0198
ACE I/D (rs4340)	mRS score at last follow-up	>55 yrs	Recessive effect of the I allele (II vs ID + DD)	3.61 (1.14–11.5)**	0.0294
ACE I/D (rs4340)	Clinical vasospasm	≤55 yrs	Recessive effect of the I allele (II vs ID + DD)	3.63 (1.04–12.7)	0.0439
ACE I/D (rs4340)	DCI	≤55 yrs	Recessive effect of the I allele (II vs ID + DD)	3.63 (1.04–12.7)	0.0439
AT2 A/C (rs11091046)	Clinical vasospasm	>55 yrs	Recessive effect of the A allele ($X^AX^A + X^AY$ vs $X^AX^C + X^CX^C + X^CY$)	3.04 (0.990–9.30)	0.0523
AT2 A/C (rs11091046)	DCI	>55 yrs	Recessive effect of the A allele ($X^AX^A + X^AY$ vs $X^AX^C + X^CX^C + X^CY$)	4.70 (1.43–15.4)	0.0111

Learning Objectives

By the conclusion of this session, participates should be able to describe the role of the renin angiotensin system in aneurysmal subarachnoid hemorrhage.