Endothelin Polymorphisms as a Risk Factor for Cerebral Aneurysm Rebleeding Following Aneurysmal Subarachnoid Hemorrhage

Paul M. Foreman; Robert M. Starke; Philipp Hendrix; Mark R. Harrigan; Winfield S. Fisher; Nilesh A. Vyas; Robert Lipsky; Minkuan Lin; Beverly C. Walters; Jean-Francois Pittet; Mali Mathru; Christoph J. Griessenauer

University of Alabama at Birmingham, University of Miami, Saarland University Medical Center, Inova Health System,

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Introduction

Aneurysm rebleeding following presentation with aneurysmal subarachnoid hemorrhage (aSAH) is associated with high mortality and poor functional outcome. While a substantial genetic contribution to aneurysm formation and rupture is known, the genetic influence on the risk of rebleeding is poorly understood.

Methods

Blood sample from all patients enrolled in the CARAS (Cerebral Aneurysm Renin Angiotensin System) study were used for genetic evaluation. The CARAS study prospectively enrolled aSAH patients at two academic institutions in the United States from 2012-2015. Common endothelin SNPs were detected using 5'exonnuclease (Taqman) genotyping assays. Analysis of associations between endothelin single nucleotide polymorphisms (SNP) and aneurysm rebleeding was performed.

Results

One hundred and forty-nine aSAH patients were included. Acute spontaneous aneurysm rebleeding occurred in 5 (3.4%) patients. Multivariable analysis identified the TT genotype for EDN1 G/T SNP (rs2070699; OR 97.4, 95% CI 3.825-2479.984, p = 0.006) as an independent risk factor for aneurysm rebleeding. Aneurysm rebleeding was associated with an unfavorable functional outcome (mRS 3-6) at last follow up in all 5 patients.

Table 3. Patients with acute spontaneous aneurysm rebleeding

Age (yrs)	M/F	rs2070699 genotype	Hunt and Hess Score	Fisher Grade	Admission Blood Pressure	Aneurysm Location	Aneurysm Size (mm)	Hijdra Score	Anti-Fibrinolytic	EVD Prior to Rebleed	Day of Rebleed	Evidence of Rebleed	Day of Aneurysm Treatment	Clip/Coil	mRS at Last Follow Up
66	M	GT	4	3	184/114	Vertebral artery	5	10	Yes	Yes	Day 0	Clinical, Imaging	Day 1	Coil	6
64	F	GG	5	3	226/127	Posterior communicating artery	15	11	Yes	Yes	Day 0	Clinical, Imaging	NA	NA	6
74	F	TT	4	3	225/91	Anterior communicating artery	7	8	No	No	Day 0	Clinical	Day 0	Coil	5
61	M	GG	4	4	177/93	Posterior inferior cerebellar artery	6	5	Yes	No	Day 0	Clinical, Imaging	Day 1	Clip	6
59	F	TT	2	3	126/64	Anterior communicating artery	4	1	No	No	Day 1	Clinical	Day 2	Coil	3

Table 3. Predictors of rebleeding in aSAH in multivariate logistic regression analysis

	OR (95% CI)	P value
	Rebleeding	
Increasing Hijdra grade	1.701 (1.146-2.524)	0.008
TT genotype (rs2070699)	97.4 (3.825-2479.984)	0.006

Conclusions

Aneurysm rebleeding following presentation with aSAH was independently associated with the TT genotype of the EDN1 G/T SNP. All patients with acute spontaneous aneurysm rebleeding suffered a poor functional outcome at last follow up.