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BDNF Val66Met Polymorphism Predicts Worse Functional Outcome After Surgery in Unruptured Brain Arteriovenous Malformation Patients

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Abstract

Background and Purpose—The Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) is associated with decreased BDNF secretion and poor outcome after acute neurological injury. We hypothesized that the Met allele is associated with worsening of functional outcome after brain arteriovenous malformation (BAVM) resection.

Methods—341 surgically-treated BAVM patients with outcome data were genotyped for Val66Met. Outcome was change in modified Rankin Scale (mRS) preoperatively versus postoperatively, dichotomized into poor (change>0) or good outcome (change≤0). Likelihood ratio test for interactions and logistic regression analysis were performed.

Results—A significant interaction (p=0.03) of Val66Met genotype and hemorrhagic presentation existed; thus, ruptured and unruptured patients were considered separately. The Met allele was associated with increased risk of poor outcome among patients presenting unruptured (OR=2.15, 95% CI=1.02–4.55, p=0.045) but not ruptured (OR=0.54, 95% CI=0.19–1.53, p=0.25), adjusting for covariates.

Conclusions—The Val66Met polymorphism is associated with worsened surgical outcome in unruptured BAVM patients, a group that currently has no good risk predictors. Further studies replicating these findings are needed.

Keywords

Brain-derived neurotrophic factor; Genetics; Arteriovenous Malformations; Outcomes; Surgery

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Disclosures
None.

Introduction

Management strategies for brain arteriovenous malformation (BAVM) often include surgical resection with varying outcomes.[1] Therefore, identifying predictors of functional outcome after BAVM resection to facilitate risk prediction is of clinical importance.

Genetic variation likely influences BAVM-related outcomes. One plausible candidate, brain-derived neurotrophic factor (BDNF), is acutely upregulated in CNS injury and increases functional recovery after CNS injury.[2, 3] The Met allele of a functional polymorphism in *BDNF*, Val66Met, affects activity-dependent BDNF secretion.[4] The Met allele has been associated with poor outcome after aneurysmal subarachnoid hemorrhage.[5] Thus, we hypothesized that Val66Met polymorphism is associated with functional outcome following BAVM resection.

Materials and Methods

341 BAVM resection patients with outcome and genotype data were analyzed. All patients signed informed consent and the study was approved by the Committee for Human Research at the University of California, San Francisco. Val66Met polymorphism (rs6265) was genotyped by PCR-based assay or microarray (Affymetrix SNP Array 6.0).

Outcome was change in modified Rankin Scale (mRS) score between preoperative and last follow-up states, dichotomized into >0 (bad outcome) versus ≤0 (good outcome).[6] The predictor variable was Val66Met genotype, dichotomized into Met/Met and Val/Met versus Val/Val groups, as previously done.[5]

Before constructing multivariate models, we evaluated whether the effect of BDNF genotype and outcome was modified by other predictors using likelihood ratio test (LRT). A significant interaction was observed between BDNF genotype and hemorrhagic presentation status (p=0.03). Thus, analyses were stratified by ruptured vs. unruptured status.

Multivariate logistic regression analysis was performed; predictors were chosen based on clinical or statistical significance (p<0.05 in univariate analysis). We also performed a sensitivity analysis restricting to Caucasians, the largest racial/ethnic subgroup, to account for potential population stratification (80 ruptured, 106 unruptured).

Results

Patient characteristics are presented in Table 1 stratified by both outcome and hemorrhagic status. Among 173 unruptured patients, those with poor outcomes had higher Spetzler-Martin scores (p<0.01) and a greater proportion of BAVMs in eloquent locations (p=0.02). In 168 ruptured patients, only Spetzler-Martin score differed significantly between outcome groups (p=0.04).

Among unruptured BAVM patients (Table 2), Met allele carriers had a two-fold higher risk of poor outcome compared to Val/Val carriers in both univariate (OR=1.98, p=0.055) and multivariate analysis (OR=2.15, p=0.045). In contrast, no increased risk was observed in ruptured patients either in univariate (OR=0.53, p=0.22) or multivariate analysis (OR=0.54, p=0.25). Sensitivity analysis restricting to Caucasians (n=186) yielded similar multivariate findings for unruptured (OR=2.79, 95% CI=1.01–7.67, p=0.048) and ruptured (OR=0.51 95% CI=0.12–2.29, p=0.38) patients. Adjusting for individual Spetzler-Martin (SM) components instead of SM score did not significantly alter the results, nor did adjustment for SM-3 (data not shown). Further sensitivity analysis adding diffuse nidus morphology, deep perforating artery supply, and smoking status to the multivariate model did not significantly

alter the BDNF genotype association with outcome among unruptured (OR=2.67, 95% CI=0.99–7.19, p=0.05, n=98) or ruptured patients (OR=0.36, 95% CI=0.05–2.34, p=0.28, n=94), despite the significant reduction in sample size.

Discussion

This study implicates the BDNF Val66Met polymorphism in functional recovery after BAVM resection in unruptured patients. Possession of the Met allele was associated with a 2-fold increased risk of worse functional outcome after surgery independent of other risk factors, whereas no increased risk was observed among ruptured patients. The effect size increased to nearly 3-fold in Caucasian patients.

One striking feature of this study is the differential effect of presenting hemorrhage on the association of Val66Met genotype with functional outcome. Possible explanations include: (1) non-linear relationship of mRS outcome and true neural injury state; (2) ruptured patients may already have elevated BDNF levels at the time of surgery due to hemorrhage, so BDNF upregulation in response to surgical injury may be less important; and (3) resection of ruptured BAVMs is less traumatic to the brain because hemorrhage facilitates resection.[6] BDNF genotype may be a less significant factor when placed in context of prior hemorrhage.

Our study is limited by a relatively small sample size within hemorrhagic presentation groups, resulting in wide confidence intervals and inability to adjust for additional variables that may influence outcome or interact with BDNF genotype. Larger studies are needed to replicate these findings and test the clinical utility of adding BDNF genotype to current risk prediction models. We were unable to explore specific functional domains using the mRS, as it is a general outcome scale. While previous studies have linked the Met allele to decreased levels of BDNF, we did not directly measure BDNF levels in this study. Finally, generalizing our results to treatment modalities other than microsurgery may not be applicable as clinical course and outcomes vary widely.[1]

In conclusion, the Met allele of BDNF Val66Met polymorphism was associated with increased risk of worse functional outcome after microsurgical resection in unruptured BAVM patients. Effect sizes for Val66Met genotype are similar to current angiographic predictors, suggesting that genetic factors could prove clinically useful. Most importantly, BDNF Val66Met genotype may prove to be an important risk factor for unruptured BAVM patients, comprising half of all cases and the subject of treatment controversy.[6]

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Table 1

Characteristics of 341 BAVM-Resected Patients by Hemorrhagic Status at Presentation and Dichotomized Functional Outcome

	Unruptured (n=173)			Ruptured (n=168)		
	Good Outcomeb (n=118)	**Poor Outcome (n=55)**	***P* Value**	**Good Outcome (n=144)**	**Poor Outcome (n=24)**	***P* Value**
Age, y ± SD	38.1 ± 16.1	41.9 ± 13.3	0.07	31.7 ± 18.3	37.5 ± 14.3	0.07
Length of follow-up, y ± SD	4.3 ± 6.6	4.2 ± 6.7	0.45	3.1 ± 6.6	3.5 ± 7.0	0.39
Spetzler-Martin score						
I	33 (28%)	6 (11%)		25 (17%)	1 (4%)	
II	47 (40%)	18 (33%)		52 (36%)	11 (46%)	
III	26 (22%)	26 (47%)		52 (36%)	6 (25%)	
IV	11 (9%)	5 (9%)		15 (11%)	5 (21%)	
V	1 (1%)	0 (0%)	< 0.01	0 (0%)	1 (4%)	0.04
BAVM size, cm ± SD	2.7 ± 1.3	3.0 ± 1.2	0.08	2.4 ± 1.5	2.8 ± 1.7	0.09
Deep venous drainage	31 (26%)	19 (35%)	0.3	74 (51%)	15 (63%)	0.2
Eloquent location	54 (46%)	36 (65%)	0.02	83 (58%)	16 (67%)	0.5
Female gender	65 (55%)	27 (49%)	0.5	73 (51%)	12 (50%)	1.0
Ethnicity						
Black	3 (3%)	1 (2%)		10 (7%)	3 (13%)	
White	76 (64%)	30 (55%)		68 (47%)	12 (50%)	
Asian	9 (8%)	8 (15%)		21 (15%)	2 (8%)	
Hispanic	29 (25%)	15 (27%)		42 (29%)	7 (29%)	
Native American	1 (1%)	1 (2%)	0.5	3 (2%)	0 (0%)	0.8
Val66Met genotype						
Val/Val	89 (75%)	34 (62%)		88 (61%)	17 (71%)	
Val/Met	27 (23%)	18 (33%)		41 (28%)	6 (25%)	
Met/Met	2 (2%)	3 (5%)	0.07	15 (10%)	1 (4%)	0.5

BAVM indicates brain arteriovenous malforation.

Table 2

Association of Val66Met Genotype and Other Risk Factors on Outcome Post-BAVM Resection Among Unruptured and Ruptured Patients

Unruptured (n=173)	**Univariate**		**Multivariate**	
Variable	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Met allele	1.98 (0.99–3.99)	0.06	2.15 (1.02–4.55)	0.05
Age, decade	1.18 (0.95–1.46)	0.13	1.34 (1.05–1.71)	0.02
Female sex	0.79 (0.41–1.49)	0.46	0.86 (0.43–1.73)	0.68
Nonwhite ethnicity	1.51 (0.79–2.89)	0.22	1.65 (0.81–3.38)	0.17
Spetzler-Martin	1.58 (1.11–2.25)	0.01	1.59 (1.09–2.32)	0.02
Length of follow-up	0.80 (0.65–0.95)	0.03	0.79 (0.63–0.99)	0.04
Ruptured (n=168)	Univariate		Multivariate	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Met allele	0.53 (0.19–1.47)	0.22	0.54 (0.19–1.53)	0.25
Age, decade	1.20 (0.94–1.52)	0.14	1.29 (0.99–1.67)	0.06
Female sex	0.97 (0.41–2.31)	0.95	1.01 (0.37–2.62)	0.99
Nonwhite ethnicity	0.89 (0.38–2.12)	0.80	1.04 (0.39–2.77)	0.94
Spetzler-Martin	1.53 (0.95–2.49)	0.08	1.39 (0.79–2.44)	0.25
Length of follow-up	0.64 (0.51–0.80)	< 0.01	0.63 (0.50–0.81)	< 0.01

BAVM indicates brain arteriovenous malformation.