Role of the Haptoglobin protein in carotid artery aneurysm formation

Jacob James Ruzevick; Christopher Mitchell Jackson; Gustavo Pradilla MD; Tomas Garzon-Muvdi MD MS; Rafael J. Tamargo MD

Department of Neurological Surgery

Johns Hopkins University School of Medicine

Introduction

Inflammation and macrophages in particular are believed to play a role in aneurysm formation. Humans have two alleles for the Hp gene, *Hp1* and *Hp2*, with the proinflammatory Hp2-2 genotype being overrepresented in inflammatory conditions. Previous clinical studies have found an association between the serum protein, haptoglobin (Hp), and the formation of abdominal aortic aneurysms. However, elucidation of a causal relationship has been limited by the lack of a physiologically relevant preclinical model of aneurysm formation. We investigated the size of aneurysms in wild-type Hp1-1 and pro-inflammatory Hp2-2 mice and found the Hp2-2 genotype to be associated with increased aneurysm size and increased numbers of macrophages infiltrating the vessel wall.

Methods

Carotid artery aneurysms (CCA) were induced in the left CCA of wild-type Hp1-1 mice and transgenic Hp2-2 mice using elastase to degrade the arterial wall of the CCA and angiotensin II to induce hypertension. There were four experimental groups: (1) sham surgery (n=11); (2) angiotensin II only (n=10); (3) elastase only (n=20); and (4) elastase + angiotensin II (n=20). Aneurysm size was determined by measuring the outer circumference and luminal circumference of the blood vessel. Macrophages that infiltrated the aneurysm wall were quantified by immunohistochemistry. Results were analyzed using a two-way ANOVA with a Bonferroni post-test.

Results

Administration of angiotensin II produced equivalent hypertension in both Hp1-1 and Hp2-2 mice. There was no statistical difference in the mean systolic blood pressure between genotypes in any of the treatment groups Concomitant administration of elastase and angiotensin II resulted in a significant increase in aneurysm size as compared to all other treatment groups. Using this model, we found that aneurysms in Hp-2-2 mice were significantly larger than aneurysms in Hp1-1 mice (p=0.02 for outer circumference, p=0.0006 for inner circumference)(Figure 1 and Figure 2). Finally, the number of infiltrating macrophages was significantly increased in aneurysms in Hp2-2 mice in the setting of vessel wall destruction and hypertension (p=0.0001) (Figure 3).

Figure 1

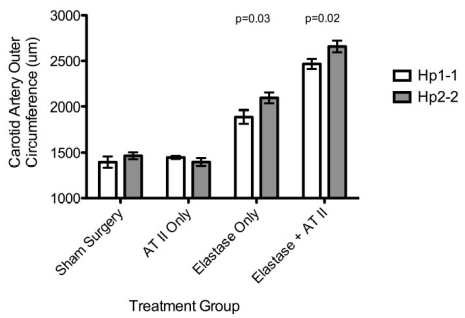

Figure 1: Mean outer circumference of common carotid artery aneurysms

Figure 2

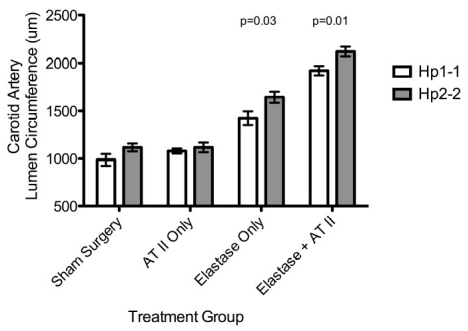

Figure 2: Mean luminal circumference of common carotid artery aneurysms

Figure 3

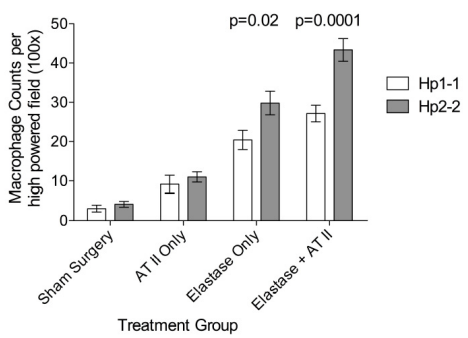

Figure 3: Counts of macrophages infiltrating the vascular wall following aneurysm formation

Conclusions

Hp2-2 mice formed aneurysms that were significantly larger and had a significantly increased number of macrophages in the aneurysm wall as compared to Hp1-1 mice. This suggests that the Hp protein is involved in aneurysm formation and that Hp genotype may be a useful biomarker in predicting aneurysm progression.

Learning Objectives

By the conclusion of this session, participants should be able to: (1) discuss the factors involved in aneurysm formation; (2) describe the importance of a pro-inflammatory state on aneurysm formation and; (3) discuss the possibility of the haptoglobin protein as a biomarker for increased aneurysm growth.

References

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