

## Family History of Aortic or Intracranial Aneurysm is associated with Abdominal Aortic Aneurysm Rupture: An Exploratory Study

Katsuyuki Hoshina\*, Atsushi Akai, Kunihiro Shigematsu, Tetsuro Miyata and Toshiaki Watanabe

Department of Vascular Surgery, University of Tokyo Hospital, Tokyo, Japan

### Abstract

**Objective:** The purpose of this study was to examine non-dynamic and non-morphological factors that may be related to abdominal aortic aneurysm (AAA) rupture.

**Methods:** Of the 205 consecutive AAA patients who underwent open surgery between 2004 and 2008 in our department, comparisons were conducted between patient groups based on the following AAA types: non-ruptured "large" AAAs with a diameter  $\geq 65$  mm (non-rupture group; n=26) and ruptured "small" AAAs with a diameter  $<65$  mm (rupture group; n=9).

**Results:** Mean age and gender were not significantly different between the 2 groups. The proportion of patients with a positive family history of abdominal aortic, thoracic aortic, or intracranial aneurysms was statistically significantly greater in the rupture group than in the non-rupture group (62% versus 11%;  $p=0.01$ ).

**Conclusion:** The present results indicate that a family history of abdominal aortic, thoracic aortic, or intracranial aneurysm might be associated with the risk of AAA rupture. Some genetic involvement in AAA rupture has been previously reported, although only a few studies have mentioned this association thus far.

**Keywords:** Rupture; Family history; Abdominal aortic aneurysm

### Introduction

The expansion rate of an abdominal aortic aneurysm (AAA) theoretically increases in proportion to its diameter, according to LaPlace's law. In the same way, the rupture risk is also thought to increase [1,2]; however, it is difficult to predict when a rupture will occur based on AAA morphology only. Hemodynamic parameters are currently the primary operative indicators for AAA; these include a diameter  $>5.5$  cm, saccular shape, and expansion rate  $>1$  cm/year [3,4]. The contribution of other reported risk factors for rupture is unknown; these factors include the female sex [5,6], a lower forced expiratory volume in 1 second [5], current smoking status [5,7], higher mean blood pressure [5], and post-transplantation status [8]. Although family history is known to have a strong association with AAA formation and development [4,9], few reports indicate that it is an independent risk factor for rupture. Recently, a sequence variant on 9p21 was reported to be associated with AAA and intracranial aneurysm, and another report subsequently detected a link to common susceptibility genes for aortic aneurysms and intracranial aneurysm [10,11]. This study aimed at retrospectively examining the non-dynamic and non-morphological factors related to the rupture of AAA with atherosclerotic pathogenesis and comparing non-ruptured large AAA with ruptured small AAA to highlight the rupture-specific factors.

This study was approved by the research ethics committee of our institution. Of the 205 consecutive patients with AAA who underwent open surgery in our department between 2004 and 2008, patients with the following types of AAA were retrospectively included: non-ruptured large AAA with a diameter  $\geq 65$  mm (non-rupture group, n=26; median 74 mm, 65-90 mm) and ruptured small AAA with a diameter  $<65$  mm (rupture group, n=9; median 50 mm, 42-60 mm). Infrarenal AAA was present in all patients, and computed tomography (CT) was performed preoperatively for all patients to measure the antero-posterior AAA diameters. AAAs associated with a saccular shape (sac-like bulging on one side of an artery), infection (diagnosed using laboratory data indicating severe inflammation or using a blood

culture), or Marfan syndrome were excluded. Comorbidities included hypertension, dyslipidemia, and diabetes mellitus, all of which required medication. In addition, the following were present: ischemic heart disease that required medication and/or interventions, cerebrovascular disease with focal neurological signs, chronic obstructive pulmonary disease, and chronic kidney disease (stages 3-5). These data, with family history, were retrospectively examined via medical records. Differences between the groups were compared using the Mann Whitney U-test for continuous variables and Chi-square tests for categorical variables. Values are reported as mean  $\pm$  standard deviation. All tests were 2-sided with statistical significance set at  $p<0.05$ .

The patient characteristics and comorbid risks are provided in Table 1. There was no significant difference in age at the time of the operation, gender, current smoking status, or ratio of comorbid risks between the 2 groups. The proportion of patients with a family history (first-degree relative with an aortic or intracranial aneurysm) was significantly different between the 2 groups (rupture group, 62%; non-rupture group, 11%;  $p=0.002$ ).

Larsson et al. previously reported that the proportion of AAA patients with a family history (first-degree relative) compared to no family history was significantly higher (8.4% vs. 4.6%), while there was no difference in family history when compared between patients

**\*Corresponding author:** Katsuyuki Hoshina, Department of Vascular Surgery, The University of Tokyo Hospital, Tokyo, Japan, Tel: +81-3-5800-8653; Fax: +81-3-3811-6822; E-mail: [traruba@gmail.com](mailto:traruba@gmail.com)

**Received** July 22, 2014; **Accepted** September 29, 2014; **Published** October 01, 2014

**Citation:** Hoshina K, Akai A, Shigematsu K, Miyat T, Watanabe T (2014) Family History of Aortic or Intracranial Aneurysm is associated with Abdominal Aortic Aneurysm Rupture: An Exploratory Study. J Vasc Med Surg 2: 159. doi: [10.4172/2329-6925.1000159](https://doi.org/10.4172/2329-6925.1000159)

**Copyright:** © 2014 Hoshina K, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Variables	Ruptured AAA (N=9)	Non-ruptured AAA (N=26)	P value
Aneurysm diameter (cm)	<6.4 (50.2 ± 6.4)	>6.5 (74.5 ± 7.8)	<0.001
Age	69.2 ± 14.7	75.0 ± 9.1	N.S.
Gender (male: female)	6:3	22:4	N.S.
Comorbidities			
Hypertension	7/9 (77%)	23/26 (88%)	N.S.
Hyperlipidemia	3/9 (33%)	13/26 (50%)	N.S.
Diabetes Mellitus	0/9 (0%)	3/26 (11%)	N.S.
Current smoking	5/9 (55%)	22/26 (84%)	N.S.
Ischemic heart disease	0/9 (0%)	9/26 (34%)	N.S.
Cerebrovascular disease	1/9 (11%)	2/26 (7%)	N.S.
Chronic kidney disease	2/9 (22%)	11/26 (42%)	N.S.
Family History	5/8 (62%)	3/26 (11%)	0.002
AAA	2	2	
TAA	1	1	
ICA	2	0	

(AAA: Abdominal Aortic Aneurysm, TAA: Thoracic Aortic Aneurysm, ICA: Intracranial Aneurysm, N.S: Not Statistically Different)

**Table 1:** Patient characteristics and comorbid risks.

with ruptured and non-ruptured AAA (7.3% vs. 8.8%) [12]. In contrast, we report that the number of patients with a family history was significantly greater in the group with a ruptured AAA compared to those without rupture. However, we included a broader definition of family history in the present study to include not only AAA but also thoracic aortic aneurysm and intracranial aneurysm based on the report by Helgadottir et al. indicating that a sequence variant on 9p21, tagged by rs10757278-G, is associated with both AAA and intracranial aneurysm [10]. Additionally, we focused only on AAAs with atherosclerotic pathogenesis and excluded dynamic and systemic factors such as initial diameter, saccular shape, infection, and genetic diseases (i.e., Marfan syndrome), which enabled us to remove the effect of these potential confounders on the association between family history and AAA rupture.

The inherent features of non-ruptured large AAA are thought to be different from those of ruptured small AAA. The definition of “large” AAA varies, and we based our definition ( $\geq 65$  mm) on that of Peppelenbosch et al. who reported significant differences in the risk of aneurysm-related death between 3 groups: 4.0-5.4 cm, 5.5-6.4 cm, and  $\geq 6.5$  cm [1]. There were 18 ruptured AAAs in 205 patients, and the 65-mm threshold divided them in half. The AAA diameters in the rupture group were regarded relatively “small”.

This study has certain limitations. We conducted the present exploratory study with a small sample from a single institute. In addition, as the pathogenesis of AAA is multifactorial, comorbid factors closely related with the atherosclerotic condition such as diabetes or lipid control should be considered in detail [13]. However, we feel that the evident difference in family history between the 2 groups indicates a genetic involvement in AAA ruptures. Another limitation is the chosen method to measure the AAA diameter; in some patients, it was difficult to evaluate the aneurysmal adventitia with plain CT. Echo-color Doppler should have been used in such difficult cases [14]. The retrospective nature of the study may have introduced selection bias. In addition, the relatively younger sample in the ruptured group might have resulted in confounding during the statistical analysis.

The results of the present study demonstrate a possible association between AAA rupture and family history of aortic or intracranial aneurysm. The broader definition of family history used in this study

might help to detect novel findings in future studies with larger samples, which we are planning to conduct.

## Funding

This research was funded in part by grants-in-aid from the Ministry of Health, Labour and Welfare, Japan.

## References

1. Peppelenbosch N, Buth J, Harris PL, van Marrewijk C, Fransen G (2004) Diameter of abdominal aortic aneurysm and outcome of endovascular aneurysm repair: does size matter? A report from EUROSTAR. *J Vasc Surg* 39: 288-297.
2. Lederle FA, Johnson GR, Wilson SE, Ballard DJ, Jordan WD Jr, et al. (2002) Rupture rate of large abdominal aortic aneurysms in patients refusing or unfit for elective repair. *JAMA* 287: 2968-2972.
3. Lederle FA, Wilson SE, Johnson GR, Reinke DB, Littooy FN, et al. (2002) Immediate repair compared with surveillance of small abdominal aortic aneurysms. *N Engl J Med* 346: 1437-1444.
4. Brewster DC, Cronenwett JL, Hallett JW Jr, Johnston KW, Krupski WC, et al. (2003) Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery. *J Vasc Surg* 37: 1106-1117.
5. Brown LC, Powell JT (1999) Risk factors for aneurysm rupture in patients kept under ultrasound surveillance. UK Small Aneurysm Trial Participants. *Ann Surg* 230: 289-296.
6. Brown PM, Zelt DT, Sobolev B (2003) The risk of rupture in untreated aneurysms: the impact of size, gender, and expansion rate. *J Vasc Surg* 37: 280-284.
7. Wilmink TB, Quick CR, Day NE (1999) The association between cigarette smoking and abdominal aortic aneurysms. *J Vasc Surg* 30: 1099-1105.
8. Englesbe MJ, Wu AH, Clowes AW, Zierler RE (2003) The prevalence and natural history of aortic aneurysms in heart and abdominal organ transplant patients. *J Vasc Surg* 37: 27-31.
9. Vlijmen-van Keulen CJ, Pals G, Rauwerda JA (2002) Familial abdominal aortic aneurysm: a systematic review of a genetic background. *Eur J Vasc Endovasc Surg* 24: 105-116.
10. Helgadottir A, Thorleifsson G, Magnusson KP, Grétarsdóttir S, Steinthorsdóttir V, et al. (2008) The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. *Nat Genet* 40: 217-224.
11. Worrall BB, Foroud T, Brown RD Jr, Connolly ES, Hornung RW, et al. (2009) Genome screen to detect linkage to common susceptibility genes for intracranial and aortic aneurysms. *Stroke* 40: 71-76.
12. Larsson E, Granath F, Swedenborg J, Hultgren R (2009) A population-based case-control study of the familial risk of abdominal aortic aneurysm. *J Vasc Surg* 49: 47-50.
13. Ciccone MM, Scicchitano P, Cameli M, et al (2014) Endothelial function in pre-diabetes, diabetes and diabetic cardiomyopathy: a review. *J Diabetes Metab* 5:364.
14. Matteo Ciccone M, K Sharma R, Scicchitano P, Cortese F, Salerno C, et al. (2014) Dolichocarotids: echo-color Doppler evaluation and clinical role. *J Atheroscler Thromb* 21: 56-63.