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PREVALENCE OF THORACIC AORTIC ANEURYSMS AND DILATATIONS IN PATIENTS WITH INTRACRANIAL ANEURYSMS

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Thoracic aortic aneurysm (TAA) is a disease with a high mortality. If not treated, complications include rupture and dissection of the thoracic aorta. TAA is often asymptomatic and it can be diagnosed incidentally when imaging studies are carried out for other reasons. Estimated prevalence of TAA is 0.16-0.34%. It has been reported that the prevalence of intracranial aneurysms (IA) in patients with TAA is 9 %. The aim of this study was to examine whether the prevalence of thoracic aortic dilatations and aneurysms is higher in patients with ruptured or unruptured IA.

This was a retrospective cohort study. Medical records of 519 patients diagnosed with ruptured or unruptured IA at the University Hospital of Turku between 2006 and 2016 were reviewed. Diameters of aorta were measured at three points using reference values by American College of Radiology. Number, shape, diameter and location of IAs were determined.

From 519 patients 94.6% had saccular and 5.4% had fusiform IA.41.6% had ruptured and 56.4% unruptured IA. Thoracic aortic dilatation (TAD) was found in 17% and TAA in 6% of patients with saccular IA. 64.2% of the dilatations occurred in the aortic arch. Patients with fusiform IA had a prevalence of 29% for TAD and 18% for TAA. It was found that higher age, rheumatoid disease and excessive alcohol consumption were associated with higher prevalence of TAD and TAA.

According to our study the prevalence of TAD and TAA in patients with IA is higher than previous reports of general population state. Our results suggest that the prevalence of TAD and TAA is higher in patients with saccular IA and a history of rheumatoid disease and/or excessive alcohol consumption. Also patients with fusiform IA had a higher prevalence of TAD and TAA.

Key words: intracranial aneurysm, thoracic aortic aneurysm

Prevalence of Thoracic Aortic Aneurysms and Dilatations in Patients with Intracranial Aneurysms.

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Abstract

Background and aims: Prevalence of intracranial aneurysms (IA) is higher in patients with aortic aneurysms. However, there are lack of studies investigating prevalence of thoracic aortic aneurysms (TAA) in patients with intracranial aneurysms. The objective of this study was to evaluate the prevalence and risk factors for thoracic aortic dilatations (TAD) and TAAs in patients with IAs.

Methods: We retrospectively reviewed data of 1777 patients with diagnosed IAs at our institution between 2006 and 2016. We included 413 patients with saccular IAs and available imaging studies (computed tomography, magnetic resonance imaging or catheter angiography) of all thoracic aortic segments. TAD was defined according to age- and sex-matched normograms, and TAA as diameter >4.0 cm.

Results: A total of 85 patients (21%) had TAD or TAA. The prevalence of TADs and TAAs were 18% (n=76) and 8% (n=32) without significant difference between unruptured and ruptured IAs (p=0.7). Of the 76 patients with TAD, 24 patients (32%) had multiple TADs and 64% of the TADs located in the aortic arch. Higher age (OR 1.04; p=0.006), rheumatoid disease (OR 4.73; p =0.009) and alcohol abuse (OR 4.77; p = 0.01) were significant risk factors for TAD/TAA.

Conclusions: The prevalence of TADs and TAAs is considerably higher in patients with IAs compared to the reports from the general population, suggesting that IAs might be associated with aortopathy. Especially IA patients with a history of rheumatoid disease and/or alcohol abuse have a high risk for TADs/TAAs.

Keywords: Thoracic aortic aneurysms; Thoracic aortic dilatations; intracranial aneurysms; rheumatoid disease; alcohol abuse

Introduction

Thoracic aortic aneurysms (TAA) are a potentially fatal disease whose complications have high mortality; 94–100% for rupture [1, 2] and 55% for acute aortic dissection.[3] TAA is typically defined as a segmental dilatation of ≥50% compared to normal diameter[4] or any dilatation above 40 mm.[5] The prevalence of asymptomatic TAA has been measured in 0.16–0.34%.[6, 7] Incidentally noted ascending aortic dilatation (4–5 cm) has been reported in 2.7% of general population.[8] Early diagnosis of TAA is difficult because 95% of patients with TAA are asymptomatic before complications.[9]

Aortic aneurysms and intracranial aneurysms (IA) share similar comorbidities and genetic risk factors,[10] and about 10% of patients with TAA also have intracranial aneurysms.[11, 12] One prior study reported prevalence of ascending TAA of 4.7% in patients with intracranial aneurysms.[13] However, larger studies evaluating the entire thoracic aorta in the patients with IA are not available.

The objective of this study was to evaluate the prevalence and risk factors for TADs and TAAs in patients with saccular IAs.

Materials and methods

This study was approved by the local institutional review board. Patient consent was not required because of the retrospective study design.

Study Subjects

We reviewed retrospectively records for 1777 patients diagnosed with ruptured or unruptured IAs at our institution between 2006 and 2016. Among them, we included 413 patients with saccular IAs and available contrast-enhanced Computed Tomography Angiography (CT-angiography), unenhanced CT, Magnetic Resonance Imaging (MRI) or catheter angiography with sufficient coverage of the all three thoracic aortic segments (ascending thoracic aorta, aortic arch and descending thoracic aorta).

Among the 413 patients, we also identified 133 patients with echocardiogram to evaluate bicuspid valve by report. Thoracic aortic dimensions were evaluated by two authors. About 40 cases per each reviewer were also examined by a board-certified radiologist from our study group to ensure reliability of measurements.

Thoracic aortic dimensions were measured perpendicular to the axis of blood flow at three points; 1. mid-ascending aorta, 2. mid-descending aorta at the level of pulmonary artery bifurcation, and 3. aortic arch at the level of maximum diameter (**Supplemental Figure 1**). Thoracic aorta was also evaluated for coarctations from imaging studies and from medical charts.

Gender/age matched and site-specific cut-off values for thoracic aortic dilatation and aneurysms were used from the study of American College of Radiology[14] (**Supplemental Table 1**). Aortic dilatation was defined as + 2 SD from normal reference value and aneurysm as diameter of >4.0 cm.

Characteristic of IAs were evaluated from digital subtraction angiography, CTA and MRA images. In patients with multiple IAs, characteristics were evaluated for ruptured or for largest unruptured IA. Maximum diameter was measured for dome height and width, and aneurysm neck. Dome to neck ratio (maximum dome width/maximum neck width) was calculated for each patient. IAs with daughter sacs or protrusions were defined irregular. IA location was categorized as follows; internal carotid artery, middle cerebral artery, anterior cerebral artery, and posterior circulation arteries.

Data from patient records were collected at the time intracranial aneurysm were first diagnosed including age, gender, smoking, alcohol consumption, hypertension, history of intracranial and aortic aneurysms in first degree relatives, diabetes, history of Turner syndrome, connective tissue disorders (Marfan syndrome, Ehler-Danlos syndrome type IV, Loyes-Dietz syndrome), rheumatoid diseases (rheumatoid arthritis, psoriatic arthritis, Sjögren's syndrome, polymyalgia rheumatica, scleroderma, spondyloarthritis, systemic lupus erythematosus) and vasculitis (Takayasu arteritis, Kawasaki

disease, Giant cell arteritis, Polyarteritis nodosa, Churg-Strauss syndrome, Henoch-Schönlein purpura, Bechet's disease) and peripheral arterial disease.

Alcohol abuse was defined as ≥288 g ethanol per week in men and ≥192 g in women or if patient was diagnosed with alcoholism (International Statistical Classification of Diseases and Related Health Problem, diagnosis code F10.2). Diabetes was defined as diabetes requiring per-oral medication or insulin. Dyslipidemia was defined as those with LDL cholesterol ≥3.0 mmol/l or total cholesterol ≥5.0 mmol/l.

Statistical analysis

Statistical analysis was performed by using IBM SPSS statistics 23 for Windows (IBM, Armonk, New York). Interclass correlation (ICC), proposed by Shrout and Fleiss,[15] was used to assess the inter-rater reliability (IRR) of imaging measurements. According to Meyer's study,[16] the following scale for ICC were used to determine the IRR: poor (<0.7), fair (0.7–0.8), good (0.8–0.9), and high (≥0.9).

Between group differences were evaluated with Chi Square or Fisher's exact test for proportions and an independent samples T-test for continuous variables and binary logistic regression. Continuous variables are reported either as mean and standard deviation or as median and interquartile range as appropriate. Multivariable binary regression was performed by including variables with a $p<0.10$ in a model with backward selection (Wald), p-values of <0.05 were considered statistically significant. Multiple imputation was used for missing data.

Results

From 1777 patients with diagnosed IA, a total of 413 patients with saccular IA and available imaging of entire thoracic aorta were included **(Figure 1)**. Available imaging modalities of thoracic aorta are represented in the Flow chart (**Figure 1)**. No patients had a history of connective tissue disorders (Marfan syndrome, Ehlers-Danlos syndrome and Loeys-Dietz syndrome), Turner syndrome or vasculitis. Baseline characteristics with normal and abnormally dilated aorta (TAD or TAA) are presented in **Table 1**. Of the 23 patients with rheumatoid disease, 15 patients had rheumatoid arthritis, five patients polymyalgia rheumatica, two patients psoriatic arthritis and one patient Sjögren's syndrome.

A total of 101 TADs and 34 TAAs were found in 76 (PR 18.4%) and 32 (PR 7.7%) patients. Altogether 85 patients (20.6%) had TAD or TAA. Multiple TADs were noted in 24 of 76 patients (31.6%) and multiple TAAs in 2 of 32 patients (6.3%) (**Figure 2)**. Altogether 21 patients had TAD in two aortic segments and three patients in all three aortic segments. Among 101 TADs, 65 (64.4%) TADs located in the aortic arch. From 133 patients with available echocardiogram, 2 patients (PR 1.5%) had BAV, but no concurrent TAD or TAA. In one patient, thoracic aortic coarctation was operated previously in childhood, in same patient TAD was found in descending thoracic aorta.

In a multivariable binary regression model (**Figure 3)**, rheumatic disease (OR 4.73; 95% CI, 1.47–15.2, p=0.009), alcohol abuse (OR 4.77; 95% CI, 1.38–16.5, p= 0.01) and higher age (OR 1.04; 95% CI, 1.01–1.06, p= 0.006) emerged as significant independent predictors of abnormally dilated aorta (TAD or TAA).

Inter-rater reliability

Both raters had good to high reliability of aortic measurements as assesses against those by a board-certified radiologist (ICC values of 0.91, 0.82, and 0.87 by T.F.; and 0.89, 0.81, and 0.84 by E.P. for ascending aorta, aortic arch, and descending aorta, respectively)

Discussion

We found that the prevalence of thoracic aortic dilatations and aneurysms is significantly higher in patients with intracranial aneurysms than in the general population based on earlier reports. As the threshold of +2SD essentially represents the 95% confidence interval, the prevalence of dilatations in the current study was almost 9-fold to the expected prevalence. We also found that IA patients with rheumatoid disease and high alcohol consumption are at a significantly higher risk of having thoracic aortic dilatations. Interestingly, 64.4% of the dilatations located in the aortic arch and 32% of patients with TAD had multiple TADs. To our knowledge, our study is the largest to date to assess the association of thoracic aortic dilatations and saccular IAs and to include all three thoracic aortic segments (aortic arch, ascending and descending aorta) with contemporary diagnostic imaging modalities.[9]

Prevalence of TADs and TAAs

In the current study, the prevalence of abnormally dilated aorta (TAD or TAA) was 20.6%. The prevalence of TADs and TAAs was 18.4% and 7.7% respectively. Goyal et al. 2015 study reported TAA prevalence of 4.7% in patients with IA. This difference may best be explained by the current study measuring all three thoracic aortic segments, while Goyal et al. 2016 were only measuring the ascending aorta.[13] Although the studies used for reference values were different, the thresholds for were very similar; accordingly, the rate of ascending aortic dilatation was virtually identical between the current study and the previous report.

In the Kuzmik et al. 2010 study, patients with TAA had a 9% prevalence of IAs and prevalence of IAs were higher when the descending aorta was aneurysmatic (33%) compared to the ascending aorta (7.1 %).[11] In their study only patients with operated TAA were included, possibly neglecting smaller thoracic aneurysms and dilatations. In addition, they did not describe aortic arch aneurysms separately. We found that nearly two-third of TADs located in the aortic arch, which is an unusual location for a TAA – typically aortic arch aneurysms account for approximately 10% of all thoracic aortic aneurysms.[17] Natural history of aortic arch aneurysms is poorly understood, but these patients have usually high age and burden of comorbidities.[18] Nearly half of patients with Turner syndrome have elongation in aortic arch,[19] but since no patients had Turner syndrome in our study, this do not explain high prevalence of aortic arch TADs. Multiple aortic lesions are usually related to aortic arch aneurysms,[20] which can explain high prevalence of multiple TADs in our study.

Finally, although BAVs are related to concomitant TAAs[21] and increased prevalence (PR 7.7%–9.8%) of IAs,[22, 23] only 2 patients (PR 1.5%) had BAV in our study without concomitant TADs or TAAs. BAV prevalence of 1.5% is comparable to normal population[24] and in line with previous studies which have evaluated prevalence of BAVs in patients with IAs.[13]

Risk factors for TAAs and TADs

TAAs and IAs shares similar risk factors, for instance connective tissue diseases such as Marfan's Syndrome, Ehler-Danlos Syndrome type IV and Loeys-Dietz syndrome,[9, 25] and habitual risk factors such as smoking and hypertension.[9, 26] Saccular IAs, TAAs and abdominal aortic aneurysms share a similar genetic background[10] and approximately 20% of TAA patients have at least one first degree relative with an arterial aneurysm.[27] Our results, however, suggest that smoking, hypertension or a positive family history of intracranial aneurysms is not an additional risk factor for TAAs or TADs. In addition, none of the patients in this study had a diagnosis of connective tissue disease, which is inconsistent with the high prevalence of TAD and TAA in our study. The absence of traditional risk

factors for aneurysms, presence of multiple thoracic aortic dilatations and the abnormally high proportion of dilatations in the aortic arch in our study suggests that there could be a hitherto unknown risk factor, genetic or acquired, shared between IAs and TAAs.

Instead, we found that rheumatoid diseases and excessive alcohol consumption are major risk factors for concomitant TAD/TAA in patients with saccular IA. There is a lack of studies related to major alcohol consumption as a risk factor for thoracic aortic aneurysms. These studies have exclusively focused on abdominal aortic aneurysms with contradictory results; some studies have found alcohol consumption to decrease[28] and others to increase[29] the risk for abdominal aortic aneurysms. Shovman et al. 2016 reported rheumatoid arthritis as a risk factor for TAA with an OR of 1.4 in the general population.[30] In the present study, the risk of TAD was 3-fold for patients with rheumatoid disease in a population with an overall prevalence of TAD almost a hundred times greater than reported for the general population. We defined rheumatoid disease beyond only rheumatoid arthritis to include other autoimmune entities which can explain this difference, although 61% categorized as having rheumatoid disease indeed had rheumatoid arthritis. Autoimmune diseases can present with aortitis, which can consequently lead to aortic aneurysm formation.[31] The relationship between rheumatoid diseases and intracranial aneurysm formation has not been described previously, although autoimmune diseases might be associated with an increased risk of subarachnoid hemorrhage.[32] However, in accordance with previous study,[13] we did not find differences in the presentation of TAA or TAD between ruptured and unruptured IAs.

Limitations

This was largest study to this day to evaluate the entire thoracic aorta in patients with IA. Only patients with widely accepted imaging modalities for TAA diagnosis were included. Because of the retrospective nature of the study, one of the limitations was potential selection bias, especially in patients with unruptured IA. In our institution, CT-angiography is usually performed to the level of

pulmonary artery during the initial diagnosis of subarachnoid hemorrhage. However, in patients with unruptured IA, chest imaging could have been performed for more various reasons. Another potential limitation is a lack of a control group of ethnically Finnish patients with measured thoracic aortic diameters and without IA, which may introduce sampling bias. We did, nonetheless, use normative reference values from a previous large study with patients of Caucasian ethnicity. Finally, we defined TAA as a dilatation of >4.0 cm which can overestimate the prevalence of TAA in our population. However, the exact threshold diameter for a dilatation to be categorized as an aneurysm is not entirely clear from the existing literature.

Conclusion

The prevalence of thoracic aortic aneurysms and dilatations is higher in patients with intracranial saccular aneurysms and especially in patients with a history of rheumatoid disease and/or alcohol abuse. Our results suggest that intracranial aneurysms and thoracic aortic aneurysms/dilatations could share a similar specific pathogenetic background beyond traditional risk factors such as smoking and hypertension.

Conflicts of interest

Dr. Gunn has received unrestricted research grant from Vifor Pharma outside the submitted work. Other authors have nothing to disclose.

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Figure legends

Figure 1. Flow chart

Abbreviations: TAD, thoracic aortic dilatation; TAA, thoracic aortic aneurysm; BAV, bicuspid aortic valve.

Figure 2. Prevalence of thoracic aortic dilatations (TAD) and aneurysms (TAA) in patients with intracranial aneurysms.

Figure 3. Predictors of thoracic aortic dilatations or aneurysms.

Abbreviations: SAH, subarachnoid hemorrhage.