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The Value of Screening in Siblings of Patients with Abdominal Aortic Aneurysm

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Objectives. *This study aimed to determine the incidence of abdominal aortic aneurysm (AAA) in a large group of siblings of Australian AAA patients to determine if screening in this group is justified.*
Methods. *1254 siblings of 400 index AAA patients were identified and offered aortic ultrasound screening. An age and sex matched control group was recruited from patients having abdominal CT scans for non-vascular indications. AAA was defined by an infrarenal aortic diameter of ≥3 cm or a ratio of the infrarenal to suprarenal aortic diameter of ≥2.0. A ratio of 1.0–1.5 was considered normal, and a ratio of >1.5 to <2.0 was considered ectatic. Aortic enlargement was defined as ectasia or aneurysm.*
Results. *276 (22%) siblings could be contacted and agreed to screening or had previously been diagnosed with AAA. All 118 controls had normal diameter aortas. 55/276 siblings had previously been diagnosed with AAA. The remaining 221 siblings underwent ultrasound screening. Overall, 30% (84/276) had enlarged aortas (5% ectasia, 25% aneurysmal); 43% of male siblings (64/150) and 16% of females siblings (20/126). The incidence was 45% in brothers of female index patients, 42% in brothers of male patients, 23% in sisters of female patients, and 14% in sisters of male index patients.*
Conclusions. *The overall incidence of aortic enlargement of 30% found in this study warrants a targeted screening approach with ultrasound for all siblings of patients with AAA. A similar targeted approach for screening of the children of AAA patients would also seem advisable.*

Key Words: Abdominal aortic aneurysm (AAA); Screening; Siblings; Ultrasound.

Introduction

Rupture of abdominal aortic aneurysm (AAA) is the 13th most common cause of death in USA and accounts for 1–2% of deaths in men over the age of 65 years.[1–3] The incidence of AAA in Australian males ranges from 4.8% in the 65–69 years age group to 10.8% in those 80 years of age or older.[4] Elective repair can be performed with mortality rates in the order of 2–6%. In contrast, the overall mortality for ruptured AAA is 80–90%.[5] Until the recent publication of the Multicentre Aneurysm Screening Study results,[6,7] screening for AAA had been controversial. Some studies have identified high incidences (15–30%) in siblings of AAA patients.[8–12] A recent Australian study by Larcos et al. from Westmead Hospital, however, found no first-degree relatives with AAA from a screened population of 52 relatives of 38 index patients with AAA and these authors questioned the role of screening.[13] This was a small study with relatively young screened recruits which we suspected did not represent the true incidence of AAA in family members.

The aim of this study was to determine the incidence of AAA in a larger group of siblings of Australian AAA patients to determine if screening programs for this group are justified.

Methods

A database of AAA patients treated at the Royal Brisbane Hospital was established and this report comprises the first 400 index cases with AAA. Family trees were constructed for the index cases to identify siblings. Permission was sought from patients to contact siblings who were contacted by either the patient or their family, with a follow-up phone call and letter advising the siblings to discuss the offer of screening with their local doctor in the first instance. If

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agreeable, the patient underwent ultrasound examination of their abdominal aorta, either locally or in the vascular laboratory at the Royal Brisbane Hospital. A copy of the ultrasound report and films were sent to the Royal Brisbane Hospital for examinations performed by the sibling's local doctor.

An age and sex matched control group of patients was recruited from patients having abdominal CT scans for non-vascular indications. Criteria for the diagnosis of AAA was an infrarenal aortic diameter of ≥ 3 cm or a ratio of the diameter of the infrarenal aortic diameter to the diameter of the suprarenal aortic diameter of ≥ 2.0. A ratio of 1.0–1.5 was considered normal, and a ratio of >1.5 to <2.0 was considered ectatic. Aortic enlargement was defined as being either ectatic or aneurysmal.

Using SPSS, statistical comparisons between groups were calculated using an unpaired t test for comparison of ages between the siblings and control patients, and a Chi square test for comparison of the incidences of aortic enlargement between the various groups (male versus female, siblings versus controls). Significance was accepted for $p < 0.05$.

Results

The 400 index patients with AAA had a mean age of 71 years (range 40–97 years) and 79% were male. Their mean AAA diameter was 5.7 cm. A total of 1254 siblings were identified from the family trees (Fig. 1). Two hundred and seventy-six of these siblings (22%) could be contacted and were agreeable to participate in the study or had previously been diagnosed with AAA. Five hundred and fifty-five siblings were deceased. Death certificate and post-mortem details were not sought for these cases because of the logistical complexity of such an undertaking and the wide geographic spread of these deceased siblings. Two hundred and ninety-three could not be contacted, because the patients did not know the whereabouts of their siblings or because they resided overseas. One hundred and thirty siblings refused the offer of AAA screening.

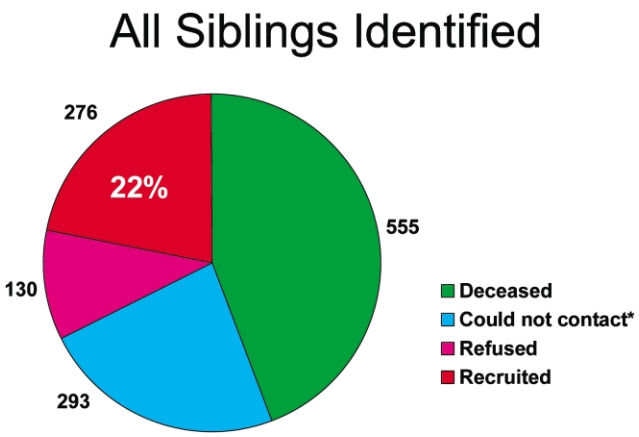

Fig. 1. 1254 siblings identified from the family trees of 400 index patients with AAA.

The 118 control patients (mean age 65 years, 52% male) were well matched with the siblings (mean age 66 years, 54% male) for age and sex (Tables 1 and 2). The index AAA patients and control patients were almost exclusively Caucasian. All 118 control patients had normal diameter infrarenal abdominal aortas.

Fifty-five of the 276 siblings had previously been diagnosed with AAA. Of these 55, 19 were deceased, nine having died from AAA rupture. The remaining 221 siblings underwent ultrasound examination of their abdominal aorta. Thirty percent (84/276) of the participating siblings had enlarged aortas (5% ectasia, 25% aneurysmal) while 70% (192/276) had normal infrarenal/suprarenal aortic diameter ratios. The 70-year mean age of those siblings with aortic enlargement was significantly older ($p < 0.05$) than the 65-year mean age of those siblings with normal aortic diameters (Table 1). Tables 2–5 detail the siblings' incidence of aortic enlargement according to their sex and the sex of the index patient. These data are of relevance in counseling patients and their siblings of the sibling's risk of harboring an AAA based on the index patient's sex and the sibling's sex. There were significantly more males ($n = 64$) than females ($n = 20$) amongst the siblings with aortic enlargement. The risk of aortic enlargement amongst the siblings was 43% for male siblings (64/150) and 16% for female siblings (20/126). Brothers of female index patients had the highest incidence of aortic enlargement at 45%. Brothers of male patients had a 42% incidence of aortic enlargement, sisters of female patients had a 23% incidence, while sisters of male index patients had the lowest incidence of aortic enlargement at 14%.

Table 1. Mean age of siblings and control patients according to whether their aorta was enlarged or normal.

	Enlarged	Normal	Total
Siblings			
All	70*	65	66
Male	69*	65	66
Female	70*	65	66
Controls			
All	–	65	65
Male	–	65	65
Female	–	65	65

*$p < 0.05$.

Table 2. Sex of siblings and control patients according to whether their aorta was enlarged or normal.

	Enlarged	Normal	Total
Siblings			
All	84	192	276
Male	64*	86	150 (54%)
Female	20*	106	126 (46%)
Controls			
All	0	118	118
Male	0	61	61 (52%)
Female	0	57	57 (48%)

*$p < 0.001$, Chi square = 21.971, power = 0.999.

Pedigree structures were consistent with a polygenic inheritance pattern, although some pedigrees showed possible dominant or recessive inheritance. Seventy-nine index patients had at least one first-degree relative (parent or sibling) also affected with AAA. Of these, 27 had one parent and one had both parents (but no sibling) affected. Sibship size (the number of children of the same parents) ranged from 2 (13 sibships) to 15 (one sibship) and the number of affected siblings of the index case ranged from 1 (50 sibships) to 5 (one sibship). Documentation of AAA in more distant relatives (half siblings, cousins, aunts, uncles etc.) was not specifically sought in this study.

Discussion

Elective repair of unruptured AAA can now be performed in many vascular surgery units with mortality rates in the order of 2–6%.[14–19] Recent data from the ASERNIP-S Australian audit of endoluminal grafting of AAA reported an early mortality rate of 2.6% in a group of 380 open AAA repairs.[16] In contrast, mortality rates for ruptured AAA have remained static for decades, with operative mortality rates for urgent repair of ruptured AAA in the order of 25–50%, and overall mortality rates for rupture of 80–90%. An excellent study from Malmo in Sweden, where there was an autopsy rate of 85% during the study, reported an overall mortality rate of 88% for 215 patients suffering from ruptured AAA. Only 61 of these patients (28%) survived to undergo surgery, with 21 ultimate survivors (12%).[5] The only strategy that can impact significantly on the overall mortality rate for ruptured AAA is to detect and repair AAA electively.

Table 3. Incidence of aortic enlargement among the 276 siblings according to the sex of the sibling.

$n = 276$	Aortic enlargement	
	Yes	No
Sib sex		
Male	64* (43%)	86 (57%)
Female	20* (16%)	106 (84%)

*$p < 0.001$, Chi square = 21.971, power = 0.999.

Table 4. Incidence of aortic enlargement among the 150 male siblings according to the sex of the index patient.

$n = 150$	Patient sex	
	Male	Female
Male sibs		
Enlarged	51 (42%)	13 (45%)
Normal	70 (58%)	16 (55%)

p = NS; $p > 0.05$, Chi square = 0.0028, power = 0.048.

Detection rates can vary considerably depending on the population screened.[8,20,21] In a population of greater than 65 year old, otherwise unselected Australian males, the incidence of AAA ranged from 4.8% in the 65–69 years age group to 10.8% in those 80 years of age or older.[4] In targeted screening programmes directed at patients with atherosclerosis in other vascular beds, the incidence of AAA ranged from 9–16% in patients with peripheral vascular disease,[22–26] up to 18% in veterans with greater than 50% carotid stenosis,[27,28] and between 5 and 9% in patients with coronary artery disease.[29,30] Wolf's study also calculated the cost of screening for AAA and reported a favourable comparison to screening for breast cancer.[22] Other studies have targeted first degree relatives of patients with AAA for screening.[8–13] Bengtsson's study from Sweden found AAA ($\geq$3.0 cm) in 29% of the brothers, and 6% of sisters of patients with AAA.[9] Webster's study in Pittsburgh USA (AAA defined as aortic diameter $>$3.0 cm or infrarenal to suprarenal aortic diameter ratio $>$1.5) detected a 25% incidence of AAA among first degree male relatives aged 55 years or older, and a 6.9% incidence in the female first degree relatives. No relatives under the age of 55 were found to have a AAA.[8] A recent Finnish study that screened 238 living first degree relatives and compared the results with controls, found a four-fold risk of AAA, but only in persons older than 60 years of age.[10] van der Lugt found a 29% incidence of AAA in brothers and a 6% incidence in sisters of AAA patients.[11] van der Graaf's study from the Netherlands found an overall AAA prevalence of 18% (12.3% new diagnoses and 5.7% prior diagnoses) in 210 brothers over the age of 50 years.[12] This study also did not identify any negative influence on psychological well-being 3 months after screening.

By contrast, a recent Australian study by Larcos et al. from Westmead Hospital found no first-degree relatives with AAA in a screened population of 52 relatives of 38 index patients with AAA.[13] Based on their results, these authors questioned the role of

Table 5. Incidence of aortic enlargement among the 126 female siblings according to the sex of the index patient.

$n = 126$	Patient sex	
	Male	Female
Female sibs		
Enlarged	14 (14%)	6 (23%)
Normal	86 (86%)	20 (77%)

p = NS; $p > 0.05$, Chi square = 0.684, power = 0.122.

screening. This was a small study with only 52 first-degree relatives screened. Of these 52 first-degree relatives, only 19 were siblings and their mean age was 60 years. The remaining 33 screened relatives were children of the AAA patients, and their mean age was a very young 48 years. Our concern that the results of this small study did not represent the true incidence of AAA in family members formed the impetus for this study. Using a definition of aortic enlargement to include ectasia (ratio of the diameter of the infrarenal aortic diameter to the diameter of the suprarenal aortic diameter of >1.5 to <2.0) and true aneurysm (infrarenal aortic diameter of ≥ 3 cm or a ratio of the diameter of the infrarenal aortic diameter to the diameter of the suprarenal aortic diameter of ≥ 2.0), our study found a 30% incidence of aortic enlargement in siblings of AAA patients. Varying definitions are used to define aneurysmal dilatation. One definition defines all infrarenal aortas measuring ≥ 3 cm as aneurysm. Others define AAA when the ratio of the diameter of the infrarenal aortic diameter to the diameter of the suprarenal aortic diameter exceeds 1.5, while others use a ratio of >2.0. Our definition of aortic enlargement (ectasia and aneurysm) encompasses all these definitions and allows comparison with the literature where these varying definitions have been used.

The siblings with aortic enlargement were significantly older (70 years) than those siblings with normal aortic diameters (65 years). The risk was 43% for male siblings and 16% for female siblings. This is a significantly increased risk compared to the reported 4.8–10.8% incidence in the elderly Australian male population. These incidences are higher than reported in some studies of first-degree relatives. This relates to the fact that only siblings were investigated in this study, and the results are comparable to other studies where only siblings were investigated.[9] The children of our index cases have not been screened as part of an organised programme, although they have been advised to undergo ultrasound screening at 5 yearly intervals once they reach the age of 50 years. Another reason that the incidences may be higher is that 55 of the siblings included in our analysis had already been diagnosed with AAA, representing a selection bias. Even if these patients are excluded from the analysis, the 13% (29/221) incidence of aortic enlargement is approximately twice the expected incidence for a patient group of this age[4] and is statistically significantly higher than the controls in this study ($p < 0.05$). The strength of the data and the resultant conclusions is also potentially affected by the fact that only 22% of all the siblings identified from the family pedigrees could be evaluated, while the remaining siblings were deceased, not able to be contacted or declined the offer of screening.

Although screening of siblings of AAA patients is logistically difficult, with many siblings uncontactable or likely to refuse screening, we believe that the overall incidence of aortic enlargement of 30% found in this study warrants a targeted screening approach with ultrasound for all siblings of patients with AAA. Asymptomatic AAA that are detected by screening can be repaired electively if and when they reach a diameter of approximately 5 cm so as to prevent the horrendous mortality that is inevitable once rupture occurs. In view of the cases of parent to offspring transmission (28 families), a similar targeted approach for screening of the children of AAA patients would also seem advisable once they reach their sixth decade of life.

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