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The Low Prevalence of Abdominal Aortic Aneurysm in Relatives in Northern Ireland☆

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Introduction. *Mortality from ruptured abdominal aortic aneurysm (AAA) remains high and has given impetus to screening. Targeted screening towards high-risk groups would increase efficacy. Relatives of previous AAA patients have been suggested as one such group. The aim of this study was therefore to determine the prevalence of AAA in relatives of previous patients in Northern Ireland.*

Patients and methods. *All living AAA patients, who underwent surgery between August 2001 and December 2005 in our unit, or were attending for follow-up of small aneurysms were contacted and asked for details of siblings and their family history. Screening by ultrasound was offered to the siblings and children over 50 years, with a defining threshold diameter for an aneurysm of 3.0 cm. Overall prevalence of AAA in the relatives was calculated. Separate prevalence rates were calculated according to relationship and gender of the patient and relative.*

Results. *513 previous patients were contacted. 132 gave details of living relatives, resulting in a total of 405 relatives suitable for screening. 105 declined a scan, leaving 300 in the study. Overall mean age of the group was 63.0 ± 8.7 years and 68% were siblings of male patients. Overall ten AAAs were detected by screening, giving a prevalence of 3.3%. No aneurysms were found in the subgroup of children, while the highest prevalence (12.5%) was found in brothers of female patients. 20 additional AAAs were reported in these 132 families, resulting in 14 of the 132 families (10.6%) having two or more members with AAA.*

Conclusion. *The prevalence of screening detected AAA in this study is lower than anticipated. The reason is unclear, but demonstrates the multifactorial nature of the aetiology and genetic complexities yet to be unravelled by future research.*

Keywords: Abdominal aortic aneurysm; Screening; Family history; Relatives.

Introduction

The mortality of ruptured abdominal aortic aneurysm (AAA) remains high despite modern advances in surgical and anaesthetic managements of the condition. This has therefore encouraged the use of ultrasonographic screening for the condition. An early diagnosis can then be made, facilitating surveillance and surgery offered to those deemed suitable. A seminal randomised controlled trial (MASS) has demonstrated definite benefit from aneurysm screening in men aged 65–74 years.[1] The same group also calculated that this nature of screening potentially reached cost-effectiveness at four years, but would increase substantially in subsequent years.[2] While population screening has demonstrated a disease prevalence of approximately 5% in men aged 65 to 74 years old, it has been suggested that targeting screening towards high-risk groups would improve the detection rate and associated cost-effectiveness.[3] The known risk factors of male sex, smoking, hypertension, previous myocardial infarction and peripheral vascular disease have been shown to increase the prevalence of AAA. Therefore, this population of patients would be high-risk for AAA, thus setting this group of patients out for targeted screening.

The reported familial tendency would suggest family members of previous AAA patients as another suitable screening sub-group.[4] This targeted screening has also been demonstrated to be cost-effective, with incremental life-years at low cost.[5] Northern Ireland provides an ideal geographical location to study

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suspected inherited diseases due its stable population, with only a small degree of migration. Overall population translocation, particularly inward, has been limited due to geographical limiting factors to significant travelling. As a result the genetic composition of the population also sets the province apart from neighbouring countries within the British Isles.

The objectives of the study were to:

1) Determine the prevalence of AAA in the first-degree relatives of previous aneurysm patients.
2) Determine the prevalence of AAA according to the gender and relationship of the patient and the relative.

Patients and Methods

Recruitment

Ethical approval and clinical indemnity were obtained from the Northern Ireland Research Ethical Committee and Belfast City Hospital (BCH) Trust respectively. The details of all patients who had undergone either open or endovascular repair of an abdominal aortic aneurysm (AAA) in the BCH Vascular and Endovascular Surgery Department between August 2001 and December 2005 were obtained from the Medical Records Department. Patients attending for routine follow-up of small aneurysms during that period were also included. The patients known to have died, either peri-operatively or subsequent to discharge, were excluded. All remaining patients were contacted by post and asked to supply details of their siblings and information regarding any family history of AAA.

Siblings and children over the age of 50 years presently residing in Northern Ireland were included. Any individual previously diagnosed with AAA was not invited for screening, but was included in subsequent prevalence calculations.

Screening

An invitation letter and patient information sheet were posted to all identified relatives. Further correspondence was sent to non-responders after two months. No financial remunerations or alternative incentives were offered. Informed written consent was obtained from all participants with a short medical history questionnaire. Screening was performed by with a 3 MHz ultrasound probe, using a Sonosite 180 Plus (Sonosite Inc, Bothwell, WA, USA) ultrasound scanner. One investigator, fully trained and validated in aortic scanning, performed all the examinations. The patients were scanned in the supine position, with alternative approaches only used when this failed to demonstrate an image. Abdominal aortic longitudinal anterior-posterior diameter of 30 mm or more was considered aneurysmal. No further review was offered to those participants below this threshold. If an AAA was detected, transverse measurements were also made. The maximum diameter was then recorded. Those with a small AAA (30-55 mm) were referred for routine follow-up at the vascular outpatient clinic, while surgery was offered if the diameter was 55 mm or more. Several images per patient, of a randomly selected proportion of all participants, including normal aortas, small and large AAA, were recorded on the Sonosite memory and then reviewed by a consultant radiologist, so that the accuracy of the ultrasonic measurements could be validated. The same radiologist also watched the screening process once per month to monitor technique and decision making of the screening.

In addition to new diagnoses made in the screening program, details of the family history provided by the patients were used to construct family trees, so that an overall prevalence of AAA in the families could be discovered.

Statistical analysis

Analysis was completed using SPSS (Version 12, SPSS Inc, Chicago, Il, USA). Normal distribution for study parameters was confirmed by histogram and Q-Q distribution plotting. Age was expressed as mean and 95% confidence intervals. An overall prevalence percentage of AAA in all participants was calculated. The prevalence was also calculated according to the relationship and gender of the patient and relative. Chi-squared test was used to analyse the difference between groups. A p value of <0.05 was considered statistically significant.

Results

Recruitment

513 patients underwent surgery for AAA in the BCH Vascular and Endovascular Unit between August 2001 and December 2005. 118 who were known to have died were excluded. 224 of the remaining 395 patients completed the family history questionnaire. 59 had no remaining siblings; 21 only had siblings living abroad; 12 never had siblings. 132 provided details of their relatives, resulting in a list of 405 relatives.

Attendance

The 405 siblings were invited to attend for a scan. One hundred and five failed to respond, refused or failed to attend two appointments, leaving 300 (74%) siblings in the study. Overall mean age was 63.3 ± 8.6 years old with some variation between each group (Table 1). The majority (68%) of siblings who attended were either a brother or sister of a male patient, reflecting the male dominance of the disease pattern. All original patients and also participating relatives were of Northern Ireland origin.

Medical details

One hundred and thirty eight were non-smokers, 109 former smokers and only 53 admitted to be currently smoking. Fourteen participants had diabetes, 27% had controlled hypertension and 29% had a history of hypercholesterolaemia with other risk factors illustrated in Fig. 1.

Aneurysms detected

Ten new AAAs were discovered, resulting in an overall prevalence in the 300 screened relatives of 3.3%. None of these were in the offsprings of patients, although this section was limited by a small number of participants. Excluding the 42 screened offsprings, the prevalence in siblings was 3.9%. If all screening participants aged below 60 years old are excluded, there are ten AAAs in 200 relatives (5.0%). The prevalence varies slightly according to the relationship with the highest prevalence found in brothers of female patients (Table 1). Although the prevalence reached 12.5% in this group of relatives, compared to 2.9% in the combined cohort of the other three sibling groups, this difference failed to reach statistical significance ($p = 0.08$). In the 84 brothers aged over 60 years six (7.1%) had an AAA. If the age threshold is increased to 65 years there were 56 brothers, with six (10.7%) having an AAA. No alteration in diagnoses was made on review of the retained images on the Sonosite memory.

The mean age of these ten relatives was 71.9 years (95% CI: 67.9–75.9 years) with a mean maximum aortic diameter of 4.4 cm (95% CI: 3.7–4.9 cm). Nine had a history of smoking, one was diabetic and overall they had a mean of three of the significant risk factors featured in Fig. 1. One man, with an AAA of 6.0 cm underwent open surgical repair without complication.

Twenty further family members previously diagnosed with AAA were identified in the family history questionnaire provided by the original patients. After inclusion of the ten new AAA diagnoses, the number of multiplex families (having two or more siblings with AAA) increased from 8 (6.1%) to 14 (10.6%) of the original 132 participating families. Ten families had 2 members with an aneurysm, 3 families with 3, and one family (of ten brothers) with 6 AAAs.

Discussion

The first report of familial occurrence of abdominal aortic aneurysm was in 1977.[6] Three brothers, being the only siblings, all presented with ruptured AAA. Norgard *et al.*,[7] using a questionnaire, reported 18% AAA prevalence in patients' families. This is similar to a prevalence of 19.4% in a New Zealand study of first-degree relatives.[8] Tilson and Seashore noted further familial clustering of 2 or more first-degree relatives, mainly males, in 50 families.[9] In 2 families 3 generations were affected, in 15 families individuals of 2 generations were affected, while in 29 families multiple siblings were affected. Verloes *et al.*[10] in 1995 demonstrated, in comparison to sporadic cases in men, a higher rate of rupture and significantly earlier age of rupture in familial male cases. The trend towards a younger age of presentation occurs in both the first and second generation of index patients with familial AAA, with morphological similarities noted in their aneurysms.[11] This has led some to suggest that familial AAA are different to the sporadic aneurysms.[12] The predilection towards aneurysm

Table 1. Results of screening according to relationship to patient

Relationship	Age (years)	Numbers invited	Numbers scanned (%)	Number of AAAs (%)	Av size (cm)
Overall	63.0 (62.2–64.4)	405	300 (74)	10 (3.3)	4.4
Brother of female patient	66.8 (63.8–70.4)	34	24 (71)	3 (12.5)	5.1
Brother of male patient	62.4 (60.5–64.2)	153	112 (73)	5 (4.5)	4.1
Sister of female patient	67.5 (64.1–70.4)	43	29 (67)	0 (0)	0
Sister of male patient	64.8 (63.3–66.9)	118	93 (79)	2 (2.2)	4.0
Son of female patient	53.9 (50.4–54.5)	12	8 (67)	0 (0)	0
Son of male patient	54.5 (50.3–61.7)	18	13 (72)	0 (0)	0
Daughter of female patient	53.4 (51.5–56.1)	10	10 (100)	0 (0)	0
Daughter of male patient	54.0 (50.7–59.7)	17	11 (65)	0 (0)	0

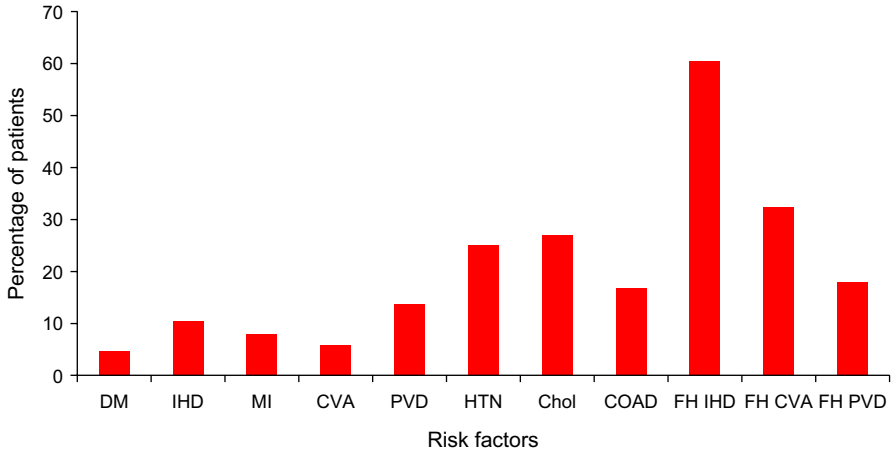

Fig. 1. Distribution of risk factors in screened relatives. IHD = Ischaemic heart disease; MI = Myocardial infarction; CVA = Cerebral vascular accident; PVD = Peripheral vascular disease; HTN = Hypertension; Chol = Hypercholesteraemia; COAD = Chronic obstructive airways disease; FH = Family history.

formation has been suggested to be a deficiency of type III collagen, after a study of a family with two brothers and the father affected by AAA.[13]

In an important paper on the subject of familial aneurysms, Johansen and Koepsell[14] compared the family history of 250 AAA patients to 250 controls. The frequency difference between 2.4% and 19.2% represented a 11.6-fold increase in the risk of aneurysmal formation in the first-degree relatives of previous AAA patients. The recommendation emanating from the authors was that a screening service should be offered to the immediate family, in order to make early diagnosis in a high-risk group.[14] A narrower profile of the targeted group was suggested by Bengtsson *et al.*,[15] with screening offered principally to sons of those who died from ruptured AAA.

There are a number of limitations in our study. Firstly, there was a disappointingly low response rate from previous patients, thus introducing a potential selection bias. However, the attendance of invitees was good in comparison to that achieved in other studies (Table 2), perhaps reflecting the shorter distances required to travel for participation. Secondly, the exclusion of AAA patients who have died may have potentially resulted in the exclusion of those with more aggressive aneurysmal disease. This is compounded by the fact that familial AAA also tend to have a higher tendency to rupture, although the overall mortality of the previous patients includes many non-aneurysm fatal events. On the same premise, it is also possible that the familial prevalence may differ between patients with large and small aneurysms, although this was not demonstrated in this study. Thirdly, the retrospective nature of the study design may have impacted upon the response rate, with the potential for poor recall of relevant family history and a clear information bias. Fourthly, social class, intra-family dynamics and relationships, are likely to influence the willingness of patients to participate in a research screening study. The overall prevalence of 3.3% is much lower than reported in other sibling screening programs, which varies from 4.1% to 25% (Table 2). This disparity is more evident when the overall 5.9% prevalence in brothers scanned in our study is compared to the 11% to 43% range of prevalence reported in these other screening programs. There is also a large variation noted in female siblings, ranging from 0% to 16%, compared to 1.7% found in this study.

The reason for the disparity is unclear. It cannot be explained by age inclusion criteria, since the lower threshold of 50 years is similar to many other studies[4,16–18] with even 40 years old used as the cut-off in other papers.[19,20] A similar aneurysmal diameter definition of 30 mm was also used in most other studies, while inclusion and exclusion criteria overall are

Table 2. Sibling screening results in other studies

Paper	Number screened	Attendance (%)	Overall	Male (%)	Female (%)
Bengtsson *et al.*[19]	87	85	15	29	5.8
Salo *et al.*[16]	241	74	4.6	1.1	0
Webster *et al.*[20]	103	51	13	21	6.7
Adamson *et al.*[27]	53	–	11	20	10.7
Adams *et al.*[4]	76	69	12	21	4
Fitzgerald *et al.*[22]	125	53	12	22	3
Van der Graaf *et al.*[17]	210	38	12	12	–
Frydman *et al.*[21]	276	22	25	43	16
Ogata *et al.*[28]	245	74	6.1	11	2.7
Jaakkola *et al.*[18]	123	–	4.1	8.9	1.3
Present study	300	74	3.3	5.9	1.6

similar to this study. The problems of poor response rates of previous patients and lack of attendance of relatives to proffered screening also beset other investigators of the familial trend, with our attendance rates being actually one of the best (Table 2). The subgroup analysis of our results by raising the age criteria of the brothers still did not bring the results into line with most other studies, suggesting a genuine phenomenon within the Northern Ireland populace. It is therefore possible that the unique genetic composition of the population has resulted in an aberration relative to the disease pathogenesis that has attenuated the familial tendency. Thus the general population disease prevalence may be similar to the rest of other western countries, as influenced by the known cardiovascular risk factors, but the genetic aetiology within the context of Northern Ireland may be limited. It is however undeniable that there is a genetic predisposition, since there are definite multiplex families identified, with evident predilection.

Frydman *et al.*[21] reported much larger prevalence rates relative to most other investigators. Interestingly they analysed their data according to the gender and relationship of the patient and siblings. Similar defining criteria of AAA were used, with comparable means of patient selection, but yet in each group the difference to our findings are marked (Fig. 2). Since overall prevalence and subgroup prevalence rates all differed, it would suggest that the phenomenon exists across the spectrum of family relationships. Fitzpatrick *et al.*[22] reported the results of a geographically closer cohort of patients. Fifteen of 125 (12%) Irish siblings were noted to have an ultrasonographically measured aortic diameter of 3 cm or more. Within this group of siblings 22% of males and 3% of females had an AAA. This difference to our results underlines the complexity of the disease's genetic predisposition and perhaps reflects the historical influences of different cultures in the genetic composition of the people of Northern Ireland. It has not been possible in the present study to determine the disease prevalence within historical and cultural groups of the inhabitants of Ulster, but future research to compare the corresponding originating countries would prove an interesting analysis and may help explain the difference illustrated by comparison to Fitzpatrick *et al.*[22]

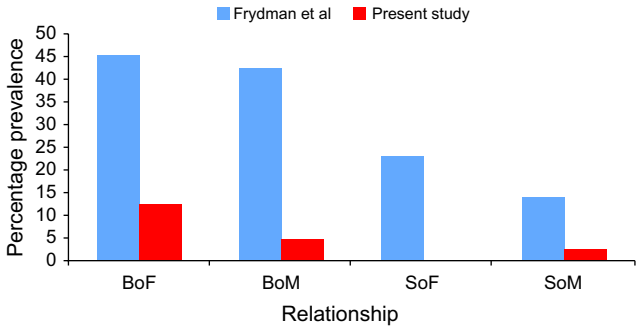

Fig. 2. Comparison of Frydman *et al.*[13] to present study, according to gender and relationship. (BoF = Brother of female patient; BoM = Brother of male patient; SoF = Sister of female patient; SoM = Sister of male patient).

The number of multiplex families (at least one affected first-degree relative of the index patient) within our cohort was 10.8%. Webster *et al.*[23] reported 15.4% multiplex families, with 21.4% demonstrating parent-offspring transmission, and after screening the actual multiplex family frequency increased to 27.9%.[20] A large multinational study into 233 multiplex families demonstrated 2.8 cases per family.[24] While most had only 2 affected individuals, there were 6 with 6, 3 with 7, and 1 with 8 affected individuals. They postulated that the genetic inheritance pattern was autosomal recessive in 72%, autosomal dominant in 25% and autosomal dominant with incomplete penetration in the rest. This variation reflects the lack of consensus or consistent evidence in available literature for a single genetic explanation. Several genetic models were compared by Majumder *et al.*,[25] with susceptibility to AAA most likely to be determined by a recessive gene at an autosomal diallelic major locus.

The reason for our low AAA prevalence in relatives is unclear. The age threshold of 50 years may have diluted the overall prevalence of the screened population. However, if those between 50 and 60 in our study are excluded, the prevalence rises only to 5.0%. Since this interval group of relatives yielded no aneurysms, it would seem prudent in future to raise the lower threshold to 60, even in the presence of family history. The very low prevalence among female relatives is predictable, but would also support limiting sibling screening to brothers, as suggested by Jaakkola *et al.*[18] The low response rate (132 of 513) of initial AAA patients demonstrates that rather than relying upon mail communication solely, it would be prudent for future researchers to adopt a multi-modal means of contacting patients, including telephone or outpatient review clinics.

Nevertheless these findings underline the multifactorial nature of aneurysm aetiology and the probable polygenetic contribution to its formation.[26] It also shows the great need for further research to be performed in the area of AAA prevalence and its genetic predisposition. The final implication, which arises from this data, is that specific screening of first-degree relatives may not be any more beneficial than population based screening, particularly within the local context.

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