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Selection for screening for familial aortic aneurysms

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The reported familial clustering of abdominal aortic aneurysm (AAA) indicates the possible rewards of family-based screening programmes with respect both to the number of asymptomatic aneurysms detected and to identifying associated genes. Ultrasonographic screening of 28 families (25 brothers and 28 sisters) was carried out together with collecting a history and a blood sample for analysis of the cholesterol level and genetic markers. Among the screened siblings six (11 per cent), all >60 years old, had an AAA ⩾3·0 cm in diameter. A further 11 siblings (21 per cent), six of whom were <60 years old, had a wide (2·5–2·9 cm) aorta. The presence of an aneurysmal or wide aorta was significantly associated with smoking (P = 0·027), male sex (P = 0·008) and a proband age of <60 years (P = 0·031). Polymorphic genetic markers for type III collagen and haptoglobin were not informative in these families. These results indicate that the efficiency of screening siblings of patients with AAA could be improved by limiting it to brothers with a smoking history and/or siblings of younger patients. The familial component appears to be greatest in these younger patients.

In all medical specialties there is an increasing emphasis on screening and preventative healthcare: prevention is better than cure. Screening for abdominal aortic aneurysm (AAA) could both prevent the catastrophic event of rupture and provide the scientific information necessary to design a cure. AAA is common in the elderly population and the incidence appears to be increasing[1]. Population screening programmes[2,3] have indicated an incidence of 1·5–4 per cent. Screening of patients with peripheral arterial disease or of siblings of patients with AAA increases the yield to >10 and >25 per cent respectively[4–6]. This last mode of screening, through family members, is perhaps the most interesting; the relatives of a patient are usually anxious to cooperate and, if AAA has a genetic basis, such screening provides the opportunity to investigate the gene(s) involved.

The increasing evidence that AAA has a genetic basis has been reviewed recently[7]. In a single family AAA has been associated with a mutation in type III collagen which has not been demonstrated in other patients with AAA[8]. The mutations associated with other collagen diseases, e.g. osteogenesis imperfecta and Ehlers–Danlos syndrome, are heterogeneous and it has been suggested that a similar situation may exist for aneurysm[7].

The elective repair of an AAA is a safe, durable procedure, yet each year the number of deaths from ruptured aneurysm increases[1]. Do we need to look for a cure? The gene for Marfan's syndrome has recently been identified and there is optimism that this will provide the basis for preventative medicine[9]. Similarly, understanding the cause of AAA could stimulate more preventative care.

Patients and methods

Consecutive patients attending this hospital for AAA repair were interviewed about their families and family histories, and a blood sample (10 ml anticoagulated with ethylenediamine tetra-acetic acid) obtained. Attention was focused on those with one or more living siblings in England and Wales. A total of 57 siblings of 28 patients (25 men, three women) were contacted. Four siblings (7 per cent) declined to participate in the screening programme.

The families were visited in their homes and a brief history taken concerning cardiovascular disease, hypertension and smoking habit. The maximum external anteroposterior infrarenal aortic diameter was measured using an Aloka 500 portable ultrasonography scanner (Keymed, Southend-on-Sea, UK) equipped with a 3·5-MHz probe. A blood sample was taken for the measurement of the cholesterol level, determination of haptoglobin phenotype, and for isolation of DNA from the white blood cells. Aortic diameters were placed into three categories: <2·5 cm (normal), 2·5–2·9 cm (wide), and ⩾3·0 cm (aneurysmal). General practitioners were advised of any finding of an aneurysmal aorta in their patient.

The polymerase chain reaction was used to amplify a portion of the type III collagen gene from the DNA isolated from the peripheral leucocytes[10,11]. The amplified fragments were digested with restriction enzymes NciI or AluI to look for the Gly–Arg-619 mutation and the common Ala–Thr-581 polymorphism[10,11].

Results were analysed using the χ^2 test with Yates' correction.

Results

A total of 53 siblings, 25 brothers and 28 sisters, were screened for AAA. Their median age was 65 (range 43–83) years. Among these siblings six aneurysmal aortas (11 per cent) and 11 wide aortas (21 per cent) were found. The aortic diameters are shown in *Figure 1*. The mean(s.d.) age of siblings with wide aortas was 63·5(9·2) years and that of those with aneurysmal aortas 70·7(11·6) years ($P = 0·095$). The two largest aneurysms have been repaired electively.

Of the 53 siblings, 34 (64 per cent) had a smoking history of >10 pack-years (i.e. at least 10 years of smoking 20 or more cigarettes per day), comprising 21 of 25 brothers (84 per cent) and 13 of 28 sisters (46 per cent). Among smokers there were four aneurysmal aortas and 11 wide aortas, compared with two aneurysmal aortas among non-smokers ($P = 0·027$). Of the 25 brothers, five had aneurysmal and eight wide aortas, compared with one aneurysmal and three wide aortas in the 28 sisters ($P = 0·008$). Eight of the probands (Charing Cross patients) had presented for elective aneurysm repair before the age of 60 years; in these families nine of 16 siblings had a wide or aneurysmal aorta compared with only eight of 37 siblings in the other families ($P = 0·031$).

The mean(s.d.) cholesterol level in the probands was 6·6(1·3) mmol l^{-1}, in the siblings with wide or aneurysmal aortas 6·5(1·1) mmol l^{-1}, and in the unaffected siblings 6·5(1·3) mmol l^{-1}. The presence of a wide or dilated aorta was not associated with a history of hypertension. The haptoglobin phenotypes of 28 probands and their siblings were determined;

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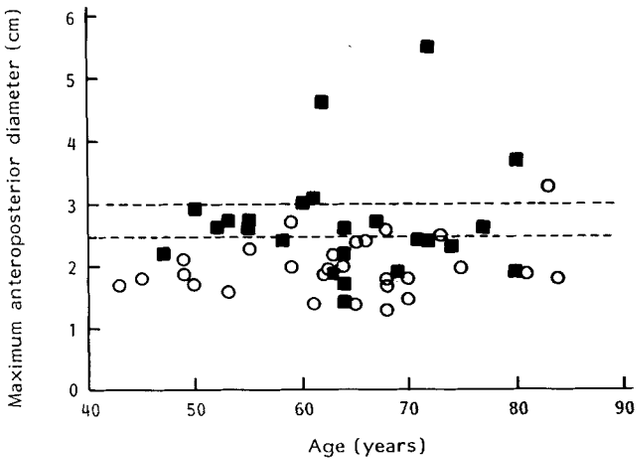

Figure 1 *Age and anteroposterior aortic diameter for 53 screened siblings.* ■, *Men;* ○, *women*

the normal frequency of the α_1 subunit (0·36) among the probands and their siblings indicated that this was not a useful marker. The Gly–Arg-619 type III collagen mutation was not observed in any of the probands. The frequency of Thr at position 581 in type III collagen is 0·32 in the normal population[11]. The frequency of Thr-581 among both the probands and their relatives was lower than this, 0·18, and indicated that this polymorphism was not useful as a marker of familial aneurysm.

Discussion

The yield of AAA from our family screening programme was much lower than that from either the Oxford or Malmö screening programmes but was similar to the yield in a recent family screening study in North America[5,6,12]. Some of these differences might be attributed to the varying ages of the siblings screened. AAA is a disease of later life. The mean age of the siblings with aneurysms detected by screening was 70·7 years, whereas half of the siblings screened in this study were <65 years old. A group of siblings with wide aortas, >1 s.d. above a mean population aortic diameter, was also defined[2,13]. Interestingly, in this group of 11 siblings with wide aortas, six were <60 years old. It has recently been suggested[14] that the mean growth rate of these wide aortas is 0·11 cm per year, so many of these siblings could have aneurysmal aortas in 5 years. If aneurysmal growth rates are dependent on control of hypertension or continued smoking the identification of wide aortas may be useful in preventative medicine.

The association between smoking and AAA has been convincingly demonstrated in both the Framingham[15] and Whitehall[16] studies. Such epidemiological evidence indicates that smoking is a more specific risk factor for AAA than for coronary heart disease. The present study again indicates that smoking is associated with a higher incidence of AAA. In a small study such as this it is not possible to assess whether male sex is a risk factor independent of smoking. Although more aneurysmal and wide aortas were found among brothers, a smoking history was twice as common among the brothers compared with sisters. With limited resources family aneurysm screening programmes could be restricted to those siblings with a long smoking history.

Perhaps the most effective way to investigate genes involved in aneurysm formation is to establish family pedigrees or collect pairs of affected siblings (who have one-quarter of their genes in common). The familial tendency for dilated aortas was most evident when the proband was <60 years old. For those wishing to pursue 'aneurysm genes' the families of younger patients may be more informative and more of the siblings may still be alive. Polymorphic genetic markers provide most information when a rare variant increases in frequency in the diseased population. Neither the haptoglobin nor the collagen markers used here was informative in this respect and we are now concentrating on alternative approaches to identify aneurysm genes.

Limited budgets are likely to preclude routine screening for AAA in the elderly population. Family screening programmes provide a high yield of wide and aneurysmal aortas. If the risk of developing an AAA depends on age, sex, smoking and aneurysm genes, selected population screening could become a part of future clinical practice.

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