How important is family history in ischaemic heart disease?

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Summary

A positive family history is an established risk factor for ischaemic heart disease, but the size of the contribution relative to classical risks is open to debate. The literature suggests that inherited factors are important in the development of premature ischaemic heart disease, but decline in importance with age. A polymorphism in the angiotensin-converting-enzyme gene was the first new genetic factor thought to contribute independently and significantly to cardiovascular risk. However, more recent large prospective studies have indicated that its contribution is smaller than was originally thought. Interventions should continue to be targeted at the reduction of important environmental factors, such as smoking cigarettes.

Introduction

The evidence for the family history as an independent risk factor in the development of ischaemic heart disease is strong. There are over fourteen studies to date confirming the clustering of cases of heart disease within families.\(^1\)\(^-\)\(^14\) This has encouraged the search for genetic factors to improve the prediction of risk and to target new areas for therapeutic intervention. Molecular genetic analysis has become a powerful and extensively-used tool, but the relative importance of genetic and environmental influences in ischaemic heart disease should be kept in perspective.

Family history in ischaemic heart disease

The relative importance of family history was studied in 1986 in the British Regional Heart Study,\(^15\) which was a prospective analysis of personal and environmental risk factors for ischaemic heart disease in males in England, Scotland and Wales. The study was based on 7735 men aged 40–59 randomly selected from age-sex registers of group general practices in 24 towns and followed for 8 years. For calculations of relative risk, men were grouped into fifths dependent upon the magnitude of the continuous variable being measured. The relative risk was calculated from the frequency of cases of confirmed ischaemic heart disease occurring in the group of men with the highest measurement compared with that in the group with the lowest measurement. The relative risk of the qualitative measurements, as with family history, was calculated from a comparison of groups with and without a history of death from ischaemic heart disease in either parent, irrespective of age. Despite this wide definition, family history was found to have a relatively small impact on risk compared to other classical factors.

Although the relative importance of family history would appear to be small, studies have varied enormously in their estimate of attributable risk, from 1.5 to 7. This variation has been due in part to a difference in definition of ‘positive family history’ (parental death from heart disease, parental and sibling death under 65 years, etc.) and to a difference in the populations studied (age range, social mix, etc.). More importantly, there has been difficulty in isolating inherited genetic risk from the confounding associations of classical risk factors that occurs in families. Two questions arise: whether the risk from a positive family history is due
Relative risk factors in ischaemic heart disease

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Relative risk</th>
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<tbody>
<tr>
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<tr>
<td>Age</td>
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<td>Total cholesterol</td>
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<tr>
<td>Diastolic BP</td>
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<td>Body mass index</td>
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<td>Family history</td>
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</tbody>
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Genetics or environment?

One of the ways in which it is possible to separate the influences of environment and genetics is by studying the impact of adoption. In 1988, a Danish study was published based upon all children born between the years 1924 to 1926 who were subsequently adopted by families who were biologically unrelated to the adoptee. They studied 960 families with follow-up until 1982. The aim was to compare the mortality rates of adoptees whose biological parents had died before the ages of 50 and 70 with the mortality rates of adoptees whose biological parents were still alive at those ages. A similar comparison was made for adoptees in relation to the death of their adoptive parents. Adoptees who had at least one biological parent who died from any cause before the age of 50 or 70 had mortality rates that were 1.7 and 1.8 times those of adoptees whose parents were both alive at those ages. The death of a biological parent before the age of 50 from a vascular cause was associated with a 4.5-fold increase in the mortality of the adolescent from the same cause. This effect was reduced if the biological parent survived to 70. Deaths of adoptive parents from vascular causes below the age of 50 increased the risk of death for the adoptees from the same cause, but this risk was not significant.

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The angiotensin-converting-enzyme gene

The potential importance of molecular medicine in defining risk and directing therapeutic intervention looked to be confirmed with the report of a polymorphism in the angiotensin-converting-enzyme gene associated with the development of myocardial
infarction.\textsuperscript{20} This discovery was preceeded by a number of observations. Levels of angiotensin-converting enzyme (ACE) are known to vary enormously between individuals—up to fivefold variation.\textsuperscript{21} However, levels remain remarkably constant on repeated measurement of any given subject. Further study revealed intrafamilial resemblance of angiotensin-converting-enzyme levels, leading to the discovery of a marker polymorphism consisting of the absence or presence of a 250 bp DNA fragment within the ACE gene.\textsuperscript{22,23} The insertion/deletion (I/D) polymorphism accounted for 47% of the total phenotypic variation of serum ACE. Cellular levels within T lymphocytes correlated well with plasma levels and also were related to the I/D polymorphism.\textsuperscript{24} Further segregation and linkage analysis confirmed that the I/D polymorphism was not itself responsible for the variation, but was in strong linkage disequilibrium with a controlling variant of the ACE gene, denoted Ss.\textsuperscript{25}

A multicentre case-control study performed in France and Northern Ireland subsequently revealed an increased frequency of the DD genotype in 610 patients who had suffered a myocardial infarction under the age of 65, compared to 733 healthy controls.\textsuperscript{20} The odds ratio of developing a myocardial infarct holding the DD genotype (as compared with the II genotype) was calculated to be 1.34. In addition, the data was analysed in terms of a low-risk group defined on the basis of a body mass index below 26 kg/m\textsuperscript{2}, and Apo B levels below 125 mg/dl, who were not being treated for hypercholesterolaemia. In this group, the odds ratio for risk associated with the DD genotype was increased to 3.2 (95\% CI 1.7–5.9, \(p<0.0001\)). The percentage of cases of myocardial infarction associated with the DD genotype was calculated to be 8\% in the total population, and 35\% in the low-risk group.

A flurry of activity ensued to examine the ACE polymorphism in many aspects of cardiology. The potential of molecular medicine appeared fulfilled in the identification of a new factor in the development of myocardial infarction which carried a significant risk and which could direct early therapeutic intervention with ACE inhibitors towards a defined population. However, evidence for the role of the ACE gene polymorphism as identified by Cambien has been drawn into some doubt.

The study by Cambien \textit{et al.} was a retrospective analysis performed 3–9 months after admission to hospital for treatment of myocardial infarction. This would have excluded the approximate 40\% of patients who fail to survive until hospital discharge.\textsuperscript{26} The first major prospective case-control study was carried out by Lindpainter \textit{et al.} based on the Physicians Health Study, which had recruited male, predominantly white US physicians into a trial of aspirin and beta-carotene in 1982.\textsuperscript{27} Blood samples from 14 916 subjects were used for gene analysis. Follow-up continued until 1992, when 387 participants had suffered an infarct and 865 men had developed angina or required revascularization. These 1250 case patients were then compared with 2340 controls matched to within 1 year for age and smoking habit. The relative risk of ischaemic heart disease conferred by the D allele in the whole group was 1.08 (95\% CI 0.9–1.2, \(p=0.16\)), consistent with no effect. Absence of significant effect was also found on analysis of the low-risk group as defined by Cambien \textit{et al.}

The Physician’s Health trial investigated the effect of the ACE polymorphism on a smaller group of patients suffering myocardial infarction at an older age than those in the earlier study. A further prospective analysis concentrated on 684 cases of acute myocardial infarction consecutively collected from coronary care units and compared with 537 controls from base populations.\textsuperscript{28} The age- and sex-matched odds ratio for myocardial infarction with DD genotype compared with D/I and II was 1.16 (95\% CI 0.82–1.65; \(p=0.44\)). The study also examined survival up to 22 months, which was important because earlier evidence had found that the DD genotype was associated with increased left ventricular dilatation following anterior myocardial infarction.\textsuperscript{29} However, there was no difference in the cumulative mortality curves between DD and D/I/II genotypes.

Finally, a meta-analysis has been performed on 14 published studies to date, involving a total of 3171 cases of acute myocardial infarction, and 5330 controls.\textsuperscript{30} The mean odds ratio across all studies was 1.26 (95\% CI 1.14–1.40, \(p<0.0001\)), giving an attributable risk estimate of 7\% to the DD genotype.

The future

Whilst it would seem that there may be an association between the DD genotype and myocardial infarction, allowing for the inevitable failings of any meta-analysis, the impact of the polymorphism is unlikely to be as significant as first reports indicated. Initial enthusiasm for the polymorphism was based on the possibility that directed therapy with inhibitors of the angiotensin-converting enzyme would selectively decrease the danger of myocardial infarction in high-risk groups. However, given the wide existing indications for ACE inhibitor use following myocardial infarction,\textsuperscript{31} any trial showing selective benefit to the DD genotype would necessarily be huge and is probably impractical.

Ischaemic heart disease is multifactoral. Family history and genetic factors represent only a proportion of the risk burden to the population. It is possible that gene–gene interactions, such as that proposed between the ACE polymorphism and the type 1 angiotensin II receptor polymorphism,\textsuperscript{32} may turn
out to be of greater significance. However, most medical interventions in ischaemic heart disease occur in patients of more advanced years, when the impact of genetic risk has declined and the environmental effects of Western lifestyles have become more important. Whilst molecular medicine has a role in defining mechanisms and directing therapeutic intervention, there remains a need to keep a balance with primary and secondary prevention strategies to reduce established environmental risk. The most benefit for patients with ischaemic heart disease accrues from stopping cigarette smoking.

References