HEREDITARY RISK FACTORS FOR ATHEROSCLEROTIC OCCLUSIVE DISEASE

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A number of basic concepts underlie this presentation. First, the development, natural history, and clinical history of all pathology are strongly influenced by an individual's genotype; hence all common disorders are hereditary to some degree. Any pathologic condition can be defined by distinct concepts: its etiology and its pathogenesis. Etiology is the study of cause, while pathogenesis is the process through which causal agents affect the clinical phenotype. Risk factors are quantitative traits, either continuous or discrete, that provide some independent prediction of the likelihood that an individual will develop a specific disease. Risk factors, which can be deleterious or protective, are determined by epidemiologic studies of populations and may indicate a specific contributor to causation or pathogenesis, or may be a somewhat remote marker for such agents. Pathogenetic factors derive from the study of biologic phenomena; the more precisely a phenotype is defined (eg, coronary atherosclerosis vs angina pectoris), the more relevant to an individual the pathogenetic factor should be. Factors that define both risk and pathogenesis are often classified as genetic or environmental, but this is a false dichotomy. Increasingly, how an individual responds to specific encounters in the environment is recognized as defined by the genotype.

Much of our understanding of risk factors for atherosclerosis has derived from research on the clinical consequences of atherosclerosis, such as myocardial infarction and stroke. Thus, factors that predispose to, or protect from, acute thrombosis, sequelae of ischemia, tissue repair, and so forth may have epidemiologic importance to clinicians but minimal relevance to the understanding of atherosclerosis.

This presentation reviews genetic factors that influence the cause and pathogenesis of atherosclerosis, the clinical consequences of which account for around 40% of deaths in the developed world. The traditional risk factors are shown in the following list.

Epidemiologic Risk Factors for Atherosclerosis

- Age
- Gender
- Estrogen deficiency
- Cigarette smoking (> 10 per day)
- Physical inactivity
- Diabetes mellitus, type I and type II
- Hypertension
- Abdominal obesity
- Family history of atherosclerotic disease in a relative less than 55 years old
- Dyslipidemia
  high total serum cholesterol
  high LDL cholesterol
  low HDL cholesterol
  high triglycerides
  high Lp(a)

Especially worthy of mention for several reasons is the family history. The lower the age criterion for determining whether the risk factor is positive or not, the more powerful it is for the fewer probands who will be defined as positive. Also, in population studies, the family history remains predictive even when all of the other factors with strong genetic contributions (lipids, diabetes, hypertension) are accounted for.

Research in the past decade has focused more on overt or possible pathogenetic factors, based on improved understanding of atherogenesis and vascular biology. Some of these factors are summarized in the next list.

Pathogenetic Factors for Atherosclerosis

- LDL cholesterol
  LDL receptor defects
  hyperapolipoprotein B
- dense LDL particles
- oxidized LDL particles
- HDL cholesterol
  hypo- and hyperlipoprotein A1
- Hyperinsulinemia and insulin resistance
- Hyperglycemia (β-glycosylation of extracellular matrix components)
- Homocysteine
  deficiency of cystathionine b-synthase or methionine synthetase
  methylene tetrahydrofolate reductase (deficiency or thermolabile variant)
  gene-environment interactions (deficiency of folate, B6, and B12)
- Vascular geometry (lesions develop at branch points due to variations in turbulence)

Determining which probands with clinical manifestations of atherosclerosis have a strong genetic contribution to their underlying disease is relatively straightforward and precise based on current capabilities (blood markers, pedigree analysis). The same holds for predicting risk in near relatives of probands. Some of the risk factors with strong genetic bases can be managed quite successfully by current approaches of diet and lifestyle modifications. Advanced understanding of vascular pathobiology will undoubtedly soon add to the list of patho-

genetic factors with a defined genetic cause, and improved methodology for genotyping will enable rapid and (perhaps) inexpensive identification of individuals with deleterious (and protective) markers. The real challenge will be to:

- perform outcome studies to determine the relative importance of specific genes and alleles;
- identify means to modulate the risks of specific alleles; and
- perform intervention trials to prove the clinical utility of both the tests and the interventions.

SUGGESTED READING

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HEREDITARY RISK FACTORS FOR ANEURYSMAL DISEASE

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Mutations in the gene for fibrillin-1 have been implicated as etiologic in aneurysms associated with Marfan syndrome, but the hereditary risk factors for more common aneurysmal conditions affecting the cerebral arteries and the aorta are uncertain. The present discussion will focus on the abdominal aortic aneurysm (AAA).

The stereotype of the AAA patient is an aging white male smoker with a positive family history for the disease. A recent ultrasound screening study of the siblings of AAA probands reaffirms this profile, with the three leading risk factors being male sex (12× increased risk), family history (4× increased risk), and age (2× increased risk).[1] Another large scale screening study of 73,451 American veterans had similar confirmatory data. The three leading "positive" risk factors for AAAs of 3.0 to 3.9 cm were smoking, family history, and age (with odds ratios of 2.72, 1.96, and 1.52, respectively); and the three leading "negative" risk factors were female sex, diabetes, and black race (with odds ratios of 0.62, 0.68, and 0.72, respectively).[2] It is possible that additional associations of AAA (for example, with inguinal hernia[3] and with elongation of the internal carotid artery)[4] might also reflect hereditary risk factors.

Several candidate genes have been considered and rejected by our group and others. Mutation in the gene for procollagen III cosegregated with AAA disease in one family,[5] but further studies revealed that mutation of this gene is an infrequent cause of AAA in a larger population.[6] We reported a polymorphism of the gene for TIMP-1 in two of six AAA patients, but the transition was in the third position of the codon. The encoded amino acid was unchanged. The role, if any, for deficiency alleles of alpha-1 antitrypsin is unclear.[7]

Considering that much recent evidence points to a role for autoimmunity in AAA degeneration, our group reported MHC Class II DR typing on a small group of North Americans (26) of mixed descent. Eighty-one percent of these individuals had a DR allele with phenylalanine residues at positions 31 and 47 of the second hypervariable region; 35% had a double dose of a putative susceptibility allele.[7] HLA DR-15 is one of the alleles[7] with the above characteristics, and HLA DR-15 has been implicated in a North American population of patients with inflammatory AAA.[8] In the more homogeneous population of Japan, DR-15 was detected in 59% of 46 AAA patients versus 28% of 50 control subjects.[9] Further study of this population suggested that HLA-DQ3 had a protective effect.

If DR-15 positive and DQ-3 negative are the high-risk serotypes, then 89% of 36 AAA patients had one or both of these features, as compared with 41% of 39 control subjects.[10]

Although genes among structural matrix proteins, proteinases, and proteinase inhibitors have been the leading candidates to date, the possible role of HLA DR and DQ genes merits more study.

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