Clinical Criteria Versus DNA Diagnosis in Heterozygous Familial Hypercholesterolemia

Is Molecular Diagnosis Superior to Clinical Diagnosis?

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More than half of all deaths in Western society are related to arteriosclerotic cardiovascular diseases. Approximately 5% of coronary artery disease (CAD) before the age of 55 years is attributable to familial hypercholesterolemia (FH), an autosomal-dominant disease. In contrast to population hypercholesterolemia, FH typically leads to a twice-normal LDL cholesterol level for age and sex and to heart attacks in early middle age. The frequency of FH is estimated to be 1 in 500, roughly half a million in the United States and >10 million persons worldwide. FH is also a very heterogeneous disease; worldwide, at least 300 mutations involving several genes divide the clinical disease into two major entities, namely, LDL receptor defects and apoB-100 defects (see Day and Humphries at the World Wide Web site http://www.ucl.ac.uk/fh for up-to-date information). However, the number of mutations within certain populations varies, due to genetic drift, founder effects, and consanguineous marriages. In the apoB gene, the arginine 3500 to glutamine mutation is also common and affects about one in 600 people. This mutation seems to be of central European origin and could not be identified in other Europeans, such as Finns and Russians.

Traditionally, the diagnosis of FH is based on clinical findings, an autosomal-dominant family history pattern of early CAD, and elevated LDL cholesterol levels. In some cases, cholesterol deposits (“xanthomata”) in the skin and tendons suggest the diagnosis. However, phenotypes overlap and family studies are complicated to perform. A genetic test for FH has utility in several applications. The FH test provides a simple yes/no answer in terms of FH diagnosis. Cholesterol concentrations, after all, are a continuous variable. The FH test is a definitive tool for family tracing. The FH test is useful in the differential diagnosis of high-risk patients. Finally, there may be some prognostic value for FH testing, in that “cholesterol-years” is a more accurate predictor of risk than is the early identification of carriers with milder mutations. However, indirect DNA diagnosis is complicated by locus heterogeneity and the high frequency of hypercholesterolemia.

In the November 1997 issue, Vuorio et al have made use of the unique geographic and historical situation of the Finnish population, comprising 180,000 individuals in North Karelia province, to perform a genetic epidemiological study to delineate the impact of FH as a determinant of CAD risk in a high-incidence area. The mean age of onset of symptomatic CAD was 42 years for men and 48 years for women. The corresponding ages at the time of first acute myocardial infarction were 47 and 59 years, respectively. The investigators also assessed the effectiveness of molecular genetic techniques in diagnosis. Their goal was the complete recruitment of patients in this population. Extensive genealogical studies by the investigators showed that one specific mutation, termed FH-North Karelia, which is characterized by a deletion of seven nucleotides from exon 6 in the LDL receptor gene, accounts for ~90% of all FH cases in this population. DNA samples were available in 95% of this group. Most important, the authors showed that FH is responsible for the relatively high incidence of CAD in Finland by demonstrating its presence in 9% of young patients with CAD in North Karelia. Interestingly, the variation in onset of CAD was mainly due to nonlipid factors, such as age, sex, and smoking habits. DNA analysis avoided the 2% false-negative and 7% false-positive diagnoses that occur with clinical criteria. These data provide the scientific background to develop case-finding programs and primary prevention strategies to decrease morbidity and mortality. They are particularly applicable in Finland, which has a well-organized public health services.

An increasingly important issue in health care systems is cost-effectiveness. In general, the efficacy of any test system is based on its sensitivity, specificity, and prognostic value. A second factor that is often ignored is pretest probability. In genetic disorders, pretest probability is generally low (1 in 500 for FH). Therefore, specificity is more important than sensitivity. Specificity is defined as the ability of a test to identify as “positive” only those individuals who actually have the disease. The test must avoid false-positive results to avoid treatment of unaffected individuals. In a situation with a high pretest probability, identification of healthy individuals as healthy is important to avoid missing the diagnosis and treatment of sick individuals. This attribute is called the sensitivity of a test. Most clinical tests are compromises between sensitivity and specificity. The main advantage of DNA diagnostics is its very high specificity compared with clinical criteria. Currently, determining the cost of DNA diagnostic tests is difficult. None of the high-throughput automated methods have been applied in those populations where FH is prevalent and all the mutations are known. As with any other diagnostic test, the costs will decrease considerably with full automation and application in reference laboratories and when large sample numbers are
examined. Currently, in a research environment the cost of a test is similar to the cost of a single month’s drug treatment. Since the test needs to be done only once in a lifetime, its cost-effectiveness seems assured. The new tools in DNA diagnostics will particularly benefit subsets of patients at high risk for premature atherosclerosis and coronary heart disease, namely, those with a positive family history.

We have recently established a new DNA assay, an oligonucleotide ligation assay, based on both the polymerase chain reaction and oligonucleotide ligation methods. We have successfully modified this assay to identify multiple mutations and to handle large numbers of samples simultaneously. The test uses mobility modifiers, which allow the method to be adapted to automated genotyping systems, thereby making it useful for analysis of large numbers of samples. The oligonucleotide ligation assay method could allow the identification of as many as 200 separate mutations in a reasonable amount of time. Because of its automation, reference laboratories will be in a position to provide this service for large numbers of patients at a reasonable price. Despite the fact that this technology needs expensive equipment, its high degree of automation is very cost-saving in terms of personnel and space.

Three recent studies have indicated that heart attacks can be reduced by one third and deaths related to heart attacks by ≈40% with drug treatment in high-risk individuals. The definition of high risk is important, because serum cholesterol levels included in this category overlap the normal range. Thus, current guidelines for managing hypercholesterolemia are likely to change. Whereas treatment regimens for secondary prevention are no longer under discussion, primary prevention is the important issue for the future. Since cholesterol lowering has been shown to be effective in almost all individuals, effectiveness is entirely dependent on risk. Consequently, cost-effectiveness of treatment considerations should be based on proper risk assessment. There is a need for primary prevention, since at least 30% of individuals with CAD never get any chance for intervention or secondary prevention because of their high, 30% sudden death rate. Currently, testing procedures for risk assessment rely on total cholesterol, LDL cholesterol, HDL cholesterol, and triglyceride determinations and other cardiovascular risk factors like hypertension, diabetes, and left ventricular hypertrophy. These tests and diagnoses are not able to provide any genetic information. We predict that genetic diagnostic screening will be of major importance in the future. In Finland the future is now.

References

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