Clinical Implications of the Molecular Basis of Familial Hypercholesterolemia and Other Inherited Dyslipidemias

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In this issue of Circulation, van der Graaf and colleagues studied 1430 children, aged 4 to 18 years, who were referred to an academic pediatric lipid clinic in the Netherlands because of dyslipidemia from July 1989 to January 2008. The objective was to determine what proportion of those with the phenotype of autosomal dominant hypercholesterolemia (ADH) had mutations in the genes encoding the low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB), and proprotein convertase subtilisin/kexin 9.

Exclusion criteria included children with secondary causes of hypercholesterolemia, a body mass index cut-off at the 75th percentile for age and sex, those referred through the national cascade screening program, and those from families with a known molecular diagnosis. Of the 269 children who remained after applying the exclusion criteria, 255 (95%) carried a functional mutation (LDLR 95%; APOB 5%). No mutations in proprotein convertase subtilisin/kexin 9 were detected. The authors concluded that in the vast majority of children with the ADH phenotype, a causative mutation can be identified, and that most of the large-effect genes underlying ADH are known. This result differed from several other reports that found widely different mutation detection rates.

Inclusion criteria for ADH included a low-density lipoprotein cholesterol (LDL-C) level >95th percentile for age and sex and an autosomal dominant inheritance pattern of hypercholesterolemia, defined as at least 1 biological parent on one side of the family with the phenotype of ADH, and carotid intima-media thickness. A meta-analysis of a number of randomized, placebo-controlled clinical trials, mostly in subjects with FH aged 10 to 17 years, found the statins to be safe and effective.

How might one resolve the conundrum of how to approach the detection of children with modestly higher LDL-C or obesity versus those with FH? The answer appears to reside in the use of universal screening. A simple measurement of total cholesterol (TC) will detect close to 90% of children with FH between 1 to 9 years of age (the optimal time for screening). The average TC and LDL-C levels in FH children before adolescence is about 300 mg/dL and 240 mg/dL, respectively. Those children with total and LDL-C levels of 240 mg/dL and 160 mg/dL, respectively, should be suspected of having an increased probability of heterozygous FH. Screening before adolescence (9 to 11 years of age) is preferred, because there is a 15% decrement of LDL-C during adolescence, which can produce false-negative results for those with FH or less marked elevations in LDL-C.

The authors used age- and sex-specific cut points to define an elevated LDL-C in children with ADH. However, a single cutpoint of 130 mg/dL during adolescence, derived from the National Cholesterol Education Program Expert Panel on Blood Cholesterol Levels in Children, was more predictive of an adult LDL-C level than was the use of multiple age- and sex-specific cutpoints from the National Health and Nutrition Examination Survey.

In a normal unselected population, 50/1000 children will have a LDL-C of >130 mg/dL, but only 2/1000 (prevalence of 1/500) will have FH. Thus, in order to detect most of those with elevated LDL-C, universal screening will...
be necessary. Initial universal screening might usefully include a measurement of TC and high-density lipoprotein cholesterol (HDL-C). Both of these measurements can be made on a nonfasting child, which most often is the case when a child presents to a pediatrician’s or general practitioner’s office. If one subtracts the apolipoprotein A-I containing HDL-C from the TC, this will provide an assessment of the cholesterol content of the APOB-containing lipoproteins, namely, very-low-density lipoproteins, intermediate density lipoproteins, LDL, and Lp(a) lipoprotein. The TC minus the HDL-C is often referred to by the rubric non-HDL cholesterol. This approach allows one to detect FH, because most of the non-HDL cholesterol will be in LDL. If the triglycerides (TG) are elevated due to increased very-low-density lipoproteins, the non-HDL cholesterol may be elevated (>144 mg/dL), despite the LDL-C being <130 mg/dL. These possibilities must be assessed by a follow-up fasting specimen and measurements of TC, TG, HDL-C, and LDL-C.

Children with elevated TG, low HDL, normal (<110 mg/dL), borderline (110 to 129 mg/dL), or moderately elevated LDL (>130 but <160 mg/dL) may be expressing the disorder familial combined hyperlipidemia (FCH), exacerbated by the presence of overweight or obesity, and often associated with insulin resistance. The authors of this article state “familial combined hyperlipidemia (FCH), another common lipid disorder, often does not exhibit its phenotype until early adulthood.” This might be true if the proband from the FCH family were ascertained through an adult with myocardial infarction. However, in a lipid clinic that includes children with dyslipidemia as probands, FCH was found by Cortner et al. to be 3 times more prevalent than FH. Additionally, even in normolipidemic adolescents, the apolipoprotein B level can be elevated despite normal LDL-C (hyperapobetalipoproteinemia). The simplest explanation for the paucity of FCH in the children with ADH studied here is that they were excluded by the criteria used by the authors. Thus, although it appears that most children with ADH have FH, it is still possible that a significant proportion of children with LDL-C >130 mg/dL may have FCH. Unfortunately, at this time no definitive single gene disorder has been described in families with FCH, and FCH may represent an ologogenic disorder. It appears that the greatest chance of discovering a monogenic defect in FCH resides in the determination of the exons in the human genome from sibships of affected children who manifest an elevated LDL-C, with or without elevated TG, or elevated TG with normal LDL-C but elevated apolipoprotein B, as a manifestation of an increased number of small, dense LDL particles.

Almost all of the children with ADH studied here had a defect in the LDLR with a minority expressing a defect in APOB, a mutation that is expressed as a defect in apolipoprotein B, the ligand on LDL for the LDLR. A previous estimate of the prevalence of familial defective APOB-100 in the European population is 1 in 1000; thus, given the prevalence of FH as 1 in 500, one might have expected a greater proportion of APOB defects in those with ADH. The dearth of APOB defects is most likely related to the lower LDL-C levels in defective apoB-100 patients than in those with FH, leading to a disproportionate exclusion of those with the APOB defect.

At the very least, this article reemphasizes the great importance of detecting children with FH. They are at the greatest risk of developing premature CVD, and therefore require earlier treatment and continued follow-up. In addition to the paramount role of pediatricians and family practitioners mentioned above, internists, cardiologists, and endocrinologists can contribute significantly by recommending that each of their patients with premature CVD have their children screened for a lipid disorder. The yield of dyslipidemic children from this approach will range from 33% to 50%.

There is a trend toward determining the molecular defect in a child suspected of having FH. This might provide some information on the effect of certain mutations on early atherosclerosis or on response to treatment. The search for a mutation in a given child is labor-intensive and expensive, because the LDLR gene must be sequenced. At this time, such an approach appears to be in the realm of research and is not ready to be incorporated into standard clinical practice. In the meantime, the phenotype of FH is usually apparent once the lipid and lipoprotein levels are known. Such an early diagnosis in childhood can lead to the institution of early and appropriate drug treatment. There is no randomized, controlled clinical trial of 50 years’ duration that demonstrates that treatment of a FH child with a statin will significantly decrease CVD in adulthood; nor is it likely that such a trial will ever occur. Nevertheless, the statins are one of the most studied drugs of all time, and their safety and efficacy, even in childhood, remains impressive. The next step will be to implement our current knowledge, starting with the systematic detection of the some 600 000 subjects in the United States who carry the gene for FH. The Dutch have been masters at this, and have demonstrated the wisdom and know-how to accomplish such a task.

Disclosures

None.

References


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