

Homozygous Familial Hypercholesterolemia: phenotype rules! Commentary on the study of Raal et al.

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Homozygous familial hypercholesterolemia (HoFH) was classically defined as a devastating metabolic disease affecting usually 1/ 1,000,000 and characterized by extremely elevated LDL-cholesterol (LDL-C) plasma levels(1, 2). This leads to early development of tendinous and cutaneous xanthomas, systemic atherosclerosis and aortic and supra-aortic valve heart disease. As a consequence, HoFH is associated with 100 times greater relative risk of atherosclerotic cardiovascular disease (ASCVD) onset in comparison with normolipidemic individuals(3).

HoFH was also described as a disease of young people since many; especially those with LDL receptor (LDLR) null mutations may not survive the first ASCVD event(4, 5). These events usually occur on the first two decades of life(1, 2) with data from a historical South African cohorts(4) showing that lipid lowering therapy consisting mostly of statins and ezetimibe associated or not with bile acid sequestrants or niacin postponed the age of first ASCVD event from approximately 13 to 28 years of age. By the age of 40, 90% of subjects had presented an ASCVD event.

Due to the devastating character of the disease HoFH patients are candidates to lipoprotein apheresis(6) or to use extremely costly and not so well tolerated

pharmacological therapies like lomitapide, a microsomal triglyceride transfer protein inhibitor or mipomersen an antisense oligonucleotide that reduces apolipoprotein B synthesis(2, 7, 8). Recently, evolocumab a monoclonal antibody that binds to proprotein convertase kexin type 9 (PCSK9) was approved to treat HoFH, however with limited efficacy(9). As an alternative, liver transplantation is a last resource that can be used to treat HoFH patients(2).

However, the advent of next generation gene sequencing (NGS)(10) and an interest in finding both Ho and heterozygous (He) FH patients to participate in clinical trials of more than welcome new treatments, has challenged some of our classical concepts about HoFH. First and foremost HoFH is more frequent than we thought, probably 1/160,000-300,000(11, 12), second the disease is much more heterogeneous than previously described with the severity of LDL-C levels depending on the type of causing mutations(2). Finally many patients with proven molecular HoFH have a phenotype compatible with heterozygous FH phenotype and worse vice-versa(13).

In this issue of Atherosclerosis, Frederick Raal and colleagues challenge our classic concepts about HoFH a bit more(14). They have analyzed a common dataset of 167 HoFH patients from different countries, mostly from South Africa and the Netherlands. In their study patient age varied from 1 year to amazingly 75 years of age. Could one imagine a HoFH surviving up to 75 years? Indeed this is awesome and rarely seen. Of course, HoFH is still a severe condition and this study can't totally discard the survival bias of less severe forms of HoFH since many patients could have died without diagnosis.

In the study of Raal et al. LDL-C levels ranged from 4.4 mmol/L to 27.2 mmol/L (170-1052 mg/dL) for untreated patients, and from 2.6 mmol/L to 20.3 mmol/L (101-785 mg/dL) for treated patients. If we consider the LDL-C criteria adopted by the European Atherosclerosis Society(2) to diagnose HoFH e.g. ≥ 13 mmol/L (≥ 500 mg/dL) and ≥ 8 mmol/L (≥ 300 mg/dL) respectively for untreated and treated patients, 27% and 31% of studied patients presented lower values. Certainly many also had untreated LDL-C < 10 mmol/L (400 mg/dL) a value recently suggested as a cutoff to diagnose HoFH by the American Heart Association(15). In this study apolipoprotein B mutations, that usually cause a milder phenotype, were excluded as a cause of HoFH and as expected the severity of LDL-C levels depended if the patient presented or not defective (LDLR activity 2-25%) or null LDL (LDLR activity $< 2\%$) receptor mutations.

Of importance there was a wide variability on the response to lipid lowering therapy meaning that many HoFH cases could be controlled by statins, ezetimibe, bile acid sequestrants before we have to appeal to the newer and more expensive treatments. This variability in response was not totally explained by LDLR mutations as previously seen(16) but might also be the subject of the effect of other genes and possibly environmental factors.

One in every three studied patients had presented a previous ASCVD event and the mean age for that to occur was 26 years old. This is compatible with the known natural history of HoFH(1) but on the other hand 2/3 of patients did not present a clinical event and shows that there is heterogeneity on ASVCD onset even in patients with HoFH. As expected those with the highest untreated LDL-C levels

had a greater chance of ASCVD onset. Certainly the presence of other risk factors, other genetic and environmental parameters might have influenced on this.

Recently there has been discussion whether the molecular diagnosis is essential to identify FH patients(17). No doubt genetic cascade screening as performed in the UK(18), Netherlands(19), Spain(20) and more recently in Brazil(21) among other countries is highly efficacious in finding unaffected FH individuals. However, unfortunately molecular testing is not universally available even considering the lower costs of next generation testing in comparison with older techniques. Also, one need to consider that what mainly causes ASCVD in FH is the severely elevated LDL-C and not the genetic defects(22). Therefore, the phenotype is more important in the clinician's point of view to identify and treat FH. This is clearly seen here in the study of Raal et al(14) where there was variability on the HoFH phenotype.

With the previously described phenotype overlap among some HoFH and HeFH patients (13, 23) one should ask how valid is in clinical practice to separate Ho from HeFH when severely elevated LDL-C levels (usually > 7.5 mmol/L) are present? Certainly, testing of family members is mandatory when one suspects of FH due to the autosomal dominant transmission independently if one suspects Ho or He FH. On the other hand, a group of severe FH patients encompassing both Ho and HeFH should be important to identify a very high risk for ASCVD population that should be treated aggressively and target for the newer and more expensive lipid lowering medications if they persist with prohibitive high LDL-C levels. In addition to very high LDL-C, severe or very high risk FH patients should also be

identified by the presence of other risk factors like smoking or hypertension, low HDL-cholesterol, high Lp(a) levels, a family history of early ASCVD(20, 22) and the presence of advanced subclinical atherosclerosis(22, 24).

Certainly, no one wants to remove the orphan disease designation that HoFH has(25), a fact that implicates in a faster way to approve newer medications most in need for HoFH patients. However, those with the more severe FH phenotype independently if they are homozygotes or not must have access to the newer and more expensive treatments.

To conclude HoFH is still a devastating disease with a huge burden of ASCVD and early mortality risk, however it is more frequent and heterogeneous than we once thought. Recognizing this heterogeneity and the overlap with HeFH is important for clinical management. Phenotype and not the genotype should be the physicians' main concern, and those with most severe phenotype have to be more aggressively treated. Unfortunately FH as a whole is still underdiagnosed and undertreated(26) and many opportunities to save lives are being lost.

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