COMMENTARY

What's so special about familial hypercholesterolaemia?

Last year the National Institute for Health and Clinical Excellence (NICE) issued clinical guidance on the diagnosis and management of familial hypercholesterolaemia.[1] The implications of this guidance for general practice are discussed by Qureshi *et al* in this issue of the *BJGP*.[2] But why do we need such guidance? We know already that we should treat high-cholesterol patients with a statin to reduce the risk of vascular disease, so what's so special about familial hypercholesterolaemia? Isn't familial hypercholesterolaemia simply the tail-end of the cholesterol distribution in a population? Epidemiologists have been telling us for years that focusing on the treatment of tail-ends is a poor preventive strategy because most events (in this case strokes and myocardial infarctions) occur to people in the middle of the population distribution simply because there are so many of them.[3] Wouldn't it be better for the NICE guidance to focus on shifting the whole population distribution of cholesterol rather than chopping off the tail?

The rationale for treating familial hypercholesterolaemia differently is the disproportionately high mortality risk, particularly in young adults, which is higher than would be predicted by the same cholesterol level in people without familial hypercholesterolaemia. Without treatment, over 50% of men and 30% of women with familial hypercholesterolaemia will have a heart attack before age 60 years.[4] This not because the atherogenic effect of high blood concentrations of low-density lipoprotein (LDL) cholesterol is any different in familial hypercholesterolaemia, but because people with familial hypercholesterolaemia are exposed to very high concentrations of LDL cholesterol from birth.[5] Most patients identified with high cholesterol in middle age, but without an LDL-receptor mutation which characterises familial hypercholesterolaemia, will have built up to their high levels over time through a combination of age, poor diet, obesity, and other risk factors. In contrast, by the time the heterozygous familial hypercholesterolaemia sufferer enters early adulthood they will have accumulated ≥20 years of continuous atherogenic exposure and are at a hundred-fold greater risk of a heart attack than other young people. Patients with homozygous familial hypercholesterolaemia (which occurs with a frequency of about 1 in a million rather than 1 in 500) are at such high risk that they may not live beyond childhood into early adulthood.

The NICE guidance is to refer all cases of suspected familial hypercholesterolaemia to a hospital specialist. GPs will wonder whether this is necessary. The suggested clinical criteria for diagnosis in sporadic adult cases are straightforward (total cholesterol >7.5mmol/l, tendon xanthomata, and family history), and so is the treatment (statin at high dose to reduce LDL-cholesterol by ≥50%). Why bother to refer patients who respond readily to treatment? The answer is twofold: the need for effective cascade screening of first-degree relatives of index cases, and the much reduced diagnostic value of the clinical criteria in these first-degree relatives[6] (reflecting the fact that their starting probability of familial hypercholesterolaemia is 50%).

Simply telling patients to advise their relatives to contact their own doctor doesn't seem to work well.[7] Direct contact from a specialist nurse (who can draw up a family tree with the help of the index case and then contact relatives directly to offer testing) is much more effective.[8,9] To make the diagnosis once the first-degree relatives have been traced, DNA testing is necessary to achieve diagnostic precision.[9]

You can't prevent death in young adulthood if you don't detect familial hypercholesterolaemia until routine cholesterol testing in middle age. So although everything that is done in the hospital lipid clinic for most index cases could be done in general practice, referral to hospital lipid clinics to initiate cascade screening is the strategy most likely to lead to identification and treatment of the estimated 85% of patients with familial hypercholesterolaemia who have not yet been identified, particularly the children who may suffer cardiac death in early adulthood if untreated. Referral may also have two other advantages: stressing the seriousness of the condition to patients and improving the treatment of those with more complex lipid abnormalities.

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Familial hypercholesterolaemia is one of the few conditions where a preventive intervention has a substantial impact on every individual receiving it, prolonging life on average by about 10 years.[10] A practice with a registered population of 10 000 may have 20 patients with heterozygous familial hypercholesterolaemia (similar to type 1 diabetes) but the problem will not have been managed as assiduously as diabetes: on average only three patients will have been detected and treated. We need to do better than this. We also have a duty to ensure that our local primary care trusts understand the number of life years that can be cost-effectively saved by cascade screening for familial hypercholesterolaemia[11] and therefore fund the screening and DNA-based diagnosis of the first-degree relatives of the index cases we identify.

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Provenance
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