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Jones J L, Lakasing E, Archontakis S. Managing familial hypercholesterolaemia.
Practitioner, 253 (1719):28–31

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Medical Publishing Ltd

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FIGURE 1
Corneal arcus, a cloudy arc around the outer fringes of the cornea, may be a sign of hyperlipidaemia

How should suspected FH be investigated?

FAMILIAL HYPERCHOLESTEROLAEMIA (FH) IS A RELATIVELY COMMON GENETIC disorder, the heterozygous form affecting 1 in 500 people in the UK, i.e. 0.2% of the population.[1] However, the vast majority of patients remain undiagnosed. It is caused by mutations in the hepatic proteins involved in the clearance of low density lipoprotein cholesterol (LDL-C) from the circulation.[1] By contrast, the homozygous form is very rare (around 1 per 1,000,000) and in practice almost all patients seen will have the heterozygous form. FH accounts for around 10% of all hyperlipidaemias.[2]

FH is a risk factor for the development of premature atherogenesis, and therefore coronary heart disease (CHD).[1]

GENETICS

Numerous mutations in at least three genes have been implicated in FH,[3] and a causative mutation is found in around three-quarters of patients with strong clinical suspicion of FH.[4] The finding of a mutation provides incontrovertible evidence for that patient and a means of identifying affected relatives;[5] however, such tests are not universally available, and screening relatives rests as much on LDL-C levels.

What are the treatment options?

PATHOPHYSIOLOGY

In FH there is a decreased concentration of LDL-C receptors on hepatocyte membranes. LDL-C clearance is thus reduced with the result that these highly atherogenic particles accumulate in the blood.[2] In the heterozygous form of the condition typical total cholesterol (TC) levels are 7-13 mmol/l (>13mmol/l in the homozygous form). High density lipoprotein cholesterol (HDL-C) levels are typically average or reduced, while triglyceride (TG) levels are usually within the normal range (< 1.7 mmol/l).

The end result is accelerated atherogenesis, with the deposition of widespread fatty plaques consisting of lipid streaks, fibrin particles and foam cells in the tunica intima of arteries – the atheromatous plaque.

The clinical corollary of this is development of CHD at an early age if untreated; this is typically in the fourth

What is the role of cascade testing?

decade in men who are heterozygous and a decade later in women. Men with FH have a >50% risk of CHD by the age of 50 and women ≥ 30% risk by the age of 60. By contrast, homozygotes have a rapid descent into CHD, manifest in early childhood and this is often fatal even when treated aggressively.

DIAGNOSIS

The diagnosis of FH rests on the Simon Broome criteria, listed in table 1, below.[6] Essentially, it requires elevation of LDL-C, plus clinical evidence of hypercholesterolaemia such as tendon xanthomata, and evidence of a family history. Patients with definite or possible FH need to undergo further testing which usually requires referral to a lipid clinic.

A complicating factor is that the Simon Broome criteria are quite rigid and may result in false negatives, so patients who actually have FH may not fulfill these particular criteria.[4] A useful approach is to use the criteria for guidance and to maintain clinical suspicion in borderline cases.
A TC > 7.5 mmol/l, or a personal or family history of premature CHD should arouse suspicion of FH.

Some practices have improved their detection of FH by trawling through their computer records to identify patients with TC >7.5 mmol/l and LDL-C >4.9 mmol/l and then assessing the patients' cardiovascular history as well as their family history.

FH is often suspected, and indeed diagnosed, in clinically well, asymptomatic subjects who may request a lipid screen on the basis of their family history, or who may be referred to their doctor following an unexpectedly abnormal profile from, for example, a screening medical. The usual systematic approach to clinical problems (history, examination, investigations and treatment) may not apply here, and the sequence: investigations, history, examination and treatment more accurately reflects the likely patient pathway.

Investigations

The initial finding of hypercholesterolaemia does not differentiate FH from other dyslipidaemias. Initial investigations are therefore required to narrow the diagnostic field. Of particular clinical importance are the dyslipidaemias secondary to other medical conditions, mainly endocrine and metabolic diseases as well as drugs, which taken collectively are quite common.[7] The list, in table 2, below is not exhaustive but covers most of the commonly encountered causes.

Many investigations, particularly haematological and biochemical, can be gainfully carried out in primary care; however, more complex tests such as DNA analysis require referral either directly to an FH genetic screening clinic or via a lipid clinic.

Therefore, in addition to the lipid profile (TC, HDL-C, LDL-C and triglycerides), baseline investigations should include:

- Urea, creatinine and electrolytes
- Estimated glomerular filtration rate
- Liver function tests
- Fasting blood glucose
- Thyroid function tests
- Full blood count
- Urinalysis for blood, protein and glucose.

The NICE guideline recommends that DNA testing should be offered to all patients with a clinical diagnosis of FH.[8] Children known to have one affected parent should be offered a DNA test by the age of ten if the family mutation is known; if it is not, then LDL-C concentration is used. If children have two affected parents (a statistical rarity) or clinical stigmata such as cutaneous lipid deposits, LDL-C should be measured around the age of five and FH considered if levels are >11 mmol/l. When excluding a diagnosis of FH a further LDL-C measurement should be taken after puberty as LDL-C levels change during puberty.

History

The key points in the history are to ascertain the family history of (usually premature) cardiovascular disease, and to check for the presence of additional risk factors such as smoking, hypertension, diabetes and, where relevant, the secondary causes

Table 1

The Simon Broome criteria for diagnosing FH

Adults: TC >7.5 mmol/l and LDL-C >4.9 mmol/l
Children under 16: TC > 6.7 mmol/l and LDL-C > 4.0 mmol/l
plus:

For definite FH
Tendon xanthomata in the patient or first- or second-degree relative
or
DNA-based evidence of FH (familial defective apo B-100, or a PCSK9 mutation)

For possible FH
Family history of MI
- below age 50 in a second-degree relative
- below age 60 in first-degree relative
or
- family history of raised cholesterol

Table 2

Causes of secondary dyslipidaemia

Endocrine/metabolic	Diabetes mellitus Hypothyroidism Cushing's disease Renal failure (acute and chronic) Liver failure (acute and chronic) Alcohol excess Obesity Anorexia Malabsorption (including ileal bypass surgery)
Altered states	Pregnancy
Other illness	Chronic infection (AIDS, tuberculosis) Lymphomas, multiple myeloma
Drugs	Beta blockers Corticosteroids Oestrogens Progestogens Thiazide diuretics Isotretinoin Ciclosporin

key points

SELECTED BY

Dr Peter Saul
GP, Wrexham and associate GP Dean for North Wales

Familial hypercholesterolaemia (FH) is a relatively common genetic disorder, the heterozygous form affecting 1 in 500 people in the UK. It is caused by mutations in the hepatic proteins involved in the clearance of LDL-C from the circulation. The homozygous form is very rare and in practice almost all patients seen will have the heterozygous form.

FH accounts for around 10% of all hyperlipidaemias. It is a risk factor for the development of premature atherogenesis, and therefore coronary heart disease.

In the heterozygous form of the condition typical TC levels are 7-13 mmol/l (>13mmol/l in the homozygous form). HDL-C levels are typically average or reduced, while triglyceride levels are usually within the normal range (< 1.7 mmol/l). The clinical corollary of this is the development of CHD at an early age if untreated; this is typically in the fourth decade in men who are heterozygous and a decade later in women.

The diagnosis of FH rests on the Simon Broome criteria, essentially, it requires elevation of LDL-C, plus clinical evidence of hypercholesterolaemia such as tendon xanthomata, and evidence of a family history. Patients with definite or possible FH need to undergo further testing which usually requires referral to a lipid clinic.

The initial finding of hypercholesterolaemia does not differentiate FH from other dyslipidaemias. Further investigations are therefore required to narrow the diagnostic field. In addition to the lipid profile (TC, HDL-C, LDL-C and triglycerides), baseline investigations should include: urea, creatinine and electrolytes, estimated glomerular filtration rate, liver function tests, fasting blood glucose, thyroid function tests, full blood count, urinalysis for blood, protein and glucose.

The key points in the history are to ascertain the family history of (usually premature) cardiovascular disease, and to check for the presence of additional risk factors. It is quite possible that some patients with FH will have symptomatic cardiovascular disease at first presentation, so enquiries should be made about suggestive symptoms such as angina and intermittent claudication.

All first-degree relatives, not just the children, of FH patients have a 50% risk of having the condition; and should be traced and tested.

NICE recommends high-intensity statin therapy as the first line of treatment. Statins are of proven efficacy in FH and have a good safety record, although myopathy or even more rarely, rhabdomyolysis may occur. The recommended target is a reduction in initial LDL-C by 50%. Most children with FH will require drug treatment by their midteens, if not earlier.

of hyperlipidaemia. A drug history must be taken. A dietary history is important: the healthy diet for patients with FH is no different from that recommended for anyone (high-fibre, low-fat, medium-carbohydrate content) but adherence to it assumes greater importance. Alcohol intake in weekly units should be recorded, as excess alcohol exacerbates an unfavourable lipid profile.

It is quite possible that some patients with FH will have symptomatic cardiovascular disease at first presentation, so enquiries should be made about suggestive symptoms such as angina and intermittent claudication. If present, appropriate management should be instigated.

Some patients present with non-classical silent angina. If the GP has a high index of suspicion that the patient has FH, the patient should be referred for a diagnostic ECG.

Examination

The core physical examination should include height and weight to calculate BMI, waist circumference, and cardiovascular examination, including blood pressure and palpation of peripheral pulses. It is particularly important to look for signs of primary hyperlipidaemia, namely tendon xanthoma (most often seen around the Achilles tendon), xanthelasma (fatty deposits usually seen around the eyelids) and corneal arcus (literally, a cloudy arc around the outer fringes of the cornea).

These signs of primary hyperlipidaemia are rarely seen in children unless they are homozygous. If these signs are going to manifest they will normally do so by the time the patient is in their 30s or 40s.

TREATMENT

Treatment of FH can be subdivided into four main components: lifestyle; drug treatment which is the mainstay of management; apheresis, an additional, invasive method of reducing LDL-C; and cascade testing for potential affected relatives.

Lifestyle

Smoking should be strongly discouraged as it accelerates atherogenesis. Smokers should be offered smoking cessation advice and, where relevant, specific pharmacotherapy with nicotine replacement therapy (NRT) or bupropion, allied to counselling.

Diet should include a fat intake comprising no more than 30% of all calories, five portions of fruit or vegetables daily, and at least two portions of oily fish a week. Omega-3 fatty acids need not be used routinely but have a role if this fish intake is not feasible.[9] Alcohol should be limited to the recommended weekly units, i.e. 21 for men and 14 for women. Physical activity should be increased to 30 minutes of at least moderate-intensity activity five times a week. In practice, any improvement from a sedentary lifestyle should be encouraged, as should weight loss in overweight and obese subjects.

Drug treatment

NICE recommends high-intensity statin therapy as the first line of treatment. Statins are of proven efficacy in FH[10,11] and have a good safety record, although myopathy or even more rarely, rhabdomyolysis may occur.[11] The recommended target is a reduction in initial LDL-C by 50%; however, lesser reductions have also been shown to reduce the risk of developing CHD.[11]

Ezetimibe, an inhibitor of intestinal cholesterol absorption, is an option for heterozygous FH patients who are intolerant of statins, and may be administered with statins if satisfactory control is not attained with monotherapy.[11] If patients are intolerant of both statins and ezetimibe, bile acid sequestrants such as cholestyramine may be considered. Other alternatives include fibrates although gemfibrozil cannot be used with statins. Finally, nicotinic acid, which inhibits cholesterol synthesis, may be used although flushing and pruritis are frequent side-effects.

Most children with FH will require drug treatment by their midteens, if not earlier.[11] Pregnancy is not associated with a worsening of outcome for the mother or fetus; however, statins are associated with a small increased risk of congenital malformations and, ideally, ought to be stopped three months before conception.[13] Management of the pregnancy should be in a joint antenatal clinic, ideally with input from a cardiologist with an interest in lipid disorders.

Apheresis

Apheresis is a type of dialysis used to reduce LDL-C concentrations. It is invariably necessary for homozygous FH patients, in whom drug treatment

alone is unlikely to be enough, and in other patients in whom there is rapidly progressive, usually symptomatic disease despite maximal drug therapy.[8] Access is usually via an arterio-venous fistula.

Cascade testing

All first-degree relatives, not just the children, of FH patients have a 50% risk of having the condition; and should be traced and tested, a process known as cascade testing. Until such services become widely available, the BHF has recommended that, relatives of a patient with FH should be advised to visit their GP to be evaluated and, preferably, referred for a DNA test.[14]

If an individual has an identified FH gene mutation, then this can be used to identify other affected relatives. If they do not, then gender and age-specific criteria for LDL-C, such as that devised by Starr and colleagues,[15] may be used to diagnose relatives. Priority should be given to first- and second-degree relatives, though ideally third-degree relatives should also be screened. This way a nationwide follow-up system can be compiled.

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Useful information

Royal Brompton and Harefield NHS Foundation Trust
GPs can refer patients with suspected FH directly to FH cascade nurse specialist Jane Jones j.jones2@rbht.nhs.uk or to lipidologist Dr Mahmoud Barbir m.barbir@rbht.nhs.uk FH clinics are held at both the Royal Brompton Hospital, London and the Harefield Hospital, Middlesex.

HEARTUK
Has a nationwide list of lipid clinics: **www.heartuk.org.uk**

NICE
Clinical Guideline 71: Identification and management of familial hypercholesterolaemia, can be downloaded from: **www.nice.org.uk**

British Heart Foundation
Provides information on FH for healthcare professionals and patients: **www.bhf.org.uk**