Familial hypercholesterolaemia

Key facts

- Familial hypercholesterolaemia (FH) is an autosomal dominant disorder characterised by high levels of serum LDL-cholesterol.
- Untreated FH can result in premature coronary artery disease.
- Clinical management, involving lipid lowering therapy, is usually provided through specialist lipid clinics, as specified by NICE guidelines.
- Statins are the first line therapy, aiming to achieve an LDL-C ≤2.5 mmol/l in primary prevention and ≤1.8 mmol/l in secondary prevention.
- FH affects 1 in 250 individuals in the UK.
- More than 260,000 people in the UK are estimated to have FH, but less than 10% of these people have been diagnosed. Of the 56,000 children estimated to have the condition, only 600 have been diagnosed.

Clinical features

- Serum cholesterol concentrations are elevated from birth, and are usually at least double the normal values.
- Premature coronary artery disease is a key feature, with a greater than 50% risk in men by age 50, and at least a 30% risk in women by age 60.
- Tendon xanthomata (virtually diagnostic); premature corneal arcus and xanthelasmas may also be present.

Diagnosis

- Distinguishing FH from common forms of hyperlipidaemia can be complex. Two main diagnostic criteria have been developed and are widely used to identify patients who may have FH. These are expressed in the following tables:

Table 1: Simon Broome diagnostic criteria for index individuals

Definite FH		
- Cholesterol concentrations as defined below, and tendon xanthomas (or evidence of xanthomas in first- or second-degree relative); or - DNA-based evidence of an LDL-receptor variant, familial defective apo B-100, or a *PCSK9* variant.		
Possible FH		
- Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative; and/or - Family history of raised total cholesterol: greater than 7.5 mmol/l in adult first- or second-degree relative, or greater than 6.7 mmol/l in child, brother or sister aged younger than 16 years.		
Cholesterol levels to be used as diagnostic criteria		
	Total cholesterol	**LDL-C**
Child/young person	>6.7 mmol/l	>4.0 mmol/l
Adult	>7.5 mmol/l	>4.9 mmol/l

Table 2: Dutch Lipid Clinic Network score for index individuals

Family history	Score	Patient score
1st degree relative with premature coronary disease/vascular disease (male <55 years old, female <60 years old) or 1st degree relative with known LDL-cholesterol above 95th percentile	1	
1st degree relative with tendinous xanthomata or arcus cornealis or children aged below 18 with LDL-cholesterol above 95th percentile	2	
Clinical history	**Score**	**Patient score**
History of premature coronary artery disease (men <55 years old, women <60 years old)	2	
History of premature cerebral/peripheral vascular disease	1	
Physical examination	**Score**	**Patient score**
Tendinous xanthoma	6	
Arcus cornealis (<45 years old)	4	
Investigation LDL-cholesterol (mmol/L)	**Score**	**Patient score**
>8.5	8	
6.5 – 8.4	5	
5.0 – 6.4	3	
4.0 – 4.9	1	
Definite FH >8, Probable FH 6-8, Possible FH 3-5, Unlikely FH <3		

Genetic basis and genetic testing

- FH is an autosomal dominant condition.
- As FH is common, sometimes both parents can have the condition. In this case, each child has:
  - a 50% (one-in-two) chance of inheriting a gene variant from only one parent, resulting in FH;
  - a 25% (one-in-four) chance of inheriting a gene variant from both parents, resulting in homozygous FH, a more severe condition with the risk of coronary heart disease in childhood; or
  - a 25% (one-in-four) chance of not having FH, as they have not inherited a gene variant from either parent.
- FH results from a gene variant in one of four genes: *LDLR, APOB, PCSK9* (all autosomal dominant genes) and *LDLRAP1* (the only gene known to cause autosomal recessive FH).
- Variants in the *LDLR* gene account for 80-95% of cases, with over 200 different genetic variants documented in the UK.
- Variants in the *APOB* gene and *PCSK9* gene occur in 5% and 2% of UK patients respectively.
- Genetic testing can be used to:
  - confirm the diagnosis in someone with possible FH (diagnostic testing); and
  - provide information about the genetic status of relatives of someone diagnosed with FH (cascade testing).

Clinical management

- NICE guidelines, updated in 2017, recommend the use of either the Simon Broome criteria (Table 1) or the Dutch Lipid Clinic Network (DLCN) (Table 2) for the identification of patients with FH.
- Secondary causes of hypercholesterolaemia (for example, diabetes, hypothyroidism, hepatic or renal disease) should be excluded before considering a diagnosis of FH.
- Family history of coronary artery disease at an earlier age than expected should be evaluated with a lipid profile.
- For an individual with definite or possible FH on the Simon Broome criteria, or with a DLCN score of 5 or greater, NICE guidelines recommend referral to a specialist lipid clinic for ongoing management.
- Patients should be started on lipid-lowering therapy at diagnosis, and given advice about lifestyle, smoking and other cardiovascular risk factors. Statins are the first-line therapy, aiming to achieve an LDL-C ≤2.5 mmol/l in primary prevention and ≤1.8 mmol/l in secondary prevention.
- Women of childbearing age should use contraception if on statins, and discuss lipid-modifying therapy with their clinician if they are planning pregnancy, as statin treatment should be stopped three months before trying to conceive.
- High risk children - those aged 10 or younger, and with one affected parent - should be offered a DNA test as soon as possible through a paediatric lipids service or a clinical genetics department.
- Cascade testing should be offered to identify affected first- and second- degree biological relatives of people with a genetic diagnosis of FH, to provide the option of early lipid control and decrease the risk of severe young onset cardiovascular disease.

Direction to further reading, guidelines and patient groups

- Marks D, Thorogood M, Neil HA, Humphries SE. A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis 2003; 168(1):1-14.
- NICE guidelines CG71: Familial hypercholesterolaemia: identification and management. Nov 2017.
- British Heart Foundation
- Heart UK

This information is intended for educational use and was current in September 2019. For clinical management, it is recommended that local guidelines and protocols are used.

Produced in collaboration with Birmingham Women's NHS Foundation Trust's Clinical Genetics department and Imperial College Healthcare NHS Trust.