1. Clinical Characteristics

1.1 Definition and prevalence

Familial hypercholesterolaemia (FH) is a dominantly inherited condition that is due to a genetic defect in one of several genes that affect receptor-mediated uptake of low density lipoprotein (LDL) (see “Molecular Genetics” below). Affected individuals suffer metabolic and clinical features (Table 1) that include impaired uptake of plasma LDL cholesterol, resulting in high cholesterol levels and increased risk of premature cardiovascular disease.

Offspring of FH patients will inherit either the normal gene or the defective gene, so the prevalence within that branch of the family will be approximately 50%. This leads to quite a high prevalence in the general population. Estimates range between 1:200 and 1:500, but some groups exhibit a “founder gene effect” that enriches the prevalence of the disorder. It is more common in Mediterranean countries, Christian Lebanese, French Canadians and Afrikaaner South Africans. In these populations the prevalence may exceed 1:100. Homozygous cases are more common in consanguineous families, and, as with compound heterozygous cases, the increased severity of hypercholesterolaemia in these cases exacerbates premature mortality. The prevalence of homozygous FH is around 1:1 million in the general population.

1.2 Clinical presentation

Index cases of FH present with one or more of the following features:

1. Severe Hypercholesterolaemia that is not explained by secondary causes;
2. A strong personal or family history of premature atherosclerotic disease;
3. Tendon Xanthomas.

Relative hypercholesterolaemia is present from birth, but levels rise with age, so diagnosis should be based on LDL-C levels and comparison to age and gender-adjusted reference intervals. Females are protected from atherosclerotic disease prior to menopause, so the natural history of premature vascular disease is delayed by about one decade in women. Additional metabolic and clinical features of FH are listed below.
Table 1: Additional metabolic and clinical features of FH

<table>
<thead>
<tr>
<th>Metabolic Features</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LDL</td>
<td>Premature CHD</td>
</tr>
<tr>
<td>Increased remnants including LDL’s precursor, IDL</td>
<td>Premature CVD</td>
</tr>
<tr>
<td>Increased Lp(a)?</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>Reduced HDL?</td>
<td>Tendon xanthomas (11%)</td>
</tr>
<tr>
<td></td>
<td>Corneal arcus (27%)</td>
</tr>
<tr>
<td></td>
<td>Xanthelasmas (12%)</td>
</tr>
</tbody>
</table>

Clearly there are many other potential causes of premature cardiovascular disease and aortic stenosis. Likewise, corneal arcus and xanthelasma are non-specific signs, however arcus in a young adult is suggestive of FH. Tendon xanthomas, which may gradually develop in Achilles tendons and extensor tendons on the dorsum of the hand, are nearly pathognomonic for FH, but they may be confounded by tendon injury, and they are rarely identifiable before adulthood.

1.3 Clinical diagnosis

Diagnosis of an index case depends on recognition of the relevant clinical features. Although the serum cholesterol level shows a moderate degree of overlap of between patients with and without FH, the presence of an elevated level in a member of an affected family is highly predictive. This is particularly the case in younger relatives. Other affected individuals can usually be identified on the basis of LDL-C levels, but studies suggest that a misdiagnosis rate of approximately 15% may apply. Several sets of diagnostic criteria have been developed, including:

a) Dutch criteria:

<table>
<thead>
<tr>
<th>Points</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>DNA Mutation, or LDL-C &gt; 8.5</td>
</tr>
<tr>
<td>6</td>
<td>Tendon xanthomas</td>
</tr>
<tr>
<td>5</td>
<td>LDL-C 6.5 – 8.4</td>
</tr>
<tr>
<td>4</td>
<td>Arcus senilis &lt; 45 yrs</td>
</tr>
<tr>
<td>3</td>
<td>LDL 5.0 – 6.4</td>
</tr>
<tr>
<td>2</td>
<td>Xanthomas or premature arcus in 1st degree relative, childhood LDL &gt; 95th percentile, or premature CHD</td>
</tr>
<tr>
<td>1</td>
<td>1st deg relative with premature CVD or LDL &gt; 95th percentile, personal history of LDL 4.0 – 4.9 or premature CVD</td>
</tr>
</tbody>
</table>

Definite: > 8 points          Probable: 6 – 8 points          Possible FH: 3-5

or
b) Modified UK criteria

1. DNA Mutation
2. Tendon xanthomas in patient or 1st/2nd degree relative
3. Family history MI <50 in 2nd degree or <60 in 1st degree relative
4. Family history of cholesterol >7.5 in 1st or 2nd deg relative
5. Cholesterol >7.5 (adult) or >6.7 (age <16)
6. LDL-C >4.9 (adult) or >4.0 (age <16)

Definite: (5 or 6) + 1  Probable: (5 or 6) + 2  Possible FH: (5 or 6) + (3 or 4)

2. Molecular Genetics

Although the clinical picture of FH will be clear-cut in many instances, the diagnostic criteria suggest that genetic testing can provide certainty of diagnosis in some cases where confounding factors such as borderline cholesterol levels, inconclusive family histories or tendon injuries have resulted in a diagnostic dilemma. Patients in whom predictive genetic tests are required should be offered genetic counseling prior to consenting to sample collection for genetic analysis. Life insurance companies cannot insist that patients have a genetic test, but they can ask for information about the patient’s medical and family history as well as the results of any tests, including lipid levels and genetic investigations, that have been performed.

2.1 FH disease genes

FH may be caused by mutation in any of several genes affecting receptor-mediated uptake of LDL, including the genes for the LDL receptor, the LDL receptor ligand (apolipoprotein B100), and a protease known as PCSK-9. A recessive form of FH due to a defect in the ARH gene for a chaperone protein, and the recessive disorder sitosterolaemia are sometimes grouped with FH. More importantly, FH has been described in association with over 1000 mutations of the LDL receptor gene. As a result, attempted genetic diagnosis in an index case may require extensive mutation detection studies.

2.2 Genetic screening

The process of trying to detect a genetic abnormality de novo is expensive and time-consuming, and failure to find a mutation is inconclusive. Nevertheless, new techniques are improving the yield. Once a mutation has been identified within a family, the process of confirming the presence or absence of that specific mutation in individual family members is much more straightforward. See further information below if you would like more details about genetic testing for FH.

3. Management

3.1 Affected individuals

FH Australasia (a subcommittee of the Australian Atherosclerosis Society) has developed management guidelines which will become available in 2009. In view of the high risk of premature cardiovascular disease, regular review of clinical symptoms and signs of CVD should be undertaken. Exercise stress testing of adults is recommended, and other forms of non-invasive testing to assist the early identification of clinically relevant atherosclerosis may become accepted practice. Diet, exercise and avoidance of smoking are mandatory, and all cardiovascular risk factors should be evaluated and treated. Consideration should be given to general measures to protect against vascular events including the use of aspirin.
Cholesterol-lowering treatment such as the statin class of drugs provides excellent control of inherited high cholesterol levels. The statins work by reducing the manufacture of cholesterol by cells. This stimulates LDL receptor gene expression. As a result, the receptors produced by the normal gene will reduce LDL cholesterol levels. The effect of statins can be enhanced by bile acid sequestrants or cholesterol absorption inhibitors such as plant sterols or ezetimibe. Many patients with FH can achieve target cholesterol levels. Statin treatment of FH males is one of the most cost-effective medical interventions available and several lines of evidence point towards major improvements in CVD event rates and total mortality of FH patients. The management of young FH patients is still evolving. Conservative measures that concentrate on diet and avoidance of smoking are safe and effective, but statin therapy should be contemplated for children from the most severely affected families. New medications such as squalene synthase inhibitors, microsomal transfer protein inhibitors and antisense oligonucleotides against apo B and PCSK 9 are under investigation in FH patients.

3.2 Asymptomatic family members

In view of the benefit of routine cholesterol-lowering therapy, the main management challenge in FH is case identification. The high rate of morbidity and mortality associated with the onset of CHD makes it inappropriate to wait until the onset of clinical symptoms. Family follow-up has been demonstrated to be an extremely cost-effective form of case detection but, unfortunately, it is often overlooked for a variety of reasons. The resources required to identify and inform family members are often beyond the scope of the primary care physician. A collaborative organization known as MEDPED (Make Early Diagnosis, Prevent Early Death), which has been established to assist with this task, may be accessed at www.athero.org.au/FH/Site/GenInfo/about.htm.

4. Further Information

For more information about any aspect of this document please contact A/Prof David Sullivan (David.Sullivan@sswahs.nsw.gov.au), Department of Biochemistry, Royal Prince Alfred Hospital Sydney, Prof Gerald Watts, Dept Medicine, Royal Perth Hospital, or Prof Ian Hamilton-Craig (ianhc@bigpond.net.au) National Chairman of MED PED Asia Pacific.

Useful contact information:
National Heart Foundation of Australia
- Health Information Service – email: health@heartfoundation.org.au, or call 1300 36 27 87 (local call cost, business hours)
- Consumer Information Sheet on familial hypercholesterolaemia http://www.heartfoundation.org.au/SiteCollectionDocuments/A_CHD_FamHypercholeste rolaemia_ISC_FINAL.pdf
Australian Atherosclerosis Society FH Subcommittee:
MEDPED (Make Early Diagnosis, Prevent Early Death) Asia Pacific:
MEDPED International:
- http://www.mped.org
NSW genetics education programme:
Australian genetics services website: