Clinical Guideline

POLYGENIC HYPERCHOLESTEROLAEMIA; INVESTIGATION AND MANAGEMENT OF PATIENTS AND THEIR RELATIVES. DEPARTMENTAL GUIDANCE

SETTING BRI Lipid Service

FOR STAFF Doctors and Familial Hypercholesterolaemia nurses

PATIENTS Adults

GUIDANCE

Definition

Polygenic hypercholesterolaemia in the context of this guidance refers to patients who have been assessed in lipid clinic as clinically having possible or probable Familial Hypercholesterolaemia (FH) and who have therefore undergone FH genetic testing, but with a negative result for FH (monogenic hypercholesterolaemia). These patients' genetic reports will include their polygenic hypercholesterolaemia single nucleotide polymorphism (SNP) score. A SNP score of ≥6 confers a high likelihood of polygenic hypercholesterolaemia, a score of 4-5 an intermediate likelihood of polygenic hypercholesterolaemia and a score of 1-3 a low risk.

This guidance does not apply to patients with clinically suspected polygenic hypercholesterolaemia who have not undergone FH genetic testing.

Clinical presentation

This group of polygenic hypercholesterolaemia patients will have presented phenotypically similarly to monogenic hypercholesterolaemia (familial hypercholesterolaemia) patients, having a high LDL-cholesterol (>4.9mmol/L) and a family history of premature cardiovascular disease.

Published research reveals that around 60% of patients with clinically suspected FH are mutation negative and an estimated 80% of these will have a high SNP score, and therefore be classified as having polygenic hypercholesterolaemia (1,2).

Cardiovascular disease risk

- *Patients diagnosed in the BRI lipid clinic with polygenic hypercholesterolaemia have a higher risk of developing cardiovascular disease than the general population, but a lower risk than patients with FH. The higher cardiovascular risk is due to them having a chronic substantially raised LDL-cholesterol rather than specifically to their SNP score.*

The risk of developing coronary heart disease correlates with the level and duration of exposure to LDL-cholesterol. (3, 4). Coronary atherosclerosis develops early in life, slowly advancing until clinical manifestations are present. Genetically confirmed polygenic hypercholesterolaemia is inherited at conception, it results in a lifelong exposure to high LDL-cholesterol concentrations and therefore a high risk of developing atherosclerosis (1, 4). These patients' cardiovascular risk

is not directly related to their SNP score, however the SNP score correlates with LDL-cholesterol levels, in that for every incremental increase in the SNP score, there is an average increase in LDL-cholesterol of 0.33mmol/L (95% CI 0.3-0.37) and therefore the chance of having an LDL-cholesterol of >4.9mmol/L also incrementally increases (1).

Population based analysis has shown that, compared to individuals with no genetic mutation and an LDL-cholesterol of <3.7mmol/L, patients with FH and an LDL-cholesterol of >4.9mmol/L have a 22-fold higher risk of coronary heart disease (CHD). Those with no FH mutation and LDL-cholesterol >4.9mmol/L have a 6 fold higher risk of CHD (5). Correspondingly, investigation with carotid ultrasound and coronary artery calcium scores demonstrated that patients with polygenic hypercholesterolaemia (confirmed high SNP scores) develop less severe preclinical carotid and cardiac atherosclerosis than those with familial hypercholesterolaemia (6).

It is important to be aware when managing this group of patients, that a very small proportion with clinically suspected FH who are mutation negative may have an as yet unidentified mutation consistent with FH. Such patients would be at very high risk of cardiovascular disease, comparable to patients with known Familial Hypercholesterolaemia (2).

Primary prevention management in Polygenic Hypercholesterolaemia patients

1 Perform a QRISK score, but with the understanding that QRISK might underestimate cardiovascular risk in this cohort of patients. If the score is ≥10%, pharmacological treatment is indicated. If the score is <10%, consider whether treatment is nevertheless appropriate, based on a review of other cardiovascular risk factors and in discussion with the patient on their preferences.

2 If statins are indicated but cannot be taken, alternative lipid lowering medication should be considered (such as ezetimibe).

3 Treat patients to NICE primary prevention targets, aiming for a reduction of ≥40% in non-HDL-cholesterol from baseline.

4 Diabetes mellitus and thyroid disease should be excluded in all patients, and investigation should include measurement of lipoprotein (a).

5 All patients should be advised on lifestyle measures to reduce their LDL-cholesterol, such as increasing exercise levels, weight loss and improvements in diet. Lifestyle advice is particularly crucial in patients where the SNP score is <6 and therefore by implication the SNP score does not correlate with their LDL-cholesterol concentration, as this may suggest that additional contributing factors for their high LDL-cholesterol.

6 In all patients, other cardiovascular risk factors should also be reviewed, including blood pressure, renal function, smoking cessation and alcohol history. Glycaemic control in patients who have diabetes should be optimised.

Investigation of relatives of a patient with an SNP score of ≥6 and advice to General Practitioners.

First degree relatives ≥18 years-old
of a patient with an SNP score of ≥6

-Perform a random (non-fasting) full lipid profile.

[Genetic cascade screening of relatives is not cost effective (1, 2)].

If non-HDL cholesterol ≥4.5 mmol/L

-Exclude secondary causes of dyslipidaemia such as diabetes mellitus or thyroid disease.

-Once thyroid disease has been excluded a statin should be offered, unless contraindicated or not tolerated. If statin indicated but cannot be taken, consider ezetimibe.

-Review other cardiovascular risk factors: blood pressure, smoking, alcohol, glycaemic control and weight management.

If non-HDL cholesterol <4.5 mmol/L

-No further action is required at present.

-Repeat lipid profile every 5 years.

REFERENCES;

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