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ENDGAMES

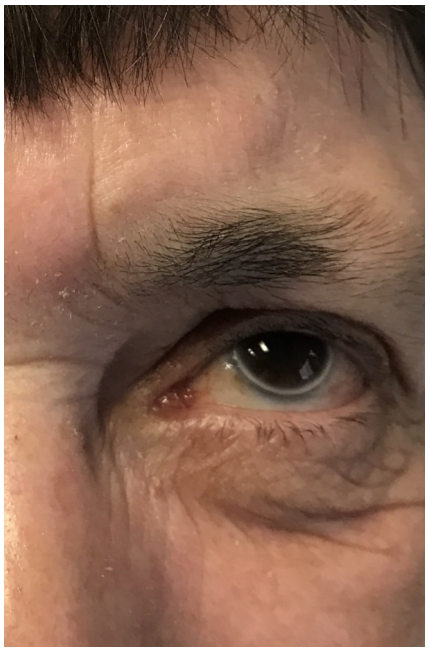
SPOT DIAGNOSIS

A keen eye for risk

Thomas J Ford *British Heart Foundation clinical research fellow*[1 2], Paul Rocchiccioli *consultant interventional cardiologist and*[1] *clinical lecturer*[1]

[1]British Heart Foundation Glasgow Cardiovascular Research Centre, Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [2]West of Scotland Regional Heart and Lung Centre, Golden Jubilee National Hospital, Clydebank, UK; Correspondence to Dr Tom Ford, tom.ford@glasgow.ac.uk

A 56 year old woman was referred to the rapid access chest pain clinic with stable angina pectoris. Her only cardiovascular risk factor was a family history of atherosclerosis, with her mother suffering from myocardial infarction at 50. Her body mass index was 20 kg/m^2 and the main abnormality on examination was the eye sign shown in . Fasting serum cholesterol and low density lipoprotein were both markedly raised at 12.2 mmol/L and 9.3 mmol/L, respectively. Triglyceride levels were relatively normal at 1.9 mmol/L. Given the history, examination, and lipid abnormality, what further blood test would confirm the underlying diagnosis?



Eye signs in cardiovascular disease: when the patient looks upward, a symmetrical abnormality is visible in both eyes

Answer

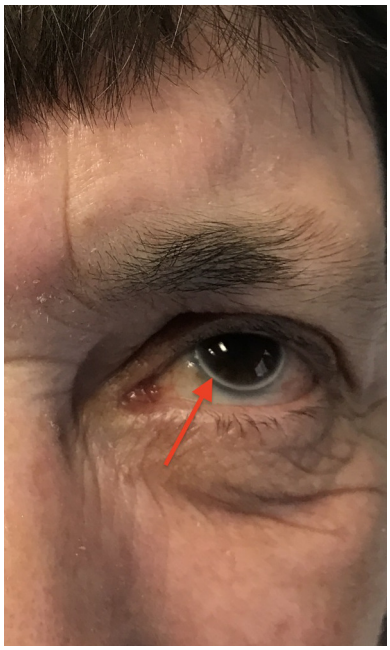
Genetic blood testing for low density lipoprotein receptor mutation to confirm the diagnosis of heterozygous familial hypercholesterolaemia.

Discussion

This presentation of premature coronary artery disease in a relatively young woman with striking corneal arcus and fasting serum cholesterol of 12.2 mmol/L is strongly suggestive of underlying heterozygous familial hypercholesterolemia. Genetic blood testing for low density lipoprotein receptor mutation would confirm the diagnosis, although the National Institute for Health and Care Excellence (NICE) recommends that this step should be performed by a specialist after genetic counselling and initiation of cascade testing.[1] Corneal arcus in this setting reflects widespread tissue lipid deposition and is correlated with both calcific atherosclerosis and xanthomatosis in patients with familial hypercholesterolemia.[2] The condition is underdiagnosed, and while physical signs including corneal arcus and tendon xanthomas are important clues, they lack sensitivity and specificity and are thus not required for diagnosis.[3] Familial screening can be helpful for early diagnosis and treatment, thus reducing the risk of premature cardiovascular events.

Initial management of heterozygous familial hypercholesterolaemia includes stabilisation with a statin. If low density lipoprotein is >3.5 mmol/L despite treatment and the patient has documented cardiovascular disease, then updated NICE guidelines suggest that fortnightly evolocumab by subcutaneous injection can be added.[4] In the absence of established cardiovascular disease these patients require greater elevations of low density lipoprotein (>5 mmol/L) to qualify for treatment with evolocumab or other proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

In the recent FOURIER trial,[5] 27 564 patients at risk of cardiovascular disease who were already on an optimal statin regime were randomised to placebo or evolocumab. Over a median follow-up of 2.2 years, the primary end point (composite of cardiovascular death, myocardial infarction, stroke, hospitalisation for unstable angina, or coronary revascularisation) was reduced in patients randomised to evolocumab compared with placebo (9.8% *v* 11.3%; hazard ratio 0.85; 95% confidence interval 0.79 to 0.92; P<0.001).



The patient looking upwards reveals a dense and striking white circumferential ring around the cornea (corneal arcus) reflecting cholesterol rich lipid deposits in the context of familial hypercholesterolaemia

Patient outcome

Molecular genetic testing showed a heterozygous defect in the low density lipoprotein receptor, confirming heterozygous familial hypercholesterolaemia. Despite stabilisation with atorvastatin 80 mg, the low density lipoprotein concentration remained >5 mmol/L. The patient was started on evolocumab.

The patient subsequently stabilised on evolocumab and atorvastatin. The most recent total cholesterol showed a reduction of 55% to 5.5 mmol/L and a reduction of low density lipoprotein of 75% to 2.3 mmol/L.

Invasive coronary angiography revealed diffuse but non-obstructive triple vessel coronary artery disease. She was randomised in the CorMicA trial (Coronary MICrovascular Angina, clinicaltrials.gov NCT03193294) with invasive metrics of coronary artery function, confirming a reduced coronary flow reserve and microvascular angina as the cause of her symptoms. Angina was much improved after targeted titration of medical treatment.

Learning points

Physicians should consider familial hypercholesterolaemia in patients with strikingly elevated cholesterol.

Physical signs including corneal arcus and tendon xanthomas are important clues, however these are not required for diagnosis (this might require genetic testing).

Patients with familial hypercholesterolaemia are at very high risk of cardiovascular complications. This is modifiable with aggressive secondary prevention including statins and possibly PCSK9 inhibitors.

We have read and understood BMJ policy on declaration of interests and declare no competing interests.

Patient consent obtained.

Provenance and peer review: not commissioned; externally peer reviewed.

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4 National Institute for Health and Care Excellence. Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. Technology appraisal guidance 394. 2016. www.nice.org.uk/guidance/ta394.

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