A physically fit woman in her thirties with exertional dyspnoea

It is easy to forget that young people may be affected by diseases usually seen in older patients. When patients have typical clinical symptoms or a high pre-test probability, we should think about them differently compared to other patients in the same age group.

Martin Prøven Bogsrud
martinbogsrud@gmail.com
Norwegian National Advisory Unit on Familial Hypercholesterolaemia
Oslo University Hospital, Rikshospitalet

Asgeir Græsdal
Vestfold Centre for Internal Medicine

Kjetil Retterstøl
Department of Nutrition
University of Oslo
and
The Lipid Clinic
Oslo University Hospital, Rikshospitalet

Kirsten B. Holven
Department of Nutrition
University of Oslo
and
Norwegian National Advisory Unit on Familial Hypercholesterolaemia
Oslo University Hospital, Rikshospitalet

A physically fit woman in her thirties noticed reduced physical capacity and breathlessness upon exercise. She contacted her general practitioner and was prescribed asthma medication, which was of uncertain benefit. A year later she also developed burning pain behind the sternum. A gastroscopy revealed grade 1 oesophagitis, and she was treated with a proton pump inhibitor. She initially responded well but the pain returned after a few weeks.

She was then referred with a diagnosis of oesophagitis to a specialist in internal medicine and for another gastroscopy in hospital. During the referral it emerged that she had familial hypercholesterolaemia and that two members of her immediate family had had early coronary artery disease. She had been taking statins from the age of 20, but had otherwise been in good health and was a non-smoker. ECG and spirometry tests performed by her general practitioner were normal. She was taking esomeprazole 40 mg × 1 and atorvastatin 40 mg × 1.

Exercise-induced asthma and oesophagitis were not unlikely diagnoses given the medical history and the patient's age. In older individuals, the same symptoms would more rapidly raise suspicion of angina pectoris.

The patient did have a potentially strong risk factor in the form of familial hypercholesterolaemia, but she had been treated with cholesterol-lowering medication from the age of 20.

Examination by specialists in internal medicine revealed a total cholesterol level of 12 mmol/l and LDL cholesterol of 10.8 mmol/l. It emerged that the patient's medication adherence had been poor –she had not taken atorvastatin for some time.

Further exploration of the medical history thus revealed that the patient's elevated cholesterol levels had not been managed as effectively as previously thought. The cholesterol levels to which she had been exposed carry a high risk of atherosclerotic coronary artery disease, i.e., the patient's pre-test risk was higher than first assumed.

In medical diagnostics, knowing the pre-test probability is of great importance as this will affect how negative test results are interpreted.

The woman's main symptom was burning pain behind the sternum. She could sometimes perform strenuous exercise without any pain; on other occasions the pain began after ten minutes but disappeared with continued exercise. She also sometimes experienced pain while at rest and often in the mornings before she got up.

A stress ECG was performed, which showed no signs of ischaemia, and the patient experienced no chest pain during the test. A supplementary examination including calcium scoring (Agatston score 23.5) was performed at a private radiology clinic.

The calcium score (Agatston score) indicates the degree of calcification of the coronary arteries as a percentage of reference values adjusted ??for sex and age, and is measured using CT without contrast. The usefulness of the calcium score when evaluating patients with possible coronary ischaemia is subject to debate (1). The score may, however, indicate whether CT-based coronary angiography (CTCA) is an option instead of referral for invasive angiography (CTCA is unsuitable with high calcium scores owing to artefacts).

The gastroscopy at the hospital also showed grade 1 oesophagitis. Although the patient's symptoms were not typical of angina, she was referred for CT-based coronary angiography because of her high pre-test risk of coronary artery disease.

The stress ECG is known to have low sensitivity (ability to detect disease), such that a negative result does not exclude coronary pathology (i.e., the test has a low negative predictive value) and further assessment is often required. When the pre-test probability of

disease is high (as in our patient), the negative predictive value decreases even further. Our patient should instead have undergone CT-based coronary angiography or invasive coronary angiography immediately.

Nevertheless, widespread availability combined with uncertainty over assessment of both symptoms and risk mean that the stress ECG is often performed in patients such as ours. A stress ECG was also performed in this case because even though a negative result would not rule out disease, a positive finding would help justify more rapid invasive treatment.

Four weeks after the first stress ECG, the woman developed central chest pains while exercising on a treadmill; she fainted and was taken by ambulance to her general practitioner. After consultation with the local hospital, the incident was judged to be a vasovagal episode. She was therefore not admitted but was instead recommended for outpatient referral. Given the possibility of angina pectoris, the general practitioner began treatment with aspirin 75 mg × 1, increased the atorvastatin dose to 80 mg × 1, and added the cholesterol absorption inhibitor ezetimibe 10 mg × 1.

Upon outpatient assessment at the local hospital a couple of weeks later, a stress ECG again showed no signs of ischaemia or chest pain. Upon suspicion of angina pectoris, metoprolol depot 50 mg × 1 was added to the medication regime plus nitroglycerine as required. A reminder was sent regarding the referral for CT-based coronary angiography, which the patient underwent three weeks later. The results showed: «Coronary artery disease in the form of calcified plaques. Cannot fully rule out coronary artery stenoses.»

Angiography four weeks later showed critical stenosis in the proximal right coronary artery, and a drug-eluting stent was implanted. The patient herself contacted the surgical clinic just two days after discharge owing to increasing chest pain, poor general condition and dizziness. She was readmitted acutely.

Recurrence of symptoms after stenting may be due to stent thrombosis; symptoms in such cases often have sudden onset. However, persistent symptoms resembling those prior to the intervention may also be due to oversight of a proximal main stem stenosis, which can occur if the catheter tip is pushed just inside the stenosis during angiography.

Angiography upon acute readmission did indeed show a left main stem stenosis at the transition to the proximal left coronary artery. The patient stated that those who performed the examination were surprised at the severity of coronary artery disease given her young age and atypical symptoms.

She underwent successful bypass surgery while in hospital, and had an uncomplicated postoperative course. Her cholesterol-lowering treatment was changed from atorvastatin 80 mg to rosuvastatin 40 mg, in addition to ezetimibe 10 mg × 1, as previously.

Atorvastatin and rosuvastatin are the most effective statins, and are about equally effective at maximum doses (2). However, there may be some individual variation in response to statins, thus switching between them may be attempted if therapeutic targets are not achieved. The cholesterol absorption inhibitor ezetimibe lowers LDL cholesterol by about another 20 % on top of statin therapy (3).

The new cholesterol-lowering PCSK9 inhibitors were not available at the time of these events, but are now a relevant adjunct therapy (4, 5).

At a check-up six months after bypass surgery, the woman was taking her medications as prescribed and had a total cholesterol level of 5.0 mmol/l and an LDL cholesterol level of 3.6 mmol/l. Over the preceding four weeks, she had become tired and breathless upon exertion. She experienced retrosternal chest pain without radiation after walking about 200 metres. She had not tried nitroglycerine. ECG and chest X-ray showed no signs of pathology.

Angiography was performed again two weeks later. A high-grade almost subtotal ostial stenosis was detected in the stented portion of the right coronary artery. A drug-eluting stent was implanted, and there has been no recurrence of her coronary artery disease to date.

In-stent stenosis is a feared complication, and the risk is particularly high upon poor adherence to antiplatelet treatment (6). We do not know whether our patient had been taking antiplatelets as prescribed, but she had previously shown poor adherence to cholesterol-lowering therapy.

Discussion

Our patient had familial hypercholesterolaemia (FH), resulting from an autosomal dominant mutation in the mechanism for LDL cholesterol uptake by the liver. Children as young as ten years of age with familial hypercholesterolaemia have increased carotid intima-media thickness compared to healthy children and siblings without the mutation (7).

New figures show that for Norwegian patients with familial hypercholesterolaemia, the average age at first hospitalisation for cardiovascular disease is 45 years, and the average age at death from cardiovascular disease is 15 years below the general population average for men and 21 years below that for women (8). In the same population, more than 90 % of individuals were shown to have established cardiovascular disease at the time of death, even if death was due to another cause (9).

Many with familial hypercholesterolaemia have only moderately elevated total cholesterol levels, but the hidden difference is that a person with the mutation will have had elevated cholesterol levels from their first years of life. This results in greater lifelong cholesterol exposure than the «ordinary high cholesterol» that arises in adulthood as a result of age and lifestyle factors. A recent study showed that individuals with the mutation are at greater risk than those with equally high cholesterol levels without such a mutation (10). This individual risk factor can easily be confirmed through genetic testing.

A genetic test is also important for tracing the condition in families. We recommend that genetic testing be considered when untreated total cholesterol levels are above 6 mmol/l in persons under 20 years of age, over 7 mmol/l in those aged 20–40 years, and over 8 mmol/l in those over 40 years. Genetic testing can be ordered by any doctor. A standard blood sample is taken and then sent to the Unit for Cardiac and Cardiovascular Genetics at Oslo University Hospital. Doctors were previously taught that peripheral cholesterol deposits are a sign of familial hypercholesterolaemia, but most persons with the condition do not have such deposits. Suspicion of familial hypercholesterolaemia should therefore be based on cholesterol levels and family history.

Effective cholesterol-lowering therapy can reduce the associated risks. If the onset of treatment is delayed, cholesterol levels must be reduced to «lower than normal» because of the high cholesterol exposure earlier in life, but ideally treatment should be started in childhood to reduce cumulative cholesterol exposure (11)

This case history illustrates the importance of knowing the pre-test probability for the diagnoses under consideration. Reduced physical capacity and breathlessness were interpreted in this case as most likely related to asthma – in older patients with the same symptoms, thoughts would turn more quickly to angina pectoris. This standard diagnostic reasoning is in line with Bayes' theorem, which states that the probability that a symptom indicates a disease (asthma or heart disease in this case) is highly dependent on the prevalence of the disease in the population in question.

Our patient's increased pre-test risk was discovered only after several consultations,

and it was therefore some time before angina pectoris was considered. Tests that would otherwise have reasonable negative predictive value have very low negative predictive value when the pre-test risk is elevated, and this must be taken into account when interpreting test results. This is well known for D-dimer, where a negative result is used to rule out disease in cases with a low pre-test probability (based on patient history and findings). However, a patient with classic deep vein thrombosis with all the cardinal signs would be referred onwards despite a negative D-dimer test. Similar reasoning should also be applied in other diagnostic scenarios.

CT-based coronary angiography is considered a reliable method for excluding coronary artery disease in patients at intermediate risk; it was thus not the optimal procedure for our patient, who was at high risk. Invasive coronary angiography is the reference method for detecting coronary artery disease and assessing severity. In retrospect, invasive testing should have been performed earlier in the disease course for our patient, but justifying invasive angiography as the initial examination of a woman in her thirties with atypical symptoms is not easy. Preventive examination or screening with, for example, CT-based coronary angiography in asymptomatic patients with a high pre-test probability of coronary artery disease (e.g. due to diabetes or familial hypercholesterolaemia) has not yet been documented.

This case history illustrates the importance of regular monitoring of persons with familial hypercholesterolaemia (and similar lifelong conditions) to ensure that established treatment plans are in fact adhered to (12). Marked regional differences have been shown in Norway with respect to the follow-up of patients with this condition (13).

The Norwegian National Advisory Unit on Familial Hypercholesterolaemia was established at Oslo University Hospital in 2014 and works to increase diagnosis and to ensure equal access to high quality treatment throughout Norway for patients with familial hypercholesterolaemia. Information on topics including referral addresses, treatment guidelines, dietary advice and ordering of genetic tests is available on our website (14).

The patient has consented to the publication of this article.

Magne Brekke (1955–2016) participated in the early stages of writing this article, but died before the article was completed. He was a specialist in radiology and head of the Angiography and Intervention Centre, Oslo University Hospital, Ullevål. We are grateful to Magne for an effective collaboration. An obituary for Magne Brekke, written by Otto A. Smiseth, Thor Edvardsen, Knut Endresen, Hilde Aarseth, Arild Mangschau, Øystein Vengen and Dag Jacobsen, was published in the May 2016 issue of this journal.

Martin Prøven Bogsrud (born 1981)
MD PhD, director of the Norwegian National Advisory Unit on Familial Hypercholesterolaemia, and general practitioner at Invivo Medical Centre.
The author has completed the ICMJE form and reports the following conflicts of interest: He has received honoraria from Amgen, Sanofi, Aegerion and MSD.

Asgeir Græsdal (born 1963)
specialist in internal medicine.
The author has completed the ICMJE form and reports no conflicts of interest.

Kjetil Retterstøl (born 1962)
MD PhD, specialist in medical biochemistry, professor and senior consultant.
The author has completed the ICMJE form and reports the following conflicts of interest: He has received honoraria from Sanofi, Mills DA, Amgen, MSD, Chiesi, Takeda, the Norwegian Society of Cardiology, the Norwegian Medical Association and the Research Council of Norway.

Kirsten B. Holven (born 1963)
PhD, nutritionist, professor, and head of research.
The author has completed the ICMJE form and reports the following conflicts of interest: She has received honoraria from Mills DA, TINE DA, Olympic Seafood, Sanofi, Amgen and Pronova.

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