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Unusual presentations to a lipid clinic

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We describe the case-histories of two young men who both presented to a lipid clinic with mixed hyperlipidaemias.

Case 1

A 33-year-old man had been referred to the lipid clinic by the dermatology unit because of planar xanthoma that been found on a skin biopsy. Apart from previously seeing the Ear, Nose and Throat department for an 18-month history of snoring, there was no other relevant medical history nor other symptoms. He was a non-smoker, rarely took alcohol and at the time was not taking any medication. On examination he was overweight with a body mass index (BMI) of 29 kg/m². His blood pressure at presentation was 140/90 mmHg and pulse 72 beats/min. He was clinically euthyroid and had planar xanthoma on his hands and tuberous xanthoma on his elbows. He had been commenced on a lipid-lowering diet and a number of investigations were performed. His fasting serum cholesterol was 12.6 mmol/l, triglyceride 5.3 mmol/l and high-density lipoprotein (HDL) cholesterol 1.31 mmol/l. Plasma urea, creatinine and fasting glucose were normal, as were his liver function tests. However, thyroid function tests showed a thyroid-stimulating hormone of 257.7 mU/l (normal range 0.3–5.0) and free thyroxine of 1.1 pmol/l (10.3–19.4). Anti-thyroglobulin and antithyroid peroxidase antibodies were 396 and 240 IU/ml, respectively (0–180 and 0–50). Apolipoprotein (apo) E phenotype performed by Western blotting showed him to be a E2/E2 homozygote. On a lipid-lowering diet instigated by a dietician and thyroxine 150 µg per day his fasting serum cholesterol improved to 5.11 mmol/l and triglyceride to 2.15 mmol/l and his thyroid function tests were rendered normal.

Case 2

A 33-year-old man was referred to the lipid clinic by his general practitioner because of hyperlipidaemia and a family history of premature coronary heart disease. His mother had hypothyroidism and pernicious anaemia. On examination he was euthyroid and had no lipid stigmata. His BMI was 31 kg/m², blood pressure was 150/92 mmHg, and pulse 72 beats/min. Initial fasting serum cholesterol was 16.49 mmol/l, triglyceride 20.83 mmol/l and HDL-cholesterol 0.59 mmol/l. His renal and liver function were normal, as was a fasting plasma glucose. However, his TSH was 37.6 mU/l and free T4 8.5 pmol/l. Anti-thyroglobulin and anti-thyroid peroxidase antibodies were 2153 and 711 IU/ml, respectively. He was commenced on thyroxine which resulted in normalisation of his thyroid function, although his fasting serum cholesterol remained elevated at 11.8 mmol/l with triglyceride of 16.7 mmol/l. His apoE phenotype also by Western blotting was E2/E2. He was subsequently started on bezafibrate 400 mg (MONO) nocte with considerable improvement in his lipids.

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Questions

- 1 What lipid disorder do these two patients display?
- 2 How can the diagnosis be confirmed?
- 3 What other conditions is this lipid disorder associated with?

Answers

QUESTION 1

They were both diagnosed as having a type III hyperlipoproteinaemia. Type III hyperlipoproteinaemia, also called broad beta or remnant dyslipidaemia, is a rare familial hyperlipidaemia whose recognition is important as it is usually responsive to therapy. The treatment is usually dietary, in conjunction with a lipid-lowering drug using a fibrate or possibly a statin.¹ The palmar striae (palmar xanthomata) are considered pathognomonic for the disorder and occur in less than 50% of patients but tubero-eruptive xanthomata, typically on the elbows and knees, as well as xanthelasma and corneal arcus have been described in this condition. Peripheral vascular disease is a typical feature of this hyperlipidaemic disorder as is premature coronary artery disease. Serum lipid determination will frequently reveal hypercholesterolaemia and hypertriglyceridaemia, often in similar molar proportions. Serum HDL cholesterol is usually low. Serum low-density lipoprotein (LDL) cholesterol may also be low due to the fact that there is reduced conversion from intermediate-density lipoprotein particles, although LDL cholesterol may also be normal or elevated.²⁻⁴

The underlying biochemical defect is one of a reduced clearance of chylomicron and VLDL remnants. This is also known as broad beta hyperlipidaemia because of the characteristic serum lipoprotein electrophoretic pattern often observed (the broad beta band that is seen being predominately remnant particles).

An association with type III/broad beta hyperlipidaemia and homozygosity for apoE2 or apoE2 variants has been described. ApoE shows three common alleles, E2, E3, and E4, coded for on chromosome 19 and which are important for the binding of remnant particles to the remnant receptor.

The mechanism for the disorder seems to be that apoE2-bearing particles have poor binding to the apoB/E (remnant) receptor and thus are not effectively cleared from the circulation.

QUESTION 2

Serum lipoprotein electrophoresis can show the classic type III picture with a broad beta band composed of remnant particles, although this is not always present. An association of type III broad beta hyperlipidaemia with homozygosity for apolipoprotein E2 has been described and thus apoE phenotyping or genotyping by a specialised laboratory can be useful, although some patients with broad beta hyperlipidaemia can show other apoE pheno-

types or variants. Another investigation that can be useful in establishing the diagnosis is ultracentrifugation to separate the lipoprotein particles. The cholesterol of the VLDL particles is then quantitated and expressed as a total of the serum triglyceride concentration. In molar terms, normal individuals show a ratio of below 0.30 while ratios over 0.30 are more likely in broad beta hyperlipidaemia, particularly if this is nearer 0.60.

QUESTION 3

It is becoming apparent that it is not just inheriting the apoE2 genotype that is important in developing broad beta hyperlipidaemia. The prevalence of the apoE2/E2 genotype is about 1 in 100 in the general population, yet only about 1 in 5–10 000 individuals manifest type III hyperlipidaemia. A concurrent increase in serum VLDL also seems necessary for the condition to be expressed, such as might occur in diabetes mellitus, hypothyroidism or obesity. Some patients may show either an autosomal recessive or dominant mode of inheritance of the condition.

The presentation of primary hypothyroidism in two young euthyroid males with type III hyperlipoproteinaemia is remarkable. It is known that the prevalence of newly diagnosed overt hypothyroidism in patients referred to a lipid clinic is approximately twice that seen in the general population.⁵ In view of our report we would suggest that secondary causes of hyperlipidaemia should be sought in a lipid clinic. In cases of type III hyperlipoproteinaemia, secondary causes such as obesity, diabetes mellitus and hypothyroidism should always be considered.

Interestingly, the lipid profile considerably improved in the first patient due to treatment of his hypothyroidism with thyroxine in conjunction with dietary measures. However, the second patient required the addition of a fibrate lipid-lowering drug. Finally, the occurrence of hyperlipidaemia in these young patients provides an unusual presentation of primary hypothyroidism which could have resulted in catastrophic sequelae in the long term if not identified.

Final diagnosis

Primary hypothyroidism in two young clinically euthyroid males with type III hyperlipoproteinaemia.

Keywords: hyperlipidaemia; hypothyroidism; hyperlipoproteinaemia

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