A first British case of fish-eye disease presenting at age 75 years: a double heterozygote for defined and new mutations affecting LCAT structure and expression

A F Winder, J S Owen, P H Pritchard, D Lloyd-Jones, D T Vallance, P White, R Wray

Abstract
Fish-eye disease is a familial syndrome with corneal opacification, major high density lipoprotein (HDL) deficiency in plasma, significant cholesterol esterification in plasma on non-HDL lipoproteins, generally without premature coronary disease. This first British male case from unrelated British parents had infarcts when aged 49 and 73 years but was asymptomatic at age 81 years, with plasma cholesterol 4.3–7.1 mmol/litre, triglycerides 1.8–2.2 mmol/litre, HDL cholesterol < 0.1 mmol/litre, apolipoprotein A-I < 0.16 g/litre, lipoprotein(a) 0.61 g/litre. Cholesterol esterification was impaired using HDL-3 and A-I proteoliposomes but not using VLDL/IDL/LDL. The findings are those of LCAT deficiency with the classic fish-eye disease defect. Most of the 22 reported cases were homozygous or heterozygous for a Thr-Ileu substitution at codon 123 of the lecithin:cholesterol acyltransferase (LCAT) gene. This patient was a double heterozygote for this mutation and a second new incompletely defined mutation affecting LCAT expression as defined by reduced mass and activity in plasma. (J Clin Pathol 1999;52:228–230)

Keywords: fish-eye disease; familial LCAT deficiency; LCAT gene mutation; corneal opacification

The term fish-eye disease was first applied to a Swedish family with massive corneal opacification resembling that of boiled fish, an excess in plasma of very low density, intermediate density, and low density lipoproteins (VLDL/IDL/LDL), and marked reduction of high density lipoproteins (HDL). Most of the 22 reported cases from 12 kindreds are homozygous or heterozygous (then with a second defect) for a Thr-Ileu substitution at codon 123 of the lecithin:cholesterol acyltransferase (LCAT) gene, associated with impaired cholesterol esterification on HDL, the usual substrate, but with activity against other lipoproteins. Clinical differences between fish-eye disease and LCAT deficiency may relate to this altered substrate specificity, or to levels of residual LCAT activity. Any lesser expression of premature coronary disease with fish-eye disease may reflect variable selective preservation of apo A-I-only HDL particles, or triglyceride enrichment of LDL.

Case report
The patient was a male who smoked heavily until admitted to hospital with his first myocardial infarct which presented with chest pain and ECG changes at 49 years of age. Discharge on anticoagulants and β blockade was followed by some breathlessness, treated hypertension, and further clinical and then confirmed infarcts at 73 and 74 years, and finally collapse and suspected Stokes–Adams attacks, for which amiodarone was briefly prescribed. Corneal clouding and mixed lipaemia with very low HDL was then noted. Tāngier disease was considered, as his tonsils had been removed when he was 17. His lipid profile (cholesterol 4.3–8.0 mmol/litre, triglycerides 1.8–3.5 mmol/litre, HDL cholesterol < 0.1 mmol/litre, and apolipoprotein A-I < 0.16 g/litre) was unresponsive to fibrates, and diet was continued. There were no other lipid deposits, or glundar or splenic enlargement. Eruptions on elbows, knees, and buttock cleft since age 25 years were controlled by steroids and appeared psoriatic rather than lipid related. Parents were unrelated. All living family members had unremarkable corneas; a brother with cloudy corneas had died aged 76.

OPHTHALMOLOGICAL FINDINGS
There were no ocular or visual symptoms; visual acuity was 6/9 in both eyes, fully corrected by spectacles for reading. There was bilateral coarse punctate corneal haze, slightly accentuated peripherally, with no clear zone or suggestion of confounding amiodarone keratopathy (fig 1). Fundi were not clearly seen but appeared normal.

LABORATORY INVESTIGATIONS
General biochemical and haematological profiles
Serum urea was 7.1–8.0 mmol/litre; other renal, electrolyte, glucose, liver, and thyroid...
Profiles were within reference ranges. There was no proteinuria. Haemoglobin was 13.3 g/dl. Blood films showed occasional spheroocytes only and no vacuolated lymphocytes (reported in a patient later defined as a double heterozygote for fish-eye disease and a functional LCAT mutation).

**Plasma lipids/lipoproteins**

These were variable off treatment, with plasma cholesterol 4.3–8.0 mmol/litre, triglycerides 1.8–3.5 mmol/litre, HDL cholesterol < 0.1 mmol/litre, apolipoprotein A-I < 0.16 g/litre, HDL band absent on lipoprotein electrophoresis, lipoprotein(a) 0.61–0.66 g/litre, all by standard methods (HDL by a heparin/manganese procedure). A lipid profile six months after withdrawal of brief ineffective lipid lowering treatment with bezafibrate or simvastatin but while on dietary advice was: cholesterol 6.0 mmol/litre, triglycerides 2.0 mmol/litre, HDL cholesterol 0.05 mmol/litre, apo A-I < 0.16 mg/100 ml. Thin layer chromatography of the plasma cholesterol fraction indicated a normal proportion of 67–72% as ester.

**Plasma LCAT activity**

Cholesterol esterification was negligible using HDL prepared by floatation or apo A-I proteoliposomes, but (in contrast to classic LCAT deficiency) was normal with the residual radiolabelled VLDL/IDL/LDL cholesterol or whole plasma as substrate, compared with heat treated and normal control samples (see fig 2).

**LCAT mass in plasma**

Band profiles on SDS-PAGE electrophoresis of enzyme purified on an anti-LCAT antibody column showed LCAT with normal mobility and apparently normal gross molecular structure but reduced mass in comparison with a series of normal reference samples.

**The LCAT gene**

PCR amplification and sequencing of the LCAT gene (PHP, UBC Vancouver) showed heterozygosity for the C→T base change at codon 123 [Thr→Ile] but no other abnormality of the coding sequence. Gross defects of the apo A-I coding sequence and an intron defect described in association with fish-eye disease were also excluded. Extensive further analysis has not identified any other intron defects; some residual areas of the large intron 5 are, however, not absolutely defined.

**Discussion**

Fish-eye disease is a misnomer, as underlying cataract giving the appearance of boiled fish and affecting visual performance was found at corneal surgery in an early case. Later cases have shown corneal clouding, no cataract, and adequate vision. Ocular appearances, together with the microscopic and biochemical findings of a corneal button (corneal surgery revealing the cataract), were essentially identical to those of authentic LCAT deficiency, with myelin figures enriched with phospholipids and free cholesterol. Special features of this case include premature coronary disease but good longevity, an absence of haematological abnormalities, and first detection in a British family—widening both clinical expression and the underlying molecular defects. A brother of the proband, who probably also had fish-eye disease, enjoyed similar longevity without premature cardiovascular disease.

The codon 123 defect has been identified in homozygous and heterozygous fish-eye disease.
states, and in heterozygotes and recombinant expression studies is associated with moderate reduction in circulating mass of LCAT but with clear corneas.\(^2\)\(^,\)\(^3\)\(^,\)\(^4\) We propose a second LCAT defect and secretion of inactive protein—with the codon 123 defect dominating the clinical phenotype—from the LCAT mass data and the lack of major structural rearrangement, and because other heterozygotes for the codon 123 defect alone have not shown the classical clinical picture of fish-eye disease. The functional status is also not established, other family members not being available for cosegregation analysis, a difficulty which has arisen in other studies of LCAT mutations.\(^2\)

The proband with definite fish-eye disease had a clinical episode consistent with myocardial infarction at the age of 49 years, but was then a heavy cigarette smoker, and his lipoprotein(a) concentrations were also well above the 90th centile, at 0.61 and 0.66 g/litre on two separate occasions. The corneal appearances had not been remarked upon by the patient or his family before he was in his seventies. In considering the variable clinical associations of major deficiency of HDL as expressed in fish-eye disease, these additional risk associations in a male patient may have contributed to the accelerated expression of cardiovascular disease and cannot necessarily be attributed to fish-eye disease, further widening the relations between HDL deficiency and cardiovascular status.

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