CORNEAL OPACIFICATIONS IN A LOW HIGH DENSITY LIPOPROTEIN SYNDROME: SUSPICION OF FISH EYE DISEASE: A CASE REPORT

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SUMMARY

A 49 year old patient with progressive massive bilateral corneal opacifications associated with a HDL (high-density-lipoprotein) deficiency is described. The opacifications started at the age of twenty and progressed slowly. They were found diffusely over the cornea, though more in the corneal periphery. A penetrating keratoplasty at the right eye was performed. The diagnosis of Fish Eye Disease was put forward on the basis of the ophthalmological, clinical, biochemical and pathological appearance. After 2 year follow-up, the graft was clear. The final distance and near vision of the right eye was 8/10 and Snellen 1 respectively.

SAMENVATTING

Een 49-jarige patiente werd gevolgd voor progressieve massieve bilaterale corneale opacificaties in het kader van een (HDL) High-Density-Lipoprotein Deficiency. De opacificaties werden opgemerkt vanaf de leeftijd van 20 jaar en namen langzaam toe. Zij waren verspreid over de hele cornea maar bevonden zich vooral in de periferie. Een penetrerende keratoplastie werd uitgevoerd aan het rechter oog. De diagnose van Fish Eye Disease werd gesteld op basis van het ophthalmologisch, klinisch, biochemisch en anatomopathologisch onderzoek. Twee jaar na de operatie toonde het biomicroscopisch onderzoek een heldere ent. De visus rechts bedroeg toen 8/10 en de patiente las Snellen 1.

RÉSUMÉ

Une patiente de 49 ans présente des opacifications cornéennes bilatérales, massives et progressives, dans le cadre d'une déficience en HDL (High-Density-Lipoprotein). Les opacifications se sont manifestées à l'âge de vingt ans et ont progressé lentement depuis. Surtout la périphérie de la cornée était atteinte, bien que les opacités étaient visibles diffusément dans la cornée. Une greffe de la cornée droite a été effectuée. Se basant sur l'examen clinique et ophtalmologique et sur les résultats de biochimie et d'anatomopathologie, le diagnostic de Fish Eye Disease a été posé. Deux ans après l'opération l'examen à la lampe à fente montrait un greffon clair. L'acuité visuelle de l'oeil droit à ce moment était de 8/10 et la patiente lisait Snellen 1.

KEY-WORDS

Corneal opacification, High-Density-Lipoprotein deficiency, Fish Eye Disease

MOTS-CLÉS

Opacifications cornéennes, déficience en HDL, Fish-Eye Disease

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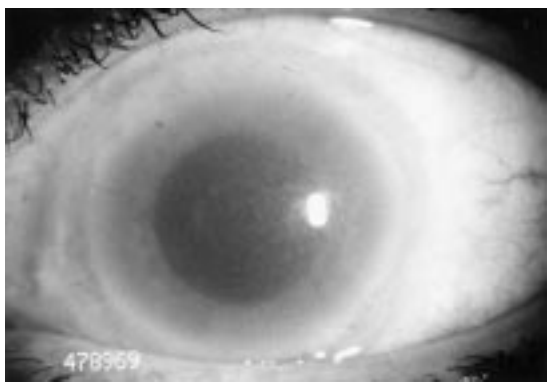
INTRODUCTION

Diffuse corneal opacification, isolated or accompanied by a corneal arc, is a common finding and often a key element in diagnosing genetic disorders of HDL metabolism, such as Lecithine-Cholesterol-Acyl Transferase (LCAT) deficiency, Fish Eye Disease, Tangier disease and apo A1 and C3 deficiency (19). For these conditions the corneal changes are evident only in homozygotes (2). Fish Eye Disease is an extremely rare genetic disorder (1,5, 11,15) characterized by a severe HDL deficiency. The underlying metabolic disorder is the dysfunction of the LCAT enzyme unable to esterify cholesterol in the HDL molecule while retaining its activity in VLDL and LDL. In the classic LCAT deficiency, however there is a lack of esterification of cholesterol in HDL, LDL and VLDL. The clinical hallmark of Fish Eye Disease is the remarkable corneal opacification. The latter was responsible for the unusual name of the disease, since in affected individuals the appearance of the eyes is similar to that of a boiled fish (13) The disease was first described in 1979 in Sweden by Carlson and Holmquist (6). Surprisingly, despite a lifelong virtual absence of HDL, the three described affected patients reached an advanced age. Autopsy findings failed to reveal the presence of extensive atherosclerosis (15). Since then, 14 homozygotic cases from nine families have been reported worlwide (6, 7, 9, 10, 13, 14, 16, 20, 21, 22).

Fig 1. Periocular xanthelasmata

CASE REPORT

A 49 year old female was referred to our department in November 1998 for marked bilateral corneal opacification: the iris appeared only as an indistinct shadow. At the age of 20, an arc on both corneae was noticed. She had periocular xanthelasmata (fig.1) on both eyelids since the age of 36, recurring after resection.
At the age of 44, her vision started to deteriorate, especially in the dark. Her mother and one of her three sisters also had xanthelasmata, however without ocular anomalies. Her two children had a normal ophthalmologic examination. Her father died from a heart attack at the age of 75, without known ophthalmologic disorder. The rest of the family history was negative for corneal opacification.
On initial examination in our department, her best vision was 7/10 and Snellen 1 in both eyes in good contrast circumstances.
On slit lamp examination corneal cloudiness was seen over the whole corneal thickness, ap-



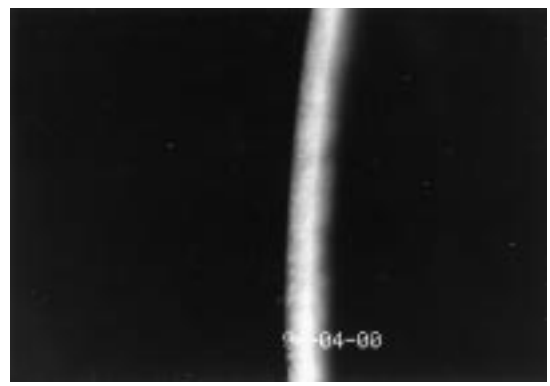


Fig 2 and 3. Slit lamp examination: corneal cloudiness over the whole corneal thickness, appearing as small, dotlike, grey white opacities in a mosaic pattern; the peripheral cornea was most involved though no distinct corneal arc is seen

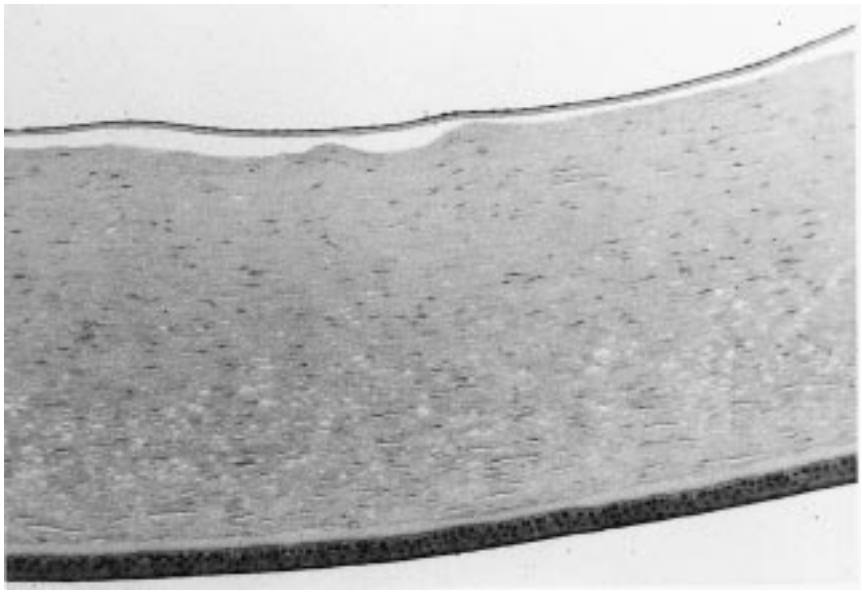


Fig 4. Light microscopy: hydropic degeneration of the epithelium in the basal layers; oedematous aspect of the stroma without signs of inflammation of neovascularisation

pearing as small, dotlike, grey white opacities in a mosaic pattern. The peripheral cornea was more involved although no distinct corneal arc was present (fig. 2-3).
Further ophthalmological examination revealed no other abnormalities.
Penetrating keratoplasty on the right eye was performed in February 1999 and the corneal tissue was submitted for pathological examination. After a 2 year follow-up, the graft remained clear and the vision of 8/10 (Snellen1) was less dependent on contrast circumstances.

PATHOLOGICAL FINDINGS

The corneal button was cut into three portions: one was fixed in formalin, embedded in paraffin and processed on routine procedure; the second part was immediately frozen and the third fixed in glutaraldehyde and processed routinely for electron microscopy. Light microscopy showed hydropic degeneration of the epithelium in the basal layers. The stroma had an oedematous aspect without signs of inflammation or neovascularisation (fig.4). The keratocytes were normal. Descemet membrane was uniformly thin and the number of endothelial

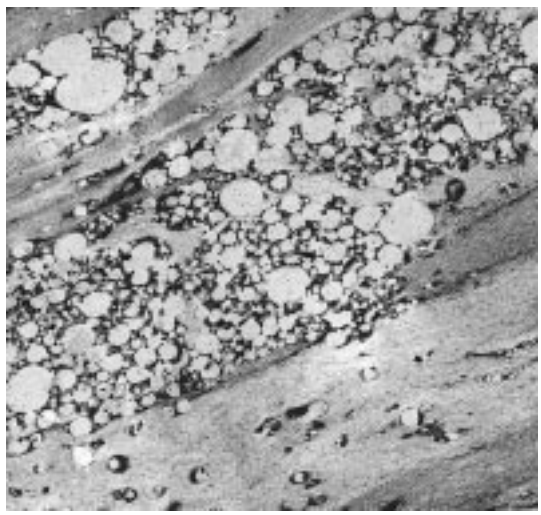


Fig 5. Electron micrograph of part of the stroma of the cornea. Large accumulations of lipid droplets in between the collagen lamels. Original magnification: x 9200.

cells was diminished. PAS, trichrome, Congo-red and oil-red O did not reveal any deposits.
On electron microscopy the whole stroma showed large and small extracellular accumulations of lipid droplets of various size (Fig.5). The structure of the collagen lamellas around these fat accumulations was altered and dense granular matrix components were present (Fig.6).

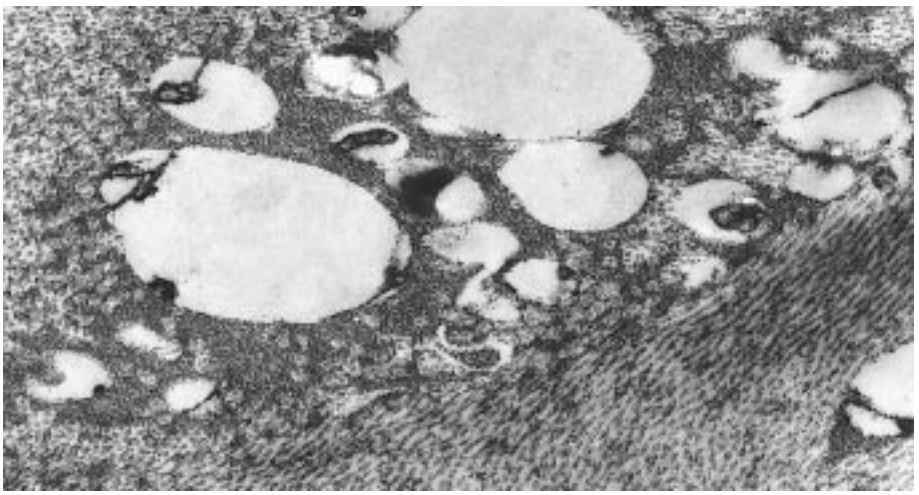


Fig 6. Electron micrograph of part of the stroma of the cornea. Detail of large and small lipid droplets surrounded by granular electron dense matrix components. Original magnification: x 36 800.

The keratocytes were normal in number and contained occasionally small lipid droplets in their cytoplasm. Numerous accumulations of small lipid droplets were especially found in Bowman's membrane and in Descemet's membrane adjacent to the stroma.

LABORATORY INVESTIGATIONS:

Haemoglobin, glucose, urea, electrolytes, renal, liver and thyroid function tests were all within normal limits. Urine examination (sediment, glucose, aceton and proteins) was normal.
Total plasmacholesterol 169 mg % (normal value 140-240 mg %), triglycerides 118 mg/dl (normal value 41-200 mg/dl), HDL cholesterol 9mg/dl (normal value 31-70 mg/dl); LDL-(Low-Density -Lipoprotein-cholesterol: 136 mg/dl (normal value: 65-175 mg/dl). Apolipoprotein A-1: 0.25 g/l (normal value 1.10-2.05 g/l). In the HDL fraction, almost no free cholesterol or esterified cholesterol was detected, whereas both forms were present in the LDL fraction.

DISCUSSION

Lipid deposition at the limbus of the cornea is a characteristic of familial and non-familial dys-

BILATERAL CORNEAL ARCUS	DIFFUSE BILATERAL CORNEAL OPACIFICATION
hyperlipoproteinemia type 2 hyperlipoproteinemia	genetic disorders of HDL metabolism - Fish Eye Disease - Apo A1 deficiency syndrome - LCAT deficiency - Tangier disease

lipoproteinaemia but in most cases it occurs without any apparent accompanying systemic abnormality (3). In the familial form, the corneal opacification can either be diffuse or arcus shaped.
A bilateral corneal arc can be a sign of hyperlipoproteinemia, especially of type 2.
Diffuse corneal opacification, either isolated or with a corneal arc, is a common finding and key element in genetic disorders of HDL metabolism, such as LCAT deficiency, fish eye disease, Tangier disease and APO A1 deficiency (2, 4, 9, 12).
In Tangier disease and LCAT deficiency there is hardly any visual impairment and in Tangier disease the corneal opacities are only evident by slit lamp examination. Systemic abnormalities are associated with both conditions (2). In our otherwise healthy patient with massive corneal opacities and visual impairment, the diagnosis of APO A-1 deficiency or more likely Fish-Eye Disease is put forward based on the partially diminished cholesterol-esterification rate. The fact that only the alpha-LCAT activity

	TANGIER DISEASE	LCAT DISEASE	Fish eye disease
Visual impairment	no	no	yes
Corneal opacities	Evident only by slit lamp examination	Evident with the naked eye	Remarkable (comparable to boiled fish eyes)
Systemic abnormalities	Yellow tonsils Hepatosplenomegaly Lymphadenopathy Neuropathy	Anaemia Proteinuria Chronic renal failure Hypertension Atherosclerosis	no
HDL	low	low	Low HDL, Apo A-1 deficiency
LCAT	Normal LCAT activity	Total LCAT deficiency (alfa and beta)	Alfa-LCAT deficiency
Differential diagnosis			Apo A-1 deficiency syndrome: with Atherosclerosis Planar xanthomas

was absent, is suggestive for Fish-Eye Disease or for Apo A-1 deficiency.

LCAT-alpha preferentially binds to HDL molecules (that contain Apolipoprotein A-1 which is the major activator of the LCAT enzyme) whereas LCAT beta esterifies LDL and VLDL molecules. The LCAT deficiency in Fish Eye Disease affects the LCAT alpha activity only (8,17,18). It is an extremely rare genetic disorder characterised by severe HDL deficiency, apo A-1 deficiency and an alpha-LCAT enzyme deficiency. However the clinical hallmark of this disease is the remarkable corneal opacification. Despite a lifelong virtual absence of HDL, which is the type of cholesterol protecting against atherosclerosis, Fish Eye Disease is not characterised by premature atherosclerosis (7) in contrast to APO A-1 deficiency which is associated with xanthomata and atherosclerosis, making a differential diagnosis possible. In this patient, neither of these two signs was present. A direct alpha-LCAT mass determination would lead to the final diagnosis.

CONCLUSION

We describe a patient with bilateral massive corneal opacities representing lipid vacuoles on pathological examination. The differential diagnosis includes genetic disorders of the HDL metabolism, such as LCAT deficiency, Tangier disease, Fish Eye Disease and Apo A-1 deficiency.The clinical and biochemical evidence points to the diagnosis of fish eye disease.

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