Coronary heart disease in a patient with cerebrotendinous xanthomatosis

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Coronary heart disease is a prevalent condition and a leading cause of death in developed countries. Most cases are due to the cluster of classical risk factors, such as smoking, diabetes, high blood pressure and dyslipidaemia. However, a few patients develop severe and premature arteriosclerosis in spite of absence of common risk factors. Here, we present the clinical, analytical and molecular features of a 36-years-old man who died from advanced ischaemic heart disease as a result of cerebrotendinous xanthomatosis (CTX), a rare condition characterized by elevation in plasma and most tissues of cholestanol and where neurological impairment is the hallmark of this disease. We discuss the relevance of heart disease and the mechanism leading to accelerate arteriosclerosis is CTX.

Keywords: cerebrotendinous xanthomatosis, coronary heart disease, atherosclerosis, cholestanol, cholesterol, Sterol 27-hydroxylase.

Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive disease resulting in the overproduction and storage of cholestanol, characterized by the appearance of tendon xanthomas, dementia, cerebellar ataxia and cataracts. The defect is caused by the absence of the sterol 27-hydroxylase enzyme (CYP27A1), involved in the biosynthesis of biliary acids and associated with incomplete oxidation of the cholesterol side chain [1, 2]. Cardiac manifestations are less remarkable, although in the case presented they were the cause of severe coronary disease resulting in death.

Case report

The patient was a 36-year-old man, who had undergone operations at the age of 9 years for bilateral cataracts and at 12 years for deformities in both ankles. At this time mental retardation was noted, as well as multiple hard subcutaneous tumours on the maxilla, forearms, sternum, both knees and the Achilles tendon. In 1992, he was referred to our hospital for study of the xanthomas. There was no history of toxic habits, cardiovascular risk factors, or allergies. The blood pressure was 110/70, the heart rate 70 b.p.m., weight 62 kg, height 1.59 m. There were no cardiopulmonary or abdominal findings of note, although xanthomas were present on the lower maxilla, sternum and both knees (Fig. 1). The level of cholesterol was 250 mg dL⁻¹, triglycerides 330 mg dL⁻¹, HDL cholesterol 41 mg dL⁻¹ and LDL cholesterol 142 mg dL⁻¹. The apolipoprotein A1 was 128 mg dL⁻¹ and apolipoprotein B100 190 mg dL⁻¹. Histopathological study of a biopsy from a xanthoma showed a dermis with lymphocyte infiltration, partially occupied by deposits of cholesterol crystals (Fig. 2). CTX was diagnosed from the
clinical data, and treatment initiated with chenodeoxycholic acid (750 mg day\(^{-1}\)), although with poor compliance. In 1993, he was admitted to another centre with an acute anterior myocardial infarction, which was treated with aspirin and β-blockers. In 1994, he was readmitted to our hospital with an inferior reinfarction, complicated by cardiac insufficiency. An echocardiogram showed a dilated left ventricle with anterior septal apical dyskinesia and inferior hypokinesia; the global ejection fraction was 34%. Cardiac catheterization, performed in 1996, revealed diffuse arteriosclerosis with 100% stenosis in the middle third of the right coronary artery, 50–70% obstruction in the left descending artery, and 70–90% in the proximal circumflex artery. Ventriculography showed an ejection fraction of 13% with multiple areas of hypokinesia, akinnesia and dyskinesia. Therapy was started with vasodilators, diuretics, digoxin and antiaggregating agents. He was readmitted in 1997 and 1999 with cardiac failure and in 2001 he was seen in the emergency department because of a prolonged episode of chest pain, dyspnoea, and cardiogenic shock, followed a few minutes later by electromechanical dissociation and death. The family refused permission for an autopsy.

The proband was the second of six children of nonconsanguineous parents. Two siblings (first and fourth) died in infancy of unknown causes. The third child, a 30-year-old woman, has bilateral cataracts and shows disseminated xanthomas; in May 2002 she was admitted to our centre with a left sylvian stroke. The fifth child, a 24-year-old man, has cataracts and epilepsy, and is receiving insulin therapy for type 1 diabetes. The sixth child, an 18-year-old man, has no apparent signs of disease.

Blood samples, obtained from all the family except the father, were anticoagulated and sent to the University of Modena for DNA analysis. The sample from the sixth child was not suitable for analysis. The mutation found in exon 8 was a single-base substitution of A for G at codon 441 [CGG (Arg) to CAG (Gln)]. Figure 3 shows the analysis of the mutation in the family and the proband. Serum cholestanol levels in the proband was 3.8 mg dL\(^{-1}\) (normal values <1 mg dL\(^{-1}\)).

**Discussion**

The molecular analysis demonstrated a mutation at position 441 in exon 8 (Arg→Gln), already reported by Kim et al. in a Japanese population [3] and seen by Garuti et al. in Italian subjects [4], determined by culture of fibroblasts, which abolish the sterol 27-hydroxylase enzyme activity.
The main symptoms of this disease involve eye, skin, and cerebral manifestations, with cardiovascular symptoms being of secondary importance. The first review to study this disease, which included 53 patients, reported the presence of cardiac disease in four, its absence in 21, with no mention made in the remaining 28 patients [5]. A recent review reported clinical cardiovascular disease in 15 of 144 patients with CTX (10.4%), including myocardial infarction (five cases), angina pectoris (one case), coronary artery disease (five cases) and ischaemic changes on the electrocardiogram (four cases) [6].

Although our patient had a myocardial infarction at the age of 38 years, there were no obvious risk factors for early arteriosclerosis, except for mild mixed dyslipaemia. Interestingly, dyslipaemia is not usually associated with CTX and the lipoprotein profile is generally referred to as ‘antiatherogenic’, with low circulating levels of cholesterol. However, prevalence of arteriosclerosis is higher than clinically reported when the disease is actively looked for. For example, four of seven patients with CTX presented lesions on the coronary angiogram, although two patients with coronary stenoses were asymptomatic [7]. Furthermore, carotid ultrasound examination enabled early detection of asymptomatic atherosclerosis in a 34-year-old woman with CTX, with plaque at both carotid bifurcations [8].

The mechanism leading to early onset arteriosclerosis in this disease is unknown. In theory, it would appear that an accumulation of cholestanol in the subendothelial region contributes to the growth of the deposits, although in an autopsy study cholestanol represented just 2.8% of all the sterols in the aortic plaque [5]. The possibility that the capacity for reverse cholesterol transport is reduced in CTX has recently been proposed. Basically, 27-hydroxylase, which is expressed in several other cells as well as in the liver, such as macrophages and endothelial cells, seems to contribute to the transport of peripheral cholesterol to the liver by transforming intracellular cholesterol into 27-hydroxycholesterol, a more polar product and which is captured by albumin. This mechanism, which is complementary to the role of HDL, is absent in CTX, so that it may well contributed to the development of arteriosclerosis [9, 10].

From the point of view of therapy, treatment consists of administration of cholic or deoxycholic acid, which reduces the levels of cholestanol in the blood and the tissues, with the subsequent neurological improvement. The role of LDL apheresis and the addition of HMG-CoA-R inhibitors remain controversial. Whilst treatment with simvastatin potentiates the reduction in cholestanol obtained with chenodeoxycholic acid [11], this combination has not been shown to improve neurological impairment or prevent atherosclerosis [8]. Although it has not yet been determined, analogy with other metabolic diseases, such as familial hypercholesterolaemia [12], would suggest that liver transplantation might be helpful.

In summary, this case of a 36-year-old man with CTX who died following several episodes of heart attacks and cardiac failure highlights the importance of early onset atherosclerosis in this disease.

Conflict of interest
None declared.

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References

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