Pinpoint skin lesions in a familial hypercholesterolaemia homozygote

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The case is reported of a 2-y-old girl referred to the outpatient lipid clinic because of a tiny cutaneous xanthoma on the dorsum of the left foot and a family history of hyperlipidaemia and coronary heart disease (CHD). Fasting serum total cholesterol levels were remarkably high (27.1 mmol l\(^{-1}\), 1050 mg dl\(^{-1}\)) and DNA analysis confirmed homozygous familial hypercholesterolaemia (class II mutation). Serum lipids were not affected by dietary intervention and cholestyramine treatment, so low-density lipoprotein apheresis was scheduled to commence at the age of 4 y.

Conclusion: An early lipid profile determination should be performed in children with a family history of premature CHD, since the physical examination may be unremarkable even in cases of severe hyperlipidaemia during the first years of life.

Key words: atherosclerosis, cutaneous xanthoma, homozygote, familial hypercholesterolaemia, LDL receptor gene

Lipoprotein abnormalities are major risk factors in the development of atherosclerosis and coronary heart disease (CHD). Therefore, children with a positive family history of dyslipidaemia and CHD should be referred for an early lipid profile determination. During the first few years of life, the physical examination is usually unremarkable, because stigmata of lipid deposition in the cornea (corneal arcus) and in tendons (xanthoma) occur later. The case is described of a girl with a tiny skin lesion on her foot and a family history of primary dyslipidaemia and CHD.

Case report

A 2-y-old girl was referred for evaluation to the Outpatient Lipid Clinic. Her parents were hypercholesterolaemic. Both of her grandfathers had suffered myocardial infarctions, at 43 and 52 y of age, respectively. On physical examination, there were no stigmata of hyperlipidaemia, except for a very small (3 × 3 mm) sallow lesion on the dorsum of the left foot (Fig. 1, arrows). The child’s fasting serum lipid profile was: total cholesterol (TC) 27.1 mmol l\(^{-1}\) (1050 mg dl\(^{-1}\)), triglycerides (TG) 1.85 mmol l\(^{-1}\) (164 mg dl\(^{-1}\)) and high-density lipoprotein cholesterol (HDL-C) 1.34 mmol l\(^{-1}\) (52 mg dl\(^{-1}\)). Apolipoprotein (Apo) A-I levels were 64 mg dl\(^{-1}\), and ApoB 595 mg dl\(^{-1}\). Her mother’s fasting serum lipids were: TC 11 mmol l\(^{-1}\) (425 mg dl\(^{-1}\)), TG 1.8 mmol l\(^{-1}\) (158 mg dl\(^{-1}\)) and HDL-C 1.1 mmol l\(^{-1}\) (42 mg dl\(^{-1}\)). Her father’s lipids were: TC 10.1 mmol l\(^{-1}\) (390 mg dl\(^{-1}\)), TG 1.5 mmol l\(^{-1}\) (135 mg dl\(^{-1}\)) and HDL-C 1.0 mmol l\(^{-1}\) (39 mg dl\(^{-1}\)). Remarkably, her 4-y-old sister was normolipidaemic. The clinical diagnosis was familial hypercholesterolaemia (FH). Dietary intervention together with oral cholestyramine (8 g daily) was initiated, but 8 wk later there was no improvement in the lipid profile. On DNA analysis, the girl was found to be an FH homozygote for the exon 11 G1646A mutation (class II mutation). She was scheduled to commence low-density lipoprotein (LDL) apheresis at the age of 4 y.

Discussion

FH is an inherited autosomal dominant disorder of lipoprotein metabolism caused by mutations in the LDL receptor gene (1). Heterozygous FH occurs in about 1 in 500 people worldwide, while homozygous FH occurs with a frequency of about 1 in 250 000. Heterozygotes have increased LDL-cholesterol (LDL-C) levels and a high risk of CHD as adults, whereas homozygotes have markedly elevated LDL-C and develop atherosclerotic cardiovascular disease as children and adolescents (1).
Over 600 different LDL receptor mutations have been described in FH patients (1, 2). FH mutations may be divided into five classes in terms of their effect on receptor function in vitro (2). Class II mutations, as in this case, are single-base changes and are associated with >2% receptor activity ("receptor-negative" FH) (2). Homozygous receptor-negative FH patients often present with cutaneous xanthomas as children. These occur in the web spaces between the fingers, and on the elbows, knees, heels and buttocks. The pinpoint cutaneous xanthoma, described in this case, indicates that the diagnosis occurred early. Survival of the untreated receptor-negative homozygous FH patient into the third decade of life is unusual (1, 2).

A trial of drug therapy with anion-exchange resins (e.g. cholestyramine) or statins may be warranted, since some patients, particularly those with class V mutations, may have a modest response (3, 4). LDL apheresis every 1–2 wk is the treatment of choice in homozygous FH (5). This may lead to the regression of xanthomas and retard the progression of atherosclerosis. However, venous access is often problematic, especially in young children, and the optimal timing for the initiation of LDL apheresis is debatable. Children who have been treated for a long period with this method have shown normal rates of growth and development (1, 5). Liver transplantation has been successfully performed in some cases of homozygous FH, while liver-directed somatic gene therapy is a promising future option, which remains experimental (1).

References

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