Corneal arcus and xanthomas in homozygous familial hypercholesterolemia: First report from China

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We report the case of a 12-year-old male who developed corneal arcus and multiple skin lesions with a 10-year history of xanthomas. The lesions appeared over his fingers, hands, elbows, knees, buttocks and feet. Laboratory studies showed a total serum cholesterol level of 752.1 mg/dL; a triglyceride level of 96.6 mg/dL; a low-density lipoprotein cholesterol level of 661.3 mg/dL. Findings were consistent with homozygous familial hypercholesterolemia. To our knowledge, this is the first such case to be reported from China.

Key words: Familial hypercholesterolemia, corneal arcus, xanthomas

Familial hypercholesterolemia (FH), a genetic disorder caused by mutations within the low-density lipoprotein (LDL) receptor gene, is characterized by an increase in plasma levels of LDL cholesterol. Homozygous FH is a rare variant, occurring with a frequency of 1:1,000,000.[1] We present a case of homozygote manifesting with corneal arcus and multiple xanthomas, which is the first reported case from China.

Case Report

A 12-year-old male, whose father was a LDL receptor (LDL-R) mutation carrier, developed corneal arcus and multiple skin lesions with a 10-year history of xanthomas. Both his parents had elevated levels of total serum cholesterol and LDL cholesterol. His elder brother died of myocardial infarction secondary to FH at the age of 7 years. Physical examination showed the presence of subcutaneous yellow nodules at the knuckles of his fingers [Fig. 1a], elbows [Fig. 1b], knees [Fig. 1c], and Achilles tendons [Fig. 1d]. They were up to 10 cm in size and partly tended to coalesce. Some other yellow nodules of varying sizes under the skin erupted over the buttocks [Fig. 1e]. This patient had no problems with his vision. Intraocular pressures were unremarkable. The ocular exam revealed a partial circumferential white-grey deposit corresponding to corneal

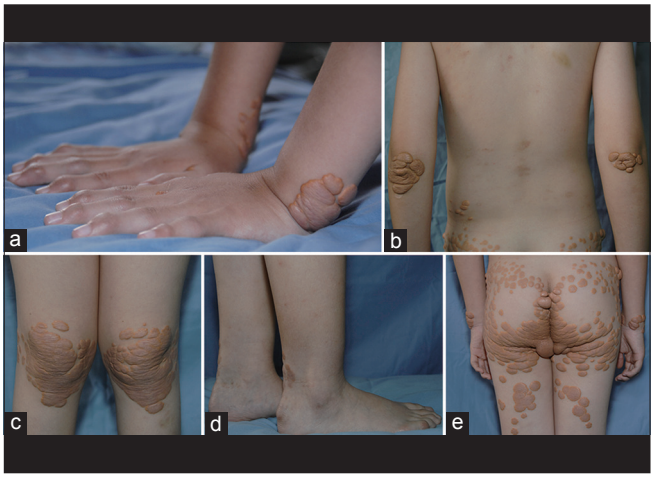

Figure 1: Findings at presentation (a) Xanthomas over the fingers (b) Xanthomas over both elbows(c) Xanthomas over both knees tending to coalesce (d) Xanthomas over the Achilles tendons (e) Xanthomas of varying sizes under the skin erupted over the buttocks

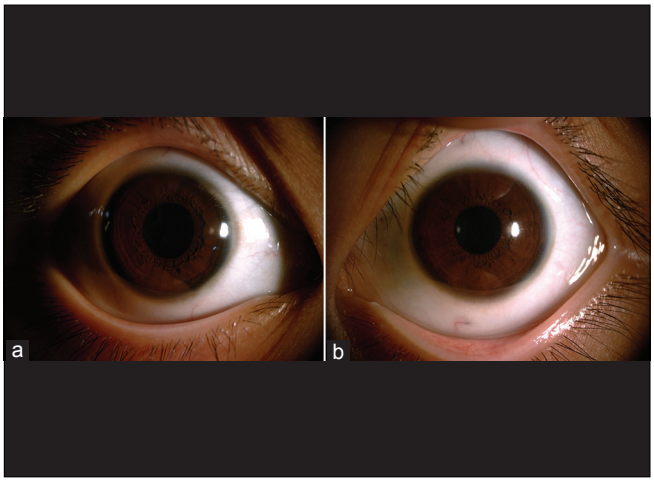

Figure 2: Findings at presentation. The ocular exam showed a partial circumferential (from 2 O'clock to 4 O'clock) white-grey deposit corresponding to corneal arcus. (a) Right eye The ocular exam showed a partial circumferential (from 2 O'clock to 4 O'clock) white-grey deposit corresponding to corneal arcus. (b) Left eye

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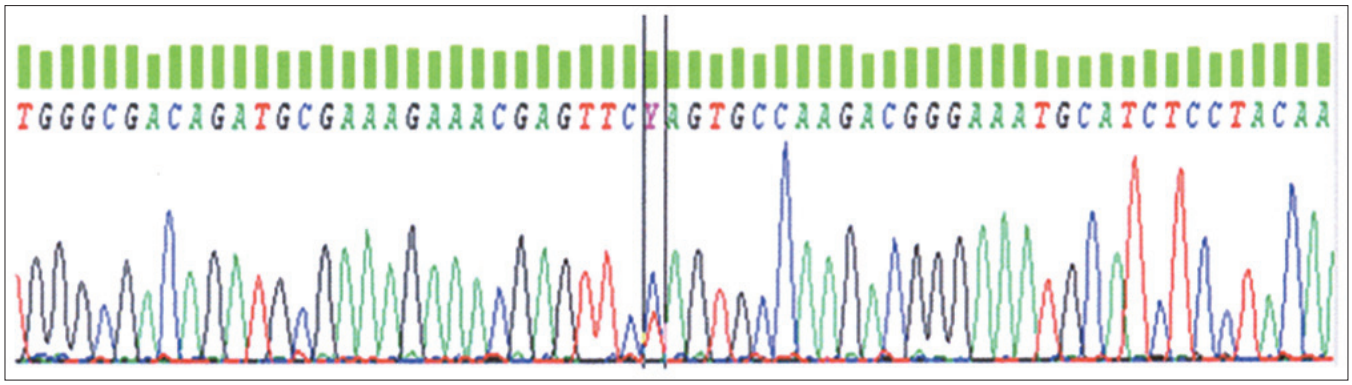

Figure 3: LDL-R nucleotide sequences. There are C > T heterozygous double peaks at 97 in the second exon of LDL-R gene

arcus [Fig. 2a and b]. Fundus examination was normal. B-scan revealed extensive plaques and enhanced intima-media thickness of common carotid arterial wall. Laboratory studies disclosed the following values: Total serum cholesterol, 752.1 mg/dL (normal range, 110-220 mg/dL); triglyceride, 96.6 mg/dL (normal range, 50-150 mg/dL); LDL cholesterol, 661.3 mg/dL (normal range, 80-140 mg/dL). Findings were consistent with type IIa hyperlipoproteinemia. As is shown in the figure [Fig. 3], there are cytosine (C)>thymine (T) heterozygous double peaks at 97 in the second exon of LDL-R gene, which is in GenBank as a known mutation of NM_001195798.1:c. 97C>T. This mutation resulted in the change from C to T 33rd codon in E2 of LDL-R gene and, thus, glutamine became the stop codon in the corresponding amino acid (NP_001182732.1:p.Gln33X). The result of genealogical analysis indicated that his father had a similar gene mutation. A diagnosis of homozygous familial hypercholesterolemia was made.

Homozygous FH is clinically characterized by cutaneous xanthomas, enlarged Achilles tendons, atherosclerosis, and corneal arcus, usually developing from early childhood.[2]

Homozygotic patients usually manifest corneal arcus before the age of 10 years. Although no significant correlations were obtained between corneal arcus and patterns of hyperlipoproteinaemia in previous observations,[3] a recent study of homozygous familial hypercholesterolemia series indicated that patients with corneal arcus had higher cholesterol-year score and was correlated with calcific atherosclerosis.[4] The exact biochemical mechanisms of corneal arcus remain controversial. One explanation is the proximity to limbal vasculature that may increase endothelial permeability to lipids via active scavenging mechanisms. Another is the temperature gradient that can alter lipid deposition as the infiltrating particles pass from limbal blood vessel into the cornea. Finally, the collagen fiber gradient might filter the lipid-rich particles.[5]

Early combination therapy with LDL apheresis, statins, and cholesterol absorption inhibitors are advised in children with homozygous FH at the highest risk.[6]

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