Abstract
Homozygous familial hypercholesterolemia is an autosomal dominant disorder of lipid metabolism, characterized by reduced clearance of low-density lipoprotein-cholesterol and a high risk of rapid development of cardiovascular diseases. Its incidence is relatively rare and estimated to be one in one million in general populations. Here, we report homozygous familial hypercholesterolemia in two Egyptian young siblings, presented with cutaneous, tendinous xanthomas, and corneal arcus. One of them has symmetric subcutaneous lipomatosis, which has not been reported before in association with familial hypercholesterolemia.

Key Words: Familial hypercholesterolemia, subcutaneous lipomatosis, xanthomas

Introduction
Familial hypercholesterolemia (FH) is an inherited autosomal dominant disorder of lipid metabolism. It is caused by a defect in chromosome 19 and characterized by raised levels of low-density lipoprotein-cholesterol (LDL-C) (“bad cholesterol”) that is passed down through families. The condition begins at birth and can cause heart attacks at an early age. Clinically, FH is characterized by deposits of cholesterol in the vascular wall, causing atheromas, and extravascularly in the form of xanthomas, especially in the skin and tendons of patients with severe hyperlipidemia. Here, we present two young Egyptian siblings with FH.

Case Report
Two young sisters of age 6 and 4 years, born to a consanguineous marriage, presented to our dermatology clinic complaining of scattered, painless, and yellowish papules and nodules since birth progressively increasing in number and size.

On examination, both children had intertriginous yellowish xanthomatous plaque in the gluteal cleft since birth (1 × 2 cm) [Figure 1a] and scattered yellowish xanthomas on both knees [Figures 1b and 2c] and elbows [Figure 1c]. In addition, the younger sister had yellowish streaks of plane xanthoma on the side and back of the neck [Figure 2a], periumbilical xanthoma [Figure 2b] and two subcutaneous soft swellings below the knees [Figure 2c]. Ophthalmologic examination revealed lipid deposition in the cornea of both patients (arcus juvenilis) [Figures 1d and 2d]. Orthopedic examination also revealed thickened Achilles tendons of both patients.

Lipid profile was done for patients, mother, and father, and it revealed elevated total and LDL-C levels with normal triglycerides and high-density lipoprotein-cholesterol (HDL-C) levels [Table 1]. Blood sugar level, thyroid function tests, complete blood count, urine analysis, and liver and renal function tests were all normal, excluding secondary hypercholesterolemia. Hematoxylin and eosin-stained sections of the biopsied lesions revealed sheets and groups of foamy xanthoma cells in the whole dermis [Figure 1 Inset].

Echocardiography of both sisters and their parents revealed no abnormality. Ultrasound for Tendo-Achilles showed fusiform thickening with intrasubstance hypoechoic areas compatible with xanthoma. Ultrasound for the subcutaneous knee swellings revealed bilateral and symmetrical subcutaneous lipomatosis on the extensor aspect of both knees. Therefore, based on clinical, laboratory, and radiological findings, the diagnosis of homozygous FH was reached.
with FH, 75% complain of tendon xanthomas, usually located in the Achilles or extensor tendons of the hands. Achilles tendon xanthomas can be detected by physical examination and better detected by ultrasonography. Therefore, arthritis and tendinitis may attract attention to the diagnosis of patients with FH.\(^3\)

Xanthomas develop because of lipid leakage from the vasculature into the surrounding tissues, where macrophages subsequently phagocytose these lipids. Because cholesterol is not degraded, it accumulates within these cells, creating foamy macrophages. The extracellular cholesterol crystallizes into the clefts, inducing an inflammatory reaction with giant cells and resultant fibrosis.\(^4\)

FH has two forms: Heterozygous and homozygous. Heterozygous FH is more common, with a reported prevalence of 1/500 and plasma LDL-C in the range of 297-425 mg/dl. Homozygous FH is rare, with a prevalence of 1/1,000,000 with plasma LDL-C of 444-1089 mg/dl.\(^5\)

Our patients—the two young sisters—were diagnosed as having homozygous FH, since their serum cholesterol level was more than 600 mg/dl; moreover, their parents have raised serum cholesterol level more than 200 mg/dl. Both cases had cutaneous and tendon xanthomas since birth, with thickened Achilles tendon, and arcus juvenilis of the cornea in the first decade of life, but fortunately, without cardiovascular complications yet. This goes with other authors who set the diagnostic criteria of homozygous FH [Table 2].

Effective FH screening by cholesterol testing should be done for all members of the extended family. The treatment of FH consists of a diet low in total and saturated fats with a combined drug therapy.\(^9\) Effective drug combinations include low doses of bile acid sequestrants together with HMG-CoA reductase

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**Table 1: Lipid profile of patient, her younger sister, father, and mother**

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<thead>
<tr>
<th></th>
<th>Father</th>
<th>Mother</th>
<th>Patient</th>
<th>Sister</th>
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<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>230</td>
<td>215</td>
<td>600</td>
<td>616</td>
</tr>
<tr>
<td>Total triglycerides (mg/dl)</td>
<td>210</td>
<td>150</td>
<td>50</td>
<td>67</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>194</td>
<td>190</td>
<td>440</td>
<td>425</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>44</td>
<td>40</td>
<td>55</td>
<td>46</td>
</tr>
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</table>

HDL-C: High-density lipoprotein-cholesterol, LDL-C: Low-density lipoprotein-cholesterol

The whole family was advised to consume a diet low in cholesterol and saturated fat and rich in unsaturated fat in addition to lipid lowering drugs. Atorvastatin was prescribed for both patients (10 mg daily) and their parents (20 mg daily). After one month of treatment, the cholesterol level was reduced to 542 mg/dl in the older patient and to 500 mg/dl in the younger patient. All patients and their parents are still under treatment and follow-up.

**Discussion**

FH is clinically diagnosed by confirming the family history and characteristic findings such as cutaneous and tendon xanthomas. Cutaneous xanthomas may initially present in the intergluteal cleft or interdigital spaces on the dorsal surface of the hands and feet. Planar surfaces over the elbows and knees are the other common sites of appearance of xanthomas.\(^2\) Of the affected individuals

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**Figure 1:** Older patient: Multiple xanthomas; intergluteal cleft (a) knees (b) elbows (c) and arcus juvenilis of corneae (d). Inset: Foamy xanthoma cells occupying the dermis (H and E, ×200)

**Figure 2:** Younger sister: Multiple xanthomas; sides and back of neck (a) periumbilical (b) knees with subcutaneous lipomatosis (c) and arcus juvenilis of corneae (d)
inhibitors or niacin or all these agents combined. A new third-generation statin, rosuvastatin demonstrated a significantly greater reduction in LDL-C as well as significantly greater increase in HDL-C compared to atorvastatin. So, aggressive treatment including diet control, lipid lowering drugs, exercise, and control of risk factors will help reduce the morbidity and mortality associated with this disease. Follow-up is mandatory for monitoring treatment and early detection of cardiovascular complications and prompt treatment.

To the best of our knowledge, the association between FH and symmetrical subcutaneous lipomatosis was not reported before, and we present our case as the first report of this association. Whether there is a genetic association between both conditions or it is an accidental combination, it requires further research. However, Rubinstein et al. reported a family with familial combined hyperlipidemia wherein the affected members had nonsymmetric subcutaneous lipomatosis, and suggested the existence of a genetic linkage between the two characteristics. Moreover, they found a correlation between the degree of hyperlipidemia and the amount of these subcutaneous lipomas.

What is new?
• We present our case as the first report of the association between homozygous FH and subcutaneous lipomas, which are interestingly symmetrically distributed.
• Is there a relationship between the amount of these lipomas and the level of hyperlipidemia? Is there a genetic linkage between those entities or an accidental association? The answers to these questions require further research.

References

Table 2: Diagnostic criteria for homozygous FH from the literature

<table>
<thead>
<tr>
<th>Publication</th>
<th>Diagnostic criteria for homozygous familial hypercholesterolemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haitas et al.</td>
<td>Hypercholesterolemia in both parents (when available) Total serum cholesterol &gt;13 mmol/L (500 mg/dl) + presence of xanthomas in the first decade of life</td>
</tr>
<tr>
<td>Goldstein</td>
<td>Unique yellow-orange cutaneous xanthomas (frequently present at birth) Tendon xanthomas, corneal arcus, generalized atherosclerosis during childhood Plasma cholesterol &gt;650 mg/dl in non-jaundiced child</td>
</tr>
<tr>
<td>Santos et al.</td>
<td>Untreated LDL&gt;500 mg/dl Plus at least one: • Genetic testing confirmation of two mutated LDL-R alleles • Tendinous and/or tuberous xanthoma prior to age 10 years • Documented elevated LDL and both parents consistent with HeFH (LDL&gt;200 mg/dl). If parent unavailable, history of CAD in first-degree relative (age: male &lt;55 years or female &lt;60 years)</td>
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LDL-R: Low-density lipoprotein receptor, HeFH: Heterozygous familial hypercholesterolemia, CAD: Coronary artery disease