Journal of Clinical Lipidology (2013) 7, 683–688

Journal of Clinical Lipidology

Case Study

Delayed diagnosis of familial hypercholesterolemia: A case report of two patients from Egypt

Areej Ahmad Alkhateeb, MSc*, Hussien Heshmat Kassem, MD, Wasseem Amin Wahba, MD, Magdy Ibrahim Algowhary, MD, PhD

Department of Cardiovascular Medicine, Asyut University Hospital, Asyut 71111, Egypt (Drs. Alkhateeb and Algowhary); and Department of Cardiovascular Medicine, Cairo University, Cairo, Egypt (Drs. Kaseem and Wahba)

KEYWORDS:
Familial hypercholesterolemia;
Homozygous familial hypercholesterolemia;
Xanthomas;
Premature atherosclerosis;
Aortic stenosis

Abstract: Two young Egyptian women with homozygous familial hypercholesterolemia (HoFH) were diagnosed after the appearance of vascular complications despite the presence of family history and suggestive clinical features. The first patient was treated by repeated surgical excisions of disfiguring tendon xanthomas diagnosed as "lipomas". The second patient, presenting with embolic ischemia, had an amputation of the forearm and repeated reconstructive surgical procedures. Each patient was diagnosed as HoFH after presenting with typical angina to a cardiologist. The first patient had severe aortic stenosis, left main and multi-vessel coronary artery disease, and died at age 21 years. The second patient had multivessel coronary artery disease that was treated by Percutaneous Coronary Intervention (PCI) with drug-eluting stents. These cases demonstrate that the delayed diagnosis of xanthomas and familial inheritance characteristic of HoFH leads to atherosclerosis and aortic stenosis early in life.

Familial hypercholesterolemia (FH) is a genetic disorder that typically exhibits autosomal dominant inheritance in which only 1 low-density lipoprotein receptor (*LDLR*) allele is abnormal. However, it can also present in a more severe form with LDL cholesterol (LDL-C) plasma concentrations that exceed 500 mg/dL. This may be due to a homozygous FH (HoFH) in which both LDL-C receptor alleles are defective or absent because of the same genetic alteration. More commonly, both receptors are found to be dysfunctional (compound heterozygosity) because of differing defects in each receptor allele. The heterozygous state (HeFH) occurs with worldwide prevalence of approximately 1 in 500 persons, whereas having abnormal genes in both alleles is rare and occurs in approximately 1 in 1 million persons.[1] A founder effect has been described in South Africa, whereby the frequency of HeFH is approximately 1 in 70 persons.[2] FH was the first genetic disorder recognized to cause early cardiovascular events and is responsible for approximately 50% of early cardiovascular disease events in untreated men by the age of 50 and 30% in untreated women by the age of 60.[3,4] The monogenic inheritance of FH was first proposed in the mid-1960s by Khachadurian et al.[5] Later on, Brown and Goldstein[6] elucidated the *LDLR* pathway, followed shortly by the cloning of the *LDLR* gene and identification of the first mutation. Since then, >1000 mutations have been identified. Most of the mutations are related to absence or dysfunction of the *LDLR* gene and other genetic variants such as defective *apolipoprotein B100* and proprotein convertase subtilisin/kexin 9 (PCSK9) genes. Here, we report 2 cases of HoFH with atypical presentations, delayed diagnosis, and undesirable outcomes.

All authors contributed equally to this work. The authors report no conflicts of interest and no sources of financial support for this report.
* Corresponding author.
E-mail address: areejalkhateeb@yahoo.com
Submitted July 17, 2013. Accepted for publication August 3, 2013.

1933-2874/$ - see front matter © 2013 National Lipid Association. All rights reserved.
http://dx.doi.org/10.1016/j.jacl.2013.08.002

Case report

The first patient was a 21-year-old, single woman from Asyut, Egypt, who attended the cardiology clinic for complaint of recurrent attacks of typical anginal pain. These episodes started at age 18 years and 6 months and occasionally were accompanied by near syncope. During childhood, she noticed the appearance of multiple painless small swellings on the front of the knees, then the ankles, and finally on the distal finger joints of both hands. These swellings progressively increased in size with age. She was treated by a plastic surgeon with a surgical excision of the recurrent swellings on the right knee, both elbows, and the back. The swellings were diagnosed as lipomata, but histologic analysis of the excised specimens was not performed. During childhood she was empirically diagnosed as having rheumatic fever because of episodic arthralgia of both knees and ankles that was preceded by fever and tonsillitis. This condition was treated with aspirin and penicillin. Menses started at age 18 years and were followed by oligomenorrhea. The patient was born to consanguineous parents, 6 living siblings were apparently healthy and did not have any skin lesions, the mother had symptoms suggestive of an acute coronary syndrome at age 40 years old, and the father had arcus cornea since childhood. Three paternal cousins were born to consanguineous parents and had similar clinical presentations as this young woman with xanthomas before

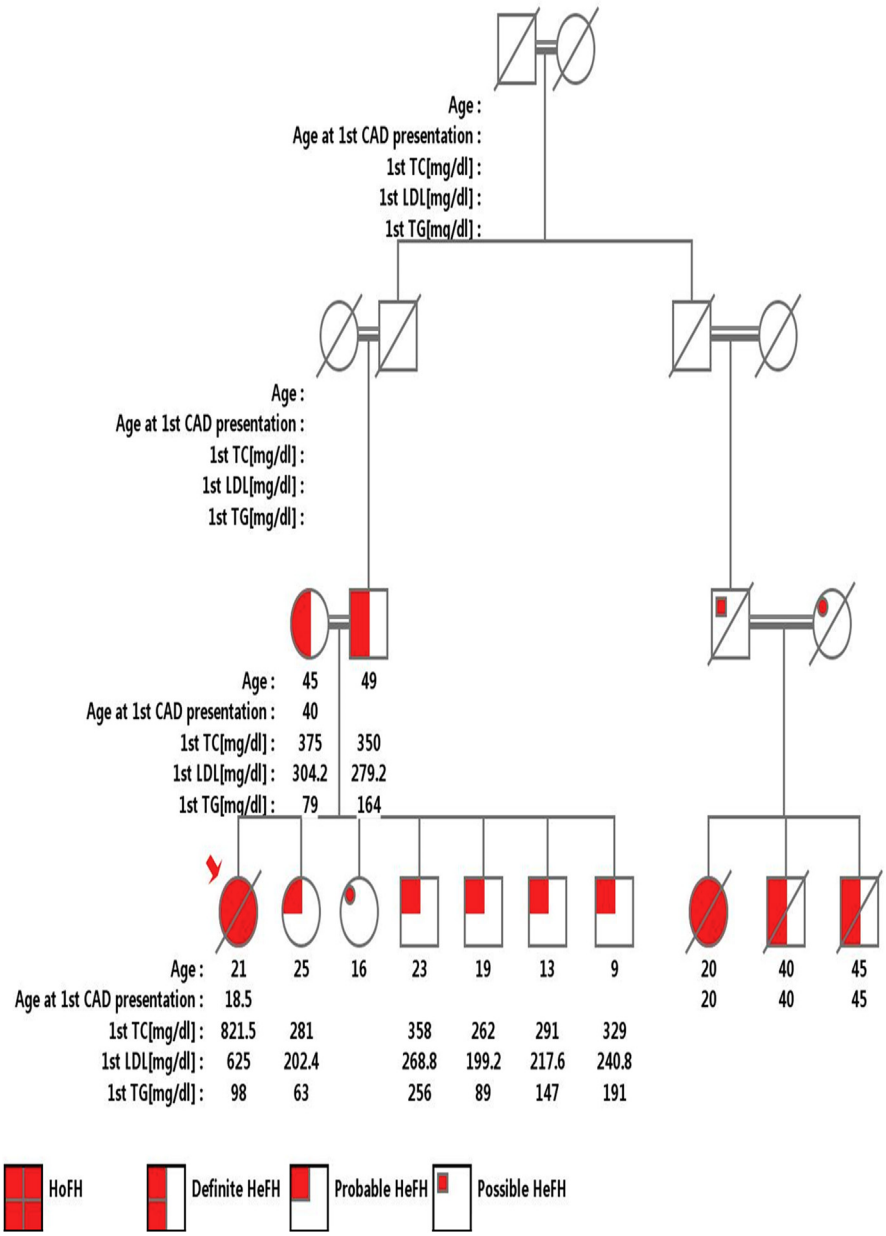

Figure 1 Genomic pedigree chart of case 1 and her family members updated in 2013. The index patient is indicated with an arrow. Men are represented by squares and women by circles. Consanguinity between the couples is indicated with a double line. Deceased persons are indicated by a diagonal line drawn through the symbol. CAD, coronary artery disease; HeFH, heterozygous familial hypercholesterolemia; HoFH, homozygous familial hypercholesterolemia; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.[7]