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Case Report

The Lifelong Burden of Homozygous Familial Hypercholesterolemia

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ABSTRACT

Homozygous familial hypercholesterolemia is caused by mutations in the low-density lipoprotein receptor gene. It is diagnosed in children or youth who present with extensive tendinous and cutaneous xanthomas and extreme elevation of low-density lipoprotein cholesterol. Untreated, premature coronary artery disease develops in the teenage years or earlier and survival to ages older than 30 years is rare. Herein we describe the clinical course of a patient with homozygous familial hypercholesterolemia treated according to the standards of care and experimental approaches. Despite aggressive therapies, atherosclerosis in all vascular beds progressed, leading to the patient's demise at age 59 years, highlighting the importance of early diagnosis and appropriate follow-up.

RÉSUMÉ

L'hypercholestérolémie familiale homozygote est causée par des mutations du gène des récepteurs des lipoprotéines de basse densité. Elle est diagnostiquée chez des enfants ou des jeunes qui présentent un grand nombre de xanthomes tendineux et cutanés et une élévation extrême du taux de cholestérol des lipoprotéines de basse densité. En l'absence de traitement, une coronaropathie prématurée s'installe à l'adolescence ou avant, et la survie du patient au-delà de 30 ans est rare. Nous décrivons ici l'évolution clinique de l'hypercholestérolémie familiale homozygote chez un patient ayant reçu les soins de référence et des traitements expérimentaux. Malgré des traitements vigoureux, l'athérosclérose a évolué dans tous les lits vasculaires, menant au décès du patient à l'âge de 59 ans, ce qui souligne l'importance d'un diagnostic précoce et d'un suivi approprié.

Homozygous familial hypercholesterolemia (HoFH) is an orphan disease, with a worldwide prevalence estimated at 1/250,000 on the basis of the prevalence of heterozygous familial hypercholesterolemia.[1] Untreated patients with severe HoFH present in childhood with extensive tendinous and cutaneous xanthomas and very premature atherosclerosis. Before the introduction of extracorporeal low-density lipoprotein (LDL) removal techniques ("LDL apheresis"), survival beyond 30 years of age was unusual.[2] Most HoFH cases are caused by homozygous or compound heterozygous mutations at the LDL receptor (*LDLR*) gene. There is marked heterogeneity in the clinical manifestations, dependent, in great part, on residual activity of the LDLR protein. Deficient or "null" mutations in *LDLR* lead to a complete absence of the LDLR function, whereas "defective" mutations lead to some residual activity and partial response to lipid-lowering medications, especially statins.

Case

The patient was born in Honduras in 1959 and was admitted in Canada as a refugee at the end of the 1980s. No medical information is available before his arrival in Canada. A novel splice-site mutation at the intron-exon 7 boundary of the *LDLR* was characterized at that time.[3] This mutation leads to a stop codon in exon 8 or to exon 8 skipping, and was associated with a 52% reduction in transcription of a dysfunctional protein or to a premature stop codon. The clinical course of the patient is summarized in Figure 1. Mean and standard error of the mean of LDL cholesterol (LDL-C) levels are shown for every year. The mean yearly LDL-C is the mean of all LDL-C values before and after LDL apheresis over a 52-week period. Although there is no "ideal" LDL-C level in the primary prevention setting, < 3.5 mmol/L is considered appropriate. In the present case, the mean yearly LDL-C was not below 5 mmol/L, which is a reflection of the difficulty in treating severe HoFH and the burden of exposure of the

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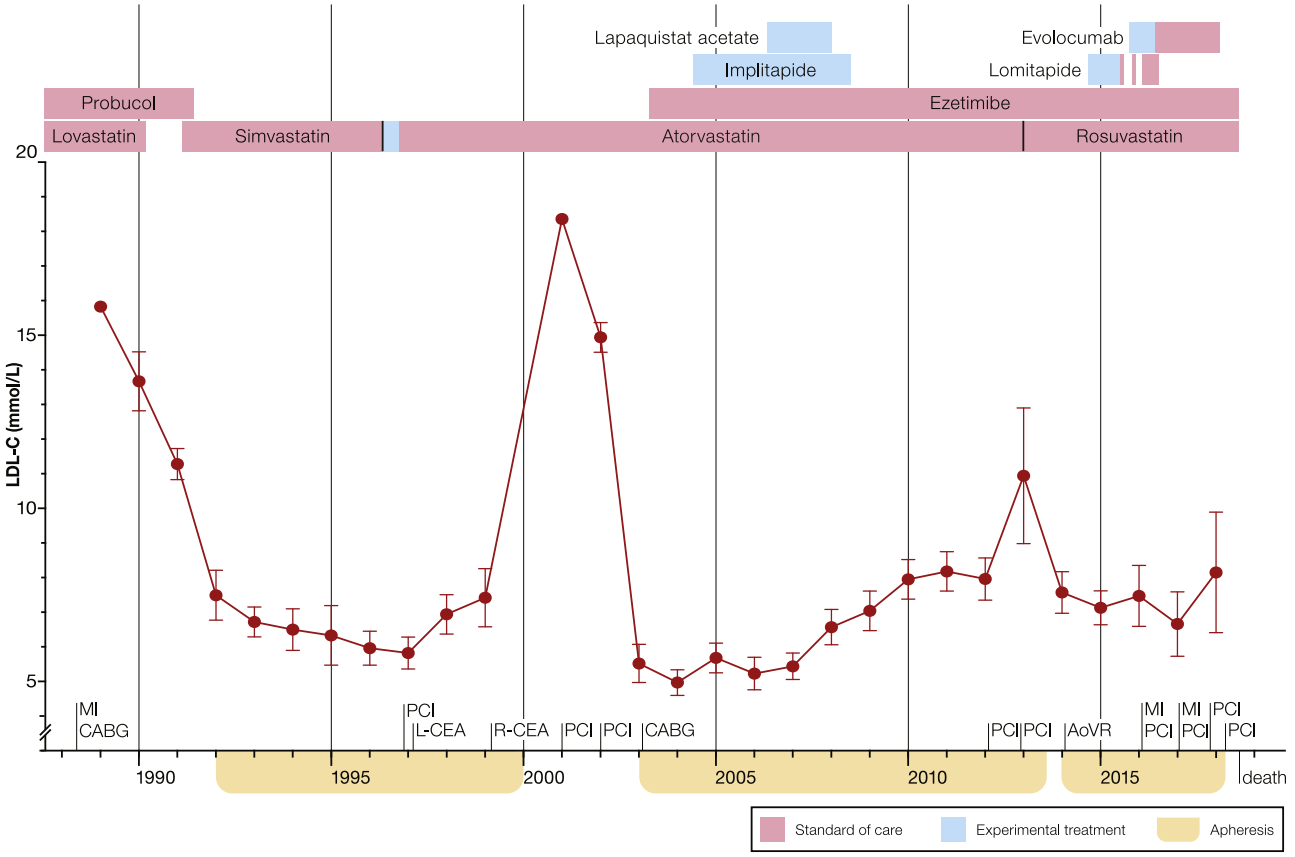

Figure 1. Clinical course. Mean and standard error of the mean of low-density lipoprotein cholesterol (LDL-C) levels are shown for every year and correspond to the mean of all LDL-C values before and after LDL-C apheresis over a 52-week period. AoVR, aortic valve replacement; CABG, coronary artery bypass surgery; CEA, carotid endarterectomy; MI, acute myocardial infarction; PCI, percutaneous coronary intervention (angioplasty); R, right.

arteries of the patient to cholesterol. Cardiovascular events are shown on the x-axis. The patient sustained a first acute myocardial infarction at age 29 years. He had subsequent myocardial infarctions at ages 56 and 57 years. The patient was admitted in August 2018 with acute cholecystitis. He sustained a cardio-respiratory arrest and could not be resuscitated. He was 59 years old, among the oldest severe HoFH survivors of whom we are aware.

LDL apheresis

The clinical features are documented in Figure 2. The top panels show the effects of extracorporeal filtration on the cutaneous and tendinous xanthomas in the right elbow (panels A and B) and right knee (panels C and D) over a 10-year period. Between 1992-2000 and 2003-2018, the patient was undergoing a 3-hour LDL apheresis session once every 2 weeks. The duration of extracorporeal LDL filtration is shown in more details in the bottom panel of Figure 1. LDL-C levels before and after LDL apheresis typically ranged from 9-12 mmol/L and 2.5-4 mmol/L, respectively. Interruptions in treatment were because of lack of availability of a filtration unit or prolonged hospitalization, which were associated with significant increases in LDL-C.

Interventions received

The patient had severe coronary artery disease and underwent multiple coronary revascularizations (x-axis, Fig. 1). The case was extensively discussed with vascular and cardiac surgeons as well as interventional cardiologists. The consensus of opinion was that further revascularizations would carry a prohibitive risk of complications and death. Panel E (Fig. 2) shows a left coronary angiogram performed in 2018 through the aortic Hemashield graft (Medi-Tech, Boston Scientific, Natick, MA), leading to a short Hemashield graft (red thick arrow) to a radial artery free graft to the left anterior descending coronary artery (red thin arrow). Panels F and G show partial (2015), then complete obstruction of the right internal carotid artery (2018; red arrow). Aortic calcifications are a frequent complication observed in HoFH individuals, often causing severe, calcific aortic stenosis with ascending aortic calcifications. In the present case, we found severe calcifications of the entire aorta from the aortic valve to the iliac vessels (panel H, red arrows).

The top panel in Figure 1 summarizes the course of medication received. Throughout the years, the patient was treated according to the standards of care (pink; higher available doses of statins and ezetimibe 10 mg/d) as well as with experimental drugs (blue). Lapaquistat acetate, an

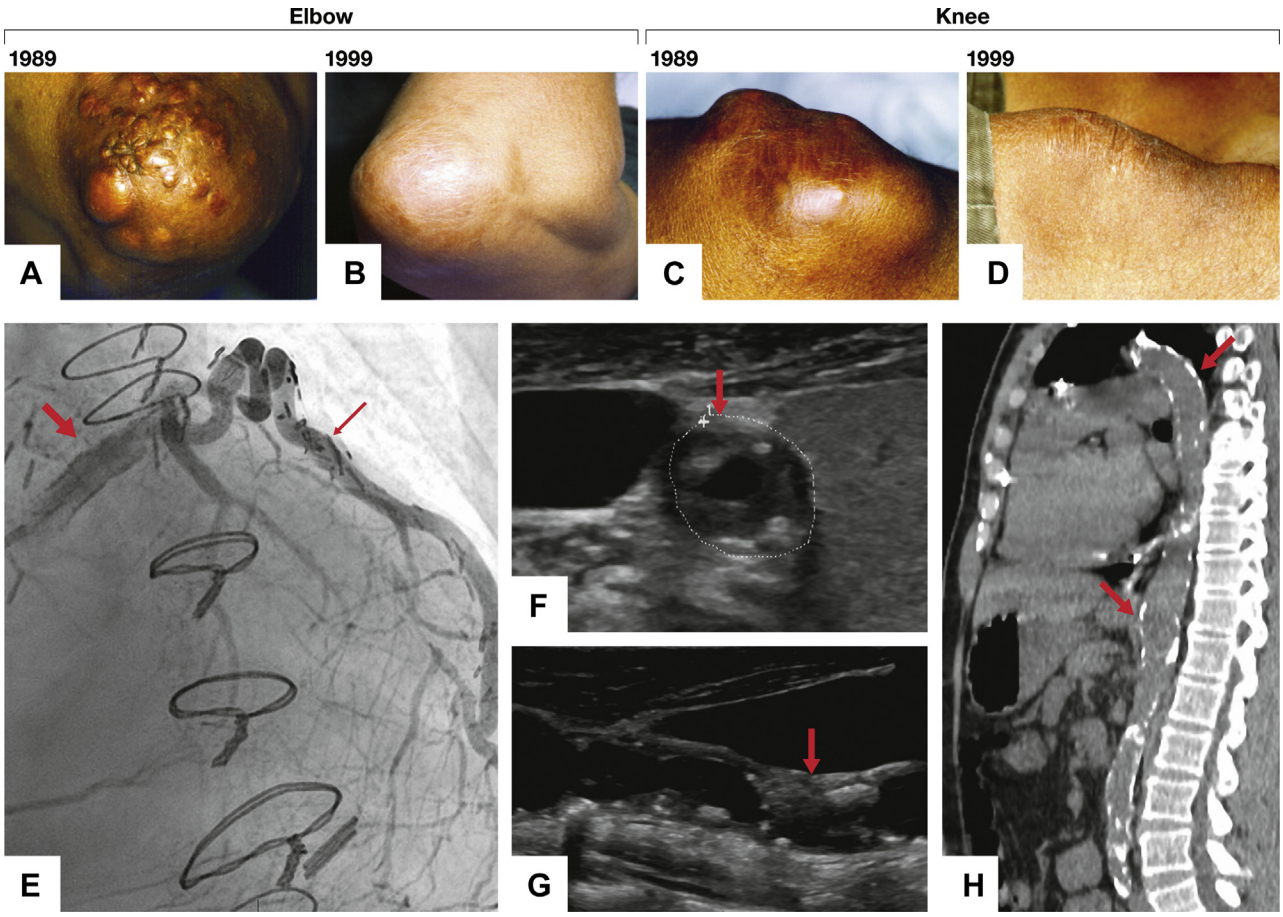

Figure 2. Clinical features. Effects of low-density lipoprotein cholesterol apheresis on the cutaneous and tendinous xanthomas in the right elbow (**A**, **B**) and right knee (**C**, **D**) over a 10-year period. (**E**) 2018 Left coronary angiogram through the aortic Hemashield graft, leading to a short Hemashield graft (**red thick arrow**) to a radial artery free graft to the left anterior descending coronary artery (**red thin arrow**). (**F**) and (**G**) show partial (2015), then complete obstruction of the right internal carotid artery (2018) (**red arrow**). (**H**) Severe calcifications of the entire aorta from the aortic valve to the iliac vessels.

inhibitor of squalene synthase, inhibits cholesterol synthesis downstream of statin-inhibited hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase. Implitapide and lomitapide, both of which inhibit the microsomal triglyceride transfer protein, were also first used in 2004 and 2014, respectively, as experimental drugs. The patient tried various doses of lomitapide (5-20 mg/d), which had to be down-titrated to 5 mg/d, then abandoned because of gastrointestinal side effects. Finally, the patient had an early access to a monoclonal antibody directed against porportein convertase subtilisin/kexin type 9 (PCSK9) (evolocumab 140 mg every 2 weeks).

Discussion

This case report highlights the clinical course of a patient with severe HoFH. Before extracorporeal LDL filtration, survival beyond age 30 years was unusual. Despite maximally tolerated medical treatment, LDL apheresis and experimental medications, the progression of atherosclerosis eventually caused the patient's demise. Clearly, more should be done with novel approaches for the treatment of HoFH.[4] The quality of life of HoFH patients is below average and the burden of disease and requirements for treatments, coupled with frequent and prolonged hospitalizations, prevent most HoFH patients from full-time employment.

The present case points out the importance of early diagnosis and appropriate follow-up of HoFH patients. HoFH cases should be referred to a centre with expertise in lipid disorders. As recently reviewed by Thompson and Parhofer,[5] LDL apheresis is still the gold standard for the treatment of HoFH and should therefore be made available in these specialized centres across Canada.

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Disclosures

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