NLA Symposium on Familial Hypercholesterolemia

NLA Symposium screening and treatment of familial hypercholesterolemia: How can we do better?
Opening and introductions

Mary McGowan, MD*

Cholesterol Treatment Center, Concord Hospital/Memorial Building, 246 Pleasant Street, Suite 210, Concord, NH 03301, USA

KEYWORDS:
Familial hypercholesterolemia; Autosomal dominant; Cardiovascular disease; Apolipoprotein B; Cascade screening; Statins; LDL apheresis; Mipomersen

Abstract: Heterozygous familial hypercholesterolemia is an autosomal dominant disorder characterized by half the normal number of low density lipoprotein (LDL) receptors and markedly elevated LDL cholesterol levels. FH is a very common disorder, affecting about one in 500 in the general population and occurring more frequently in certain ethnic groups. Untreated, roughly 50% of men and 25% of women who have FH will have had their first myocardial infarction or other cardiovascular event by the age of 50. Since roughly half of an affected individual’s first degree relatives will also have FH, Cascade Screening represents an important tool for patient identification. Although treating FH represents a clinical challenge, most affected patients can be managed with currently available treatment modalities including statins, resins, cholesterol absorption inhibitors, and niacin. LDL apheresis is an option for individuals who fail currently available oral prescription therapies. And mipomersen is an antisense therapy designed to inhibit apolipoprotein B (apo B) synthesis. This agent is currently being studied in FH patients who fail to achieve target LDL cholesterol levels with the aforementioned prescription therapies.

Introduction

This symposium on familial hypercholesterolemia (FH) was sponsored jointly by the National Lipid Association and the International MedPed Foundation. The symposium consisted of presentations given at the Annual Scientific Sessions of The National Lipid Association in Chicago, May 2010. The purpose of the symposium was to encourage physicians and other health care workers to make an early diagnosis and thereby prevent early death in FH. The speakers have summarized their talks in the articles that follow. The symposium was sponsored by an unrestricted grant from the Genzyme Corporation.

Heterozygous FH is an autosomal-dominant disorder characterized by a defective allele of the gene coding for the low-density lipoprotein (LDL) receptor. Those who are affected usually express one-half the normal number of LDL receptors, with a concomitant reduction in clearance of LDL into the liver and markedly elevated LDL cholesterol. It is caused by 1 of the 900 or more different mutations found in the LDL receptor gene. It is a very common disorder, affecting approximately 1 in 500 in the general population, and it is much more frequent in certain ethnic populations. Where I live in New Hampshire, we have a large French–Canadian population. FH is very common in this population. It is also frequently found in Christian Lebanese, Afrikaners in South Africa, and the Finnish population.

* Corresponding author.
E-mail addresses: mmcgowan@crhc.org; mpfmcgowan@gmail.com
Submitted July 21, 2010. Accepted for publication August 12, 2010.

1933-2874/S - see front matter © 2010 Published by Elsevier Inc on behalf of the National Lipid Association.
doi:10.1016/j.jacl.2010.08.016
Untreated, roughly 50% of men and 25% of women who have FH will have had their first myocardial infarction or cardiovascular event by the time they are 50 years of age, and sometimes, it is much earlier than that. But FH is very treatable, and the earlier in life we begin treatment, the better.

Unfortunately, often, even people who have very strong family histories of premature cardiovascular disease are not screened, and they don’t learn that they have FH until they themselves have had their first event, or they might not even learn at that point. Today, we are going to hear from four physician—scientists who work with FH patients; they are going to tell us about the challenges of treating this disorder and discuss current and future therapies.

But before we hear about this from our experts, I would like to present a statement by Katherine Wilemon, the ultimate expert! She is a young woman with FH who has agreed to tell us her story. I am very pleased to have her personal contribution to this symposium.

Ms. Katherine Wilemon: Well, I discovered that I had hyperlipidemia when I was 15 years old. I had extreme swelling in my Achilles tendons. It was actually very painful, and I went to my primary care physician, and after a battery of blood tests, they found that my cholesterol total was 385 mg/dL. At that point, the interesting thing is that FH really was not mentioned; it was just presented as hyperlipidemia, which was the case for years of my life. I really did not meet anyone who understood what I had until about 2 years ago, but in the meantime, at the age of 38, I did have a myocardial infarction with 100% occlusion of my left anterior descending artery. I now know also that my 3-year-old daughter has FH.

The interesting thing that I would like to share about my experience is that even with my elevated cholesterol, when I started to have mild angina, no one suspected heart disease. And at this point, my cholesterol was in excess of 600 mg/dL. It was more than 600 mg/dL because I had been on fertility medications for several years, which no one mentioned might greatly elevate my already very high cholesterol.

So I was not feeling well. I went to my reproductive endocrinologist and said, “I am not well, something is wrong. I don’t know if I can keep doing this, are you all checking my blood cholesterol level given my history?” I was getting blood tests all the time. But they were not checking and so we checked. That is when we discovered that my cholesterol was more than 600 mg/dL. So they sent me to a cardiologist who did a computed tomography angiogram looking for calcification. He did not see any and we did a stress test. I had started to have some symptoms, and in the next 6 or so months, started to have more.

And then, interestingly enough, I was out gardening one day, and I was bitten by a spider, and I have a phobia of spiders. So I could just feel my blood pressure shoot up, and I knew that something was wrong. I did not feel right afterwards. I called the EMT for the first time in my life, told the EMT about my history, told them that my cholesterol was greater than 600 mg/dL. They probably thought I did not know what the heck I was talking about since that is so high, and he looked at me and he said, “Sweetie, if it was your husband maybe, but there is no way you are having a heart attack.” That was the beginning of about a 5-week journey where mild symptoms had turned into crushing heart pain anytime I tried to go up my stairwell or go up any incline, radiating down my right arm, not my left.

Needless to say, a well-known hospital in Los Angeles turned me away, even given my history, when I went in that initial time. I then flew to Bermuda with my husband on a business trip and luckily got back to the States but could not do anything, could not even honestly walk upstairs without crying. So I immediately went to see a kind of a doc-in-the-box when we landed back in the country. He said, “You know, you look tired, you look stressed; let me give you some Zantac in case it is heartburn,” because I was also having burning in my chest. And I went to my primary care physician, who said, “You have been doing fine; I really think there are people who just, have high cholesterol and they live with it.”

So I had my husband take me to the emergency room one Sunday morning because I woke up with crushing pain, and I got turned away again. So I went to my cardiologist because I had a recent stress test and this computed tomography angiogram, and he said, “I think it is inflammation.” I have enough background in the natural sciences that I said, “This is vascular: I move, it hurts, I stop, it recedes. This is not inflammation and I am not going to leave until you put me on a stress test.”

This was my cardiologist who knew my history, but I really felt like I had to advocate for myself. I am honored to be up here to be able to share my story, but I also feel frankly quite blessed to be here at all. So that is my journey, and I hope to make a difference so that other people don’t die needlessly.

Dr. Mary McGowan: Thank you so much for your moving account, Ms. Wilemon. The initial presentations discussing the challenges of FH screening were given by Dr. Paul Hopkins and Dr. Joep Defesche. Dr. Hopkins has spent his career working to prevent coronary artery disease in people with FH. He has worked in the Department of Cardiovascular Genetics at the University of Utah since 1978. He has conducted multiple National Institutes of Health-funded studies focusing on the genetics of cardiovascular disease, and from 1998 to 2004, Dr. Hopkins was the International Chair for the MedPed program, which stands for “Make Early Diagnoses to Prevent Early Disease.” This organization, started by the late Dr. Roger Williams, is dedicated to finding, educating, and helping to prevent premature cardiovascular disease in persons with FH.

The second article is from a presentation by Dr. Joep Defesche, who studied cell biology and molecular biology at Erasmus University Medical Center in Rotterdam. He subsequently joined the European Molecular Biology Laboratories in Heidelberg, Germany. Since 1989, he has worked in the Department of Vascular Medicine at the University of Amsterdam studying lipoprotein disorders, and in 1994, along with Dr. John Kastelein, organized the
Foundation for the Identification of Persons with Inherited Hypercholesterolemia. This foundation screens patients throughout the Netherlands for FH. Since 1997, he has headed a DNA diagnostic laboratory for the screening for genetic dyslipidemias. He is also Chair of the steering committee for MedPed, the task force for the International MedPed Foundation.

In the third article in this series, Dr. Linda Hemphill will discuss the effects of current drug therapy in this disorder and the use of lipid apheresis in those without adequate response to diet and drugs. Dr. Hemphill has had a very large experience in managing FH as a faculty member at Harvard Medical School and a member of the Cardiology Division of the Massachusetts General Hospital.

The final article from this symposium examines developments in pharmacotherapy for the future. Dr. Ann Goldberg from Washington University in St. Louis and the Barnes Hospital will review some of the promising agents that may provide totally new approaches to reducing LDL in human plasma and therefore more effective therapy for familial hypercholesterolemia.

(Please see the transcript of the question-and-answer session that followed these presentations in this Journal after the article by Dr. Goldberg.)