CASE REPORT

Genetic testing for a patient with suspected familial hypercholesterolaemia

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SUMMARY

Familial hypercholesterolaemia (FH) is a genetic condition that results in elevated low-density lipoprotein (LDL) cholesterol (LDL-C) levels with consequent increased risk for premature cardiovascular disease events. Although it is considered an autosomal-dominant genetic condition, the underlying genetic causes of FH can be complex. Currently most guidelines rely on clinical criteria to diagnose FH. But this approach has some pitfalls. We present a patient who was not formally diagnosed with FH using commonly used and well-accepted clinical criteria but via genetic testing was found to have a mutation for this disorder. This case brings to fore the challenges clinicians face in diagnosing and managing such unusual cases optimally. Through this case report, we hope to stimulate a debate among clinicians as well as other stakeholders regarding the need to develop more efficient ways of selecting patients for genetic testing in response to elevated LDL levels.

BACKGROUND

Familial hypercholesterolaemia (FH) is primarily an autosomal-dominant genetic condition resulting from mutations in genes involved in the process of low-density lipoprotein cholesterol (LDL-C) metabolism.^{1 2} While mutations in the LDL receptor, apolipoprotein-B100 (Apo-B) and proprotein convertase subtilisin/kexin (PCSK9) genes are the most common mutations associated with the diagnosis of FH, >1600 genetic mutations associated with FH have been identified.³ Prior to the introduction of statins, several studies showed a higher risk of premature coronary heart disease (CHD) in patients with FH. Although some of these historical studies were weak in their methods and may have defined FH based on a much higher LDL-C level than those used currently, they do imply a higher risk of early CHD and death in patients with FH.⁴ Mundal *et al* in a recent study have tried to confirm this higher risk of CHD in patients with FH and explored the impact of age on it. They found that the highest excess risk of CHD was in the youngest age group of 25–39 years.⁵ Early diagnosis and appropriate therapy can help reduce their risk for cardiovascular disease (CVD). Despite this, the proportion of patients who are diagnosed and receive optimal therapy is very low across the world.² Thus, there is an urgent need for early and proper diagnosis of FH cases in the community. Currently, three diagnostic criteria, Simon-Broome, Dutch Lipid Clinic Network (DLCN),

and Make Early Diagnosis to Prevent Early Death (MEDPED), are widely used to diagnose FH.^{6–8} As our knowledge of genetics improves over the years it has become clear that the genetic basis for FH is complex. Genetic testing can be a valuable resource in the diagnosis of FH and to recognise the specific mutations responsible for the condition in an individual. We present a case in which genetic testing had unexpected results with a hope to stimulate a debate on what role genetic testing should play in the diagnosis and management of FH.

CASE PRESENTATION

Our case is of a 56-year-old Caucasian woman diagnosed with obesity, hypertension and obstructive sleep apnoea. She was first diagnosed with dyslipidaemia in 1999 and has since been prescribed a series of lipid-modifying agents including atorvastatin, rosuvastatin, pravastatin, ezetimibe, nicotinic acid and fenofibrate each one of which was associated with significant intolerance and had to be withheld. She has no history of any cardiovascular events or any other significant medical conditions. She does not smoke, does not exercise routinely and drinks alcohol moderately. She eats three servings of fruits and vegetables every day, pork 1–2 times/week and seafood rarely. Her mother and maternal grandmother had coronary artery disease (CAD) in the form of myocardial infarction with her mother having a myocardial infarction in her 60s and dying at the age of 71 and grandmother's details unknown, but there is no other family history of CVD. Her physical examination revealed blood pressure of 129/68 mm Hg, pulse 90/min, height 5'5", weight 202 lbs and body mass index (BMI) 33.6. She had no xanthomas or xanthelasmas, arcus senilis or rash.

INVESTIGATIONS

Between 2013 and 2016, her total cholesterol levels were between 260 and 300 mg/dL and her LDL-C levels were between 165 and 220 mg/dL. Her blood and urine tests ruled out thyroid, renal or hepatic disease.

DIFFERENTIAL AND TREATMENT

As per the American College of Cardiology (ACC) and American Heart Association (AHA) atherosclerotic CVD (ASCVD) risk calculator, her 10-year risk for CVD was determined to be 3.7%. She was advised regarding all the lifestyle changes, including being seen by a registered dietitian (RD),

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to reduce her cholesterol levels and her risk for CVD events. She was provided with information on the current Dietary Guidelines for Americans with a recommendation for eating at least four servings of vegetables/day and seafood at least twice/week. Since, at least two of her fasting LDL-C levels were >190 mg/dL, she was diagnosed as a case of possible FH as she did not meet the Simon-Broome, DLCN or MEDPED criteria but did so based on the American Heart Association diagnosis recommendation. Following this, she was placed on several different alternative statin medications and she was not able to tolerate any of the statins to lower her LDL-C to acceptable levels. So, after discussion with the patient, alirocumab 75 mg every 2 weeks was prescribed but her insurer denied coverage due to not having a definite diagnosis of FH per the Simon-Broome or DLCN criteria. A carotid Doppler to evaluate a faint carotid bruit revealed very minimal plaque but no significant stenosis (1%–15%). Her insurance company again denied coverage for alirocumab due to lack of demonstrated clinical CVD or definite FH but offered to cover expenses for genetic testing. Thus, genetic studies were performed after formal consultation by a genetic counsellor.

OUTCOME AND FOLLOW-UP

She was found to have a pathological variant (mutation) in an apo-B gene via testing by Ambry Genetics that included next-generation sequencing (NGS) of the *APOB*, *LDLR*, *PCSK9* and *LDLRAP1* genes (also deletion/duplication analysis of the *APOB*, *LDLR*, and *PCSK9* genes) and analysis of the pharmacogenetic c.521T>C SNP in the *SLCO1B1* gene. Her specific mutation is designated c.10580G>A (also known as p. R3527Q). The test for a SNP in *SLCO1B1* gene (for statin intolerance) was negative. This genetic analysis confirmed her diagnosis of FH, and she was started on evolocumab 140 mg every 2 weeks (changed from alirocumab due to results of the FOURIER Study being published) following approval from her insurer.⁹ She was educated regarding what a diagnosis of FH meant for her CVD health, the importance of having her first-degree relatives evaluated for FH and advised to become further educated regarding FH via the FH Foundation Website (thefhfoundation.org). Her LDL was 115 mg/dL in February 2018 and she has been injecting as well as tolerating evolocumab well since July 2017. She has not had any CVD events.

DISCUSSION

In our case, LDL-C levels were only modestly raised above a commonly used threshold of 190 mg/dL, and the patient barely fulfilled any of the current phenotypic criteria for the diagnosis of FH. According to the MEDPED criteria, she was an unlikely case of FH,⁶ as per the Simon Broome Criteria, she would be a probable case of FH.⁷ As per the DLCN criteria since she had a first-degree relative with possible premature CAD as it is not known if they were age ≤ 65 (1 point), and LDL-C levels between 190 and 250 mg/dL (three points), she scores a potential total of 4 points giving her a possible diagnosis of FH.⁸ Although she did not fulfil any of these clinical criteria to be diagnosed of FH, her genetic studies confirmed FH enabling her to be approved for evolocumab through her insurance. Genetic testing was considered only after her insurer denied coverage for a PCSK9 inhibitor. Thus, the case highlights an important role that genetic tests can play in the management of FH. It raises the questions: What role does genetic testing play in the diagnosis and management of FH and should we genetically screen more patients with elevated LDL-C levels for FH and on what basis?

Three different diagnostic criteria are widely used to establish the diagnosis of FH. These are the MEDPED criteria, the Simon Broome Criteria and the DLCN FH criteria.^{6–8} These clinical criteria are not able to diagnose all the patients with FH and all patients with an FH-related mutation may not fulfil all these clinical criteria.¹⁰ Using them, patients with suspected FH can fall into one of three categories: (a) patients who fulfil clinical criteria for diagnosis and also have a mutation diagnosis; (b) patients who do not fulfil clinical criteria but still have a mutation diagnosis for FH (our patient fits this description); (c) patients who fulfil clinical criteria but do not have a known mutation. Currently, genetic studies are not mandatory for diagnosis and treatment of FH but are encouraged by most guidelines. But as seen in our case, genetic testing could still play a role in diagnosis and management of certain individuals with suspected FH.

Although the genetic basis behind FH continues to get more complex as we know more about it, genetic testing is an important component of diagnosing FH and offers some additional benefits as discussed further. Tada *et al* have outlined the prevalence of CAD in four subgroups of patients with suspected FH. The likelihood of CAD in patients who have no clinical signs of FH but have a positive mutation for FH is 3.4 times that of patients who lack both clinical signs as well as a mutation diagnosis.¹¹ Studies have shown that the risk of atherosclerosis and subsequent CVD may be different depending on the genetic mutations underlying the hypercholesterolaemia.^{12,13} Patients who have severe hypercholesterolaemia and a family history of early CVD and also have a mutational diagnosis have more severe atherosclerosis than their counterparts who do not have a mutational diagnosis.¹⁴ Thus, genetic studies can help us better assess cardiovascular risk in patients of FH. Genetic studies may aid in getting patients approved for expensive but effective lipid-lowering agents. Most insurers in the USA mandate demonstration of clinical CVD or a definite diagnosis of FH per the Simon-Broome or DLCN criteria before they will authorise PCSK9 inhibitors. This could be especially important in patients who demonstrate intolerance to various statins (like ours) or fail to achieve optimal lipid goals despite maximal statin therapy. Some research also relates to the motivation of patients to abide by lipid-lowering agents after a genetic diagnosis. Marina *et al* showed that patients who underwent genetic screening had better long-term adherence with lipid-lowering treatment and positive attitudes toward genetic screening.¹⁵ Conducting genetic tests in a patient also enables us to proceed with cascade screening of family members and genetic counselling of the patient as well as the first-degree relatives if a mutation diagnosis is obtained. Identifying the specific mutation in the proband makes it much more cost-effective to screen first-degree relatives. Cascade screening has been demonstrated as the most cost-efficient screening strategy for diagnosing FH.¹⁶ But cascade screening also raises several ethical issues related to patient's rights to privacy and possibility of discrimination. On a population level, genetic testing can also add to our knowledge regarding prevalence of various types of FH-related mutations among communities potentially allowing us to build new screening strategies while allocating our resources and efforts appropriately.

Despite the benefits that genetic evaluations offer, there are various drawbacks and issues. First and foremost, genetic testing is still expensive and widespread population-based use is not feasible. Genetic counselling needs to be offered to patients both before and after genetic testing, which further adds to the costs and challenges with feasibility. Thus, carefully selecting patients to maximise the utility of genetic testing in FH is key. Also, genetic testing has its limitations. There is an extensive literature on the variable yield rates for a mutation diagnosis based on

various criteria used for FH phenotype. The mutation identification rate has ranged from 50% in patients with a possible FH phenotype to 86% when patients with a more definitive FH phenotype are included.^{17 18} Furthermore, LDL-C cut-off values are widely used as a basis for diagnosis of FH and for advising genetic studies in patients with suspected FH. But the discriminatory capacity of LDL-C levels has been questioned in a recent study by Huijgen *et al.* They demonstrated that the clinical utility of LDL-C levels in predicting genetic FH is contingent on the prevalence of particular mutations in a population, suggesting that LDL-C may not be an ideal predictor in populations where there is a high prevalence of mild mutations.¹⁹ Thus, applying LDL-C cut-off values for genetic testing would require further data on the prevalence of genetic diversity within a population. This counterintuitively suggests that widespread genetic testing might help us gather such data and enhance our ability to take a very personalised approach in making decisions regarding those who would benefit from such testing. In a recent study, Khara *et al* demonstrated that using LDL-C levels as the sole basis for genetic testing may not be an efficient strategy. Their study demonstrated that only 2% of patients with severe hypercholesterolaemia (LDL-C levels ≥ 190 mg/dL) had a genetic mutation for FH.³ Hence, the strategy of advising genetic tests in patients solely based on elevated LDL-C is clearly not efficient. Thus, it is critical to note that while a mutation diagnosis may be of benefit, an absence of mutation does not rule out FH or suggest that the CVD risk in a patient may be any less important.

The somewhat surprising but illuminating genetic findings of this case draw attention to the role of genetic testing in the diagnosis and management of FH by clinicians, as well as the

motivation of patients for screening and their access to treatment. We believe that as our knowledge of genetics underlying FH continues to grow, it is imperative that we develop comprehensive guidelines for selecting patients with suspected FH to undergo genetic testing both on an individual basis and as a screening tool. One way of selecting patients for genetic testing could be based on their score from the DLCN criteria. Patients who have a score between 3 and 8 (ie, patients who would be considered possible or probable FH) should be offered genetic testing. Although such an approach may have a low yield of patients with a mutation diagnosis, nevertheless, we will still be able to diagnose some of these who may be at a higher risk of CHD and may need aggressive treatment.³ From recent research like the one published by Sharifi *et al*, other cardiovascular risk stratification data in FH could also be used to parse out patients who are at a higher risk of CHD for genetic testing.²⁰

Contributors RB and VM: had the opportunity to review the case and initiated writing this case study, both of them contributed specifics of this case from a clinical stand-point and its management. GW: overviewed the manuscript and added his expert views on role of motivation in decision making in the case regarding going ahead with genetic testing. KM: was closely involved in the management of this case as a pharmacy specialist and contributed on aspects related to pharmacy and insurance approval of drugs as well as on genetic counseling. All authors edited and reviewed the final manuscript.

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Patient's perspective

Having my grandmother die of heart disease at the age of 63 and watch my mother suffer from heart disease, I tried to do everything I could to stay healthy. From a young age, I was active outdoors and took aerobics classes in my 20s to early 40s. As active as I was then, I still had high cholesterol levels. Since having the genetic testing done and found to have the gene that can cause FH, I am now on a new medication that has brought my levels down without causing significant side effects. I have since changed my diet to exclude meat and eating more vegetables and legumes. Because of this, I have lost some weight and finally feel like I am headed in the right direction. Genetic testing could also benefit my children and other generations. If they were able to be diagnosed and treated earlier, it may contribute to a healthier ageing process.

Learning points

- Genetic analysis can be of clinical benefit in patients with suspected familial hypercholesterolaemia (FH) even though they may not fulfil the phenotypic criteria for an FH diagnosis. Such analysis can help establish a definitive diagnosis, enhance family member screening, risk stratify patients appropriately and clarify the cause for statin intolerance.
- Genetic tests for FH are expensive and can raise ethical issues but can still hold value in the form of motivating patients and improving access to appropriate medications.
- There is a need for developing appropriate guideline for clinicians to efficiently select such patients for genetic testing for FH.

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