Hui: a partnership in practice in familial hypercholesterolemia

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ABSTRACT

AIMS: To empower a large whānau (extended family) with a history of severe premature heart disease and familial hypercholesterolemia (FH).

METHODS: After broad consultation a Hui was held to discuss how to better manage this issue to ensure present and future generations were appropriately screened and treated.

RESULTS: A closed social media page with detailed information on how to manage and screen FH that includes a family tree (for those who consent) has been created. The whānau, facilitated by health professionals, have ownership of their health. This has led to an uptake of screening and treatment for FH with whānau who are now able to inform local health professionals about their disorder.

CONCLUSION: FH is the most common dominant genetic disorder in humans and causes premature heart disease and death. Current approaches are dependent on index patients presenting for cascade screening and do not incorporate the needs and views of the extended whānau. Establishing a partnership with the whānau and giving back control of health information is crucial to ensure equity. A national systematic programme is also needed to manage this condition with important health outcomes that can be averted if treated from a young age.

Familial hypercholesterolemia (FH) is the most common dominant genetic disorder in humans and causes premature heart disease and death. The incidence of heterozygous FH in the general global population is 1:250;[1] however, rates in Māori are not known. It is characterised by very high-level low-density lipoprotein-cholesterol (LDL-c), systemic manifestation of cholesterol deposition (tendon xanthoma, xanthlasma and arcus cornealis). Three clinical definitions for FH are used to identify people with possible FH;[2–4] the most commonly used are the Dutch Lipid Clinic and Simon Broome criteria.[5]Early detection and treatment of individuals with this disorder is important to prevent the early development of cardiovascular disease. Current guidelines recommend screening of high-risk individuals, and then cascade screening of family members in childhood. [6] Cascade screening using the genetic test is recommended once the proband for DNA testing is identified. Studies have shown that 15–20% of family members are incorrectly classified based on cholesterol testing alone.[7] Treatment of gene positive offspring is recommended to start at the age of 8–10 years with the aim of reaching a target LDL-c <3.5mmol/L or to less than 50% if the target is not achievable.[6,8] Early identification of FH in children is vital as children with FH can have normal life expectancies if treatment is started early.[9] The most common mutation causing FH is in the LDL receptor, identified in ~90% of cases. The LDL receptor mediates endocytosis of LDL-c into cells including hepatocytes.

A number of medications are recommended to treat FH; intensive statin therapy, ezetimibe and protein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. At present, New Zealand has a limited range of drugs to treat hypercholesterolemia. For example, rosuvastatin, the most potent statin, or PCSK9 inhibitors are not funded for FH, limiting choice in individuals at very high risk of premature heart disease (See Figure 1, patient experience). Studies suggest that

Figure 1: Patient experiences.

I am a very physically active and fit woman in my early 30s. My cholesterol levels were well controlled on the atorvastatin and ezetimibe tablets, but I had extreme fatigue and a 'cloudy mind'. I would sleep from 3pm to 6pm, eat my dinner and sleep right through the night. If I exercised it would take my body two days to recover from fatigue. I was experiencing short-term memory loss consistently every day. At first I thought it was lack of sleep or 'mummy brain'. I was unable to hold conversations with people because my mind couldn't keep up. A lot of conversations went over my head.
Because of all these symptoms I decided to try Rosuvastatin, which is not funded. I had none of the previous symptoms; however, I experienced difficulty with the monthly price. And because the price kept increasing and I was unable to afford this. I stopped it altogether after the second month.
Unfortunately, my cholesterol levels were high, so I restarted rosuvastatin. Realistically because of the price, I probably will eventually end up back on atorvastatin and it scares me. I'm afraid of what it's going to do with my brain as I age.

expensive medications like PCSK9 inhibitors are cost effective as they significantly reduce cardiovascular events in FH.[10]

LDLR:c.2312-3C>A splicing mutation

A specific mutation in the LDL receptor, LDLR:c.2312-3C>A splicing mutation, was described in a Māori man who was working in western Australia who presented with coronary artery disease in his 30s. He had a strong whānau (extended family) history of premature death from heart disease.[11] He described a whānau blighted by premature heart disease and death and a whānau legend of "a white woman" who had married their Māori ancestor at the turn of the 20th century who had "brought a curse on them". The gene has been traced back to whānau with origins in Valencia (in eastern Spain), with an ancestor moving to northern France during the 1600s. Descendants then migrated to England, and subsequently to New Zealand whereupon one ancestor married a Māori man and then moved to in a remote area of New Zealand. This union resulted in a very large whānau afflicted with premature heart disease and death. Endocrinologists visited this remote area and tested a number of members of the whānau and confirmed the presence of this mutation. However, no systemic screening and treatment was initiated as no national system was in place to manage this.

In 2018, three members of the extended whānau presented to the cardiology department at Auckland City Hospital with very high LDL-c; one male in his early 30s with significant atherosclerosis requiring stents and two females in their 20s with tendon xanthomata. They all told a story of a large extended whānau affected by premature heart disease with high rates of premature death. They remembered the endocrinologists that had visited the whānau about 15 years earlier who had taken samples, but they were not sure of the diagnosis. Contact was made with the Christchurch Laboratory who had records of an identified LDL-c receptor mutation in this whānau. Confirmation of the presence of the same mutation was made in the three index patients. This revealed issues in the health system in terms of systemic screening and treatment of whānau now scattered across the country and the world.

The consequence of a lack of a national strategy for FH has resulted in a fragmented and disparate service for patients (Figure 2, practice nurse experience). There are pockets of experts in some places, but there is also little awareness of how to treat and manage this condition in the general medical community. For example, few clinicians without a specific interest in FH understand that genetic testing and treatment needs to be implemented in childhood (Figure 3, patient experience).

There was no prospect of a national service in the near future; however, a solution for this whānau was needed urgently.

Figure 2: Rural nurse experience.

I have been here for 35 years and was aware from the start that some research had been done by a cardiologist at the University Of Auckland School Of Medicine in the late 1970s. Therefore, as health providers we knew that it was likely a heredity gene (even though it was prior to the possibility of genetic mutation identification). We were constantly reminded of the impact of this mutation on the family by photos and in discussion about husbands, children, aunts and uncles who had suffered a sudden and catastrophic cardiac event at an early age. We considered every Tangihanga to be a health system failure.

Therefore, in primary care the families have always been a target for us, but we struggled with secondary care response and with compliance with statins due to the high doses required and follow on side effects. We had found that atorvastatin worked better than simvastatin and then at one stage Pharmac took atorvastatin off the subsidised list which was a frustration. As well most of the patient information focused on healthy food choices resulting in some erroneously believing that if they made dietary changes then medication would be unnecessary.

It has also been difficult when the family are no longer registered with us and their new GP does not understand the condition. One example was that I had a man in his 50s who had very high LDLs up until the age of 50 and would not take statins—he moved to Auckland and over the last five years has been compliant with medication. I wrote to his GP and asked if he would refer him to cardiology and explained why—his response was to send me a photo of his normal lipid profile—he did not understand that it was likely that 50 years of very high lipids had already caused significant damage—he did not refer—we are afraid of an unnecessary event at some stage as he ages.

The identification of the genetic variant has instilled us with renewed confidence that we will be able to play a part in improving health outcomes for this family. The willingness of the secondary care provider to visit the Marae to provide education and develop a culturally appropriate plan of care has been very effective. We no longer feel that we are fighting the battle on our own. The health system taking a family centred approach has resulted in an effective referral and treatment pathway for this extended family that will certainly save lives.

Methods

Consultation with a broad range of invested stakeholders was undertaken to determine how to best ensure that the whānau were empowered to manage this condition across generations and geography. Initial consultation was with index whānau and then kaumātua (elders). Then broader consultation was with the national genetic services, the paediatric metabolic department and the director of Māori Health Research at the Waitemata and Auckland District Health Boards (DHB) Dr Helen Wihongi. The discussion with Dr Wihongi focused on how to ensure that tikanga Māori (custom, ethics) was taken into account especially around the issues regarding taking

Figure 3: Patient experience.

I have the genetic mutation and my 13-year-old son has very high cholesterol levels. My GP referred him to the hospital paediatric department for testing and surveillance. I had to take two days off work specifically for an appointment because of the distance to the hospital. When we arrived the doctor told us she didn't know why he was there because he has no existing heart disease. I proceeded to tell them about familial hypercholesterolemia and how we now know the specific mutation and its great news for our family. I explained that my son is on a statin, even though he is a young boy and our understanding was that he needs to have his heart health and progress monitored very closely. I also said that he needed blood tests for the gene. The doctor looked at me dumbfounded and was embarrassed. She apologised, arranged a blood test and booked another appointment with another specialist. I had to take another two days off work for the second appointment. This specialist told us everything we already knew, and sent us on our way with pamphlets. It felt like a waste of time.

and storing of blood, as well as who owned the data. We reviewed the current consent form used by the genetic services to ensure this explained that blood samples may be stored and that this may have implications for the whakapapa (genealogy). The form also explains that the samples are kept in New Zealand and are not given to third parties. There is currently no national genetic database for FH in New Zealand so no one currently holds the data other than the treating physician and laboratory. We also discussed how to balance the needs of the extended whānau and the privacy of the individual. The genetic and metabolic services provided support for cascade screening and were happy to be part of the hui. The local general practice was also consulted to assess their needs and opinions on how best to move forward.

Hui

A hui (social gathering) was organised to inform the whānau about the genetic mutation and discuss how best to manage this to ensure access to testing and treatments. This was attended by the whānau, kaumātua, doctors and nurses from the local health practice, the national genetic services, a doctor from ADHB and a health science student.

On arrival at the marae (meeting ground) there was a pōwhiri (formal welcome), which included a karanga (call) to the manuhiri (guests), and a response. After a number of speeches and songs by the men, we all introduced ourselves. After a mihi (introduction) and waiata (song) the doctor gave a talk that centred on what FH is, what age to screen and treat FH, how the gene is transmitted, how to organise testing and risks and benefits of treatment. The geneticists then explained genetic and cascade testing and how it is undertaken. The formal presentations by the doctors and geneticists lasted two hours, and the rest of the hui was comprised of open discussions. There was also a need to acknowledge the past. The whānau felt used and let down by previous doctors who had visited and taken samples but gave no information on how to prevent further deaths. This had to be acknowledged by the medical team. The pace of discussions was driven primarily by the needs of the whānau. For example, when the doctor spoke too fast or used medical terms, the whānau backtracked by asking questions. There was a strong feeling that decisions on how to manage this issue could not be made in haste, and that we were all in this together (He waka eke noa (A canoe which we are all in with no exception)). There was agreement that for any solution to work, it needed to be acceptable to everyone and according to the Kaupapa Māori principles of self-determination, involvement of the whānau and āta (respectful relationships).

Issues discussed were:

- Who should have access to the information and how to balance the rights of the individual vs the rights of the whānau
- How to cascade screen whānau and ensure this is done in perpetuity
- How to ensure whānau members living in other counties access the information
- How to ensure whānau is updated on new information regarding treatment
- How to access novel agents shown to work in FH
- Can PHARMAC be approached for access for new medications for this whānau under Te Tiriti o Waitangi obligations
- How to manage blood samples, ethical issues with privacy and storage of blood

Results

A whānau member was nominated to run a closed social media page for the whānau that includes a family tree. The closed social media page can only be accessed by members and Facebook administration. The Facebook administrators monitor closed sites only to “promote safety and security on and off of our products”. Data is not given to third parties. The whānau member acts as a gatekeeper so that new posts can be sent to them and can only be uploaded by them. All extended whānau are invited to be part of this Facebook site, and the addition of the genetic test result to the family tree is completely up the individual. A printable letter to show health professionals was created with general information about FH, diagnosis and treatment, the proband identified and steps for genetic testing (Figure 4).

Figure 4:

Your patient belongs to a family who carry a mutation on gene LDLR c.2312-3C>A. This causes a medical condition called 'familial hypercholesterolaemia' (FH). The key to preventing premature heart disease and death is early diagnosis and treatment to achieve normal life expectancy.
Individuals of this whānau who have the mutation develop heart disease in their 20s and 30s. Life expectancy in untreated individuals is approximately 30–40 years for heterozygous individuals (HeFH). Homozygous individuals (HoFH) manifest cardiovascular diseases in childhood or adolescence.

1. **What is familial hypercholesterolaemia?**
   FH is an autosomal **dominant** disorder that leads to premature coronary heart disease and atherosclerosis.
- Mutations result in markedly reduced hepatic capacity to clear atherogenic cholesterol-rich lipoproteins (LDL) from the blood resulting in LDL cholesterol (LDL-C) accumulation in arteries from childhood (extreme cases have LDL-C exceeding 13mmol/L).
- The sustained exposure of the arterial wall to elevated LDL-C levels accelerates cholesterol deposition and vascular inflammation leading to stroke, atherosclerosis and CHD.

2. **Treatment—the key is early diagnosis and treatment**

- A healthy lifestyle (smoking cessation, high fruit/veg diet, exercise)
- **Genetic screening** of children for the gene mutation should be done at ages **8–10** years (or diagnosis). There is a 20% chance that you will miss a gene mutation if you base your decision to do a genetic test based on cholesterol levels only.
- Aim to reduce LDL by 50% or to **<3.5mmol/L** for **children** and **<2.5mmol/L** for **healthy adults** and **<1.8mmol/L** if someone already has **heart disease or diabetes. If this cannot be achieved aim to reduce LDL-c by 50%**.
- **Pregnancy/ breastfeeding—**do not prescribe statins in pregnant/breast feeding woman—restart statins once able.
- Medication dosage must be prescribed at the **highest possible tolerated dose for that patient**:
  - Statin (atorvastatin, rosuvastatin): 58–60% LDL decrease
  - Ezetimibe: 10–15% LDL decrease
  - PCSK-9 inhibitors: twice monthly injection decreases LDL by 50–60%
  - Bempodoic acid: 30–40% LDL decrease (currently unavailable in New Zealand)
  - Inclisiran: twice yearly—in clinical trials decreases LDL-c buy 54%

3. **Blood testing for gene mutation**
   There is a 50% chance of children of FH carriers inheriting the mutated genes.
- All children of FH individuals should be genetically tested/cascade-based screening to identify LDLR mutation carriers.
- Cascade-based screening is more effective and provides earlier diagnoses than lipid-profile testing which can give hard to interpret results and is based on cholesterol levels which fluctuate with age.

4. **Steps for genetic testing**

1. Fill out attached consent and lab form with blood sample.
2. Send to National Genetic Screening Services in Christchurch and email them in advance to raise this sample to their attention.
3. Begin treatment once mutation is confirmed.

For more information contact Jocelyne Benatar on 021893886 or jbenatar@adhb.govt.nz
Nga mihi,
Jocelyne Benatar and the whānau

A consent form for testing and a pre-filled laboratory form with the proband are also available. The consent form is the standard consent form used by the National Genetic Services for New Zealand. It requires specific and separate consent for storage of samples. As new treatments become available, the ADHB doctor sends the information to the gatekeeper who then uploads this to keep extended whānau informed of latest treatments. The clinician has no access to the Facebook page but is in close contact with the moderator to address concerns, misinformation and misconceptions about FH and treatments to lower cholesterol.

This whānau social media page will also engage with whakahekenga (descendants) within the whānau in the long term. This will allow all to make informed decisions on the need to be tested, especially if no data is available about their immediate whānau.

At present, the social media page is active with a number of whānau members active on it. As a direct result, genetic testing and appropriate treatment has been initiated in 17 whānau members. Intensive statin treatment has been initiated in two children and a couple of young adults; this has the potential to ensure they reach normal life expectancy. The hope is that testing will be extended to all young children when they reach the age of eight. Only one surviving whānau member over the age of 50 has been found to have the mutation; however, this LDL-c is lower than others with the mutation.

Results of genetic tests are known only to the testing laboratory, the treating physician and the person tested. Results of genetic tests are only sent to the ADHB doctor if this is specifically requested by the patient. No data is centrally held by genetic services at this point as there is no national genetic service for FH. This ensures data for and about this Māori whānau can be safeguarded and protected from parties who are not directly involved with their care.

Discussion

The experience of this whānau underscores a number of issues. The first is that there is no systematic national approach to FH in New Zealand. It is not possible for clinicians to test and treat families from other DHBs or refer them to a national screening service as none exists. In this particular instance, testing was undertaken by clinicians from another DHB for research purposes, but there was no ability to refer for clinical follow up, cascade screening or appropriate treatment. A missed opportunity resulted to prevent premature cardiovascular events and led to an injustice perpetrated on the whānau. This resulted in inequity though three pathways; ongoing exposure to a modifiable and potent risk factor for CVD, difference in the quality of care received and differential access to healthcare.[12] Had the whānau lived within the researchers' DHB, they would have been appropriately managed. A priority of the hui was acknowledging that there had been an injustice and that that this had led to ongoing harm. The whānau wanted assurances it would never happen to them again and that measures were put in place to ensure that the whānau had ownership and control of their health information.

A second issue is that the system prioritises the needs and privacy of the individual over the whānau. This Westernised approach to health ignores the cornerstone of health; taha whānau (family health).[13] In this instance, if one person misses testing, other members of the whānau further down the 'cascade stream', such as children will not be tested. This may be useful in societies where the needs of the individual are paramount, but not where the collective is just as important.

Despite calls over a number of years for a national screening registry for FH,[14] none has eventuated. The argument for a registry is that it will allow for efficient screening and treatment of gene positive children and young adults to prevent future cardiovascular events. The argument against this is that it is a common genetic disorder picked up by a cheap lipid test, and that gene testing may be prohibitively expensive for the country. This approach ignores the benefits of cascade screening and treating gene positive children. It has resulted in a haphazard approach to FH with disparity in care across the country. For this whānau it has led to ongoing hurt caused by young family members developing often fatal premature heart disease.

Conclusion

FH is the most common dominant genetic disorder in humans and causes premature heart disease and death. Current approaches in New Zealand are dependent on index patients presenting for cascade screening and do not incorporate the needs and views of the extended whānau. Establishing a partnership with the whānau and giving back control of health information is crucial to ensure equity. A national systematic programme is also needed to manage this condition with important health outcomes that can be averted if treated from a young age.

Competing interests:
Nil.

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