Hereditary Hyperlipidemia in Malaysia: A historical Perspective of Six Decade of Research and Treatment

Khoo K L, MBBS (S'pore), MD (S'pore), FRCP (Lon), FAMM (Mal)

In 1950, coronary heart disease (CHD) occupied the third place as a cause of death in Malaysia. By the 1970s, it emerged as the number one killer and has remained so ever since[1]. One of the earliest clinical reports on CHD was in 1957 by Pallister who described 89 cases of CHD in Penang General Hospital between 1952 and 1955[2]. Thereafter, there were various publications that focused on cholesterol and nutrition of aborigines in Malaysia[3]. Many of these studies discussed the risks of hypertension, diabetes and smoking, but none of them have alluded to raised blood cholesterol as a risk factor for CHD. One of the first times cholesterol became the focus of a study was in 1961 when Chong presented a paper that provided some details of serum lipids (cholesterol, phospholipid and beta/alpha lipoprotein ratios) of healthy male Chinese, Malay and Indian adults[4]. In 1971, Chong reported that the mean TC level for all major ethnic groups was 5 mmol/L[5].

Meanwhile, Fredrickson, Levy and Lees in the US had compiled integrated information to derive a rational approach to the classification and treatment of hypercholesterolaemic patients based on measurements of cholesterol, triglycerides and lipoprotein electrophoresis[6]. This was subsequently adopted by the World Health Organization (WHO) as a classification for hyperlipoproteinaemia[7,8].

Studies also showed that growing urbanisation and industrialisation affected the rise in levels of serum TC and a concomitant rise in CHD in Malaysia[9]. Today, the term is 'Target Lipid Values'. It is more specific and directed at the various risk categories for CHD. Furthermore, LDL has become the benchmark laboratory test that helps physicians when suggesting treatment options. Current target values of LDL depend on the level of CHD risk. Those who have very high risk of CHD should have an LDL target that is less than 1.8 mmol/L. Those who have a moderate risk should have a LDL target of below 2.6 mmol/L. Those who have a low risk of developing CHD should have a LDL target of between 3.3 and 4.2 mmol/L.

Until the mid-1970s there were no specific genetic markers for the hyperlipoproteinaemia, and reliance was placed on lipids and lipoproteins, family history and certain physical findings. With further research over the next few years, familial combined hyperlipoproteinaemia was identified as a disorder genetically distinct from both FH and familial hypertriglyceridemia. In one family, the affected members may have more than one lipoprotein phenotype [10-13].

Meanwhile, researchers in Malaysia and Singapore showed an interest in the genetic causes of FH following the work of Fredrickson and, subsequently, Goldstein and Brown (see below). As such, multiple single case studies of inherited FH were published in Malaysia and Singapore between 1969 and 1973 [14-20]. However, the first extensive publication of this disease in Malaysia was by Khoo who reported 117 families with genetic dyslipidaemia in 1983[14]. The majority of subjects were found to be Type II FH which was consistent with the West. In addition, there were also ambiguous cases which belonged to the other types of dyslipidaemia as classified by Frederickson. At the time, other than a three-part change in a patient's lifestyle (dietary modification, weight management and physical activity), they were administered Bile acid sequestrants, niacin and fibrates to lower their cholesterol levels. Then came statins which resulted in at least a 25 per cent reduction in the chances of developing a heart attack[21].

The biggest challenge was the cost of the medication, espcially statins as they were expensive. For familial hyperlipidemia (FH) patients, statins are necessary for life. In 2000, the Inherited Cholesterol Disorder (ICD) Club was set up under the auspices of the Heart Foundation of Malaysia[22]. Fortunately, Merck, Sharp and Dohme (MSD) agreed to supply statins to FH subjects at a subsidised price from the Heart Foundation of Malaysia.

Meanwhile, there were patients who were unable to reach target lipid levels in spite of being administered statins. To identify them and the treatment options provided, it was necessary to understand the advances in medical technology since 1980 and, in particular, molecular genetics.

Molecular Genetics (1980-2013)

By the mid-1970s, Joseph L. Goldstein and Michael S. Brown discovered a protein called 'LDL receptors'[23]. Two-thirds of LDL is cleared through these LDL receptors. Some people have a genetic defect in their LDL receptors which leads to less LDL being removed from the bloodstream. If the patient is diagnosed as having Heterozygous FH, the liver has only 50 per cent of functioning LDL receptors; hence, it is unable to take up the excess LDL, resulting in plasma LDL levels twice the normal level. If the patient is diagnosed as having Homozygous FH, he has no functioning LDL receptors. This means that no excess LDL is taken up and the plasma cholesterol in these patients is four times the normal level.

Corresponding Author: Khoo Kah Lin
Email: kahlinkhoo@gmail.com

Today, there are 3 different ways of looking at the criteria for making a diagnosis of FH, namely, Dutch Lipid Clinic Network Criteria[24], Diagnostic criteria for FH using the Simon Broome register[25,26] and the MEDPED[27] criteria for diagnosis of FH. One of the most significant signs that someone is suffering from FH is that together with elevated with LDL levels, he will also have thickened tendo Achilles. In fact, in the Dutch Lipid Clinic Network, tendinous xanthoma is given the second highest score after LDL levels.

Following the discovery of the LDL receptor gene, Innerarity, in 1987, found that a defective apo B-100 gene produced an abnormal protein which could not bind to the LDL receptor resulting in the inability to remove the LDL and cause FH (also known as Familial Defective apolipoprotein B-100 – FDB)[28]. Generally, FDB in a European population ranged from 1 in 500 to 1 in 700 for the heterozygote. What about us in Asia? Did our FH patients have such a problem?

In 2000, Win Mar Kyi *et al.* reported 62 Malay subjects with hyperlipidaemia and could not find the apo B R3500Q mutation of the FDB-100 and concluded that the Apo B R3500Q mutation did not appear to be a common cause of hypercholesterolaemia in Kelantanese Malays[29]. In the same year, Khoo *et al* published an article called 'Low-density lipoprotein receptor gene mutations in a Southeast Asian population with familial hypercholesterolaemia'[30]. This is the first such study in a South East Asian population comprising of Malays, Chinese and Indians. The majority of the 86 subjects had no LDL receptor gene mutation. Neither did they have the apo B-100 mutation. 22 patients with a LDL receptor gene mutation had significantly more xanthomas and a higher incidence of CHD. But, their levels of LDL were significantly different.

The conundrum was this: there appeared to be no co-relation between the type of gene mutation and LDL levels and clinical signs of CHD. So, if they do not have any of the recognisable mutations (LDL, LDL receptors and apo B-100), what did they have that caused them to have elevated levels of LDL? Was it a mutation of a gene we do not know about or were they having elevated cholesterol levels because of other non-genetic factors? These questions have to be viewed against the backdrop of a 1997 study where FDB was described in four in a mixed cohort of 163 Malaysians with high cholesterol[31].

What all this research suggested was as follows: While FDB was a common condition in Europe, it was not so in Asia. This then led to the exciting question: Could it be that there was a presence of a third gene in the Southeast Asian population that led to a disorder resembling a milder form of FH? That said, the research also offered a genetic basis as to why Asian patients with FH have lower LDL levels and less premature CHD than their Western counterparts. This is probably due to other factors such as diet, exercise and concomitant diseases such as diabetes and metabolic syndromes.

There are other genes that are found to raise the LDL level, namely, the PCSK9 gene, LDLR adaptor protein gene and ABCG5 / ABCG8 gene. In recent years, researchers in this field have demonstrated that they can raise the LDL levels, but have not been described in our population. In addition to LDL receptor genes, the presence of high cholesterol is due to lipase mutation genes which cause raise triglycerides. In 2000, three Chinese families were found to have hypertriglyceridaemia which was due to a defect in the LPL gene[32]. Furthermore, in subsequent DNA studies, two patients were found to have extremely low HDL. A full DNA analysis revealed a defect in the ABCA1 gene. In effect, this was one of the few cases in Malaysia, and worldwide, of Tangier Disease.

When a patient exercises, controls his diet and takes the maximum amount of medication, but his LDL levels remain high, he is thought to be suffering from resistant hypercholesterolaemia. The treatment of choice for such patients is LDL apheresis[33,34].

In 2004, a programme called Cholesterol Dialysis Programme was set up under the auspices of the Heart Foundation of Malaysia. Currently, this is the only LDL Apheresis centre in South East Asia. Sau Seng Lam Foundation, a charitable organisation, agreed to offer a special room at their premises for the use of FH patients for this programme. The people at B. Braun provided the Heparin-Induced Extracorporeal Low-Density Lipoprotein Precipitation (HELP) machine. In addition, they would supply the necessary solutions and provide technical training to the technicians. The Nephrology Department of the University of Malaya agreed to look after the HELP machine as they were already looking after the machines for renal dialysis at the centre.

The efficacy of the LDL Apheresis treatment was measured by the percentage reduction of the LDL cholesterol with each treatment. It was found that mean LDL cholesterol reduction was 52.44 per cent. The study was conducted over 8 years. There was no new onset of angina or CHD in all the patients, skin xanthomas were reduced and there was no increase in the intensity of the bruit in the neck, chest and abdomen.

For now, in Malaysia, as it is internationally, LDL Apheresis remains the safest method of treating patients who are diagnosed as having resistant hypercholesterolaemia.

CONCLUSION

Incidence of CHD over the last 60 years has risen and become the main cause of health-related death in Malaysia. Studies of the local population indicate that raised cholesterol levels is a high risk of CHD and there is an increased awareness of this. Treatment and management of patients with high cholesterol include lifestyle modification and drug therapy. For FH patients, treatment may include LDL apheresis. WHO reports that there is an estimated 10 million individuals with FH worldwide. In Malaysia, this number is 1 in 500 for Heterozygote FH and 1 in a million in Homozygous FH[35]. With a population of 28 million, this is an estimated 56,000 Malaysians with FH. In cases of Resistant Hypercholesterolaemia, it has been shown that a combination of statins and new drugs seem to have had an additional effect on lowering the LDL levels to appropriate

levels. Together with genetic studies, trials are underway to combine drugs and statins to create treatment programmes that ensure that approximately 45 per cent of LDL Apheresis can be avoided. This is good news for all FH patients and their health care providers.

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