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CASE REPORT

A successful pregnancy outcome of homozygous familial hypercholesterolaemia patient on statin therapy

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Abstract

Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disorder of lipoprotein metabolism mainly due to mutation of the low-density lipoprotein (LDL)-receptor gene (*LDLR*). It is a life-threatening disease that causes accelerated, multi-vessel atherosclerosis presented in early childhood. Pregnancy in HoFH may pose early coronary morbidity and mortality to both the foetus and mother. The combination of HoFH and pregnancy can be a fatal condition. While statins are very effective in lowering low-density lipoprotein cholesterol (LDL-C) levels, they are generally contraindicated during pregnancy, thus their use during pregnancy is uncommon. On the other hand, lipid apheresis (LA) has turned into an effective treatment to control cholesterol level amid pregnancy. However, the procedure is not widely available in our region. To date, there are scarcely documented case reports of HoFH in pregnancy in which the majority of them underwent LA to keep LDL-C at a low level. We report a rare case of successful pregnancy outcome of HoFH patient treated with lipid-lowering drugs including statin without LA therapy. Apart from that, we also discussed the genetic findings of the proband and all screened family members in which to the best of our knowledge, the first study using the whole-exome sequencing technique to identify the causative gene mutations for familial hypercholesterolaemia among the Malaysian population.

Keywords: Homozygous familial hypercholesterolaemia, *LDLR* gene, lipid apheresis, pregnancy, statin

INTRODUCTION

Homozygous familial hypercholesterolaemia (HoFH) is a rare genetic disorder of lipoprotein metabolism mainly due to mutation of low-density lipoprotein (LDL)-receptor gene (*LDLR*). This condition is a potentially life-threatening disease that can cause accelerated multivessel atherosclerosis leading to coronary artery disease (CAD). Pregnancy in HoFH patients carries high and early coronary morbidity and mortality to both the foetus and mother. Although statins are highly effective in lowering LDL cholesterol levels of hypercholesterolaemic patients, they are contraindicated during pregnancy. Thus, their use during pregnancy is uncommon. On the other hand, lipid apheresis (LA) has become an effective treatment to control cholesterol level during pregnancy. However, the procedure is not widely available in the Asian region. To date, there is a scarcity of case reports on the management of HoFH in pregnancy. The majority of such cases reported thus far, indicated that such patients underwent LA therapy throughout pregnancy. This case report illustrates a rare successful pregnancy outcome of a HoFH patient who refused LA therapy. The genetic analysis of the proband and her family members who underwent familial hypercholesterolaemia (FH) family cascade screening was also discussed. A written informed consent was obtained from the

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patient to include her information and photos in this case report.

CASE REPORT

A 28-year-old Malay lady was detected to have severe hypercholesterolaemia at the age of 12 years old during a family cascade screening. Her baseline total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were 20.0 and 18.0 mmol/L, respectively, but was otherwise healthy at that time. At the age of 21 years old, she developed hypertension. Her condition worsened about 4 years later, where she was diagnosed to have CAD with left main-stem coronary artery stenosis with moderate aortic valve stenosis. She was a non-smoker, euglycaemic and practiced a healthy diet. Clinically, the patient was slim with bilateral grade 2 corneal arcus. In addition, there were multiple xanthomata over the hands (knuckles and interdigital web), feet (dorsum and Achilles tendon) and elbows as shown in Figure 1. Her parents are of consanguineous marriage where they are cousins and reside in the same village. Both parents also suffered from hypercholesterolaemia (LDL-C 7.3 and 6.2 mmol/L in her mother and father respectively). Her father had premature CAD at the age of 40 years. One elder sister also had severe hypercholesterolaemia (pre-treatment LDL-C = 15.3mmol/L), premature CAD, and had an angioplasty done at the age of 31 years. A younger brother also had hypercholesterolaemia (LDL-C = 6.2 mmol/L). Two of her siblings died at a very young age, and one sibling was born stillbirth. The family tree is illustrated in Figure 2.

Her family members were screened for full lipid profile and proceeded with genetic testing using whole-exome sequencing for identification of genetic mutations. The proband was identified to have one homozygous *LDLR* splice site mutation c.1187-2A>G (rs879254823) which is located at the 3′ splice site of intron 8 in *LDLR* gene. Her elder sister, also a case of HoFH, inherits the same homozygous c.1187-2A>G mutation, as reported in the proband. Both parents and her younger brother carry a heterozygous variant of the same mutation, whilst the eldest sister does not carry the pathogenic *LDLR* variant. No nonsense or frameshift mutations were identified in the *LDLR* gene sequence. Neither pathogenic *APOB* nor *PCSK9* variants were detected in all family members. All FH-affected family members also carry an *LDLR* synonymous variant, p.Pro539Pro (rs5929), located in exon 11 of the *LDLR* gene, which shows identical zygosity with c.1187-2A>G

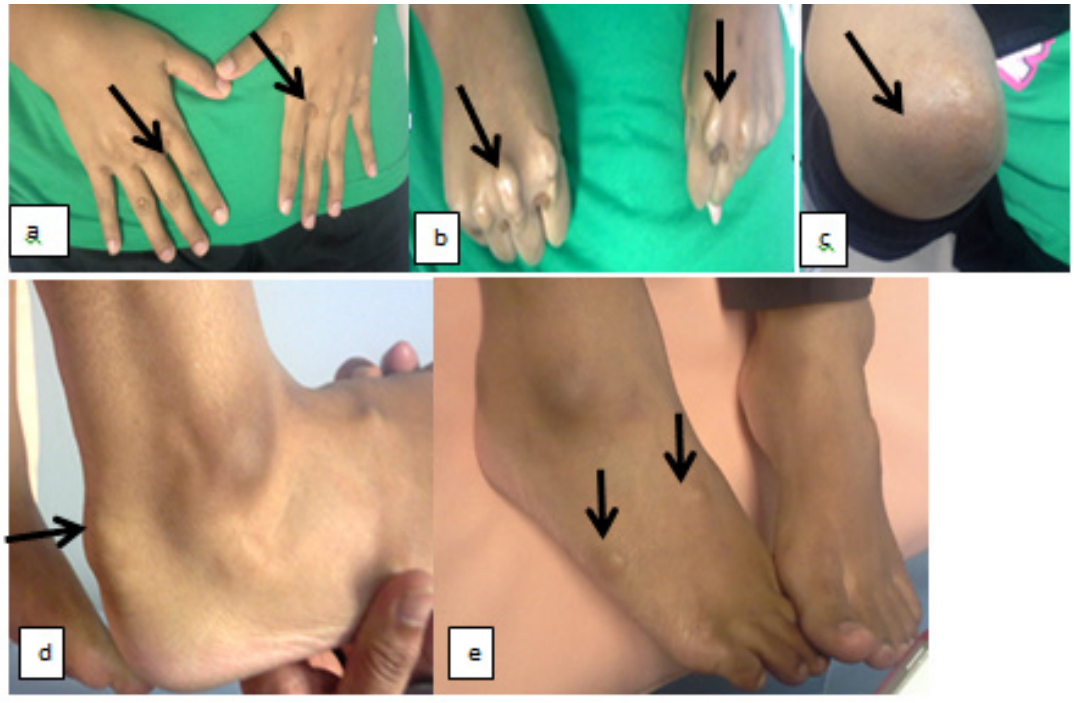

FIG. 1: Xanthomata at multiple sites indicated by the arrows. a) interdigital b) knuckles c) elbow d) Achilles tendon e) dorsum of foot.

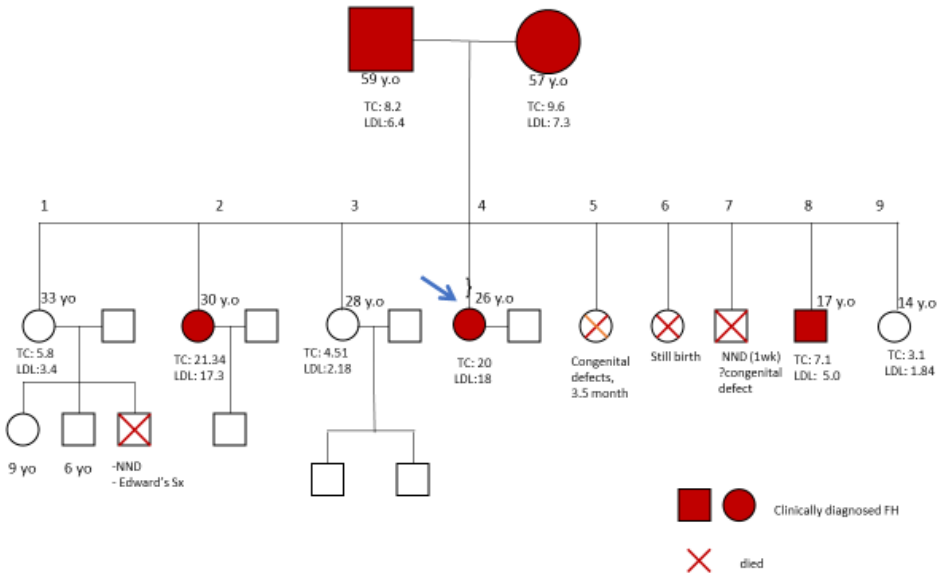

FIG. 2: Pedigree of proband's family with baseline total cholesterol and LDL (mmol/L).

mutation (Table 1).

The proband's LDL-C became even more difficult to control as she became pregnant. During pre-pregnancy, the patient was given cholestyramine, colesevelam, rosuvastatin, and ezetimibe at maximum dose. However, she only managed to achieve a maximal LDL-C reduction of about 20%. She presented a non-ST-elevation myocardial infarction at 7 weeks of pregnancy and symptoms of being easily fatigued. In view of her worsening LDL-C and risk of developing subsequent acute coronary event, the patient was advised for therapeutic abortion, but she refused. Statin administration was halted temporarily during the 1st trimester of pregnancy and restarted in the 2nd trimester. The highest TC and LDL-C level reached 21.0 mmol/L and 19.1 mmol/L during the second trimester of her pregnancy. A drug-eluting stent angioplasty was performed during her second trimester of pregnancy. Serial ultrasound monitoring was done to ensure good growth and foetal well-being. Elective caesarean section with bilateral tubal ligation was performed at 34 weeks without any intrapartum complications. The patient delivered a healthy baby girl with a birth weight of 2.2 kg. During the post-pregnancy period, her TC and LDL-C were still difficult to control. The patient was counselled again for LA but still refused. Alirocumab 75 mg subcutaneously once every two weeks was added but without much improvement in the LDL-C levels. The data of her lipid profile was presented in Figure 3.

DISCUSSION

FH is an autosomal dominant genetic defect characterised by marked elevation of LDL-C, xanthomata, and association with premature CAD. Unlike heterozygous FH (HeFH) with a prevalence of 1:100 in Malaysia[1], HoFH is a very rare form of FH, featuring a worldwide prevalence of 1:1,000,000. However, more recent reports showed a prevalence of 1:160,000 to 300,000 populations.[2] In Malaysia, with a recent population of about 32 million[3], taking into account 1:160,000 prevalence, 200 individuals are estimated to be affected with HoFH. However, the majority remains undiagnosed and very few cases of HoFH have been reported in Malaysia.[4,5]

High concentrations of LDL-C levels during pregnancy may result in serious consequences for both the foetus and mother. This condition may increase the risk of acute myocardial ischaemia for women with underlying CAD and cause foetal intrauterine growth restriction. Some studies showed that maternal hyperlipidaemia may induce acute atherosclerosis in the uteroplacental spiral arteries that together with hypercoagulation, may result in local thrombosis and placental infarctions, leading to placental insufficiency and subsequent foetal compromise.[6] Thus, it is very crucial to maintain LDL-C at a low level as possible to avoid all those effects and complications.

To the best of our knowledge, this study

Table 1: Genetic analysis of the proband and family members

Family Relationship	Chromosome sequence	Zygosity Variant	dbSNP ID	Classification
Proband	chr19:11223952	c.1187-2A>G Homozygous	rs879254823	Pathogenic/ Likely pathogenic
	chr19:11226800	c.1617C>T p.Pro539Pro Homozygous	rs5929	Benign
Father	chr19:11223952	c.1187-2A>G Heterozygous	rs879254823	Pathogenic
	chr19:11226800	c.1617C>T p.Pro539Pro Heterozygous	rs5929	Benign
Mother	chr19:11223952	c.1187-2A>G Heterozygous	rs879254823	Pathogenic
Older sister 1	-	-	-	-
Older sister 2	chr19:11223952	c.1187-2A>G Homozygous	rs879254823	Pathogenic
	chr19:11226800	c.1617C>T p.Pro539Pro Homozygous	rs5929	Benign
Younger Brother	chr19:11223952	c.1187-2A>G Heterozygous	rs879254823	Pathogenic/ Likely pathogenic
	chr19:11226800	c.1617C>T p.Pro539Pro Heterozygous	rs5929	Benign

is one of the few case reports on a successful pregnancy outcome of HoFH patients treated with statin without LA intervention. Although LA is considered the most effective modality to control LDL-C levels during pregnancy in HoFH patients, it may be accompanied by untoward effects, such as haemodynamic compromise. In our case, this patient refused to undergo such a procedure partly because of cosmetic disfigurement, financial constraint and logistic issue. Statins on the other hand are contraindicated during pregnancy which are rated as "Pregnancy Category X" drugs, which signifies that studies have shown they may cause birth defects and that the risks clearly outweigh any benefit. However, reports on the teratogenic effect are scarce and conflicting. Recent studies showed the absence of consistent teratogenic pattern in human or animal models who was given the standard statin regime.[7]

This case is considered a very high-risk pregnancy. Ideally, childbearing-age women with FH on lipid-lowering therapy should receive pre-pregnancy counselling and contraception advice. The preferred methods for contraception in women with FH are low-dose oestrogen oral agents, intrauterine devices, and barrier techniques, although, in women older than 35 years of age, the latter two methods are preferable.[8] Several cases reported repeated pregnancies in HoFH patients who received LA during pregnancies with a successful outcome, thus suggesting that LA during pregnancy may inspire patients to bear more than one offspring.[9] Thus, despite high-risk pregnancy in HoFH patients, LA therapy shows feasibility in assisting safe pregnancy with a good outcome for both mothers and infants.

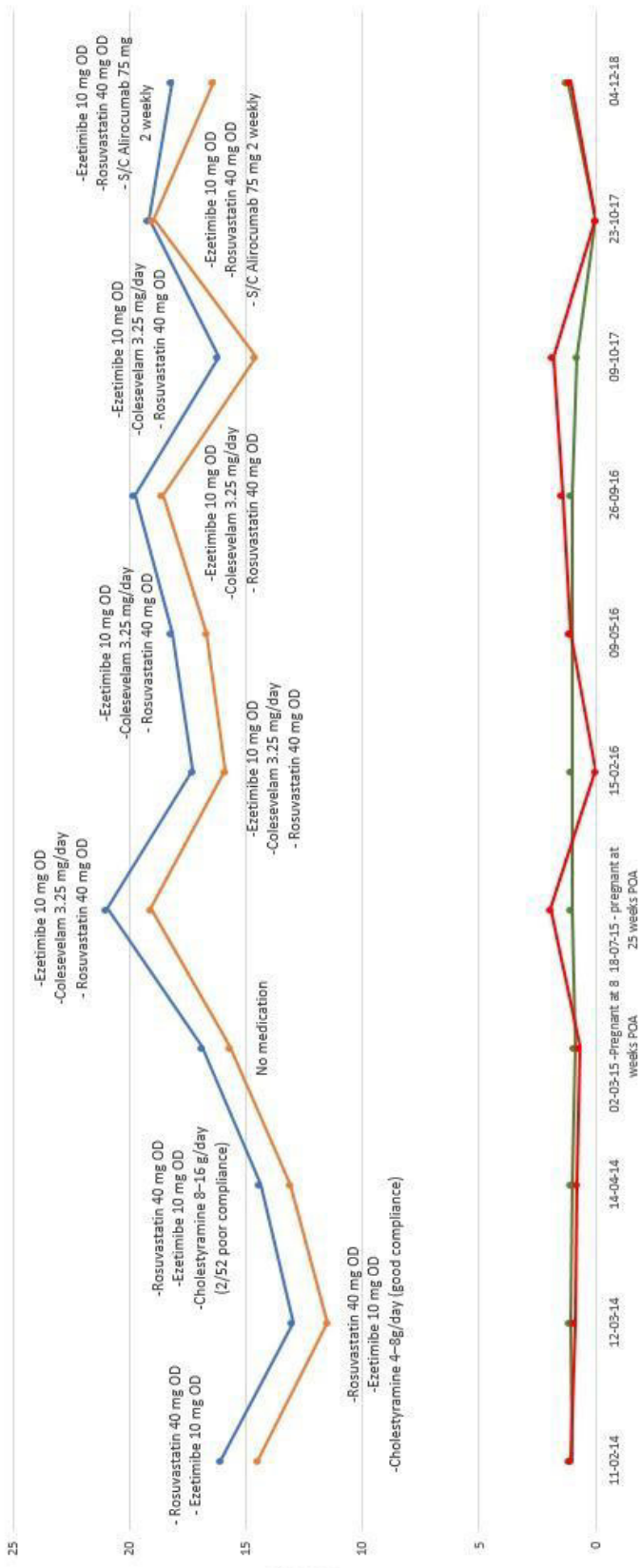

FIG. 3: Lipid profile and prescribed medications of the patient. TC: Total cholesterol, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: Triglycerides, S/C: subcutaneous, OD: once a day.

The patient in this case report was identified to carry a well-documented pathogenic *LDLR* c.1187-2A>G variant, leading to skipping of the entire exon 3 and inclusion of intron 3 during mRNA splicing, resulting in the production of a non-functional LDL receptor.[10] We also notice the presence of allele-dose effect *LDLR* c.1187-2A>G, where heterozygous mutation of this variant in the patient's father, mother, and the younger brother was manifested as a less severe phenotype (LDL-C: 6.2 - 7.3 mmol/L), which are approximately half of that of the homozygous proband (18.0 mmol/L). Homozygous *LDLR* variants are rarely identified in the Malaysian population. So far, two pathogenic homozygous *LDLR*, c.763T>A (C255S) at exon 5 and c.2209A>G (R716G) at exon 15, have been previously identified among Malaysian FH patients.[4,11]

On the other hand, homozygous *LDLR* p.Pro539Pro, which features identical zygosity with c.1187-2A>G in this present study, presented different pathogenicity. There are multiple evidence, such as *in silico* analyses and population frequency data obtained from the 1000 Genome and ExAC Browser, indicating that p.Pro539Pro is a benign variant. Although p.Pro539Pro was co-segregated in the affected family members in this case report, it has been identified among Malaysian normolipidaemic control subjects in previous studies.[12,13] Furthermore, a previous Taiwanese population study demonstrated that this synonymous mutation is associated with low LDL-C level.[14] PCSK9 inhibitor is a monoclonal antibody lipid-lowering agent that suppresses PCSK9 circulating enzyme from facilitating the intracellular degradation of the LDL receptor. Alirocumab was administered to the proband according to the updated Malaysian Guidelines in managing very-high-risk dyslipidaemic patients with uncontrolled LDL-C levels[15] before her *LDLR* genotype were identified. Subsequent next-generation sequencing analysis revealed that the proband carries a homozygous *LDLR* mutation. Despite the administration of PCSK9 inhibitor, the proband's LDL-C showed no reduction (Table 2) even after 8 weeks of alirocumab treatment, suggesting that this class of lipid-lowering therapy is ineffective for such type of homozygous *LDLR* mutation. Suppression of PCSK9 had minimal impact on homozygous *LDLR* mutation which could be due to the fact that the majority of the LDL receptors in this proband are defective.[16]

A finding from ODYSSEY HIGH FH clinical trial demonstrated a 23% LDL-C reduction among patients with homozygous *LDLR*-defective mutation treated with alirocumab 150 mg once every 2 weeks for 12 weeks duration.[17] This reduction was about half of the efficacy (>50% LDL-C reduction) observed with HeFH patients given with alirocumab 75–150 mg once every 2 weeks for 24 weeks duration, as reported in ODYSSEY FH I and II clinical trials.[8] Another type of PCSK9 inhibitor, evolocumab, was reported to demonstrate a better efficacy than alirocumab. Two clinical trials showed that when 420 mg evolocumab was given monthly to homozygous and heterozygous *LDLR*-defective patients for 12 weeks the LDL-C level was reduced by 32% - 59%.[18,19]

Following Mendel's laws of inheritance, children with HoFH mother will definitely inherit one of the FH alleles. Thus, lipid screening is crucial to these children as they will develop into HeFH in their later life. Therefore, a lipid screening to the child of this patient will be arranged when the infant reaches 2 years old, as recommended.[20]

CONCLUSION

In conclusion, as pregnancy and delivery in women with HoFH are extremely risky, more case reports should be documented to guide the future therapeutic decision. Family cascade screening is recommended for first-degree relatives and extended family members who may have inherited the same mutation as the proband. Hence, early detection and intervention can be implemented and improve overall clinical outcome. A genetic diagnosis may provide important information concerning molecular confirmation of diagnosis, the severity of disease and response to treatment. HoFH patients in pregnancy are ideally managed by a multidisciplinary team. Proper guidelines on best practices in managing such cases are warranted.

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Conflict of interest: The authors declare no conflict of interest.

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