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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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 zygorosity 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
difluprednate, 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 Malaysia1, 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 million3, 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
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.

Table 1: Genetic analysis of the proband and family members

<table>
<thead>
<tr>
<th>Family Relationship</th>
<th>Chromosome sequence</th>
<th>Zygosity Variant</th>
<th>dbSNP ID</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proband</td>
<td>chr19:11223952</td>
<td>c.1187-2A&gt;G</td>
<td>rs879254823</td>
<td>Pathogenic/Likely pathogenic</td>
</tr>
<tr>
<td></td>
<td>chr19:11226800</td>
<td>c.1617C&gt;T</td>
<td>rs5929</td>
<td>Benign</td>
</tr>
<tr>
<td>Father</td>
<td>chr19:11223952</td>
<td>c.1187-2A&gt;G</td>
<td>rs879254823</td>
<td>Pathogenic</td>
</tr>
<tr>
<td></td>
<td>chr19:11226800</td>
<td>c.1617C&gt;T</td>
<td>rs5929</td>
<td>Benign</td>
</tr>
<tr>
<td>Mother</td>
<td>chr19:11223952</td>
<td>c.1187-2A&gt;G</td>
<td>rs879254823</td>
<td>Pathogenic</td>
</tr>
<tr>
<td>Older sister 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Older sister 2</td>
<td>chr19:11223952</td>
<td>c.1187-2A&gt;G</td>
<td>rs879254823</td>
<td>Pathogenic</td>
</tr>
<tr>
<td></td>
<td>chr19:11226800</td>
<td>c.1617C&gt;T</td>
<td>rs5929</td>
<td>Benign</td>
</tr>
<tr>
<td>Younger Brother</td>
<td>chr19:11223952</td>
<td>c.1187-2A&gt;G</td>
<td>rs879254823</td>
<td>Pathogenic/Likely pathogenic</td>
</tr>
<tr>
<td></td>
<td>chr19:11226800</td>
<td>c.1617C&gt;T</td>
<td>rs5929</td>
<td>Benign</td>
</tr>
</tbody>
</table>
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 \textit{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.\textsuperscript{10} We also notice the presence of allele-dose effect \textit{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 \textit{LDLR} variants are rarely identified in the Malaysian population. So far, two pathogenic homozygous \textit{LDLR}, c.763T>A (C255S) at exon 5 and c.2209A>G (R716G) at exon 15, have been previously identified among Malaysian FH patients.\textsuperscript{4,11}

On the other hand, homozygous \textit{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 \textit{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.\textsuperscript{12,13} Furthermore, a previous Taiwanese population study demonstrated that this synonymous mutation is associated with low LDL-C level.\textsuperscript{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\textsuperscript{15} before her \textit{LDLR} genotype were identified. Subsequent next-generation sequencing analysis revealed that the proband carries a homozygous \textit{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 \textit{LDLR} mutation. Suppression of PCSK9 had minimal impact on homozygous \textit{LDLR} mutation which could be due to the fact that the majority of the LDL receptors in this proband are defective.\textsuperscript{16}

A finding from ODYSSEY HIGH FH clinical trial demonstrated a 23% LDL-C reduction among patients with homozygous \textit{LDLR}-defective mutation treated with alirocumab 150 mg once every 2 weeks for 12 weeks duration.\textsuperscript{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.\textsuperscript{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 \textit{LDLR}-defective patients for 12 weeks the LDL-C level was reduced by 32% - 59%.\textsuperscript{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.\textsuperscript{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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**Authors’ contributions:** NAMK collected the data and wrote the article. CYA, AAK and ARS contributed in collecting data and reviewing the
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article. HMN conceived the study and contributed to reviewing and editing the article. All authors have read and approved the final article.

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

REFERENCES