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Case Study

SARS-CoV-2 infection-related deregulation of blood lipids in a patient with -/-LDLR familial homozygous hypercholesterolemia: A case report

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KEYWORDS
SARS-CoV-2;
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Case report

Abstract:

Background: The effect of SARS-CoV-2 infection in blood lipids of homozygous familial hypercholesterolemia (HoFH) has not been explored.

Case summary: We report a case of a 43-year-old male patient with -/-LDLR HoFH with previous history of premature coronary artery disease, coronary artery bypass graft (CABG) and surgical repair of aortic valve stenosis. He presented with an abrupt decrease of his blood lipid levels during acute infection with SARS-CoV2 and subsequently a rebound increase above pre-infection levels, refractory to treatment including LDL-apheresis, statin, ezetimibe and lomitapide up-titration to maximum tolerated doses. Markers of liver stiffness were closely monitored, increased at 9 months and decreased at 18 months after the infection. Potential interactions of hypolipidemic treatment with the viral replication process during the acute phase, as well as therapeutic dilemmas occurring in the post infection period are discussed.

Introduction

SARS-CoV-2 infection or Coronavirus disease 2019 (COVID-19) has been shown to alter lipid metabolism in the acute and the post-infection period.[1] In contrast to accumulating evidence on the effect of the SARS-CoV-2 infection on blood lipid levels in the general population, rel-

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evant data is lacking for homozygous familial hypercholesterolemia (HoFH) patients. In the present work, we aim to describe a rare case of a HoFH patient, showing substantial changes in his lipid profile during and after SARS-CoV-2 infection. This case report is structured according to CARE guidelines.[2]

Case presentation

A case of a 43-year-old man with HoFH (LDLR-/-) is presented, who was diagnosed at early childhood, as a true homozygous for the c.1285G>A (p.Val 429 Met) variant in low-density lipoprotein (LDL) receptor gene known as Afrikaner-2 or V408M. Highest known pre-treatment LDL-C levels were 709 mg/dL. Both parents of the patient bear a diagnosis of heterozygous dyslipidemia based on clinical criteria and receive appropriate treatment. Neither of the parents has been genetically tested, and they are not related. True homozygotes have no functional LDL receptor on their cell surface, resulting in dramatic increases in circulating LDL-C levels and consequently premature cardiovascular disease.[3] Accordingly, previous history includes premature coronary artery disease and aortic valve stenosis. Specifically, at the age of 12, he underwent triple coronary artery bypass grafting (CABG) surgery and intraoperative repair of supravalvular aortic stenosis. Since then, his treatment regimen has included weekly LDL- apheresis treatments and maximum dose of high-intensity statin. At age 34, he underwent aortic arch and sub-valvular stenosis surgical correction, concomitantly with right ventricular outflow tract restoration, aortic valve and arch prosthetic replacement by an artificial prosthesis with a diameter of 21 mm and built-in new aortic valve. After the operation, the patient was referred to our Unit and his treatment regimen was progressively titrated to rosuvastatin 40 mg, ezetimibe 10 mg, lomitapide 20 mg once daily, warfarin 5mg and metoprolol 25 mg twice daily, combined with weekly LDL-apheresis.

On March 9, due to upper respiratory symptoms, the patient missed his scheduled session of apheresis (last apheresis session one week earlier, pre-apheresis LDL-C=54 mg/dL). Three days later, the patient tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction (rt-PCR). Due to his severe medical history, he was admitted to hospital 7 days after initial diagnosis, where he was treated as an inpatient for one week. His infection was characterized by mild pulmonary infection, not requiring oxygen therapy. He received iv ceftriaxone 2 g/day for 7 days. Rosuvastatin and ezetimibe therapy was discontinued, due to increased CPK levels, which was attributed to pharmacological interaction with ceftriaxone and/or disease-related rhabdomyolysis, while he remained on lomitapide and warfarin treatment. The patient also missed, another LDL- apheresis session before hospitalization due to SARS-CoV-2 infection symptoms. As shown in the Table and despite the missed sessions and evidence showing that reductions in lipid levels are usually associated with the severity of COVID-19 in non-HoFH patients,[4] we observed unexpectedly low levels for all lipoproteins for this patent's mild disease course (LDL-C 9 mg/dl). Given the severe history of this HoFH patient with established atherosclerotic cardiovascular disease and previously reported coronary artery endotheliitis in COVID-19,[5] he underwent LDL-apheresis on the 5th day of hospitalization. This was also decided on the basis that discontinuation of hypolipidemic treatment and particularly of apheresis is associated with non-linear kinetics of LDL-C with steep increases between sessions.[6] Ten days after his discharge, LDL-apheresis was re-introduced while his pre-apheresis LDL-C remained extremely low (15 mg/dl). We chose to re-introduce LDL-apheresis for the same reasons we did during hospitalization.

In the following weeks, LDL-C was progressively increasing, reaching levels above those before infection (pre-apheresis LDL-C 105 mg/dl as compared to 54 mg/dl, Table 1), despite re-introduction of full dose of statin-ezetimibe, lomitapide 20 mg once daily and weekly apheresis sessions. Lomitapide was up-titrated to the maximum tolerated dose of 30 mg once daily (Fig. 1). In order to provide a comparative magnitude of change in lipoprotein levels of our HoFH patient versus non-HoFH controls, we analyzed data from a cohort of non-FH patients with acute COVID-19 admitted to our hospital. All of these patients gave informed consent, and the registry has been approved by the local ethics committee. The demographic characteristics of those patients are provided in the **Supplementary Table.** The majority of these patients received corticosteroids and required non-invasive mechanical ventilation or high-flow nasal canula (53%, median WHO severity scale= 5, interquartile range: 5-5) indicating severe disease. Admission and 3 months post-infection lipid levels were measured. Although pre-admission levels were not available, we observed comparable trends to our HoFH patient (Fig. 1).

Due to persistent moderately elevated liver enzymes during the acute and post-infection period, we performed a closer than routinely recommended serial follow-up of liver function tests, showing progressive increase in liver stiffness and hepatic steatosis by liver elastography. Moreover, liver MRI (9 months after COVID-19) indicated hepatic steatosis, not present in pre-infection imaging. After excluding other causes of hepatic steatosis, gastrointestinal (GI) specialist consultation suggested to continue lomitapide treatment and monitor liver enzymes and elastography findings. Two follow-up elastographies 15 months and 18 months later indicated improvement in liver fibrosis with concomitant decrease of liver enzyme levels and pre-apheresis LDL-C at 70 mg/dL (Table 1).

Discussion

We present a case of a HoFH patient with associated severe cardiovascular disease, who presented an extreme decrease in his lipoprotein levels during and shortly after SARS-CoV-2 infection and a rebound phenomenon which was observed during the late post-infection period.

Table 1 Prospective changes in lipid panel before, during and after SARS-CoV2 infection from 03.02.2021 to 05.24.2022. Abbreviations: COVID-19= Coronavirus disease 2019, LDL= low-density lipoprotein, HDL=high-density lipoprotein, ALT= alanine aminotransferase, CPK= creatine phosphokinase.

Condition	Pre-infection	During hospitalization (10 days after testing positive for COVID-19)	One week after hospital discharge	Two weeks after hospital discharge-	Two months after hospital discharge	One month after up-titration to maximum rosuvastatin	Seven months after infection	After 4 weeks of maximum tolerated dose of lomitapide	Fourteen months after the infection
LDL cholesterol before apheresis (mg/dL)	54	9	15	18	62	105	69	44	70
HDL cholesterol (mg/dL)	46	39	44	45	58	56	29	38	54
Total cholesterol (mg/dL)	109	51	68	66	115	164	115	98	137
Triglycerides (mg/dL)	26	34	14	19	23	46	39	88	72
ALT (U/L)	44	106	90	56	36	35	55	55	49
Treatment									
Rosuvastatin	40 mg	-	-	20 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Ezetimibe	10 mg	-	-	10 mg	10 mg	10 mg	10 mg	10 mg	10 mg
Lomitapide	20 mg	20 mg	20 mg	20 mg	20 mg	30 mg	30 mg	30 mg	30 mg

Current literature suggests a bi-directional association of lipids and lipoproteins with SARS-CoV-2 infection. The binding of spike glycoprotein of SARS-CoV-2 to angiotensin-converting enzyme-2 receptor is mediated by lipid rafts, which are plasma membrane domains rich in cholesterol.[7] On the other hand, dyslipidemia creates a pro-inflammatory substrate, which leads to exaggerated inflammasome activation and release of cytokines such as IL-1b and IL-18 during the acute infection.[8] In addition, SARS-CoV-2, a flavi-virus, requires lipid metabolic pathways of the host cell for its replication, disrupting lipid homeostasis in sub-cellular level. In detail, SARS-CoV-2 has been shown to consume lipoprotein components and cause functional deficiency of TMEM41B, which has been suggested to regulate autophagy and cellular lipid metabolism.[9,10]

Current evidence shows that SARS-CoV-2 infection severity is associated with decreased levels of serum cholesterol, LDL-C and HDL-C, which return to normal or even increase to abnormal levels after the infection's resolution.[11,12] It has also been previously reported that viral infections lead to increased production of free radicals in host cells.[8] Furthermore, the combination of SARS-CoV-2 infection and the excess of proinflammatory cytokines can affect liver function, impairing cholesterol metabolism.[8] Collectively, these mechanisms could explain the low levels of lipids observed in the acute COVID-19 and their association with disease severity. Along this line, trends of increasing lipoprotein levels during the post-infection period were observed in a cohort of 66 non-HoFH hospitalized patients due to SARS-CoV-2 infection in our institution (Fig. 1). In our HoFH case, despite the mild severity of the disease and the omission of 2 apheresis sessions, unexpectedly low levels of lipids were observed (Table 1). Such, lipoprotein levels may initially seem incompatible with those observed in HoFH. However, 1) LDL-C levels were serially measured in the same certified lab, 2) very low levels were twice confirmed on 2 different days and gradually changed over time (Table 1) and 3) all lipoproteins followed the same trend showing decreases >50% except for HDL-C which decreased by >15% (Fig. 1). From a mechanistic point of view, this finding could be possibly explained by critically decreased availability of LDL-C in this patient related to an additive effect of altered cellular metabolism caused by SARS-CoV-2 with the already potent effect of his hypolipidemic treatment synergistically targeting LDL-C (ie reduced cholesterol synthesis by statins, LDL-C re-absorption by ezetimibe and VLDL synthesis by lomitapide). To that end, the observed hepatic steatosis during this patient's post-infection follow-up, could be associated with lipid accumulation within hepatocytes, inflammatory responses during acute COVID-19 as well as potential adverse effects of hypolipidemic treatment.[14]

The effect of hypolipidemic treatment in patients with SARS-CoV-2 infection is a field of intense research. Statins have been considered as a potentially beneficial drug class in COVID-19 patients, since pre-hospital statin use has been associated with reduced inflammatory responses, as evident by lower levels of CRP and IL-6.[15] It has been proposed that statins might significantly reduce the attachment and internalization of SARS-CoV-2 by lowering membrane cholesterol levels.[15,16] In addition, statins exert antithrombotic and antioxidative properties, which could be of clinical importance in COVID-19 patients, who present a pro-thrombotic state.[16] Other hypolipidemic treatments, such as fibrates and niacin, have been tested in clinical trials as potential thera-

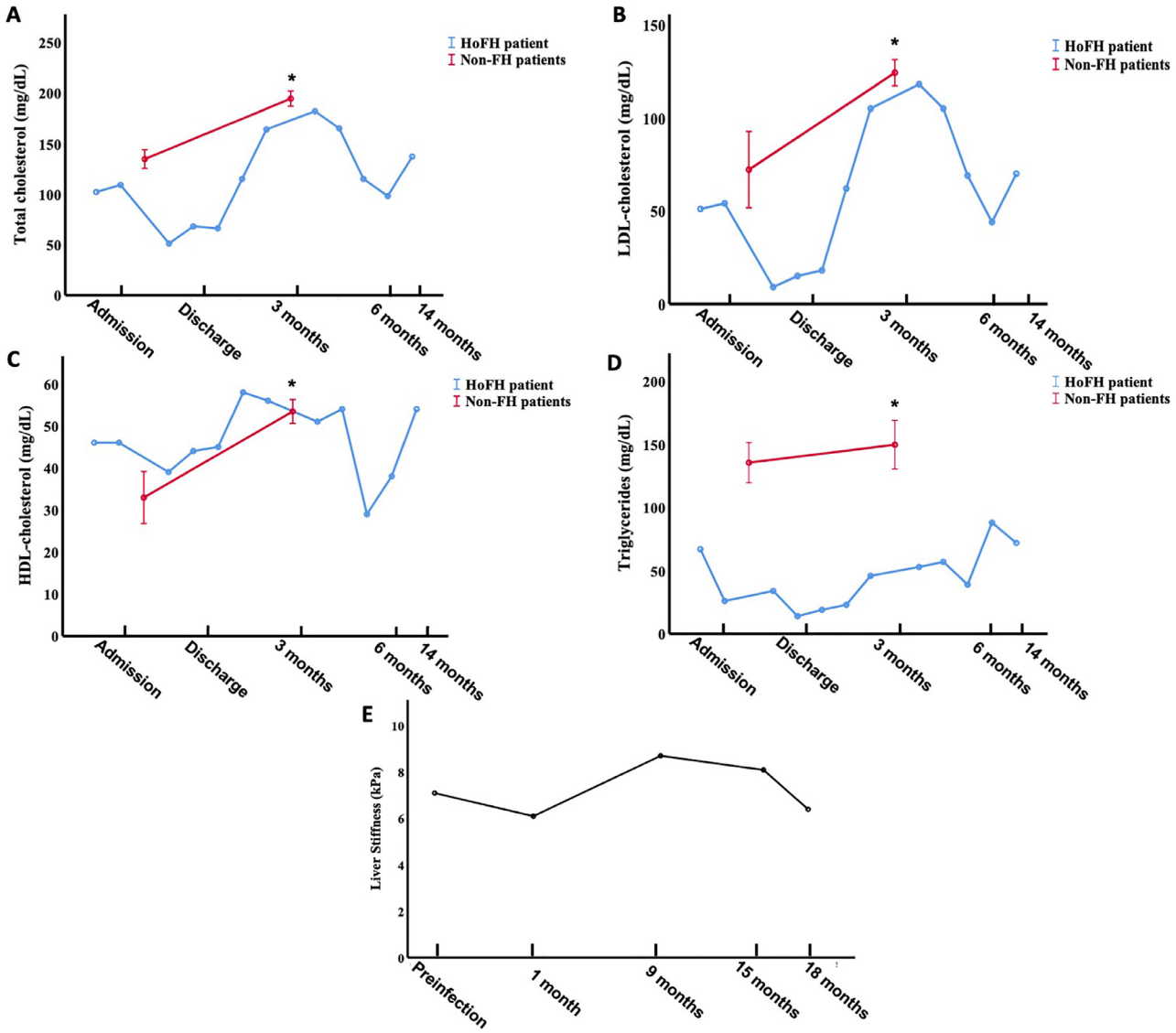

Figure 1 Prospective changes in A) Total cholesterol, B) LDL cholesterol, C) HDL cholesterol, D) Triglycerides from pre-infection period to 14 months after E) Liver stiffness from pre-infection period to 18 months after. The blue line corresponds to the patient presented in the report, while the red line corresponds to a non-HoFH population hospitalized in our institution for SARS-CoV-2 infection. Error bars represent 95% confidence interval of the mean. * Indicates statistically significant difference. Abbreviations: LDL= low-density lipoprotein, HDL=high-density lipoprotein, n/s= non-significant.

peutic interventions in patients with COVID-19, with limited results.[17] The existing data correlating PCSK9 inhibitors and COVID-19 are inadequate while LDL-apheresis and lomitapide treatment has not been studied in patients with SARS-CoV-2 infection yet. Notably, lomitapide discontinuation is suggested when CYP3A4-interacting drugs are prescribed, during SARS-CoV-2 infection, such as antiviral drugs or certain antibiotics.[13,17] In our case, no drug interacting with lomitapide's mechanism of action and metabolism was prescribed, eliminating the possibility of augmented lomitapide effect due to interactions. Moreover, rosuvastatin and ezetimibe were discontinued during hospitalization, but only a few days before the unexpectedly low lipid levels. Thus, their contribution in the observed reductions in blood lipid levels cannot be ruled out. Collectively, this phenomenon could be attributed to the synergistic effect of SARS-CoV-2 infection on lipid metabolism and hypolipidemic treatment.

As already known, HoFH patients require very tight and timely lipid control, due to their extremely high cardiovascular risk.[13,17,] The present case highlights the importance of close monitoring of lipid levels and hypolipidemic treatment adjustments during an acute infection and recovery period to address dramatic changes in circulating lipids. In our case, all lipoproteins were decreased during the acute infection as also supported in the literature for non-FH patients[1,18,] while later we observed an overshoot reaction with increasing lipoproteins and a similar pattern[1], including HDL-C. Whether the following decrease of all lipoprotein levels reflects adaptive

mechanisms to reach initial baseline levels merits further investigation.

As shown by the present case, hepatic injury may result from SARS-CoV-2 infection as well as from interactions with hypolipidemic drugs administered in HoFH and their up-titration due to rebound increases after infection.[18,19] Based on current literature, suggesting that liver stiffness may precipitate after SARS-CoV-2 infection,[20] and on our observations, it would be reasonable for HoFH patients after SARS-CoV-2 infection to be more closely monitored than already recommended for liver function and signs of fibrosis or steatosis particularly when considering up-titration of lomitapide. A multidisciplinary team of lipidologists, cardiologists, and GI specialists was involved in this case to secure optimal management of multiple challenges related to his infection.

In conclusion, this is the first case to show extreme perturbations in blood lipid levels induced by SARS-CoV-2 infection in a HoFH patient during the acute and recovery phase. It should be acknowledged that the present case does not provide sufficient evidence to separate the blood lipid changes associated directly or indirectly with the virus versus the host's genetic predisposition or the treatment and should trigger further research to this direction.

Consent for publication

This case report was specifically discussed with the patient and informed consent was obtained.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2023.02.001.

CRediT authorship contribution statement

Dimitrios Bampatsias: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. **Maria-Angeliki Dimopoulou:** Conceptualization, Investigation, Formal analysis, Writing – original draft. **Dimitrios Karagiannakis:** Writing – review & editing. **Alexandros Sianis:** Writing – review & editing. **Eleni Korompoki:** Data curation, Writing – review & editing. **Kanella Kantreva:** Data curation, Writing – review & editing. **Erasmia Psimenou:** Writing – review & editing. **Georgia Trakada:** Writing – review & editing. **George Papatheodoridis:** Writing – review & editing. **Kimon Stamatelopoulos:** Conceptualization, Supervision, Writing – review & editing.

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