Recurrent coronary syndromes in a patient with isolated very-high lipoprotein (a) and the prothrombin genetic variant rs1799963 (G20210A): a case report

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Background
Elevated lipoprotein (a) [Lp(a)] is an under-diagnosed genetically inherited risk factor for coronary heart disease (CHD) and calcific aortic valve stenosis. Premature myocardial infarction (MI) could stem from the association between elevated Lp(a) and other non-traditional cardiovascular risk factors.

Case summary
Here, we report a male patient with extremely high Lp(a) plasma levels [610 nmol/L (244 mg/dL); normal <75 nmol/L (<30 mg/dL)] associated with the prothrombin genetic variant rs1799963 (G20210A) and no other CHD risk factor. At the age of 32, he suffered recurrent episodes of MI treated by coronary angioplasty and drug eluting stents. The patient who was initially prescribed antiplatelet therapy, beta-blockers, and statins, has subsequently been treated by lipoprotein apheresis every fortnight for 43 months. He has never experienced any recurrent episode of angina or chest pain since.

Discussion
The rare association between extremely elevated circulating Lp(a) levels and prothrombotic genetic variants of coagulation factors appears to be a deadly combination that can only be adequately treated by antiplatelet therapy and lipoprotein apheresis.

Keywords
Case report • Acute coronary syndromes • Lipoprotein (a) • Prothrombin

Learning points
• Genetic variants of coagulation factors associated with extremely high lipoprotein (a) [Lp(a)] is a rare and deleterious combination that can lead to recurrent myocardial infarction in young individuals.
• The optimal treatment option appears to be the combined use of antiplatelet therapy and lipoproteinpheresis until drugs specifically aimed at reducing Lp(a), and currently under development, are approved.
**Introduction**

Lipoprotein (a) \([\text{Lp}(a)]\) is regarded as more atherogenic than low-density lipoproteins (LDL) because it contains all the components of LDL but also oxidized phospholipids and apolipoprotein(a) \([\text{apo}(a)]\), a unique protein structurally similar to plasminogen, with atherothrombotic, proinflammatory, and antifibrinolytic properties. Lipoprotein (a) is the single most common genetically-inherited risk factor for coronary heart disease (CHD) and it is also causative of calcific aortic valve stenosis.\(^1\) Lipoprotein (a) levels above 75 nmol/L (30 mg/dL) are considered pro-atherothrombotic and are found in 20% of the population.\(^2\) Here, we report a young patient with severe recurrent episodes of coronary syndromes presenting with very-high circulating Lp(a) levels and the prothrombin \(\text{rs}1799963 (\text{G20210A})\) genetic variant associated with an increased risk of thromboembolism.\(^3\)

**Timeline**

| Time        | Events                                                                 |
|-------------|------------------------------------------------------------------------|
| Day 1       | Onset of chest pain. Clinical and biological presentation of an acute coronary syndrome with ST-elevation myocardial infarction. Cardiac computed tomography revealed complete occlusion of the right coronary artery (RCA) and suspicion of multi-vessel coronary disease. Coronary angiography was performed followed by recanalizations with drug-eluting stents of (i) the distal RCA, (ii) the left anterior descending artery, (iii) the ramus intermedius artery, and (iv) the circumflex artery. |
| Day 5       | Patient stable, no recurrent angina.                                    |
| 2 months    | Standard lipid biological tests normal.                                 |
| 5 months    | Stress echography revealed no coronary insufficiency and no left ventricular dysfunction. New acute coronary syndrome. Angiography revealed severe double stenosis of the proximal and distal RCA treated by two drug-eluting stents. |
| 6 months    | Detection of very-high levels of plasma lipoprotein (a) and of a \(\text{rs}1799963 (\text{G20210A})\) polymorphism on the prothrombin gene. Onset of lipoprotein apheresis treatment every fortnight. |
| 12 months   | No recurrent chest-pain. Echo stress control normal. Ejection fraction stable at 71%. |
| 24 months   | No recurrent chest-pain. Echo stress control normal.                   |
| 54 months   | Myocardial perfusion scintigraphy control normal. Coronary angiography control showed a stable zone of 30% restenosis in the area of RCA stents. |

**Case presentation**

A 32-year-old Caucasian man presented to our department with acute chest pain. The patient experienced an episode of severe angina for 50 min. His past medical history included migraines until the age of 16 with symptomatic treatment. The patient was otherwise healthy (non-smoker, exercised daily, no diabetes, and not hypertensive) with a family history of heart disease (maternal grandfather underwent coronary bypass at age 51). Serum troponin level was positive at 0.419 ng/mL (reference range 0.00–0.04 ng/mL), and biological tests showed normal lipids with LDL-cholesterol at 2.9 mmol/L (reference range 2.6–5.7 mmol/L) or 112.1 mg/dL.

Physical examination did not show any sign of cardiac insufficiency. Electrocardiogram demonstrated sinus rhythm at 77/min and ST-segment elevation in leads I, v2, v3, v4 and fragmented QRS in v3, v4 suggestive of high lateral wall myocardial infarction (MI) (Figure 1A). Since the patient was young and otherwise healthy, a cardiac computed tomography (CT) was performed initially. It revealed triple-vessel coronary disease with right coronary artery (RCA) occlusion and severe stenosis at the origin of the left anterior descending artery (LAD) (Figure 1B). Coronary angiogram confirmed myocardial CT findings with total RCA occlusion, 50–70% stenosis of the proximal LAD at its bifurcation to diagonal artery, 70–90% stenosis of the circumflex artery, 70–90% stenosis of the ramus intermedius and marginal arteries (Figure 1C and D). Two-dimensional echo examination showed 70% left ventricular (LV) ejection fraction with no dyskinesia, no LV hypertrophy, no valve pathology, and an absence of pericardial effusion. As coronary artery bypass grafting was not an available option, coronary multi-vessel angioplasty was performed in emergency. Full revascularization by percutaneous coronary intervention has given excellent results\(^4\) and has therefore become our institutional practice in particular for young patients with no overt cardiovascular risk factor and not in cardiogenic shock. Recanalizations with drug eluting stents of the distal RCA (Everolimus, Promus Element Plus, 2.75 × 16 mm, Boston Scientific), proximal LAD (Everolimus, Promus Element Plus, 2.75 × 24 mm, Boston Scientific), ramus intermedius artery (Everolimus, Promus Element Plus, 2.75 × 16 mm, Boston Scientific), and circumflex artery ( Zotarolimus, Resolute Integrity, 2.75 × 18 mm, Medtronic) were performed (Figure 1E and F). The patient was stabilized and asymptomatic. He was prescribed lipid-lowering medication (atorvastatin 80 mg), beta-blocker (bisoprolol 2.5 mg), and antiplatelet therapy (aspirin 100 mg + clopidogrel 75 mg). Stress cardiac test performed 2 months later was normal.

The patient suffered a new angina episode without ST-elevation and serum troponin level at 0.562 ng/mL 5 months later, and coronary angiogram revealed severe double stenosis of the proximal and distal RCA likely resulting from the progression of mild pre-existing lesions. Proximal and distal RCA were treated with two drug-eluting stents (Everolimus, Promus Element Plus, 3.50 × 8 mm and 3.00 × 28 mm, respectively). A series of biological investigations were undertaken showing the absence of anti-DNA, antinuclear, anticardiolipin, anti-beta-2 glycoprotein, and antineutrophil cytoplasmic antibodies. We found the \(\text{rs}1799963\) genetic variant on the prothrombin gene (G20210A), a polymorphism known to increase the risk of venous thromboembolism. We also found extremely high levels of \(\text{Lp}(a)\) at 610 nmol/L (reference range <75 nmol/L) or 244 mg/dL despite an otherwise normal lipoprotein profile (total cholesterol 3.49 mmol/L (reference range 3.0–5.2 mmol/L) or 135 mg/dL, triglycerides 0.62 mmol/L (reference range 0.50–1.70 mmol/L) or 55 mg/dL, HDL-cholesterol 1.33 mmol/L (reference range 0.90–1.60 mmol/L) or...
51 mg/dL, LDL-cholesterol 1.88 mmol/L (reference range 2.6–5.7 mmol/L) or 73 mg/dL, apolipoprotein B100 76 mg/dL (reference range 40–125 mg/dL), and apolipoprotein A-I 138 mg/dL (reference range >120 mg/dL).

The patient medication was changed for atorvastatin 80 mg, antiplatelet therapy (aspirin 75 mg + 2 × 90 mg ticagrelor), and a beta-blocker (bisoprolol 2.5 mg). An arterio-venous fistula was created to allow efficient extracorporeal removal of lipoproteins from blood.

**Figure 1** Clinical presentation of a 32-year-old Caucasian man before and after recanalization for an acute coronary syndrome. (A) Baseline admission electrocardiogram showing ST-elevation in leads I and V2, V3, V4. (B) Computed tomography scan. Proximal anterior LAD showing 70% stenosis and calcifications of the aortic valve (arrow) and at the origin of the left anterior descending artery. (C) Proximal anterior LAD showing 50–70% stenosis at its bifurcation to diagonal artery, 70–90% stenosis of the circumflex artery, 70–90% stenosis of the ramus intermedius, and severe stenosis of the marginal artery. (D) Right coronary artery occlusion. (E) Proximal LAD, ramus intermedius artery, and circumflex artery stentings. (F) Right coronary artery stenting.
The patient was treated by double filtration plasmapheresis (DFPP). This procedure was performed using the Plasauto plasmapheresis system with plasma separator Plasmaflo OP-08W and plasma fractionator Cascadeflo EC-50W (Asahi Medical Co., Ltd, Tokyo, Japan). The processed plasma volume was 4L/session. This DFPP was performed every fortnight. His Lp(a) levels are on average 237 ± 45 nmol/L (95 ± 18 mg/dL) before and drop down to 63 ± 10 nmol/L (25 ± 3 mg/dL) after each apheresis procedure (reduction rate of 73% per session and 90% vs. baseline) with apolipoprotein B100 levels of 62 ± 33 and 17 ± 9 mg/dL, respectively. Since initiation of apheresis (43 months in total), the patient never experienced any recurrent episode of angina or chest pain. A coronary angiogram performed in January 2018 showed no restenosis in the left coronary arteries (Figure 2A) but a small-stabilized zone of restenosis affecting approximately 30% of the area within the RCA drug-eluting stent (Figure 2B). Scintigraphy showed normal myocardial perfusion in relaxed and stress states (not shown), whereas cardiac magnetic resonance imaging showed the sequelae of initial MIs in the inferior and apex zones (Supplementary material online, Video S1). Doppler ultrasound imaging indicated that abdominal aorta, extra-cranial arteries, and lower limb arteries are normal.

**Discussion**

Besides isolated Lp(a)-hyperlipoproteinaemia, our patient carries the prothrombin rs1799963 genetic variant associated with an increased risk of venous thromboembolism as well as with an increased overall risk of MI, an association markedly increased in young individuals and for which antiplatelet therapies seem to be the adequate treatment. However, MI in healthy and fit young individuals often occurs in patients with familial hypercholesterolaemia (FH), a genetic condition resulting either from the presence of mutations on the LDL receptor gene, or occasionally from the presence of mutations on genes coding for apolipoprotein B100, Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9), or the LDL receptor adaptor protein. These mutations systematically impair LDL-cholesterol removal from the blood. Combination of statins, ezetimibe and the recent PCSK9 inhibitors is the gold standard treatment to sharply reduce LDL-cholesterol levels and CHD risk in FH patients. Lipoprotein apheresis is sometimes required to treat the most severe forms of FH, in particular homozygotes.

Unfortunately, neither statins nor ezetimibe reduce Lp(a), whereas PCSK9 inhibitors lower Lp(a) by 20–30%. Lipoprotein apheresis is therefore the only suitable treatment to bring individuals with isolated Lp(a)-hyperlipoproteinaemia such as our patient, as close as possible to the Lp(a) cut-point of 75 nmol/L (30 mg/dL) to substantially reduce their CHD risk. In that respect, a randomized crossover trial of 20 patients with refractory angina and Lp(a) levels above 125 nmol/L (50 mg/dL) recently showed that lipoprotein apheresis improves myocardial perfusion reserve, exercise capacity, angina symptoms, quality of life, and reduces carotid wall volume. Injectable therapies such as antisense oligonucleotides that specifically target hepatic apo(a) messenger RNA, and hence obliterate apo(a) protein synthesis, are currently being developed. As they consistently reduce circulating Lp(a) by 90% in phase II trials, these new drugs will certainly become a robust alternative to the long, invasive, and costly apheresis procedures for patients with extreme Lp(a) levels.

**Supplementary material**

Supplementary material is available at European Heart Journal - Case Reports online.

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**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The author(s) confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.
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