Saudi Journal of Ophthalmology (2016) 30, 250–252

Case report

# Central retinal vein occlusion associated with high blood levels of lipoprotein (a). Is lipoprotein (a) a reliable marker for identification of predisposed individuals?

Piergiacomo Grassi [a,*]; Alberto Salicone [b]; Lorenzo Motta [b]; Mario Salvatore Motta [b]

## Abstract

To report a case of central retinal vein occlusion (CRVO) associated with abnormal elevation of Lipoprotein (a) [Lp(a)] plasma levels, without local or systemic risk factors.
A 74-year-old man was referred to our department for cataract surgery in his left eye, and his anamnesis was negative for systemic diseases. Two months later, the patient presented with sudden visual loss in his operated eye, and comprehensive ophthalmic examination was performed, including Fluorescein Angiography (FA) and Optical Coherent Tomography (OCT). Serum concentrations of anticardiolipin and antiphospholipids antibodies, homocysteine and Lp(a) were measured.
Ophthalmoscopy showed the classic features of acute CRVO, FA and OCT confirmed the initial diagnosis. Blood tests were negative for hyperhomocysteinemia, anticardiolipin and antiphospholipids antibodies, and an abnormal Lp(a) plasma concentration of 1.7 g/L was found. The patient was sent to the internist for further investigation and treatment.
Lp(a) can be an useful marker for early identification of predisposed individuals to CRVO and may be involved in its pathogenesis, presumably through its pro-atherogenic and antifibrinolytic action.

**Keywords**: Central retinal vein occlusion, Hypercoagulability, Lipoprotein (a)


http://dx.doi.org/10.1016/j.sjopt.2016.11.001

## Introduction

Retinal vein occlusion (RVO) is the second most common retinal vascular disorder after diabetic retinopathy. There are two types of RVO, central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO). In CRVO, the major outflow channel of the eye is obstructed, resulting in effects throughout the whole retina. In BRVO, a tributary of the central retinal vein is obstructed and only the portion of the retina that is drained by the tributary is affected.[1] Besides standard therapeutic options such as laser photocoagulation and intravitreal injections, the management of RVO includes the identification and correction of systemic vascular risk factors even if no data are available on the possible role of antithrombotic strategies in the long-term prevention of recurrent RVO.[2] Risk factors for RVO lead to diffuse vascular endothelium damage that predisposes to thrombosis and include hypertension, diabetes mellitus, disorders of lipid metabo-

Received 28 May 2015; accepted 2 November 2016; available online 10 November 2016.

[a] Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Napoli ''Federico II'', Via Pansini n. 5, 80131 Naples, NA, Italy
[b] Ophthalmology Unit, ''San Leonardo'' Hospital, Viale Europa 79, 80053 Castellammare di Stabia, NA, Italy

* Corresponding author. Fax: +39 081 7462471.
e-mail address: pjgrassi@libero.it (P. Grassi).

Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

Production and hosting by Elsevier

Access this article online:
www.saudiophthaljournal.com
www.sciencedirect.com

lism, obesity, atherosclerosis, smoking, age >65, open angle glaucoma, and conditions that promote a hypercoagulable state such as deficiency of protein C, protein S, antithrombin III, and activated protein C resistance. Hyperhomocysteinemia and vitamins involved in methionine metabolism, altered fibrinolysis pathway [elevated levels of PAI-1 and Lp(a)], together with hemorheologic modifications have been recently consistently associated with the disease.[2] Few studies, with conflicting results and conducted in limited study populations, have hypothesized the role of high levels of Lp(a) in the occurrence of RVO.[3,4] We report a case of ischemic CRVO, presenting in a patient with anamnesis negative to all classic risk factors, except for a significant increase in Lp(a) levels. The aim of this study was to underline the potential role of Lp(a) as an independent and highly predictive risk factor for CRVO.

## Case report

A 74-year-old man was referred to our department for cataract surgery in his left eye. The patient was in good health, taking no medications. His right eye was aphakic because of a traumatic cataract removal about twenty years before. Best corrected visual acuity (BCVA) was 20/30 in his right eye and 20/100 in his left eye. Slit lamp examination detected no other ocular abnormalities except for a dense nuclear cataract in his left eye. Intraocular pressure (IOP) and dilated fundoscopy were normal in both eyes. He underwent routine uneventful coaxial micro incisional cataract surgery (MICS) in his left eye. After 2 months, the patient complained of sudden visual loss in his left eye, and comprehensive ophthalmic examination was performed. Fundoscopy showed the classic features of acute ischemic CRVO: dilated and tortuous veins, capillary occlusion, papillary and macular edema, hemorrhages, exudates and cotton wool patches. Fluorescein Angiography (FA) and Optical Coherent Tomography (OCT) confirmed the initial diagnosis. Blood tests were negative for hyperhomocysteinemia, anticardiolipin and antiphospholipids antibodies, and an abnormal Lp(a) plasma concentration of 1.7 g/L was found. The patient was sent to the internist for further investigation and eventual treatment.

## Discussion

Lp(a) was first isolated by Berg in 1963.[5] Lp(a) is a hepatocytes-synthesized lipoprotein structurally related to low-density lipoproteins (LDL) and contains, in addition to cholesterol and apolipoprotein B-100, a surface glycoprotein, apolipoprotein (a) (Apo A), responsible for its characteristic properties; in fact, the primary structure of Apo A is similar to that of plasminogen, a key player in the physiological fibrinolysis. DNA of Apo A and DNA of plasminogen are structurally similar and are both located on chromosome 6. The plasma levels of Lp(a) are genetically determined and extremely variable from one subject to another (from 0.001 to 3 g/L), but very stable over life in the same individual. This rate is independent of age, sex, smoking, diet, cholesterol and triglycerides circulating and depends very few on environmental factors. Lp(a) is considered an independent risk factor for thromboembolic diseases.[3] The pathophysiological mechanisms discussed are based on a dual role of Lp(a): an atherogenic role and an antifibrinolytic role; in fact Lp(a) and its cholesterol are taken up by macrophages that become foam cells and colonize the vascular endothelium, thus initiating the process of atherosclerosis. On the other hand, due to the structural analogy between Apo A and plasminogen, Lp(a) presents a striking homology with plasminogen and may therefore compete with binding of plasminogen at fibrin, leading to fibrinolytic system dysfunction. In addition, by inhibiting competitively the binding of plasminogen to its receptors on the surface of endothelial cells, Lp(a) prevents also the activation of plasminogen by t-PA. Due to this interaction with fibrinolytic pathway, Lp(a) has a role in thrombosis in vivo.[3]

Many studies show that elevated levels of Lp(a) constitute a risk factor for coronary and brain thromboembolic diseases.[3] The great interindividual variability in plasma levels of Lp(a) precludes defining normal values, but the rate of Lp(a) is generally considered pathological when it exceeds 0.3 g/L, which is the threshold value beyond which the risk of heart attack increases. Regarding the risk for RVO, the threshold value could be 0.1 g/L according to the literature.[3] In our case, blood levels of Lp(a) were 1.7 g/L and they represented the only significantly increased marker of a thrombotic disease. Surprisingly, RVO occurred in a no-smoker, no-hyperlipidemic and normotensive patient. Hypertension, smoking, atherosclerosis and diabetes mellitus are nonspecific markers for RVO, whereas dyslipidemia and hyperhomocysteinemia are independent risk factors for the occurrence of recurrent CRVO, as shown by Sodi et al.[6]; in fact, hypercholesterolemia, hypertriglyceridemia, fasting and postmethionine hyperhomocysteinemia are more prevalent in recurrent CRVO patients.[6] Marcucci et al. put in evidence that also vitamins involved in methionine metabolism and alterations in the fibrinolysis pathway (elevated levels of PAI-1, deficiency of protein C, of protein S, of antithrombin III, activated protein C resistance) appear to play a significant role in the pathogenesis of this disease.[2] Elevated levels of soluble endothelial protein C receptor also seem to be an important candidate risk factor for CRVO, as shown by Gumus et al.[7] Lp(a) has been shown to be correlated with cardiovascular disorders and is considered as an emerging thrombophilic risk factor in the pathogenesis of RVO. In fact, circulating concentrations of Lp(a) were found to be significantly different in a large population of RVO patients when compared to healthy subjects, independently from other traditional and emerging risk factors, suggesting that Lp(a) may play an important and independent role in its pathogenesis.[8] Our study found elevated levels of Lp(a) in one patient with ischemic CRVO, confirming the hypothesis that Lp(a) may have an independent role in the pathogenesis of this disease, presumably through its pro-atherogenic and antifibrinolytic action. Plasma levels of Lp(a) mainly depend on genetic factors and very few on environmental factors. This probably explains why the therapeutic methods used against hyperlipoproteinemias usually have no influence on plasma levels of Lp(a) (diet, bile salts chelating resins, HMG CoA reductase, fish oils, fibrates). Nicotinic acid would cause a decrease of almost 34% of the concentration of Lp(a), but only the LDL-apheresis resulted in a decrease of large amplitude. The current lack of effective treatments known to reduce levels of Lp (a) or to fight against the consequences of its pathological elevation makes the determination of systemic Lp(a) currently of limited value in clinical practice.

In conclusion, identification of independent and highly predictive risk factors for RVO is nowadays still a big challenge. The main goals are the preservation of visual acuity and of visual field, and the prevention of relapses. This study emphasizes the importance of a systematic control of Lp(a) blood values, which could be useful for an early identification of predisposed individuals to CRVO and BRVO, despite their young age or the absence of other well-known risk factors. Systematic prospective studies are needed to confirm these hypotheses and to clarify the proper role of Lp(a) in relation to other risk factors for RVO.

## Conflict of interest

No conflicting relationship exists for any author.

## References

1. Channa R, Smith M, Campochiaro PA. Treatment of macular edema due to retinal vein occlusions. *Clin Ophthalmol* 2011;**5**:705–13 Epub 2011 May 24.
2. Marcucci R, Sofi F, Grifoni E, Sodi A, Prisco D. Retinal vein occlusions: a review for the internist. *Intern Emerg Med* 2011;**6**(4):307–14 Epub 2010 Dec 14.
3. Ribeaudeau-Saindelle F, Glacet-Bernard A, Lelong F, Coscas G, Soubrane G. Retinal vein occlusion and lipoprotein (a). *J Fr Ophtalmol* 1998;**21**(4):245–50.
4. Bandello F, Viganò D'Angelo S, Parlavecchia M, et al. Hypercoagulability and high lipoprotein(a) levels in patients with central retinal vein occlusion. *Thromb Haemost* 1994;**72**(1):39–43.
5. Berg K. A new serum type system in man- the LP system. *Acta Pathol Microbiol Stand* 1963;**59**:369–89.
6. Sodi A, Giambene B, Marcucci R, et al. Atherosclerotic and thrombophilic risk factors in patients with recurrent central retinal vein occlusion. *Eur J Ophthalmol* 2008;**18**(2):233–8.
7. Gumus K, Kadayifcilar S, Eldem B, et al. Is elevated level of soluble endothelial protein C receptor a new risk factor for retinal vein occlusion? *Clin Exp Ophthalmol* 2006;**34**(4):305–11.
8. Sofi F, Marcucci R, Fedi S, et al. High lipoprotein (a) levels are associated with an increased risk of retinal vein occlusion. *Atherosclerosis* 2010;**210**(1):278–81 Epub 2009 Nov.