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# Central Retinal Vein Occlusion in an Army Ranger with Glucose-6-Phosphate Dehydrogenase Deficiency

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**Abstract**

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most prevalent human enzyme deficiency, affecting an estimated 400 million people worldwide. G6PD deficiency increases erythrocyte vulnerability to oxidative stress and may precipitate episodes of hemolysis when individuals are exposed to triggering agents. Although central retinal vein occlusion (CRVO) does occur in G6PD-deficient individuals, G6PD-deficient individuals exposed to oxidative stressors have not been previously reported to have an increase in CRVO incidence. This is a case of an Army Ranger who deployed to Afghanistan with unrecognized G6PD deficiency and was placed on primaquine following his return to the United States and subsequently developed CRVO. Primaquine is a well-recognized cause of hemolysis in individuals with G6PD deficiency. Hemolytic anemia may contribute to thrombosis as a result of increased erythrocyte aggregation and erythrocyte-endothelium interaction. This case underscores the continued need for routine G6PD screening and avoidance of known triggers in G6PD-deficient individuals.

## Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme disorder in the world, with over 440 genetic variants and more than 400 million people affected worldwide.[1,2,3] G6PD-deficient individuals can develop acute hemolytic anemia and other associated reactions when exposed to oxidative stressors including infections, toxins, foodstuffs, and medications. According to existing literature regarding the occurrence of retinal vein occlusions in this population, G6PD-deficient individuals are postulated to have a significantly lower risk of developing central retinal vein occlusion (CRVO).[4] However, the literature does not state the risk of CRVO development in a G6PD-deficient individual with an on-going oxidative stressor. Retinal vein occlusion, which includes branch retinal vein occlusion and CRVO, is the second most common sight-threatening retinal vascular disorder worldwide following diabetic retinopathy.[5] This case presents a patient with unrecognized G6PD deficiency who was placed on primaquine for malaria prophylaxis and subsequently developed a CRVO.

## Case Report

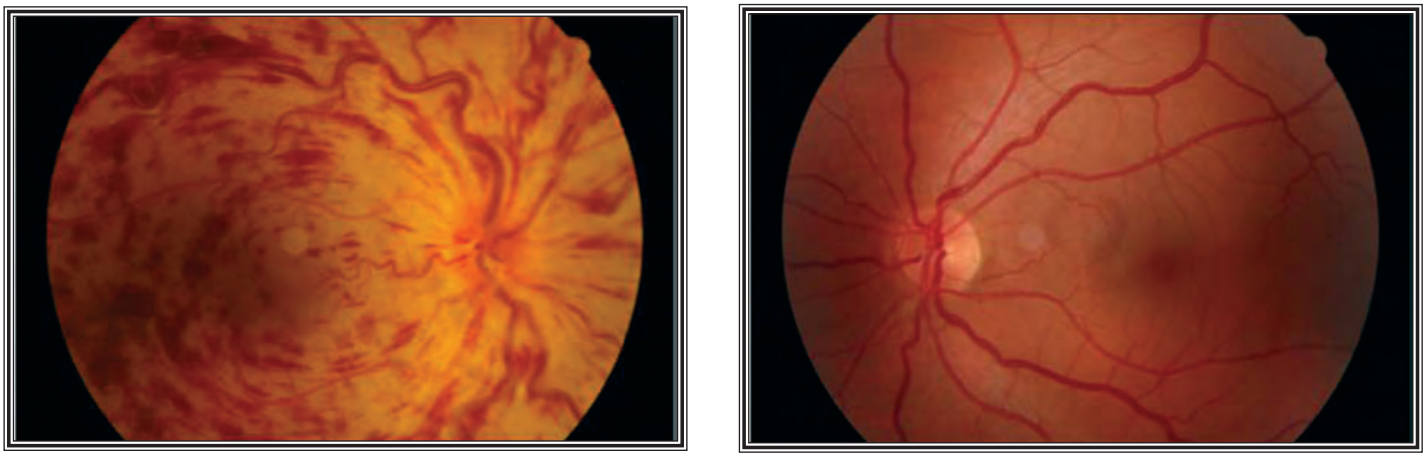
A 35-year-old active duty Army Ranger of Mediterranean descent presented to his primary care provider with the chief complaint of constant blurred vision in his right eye with associated symptoms of photophobia and a "seasick" sensation upon awakening one morning. These symptoms continued to progressively worsen up until the time of his presentation two weeks later. He denied ocular pain or any other symptoms at the time of his initial evaluation.

The patient's past medical history was unremarkable except for intermittent mild normocytic normochromic anemia of unknown origin initially noted on a routine physical examination five years earlier. The patient denied any history of visual complaints, treatment for ophthalmologic conditions, tobacco use, drug allergies, and prior medication complications.

The patient's recent medication history consisted of doxycycline 100mg daily for malaria chemoprophylaxis, which he consumed before, during, and after a three month deployment to Afghanistan. He also consumed a two-week course of primaquine base 15mg daily concomitantly during the last two weeks of his doxycycline regimen. Both medications were completed the month prior to symptom onset. The patient stated that he was compliant with the medication regimens.

The physical examination at the time of presentation revealed a distance visual acuity without correction of 20/200 OD and 20/20 OS. His medical record denoted that he had previously maintained a visual acuity of 20/20 bilaterally without correction. The remainder of his physical exam was unremarkable to include stable vital signs with a normal blood pressure. He was referred to an ophthalmologist who confirmed the decreased vision in the right eye and also noted an afferent pupillary defect, or Marcus Gunn reaction, of the right pupil. Additionally, the right eye fundoscopic examination was remarkable for dilated, tortuous veins, diffuse four-quadrant intraretinal hemorrhage, and macular edema. (Figure) The remainder of the ophthalmologic exam was normal to include noncontact tonometry intraocular pressures of 14mmHg in each eye and an unremarkable slit lamp examination.

The ophthalmologist diagnosed nonischemic CRVO, and the patient was given a two-week course of brimonidine 0.2% one drop twice a day, Cosopt™ (dorzolamide 2% and timolol 0.5%) one drop twice a day, latanoprost 0.005% one drop



OD – Central Retinal Vein Occlusion OS – Normal

**Figure.** Bilateral fundoscopic evaluation of patient's eyes. OS is normal and OD is remarkable for dilated tortuous veins, diffuse intraretinal hemorrhage, and macular edema ("blood and thunder" fundus), which is characteristic of central retinal vein occlusion.

at bedtime, and acetazolamide 500mg one capsule daily. The patient was also started on aspirin 325mg one tablet daily, which he continued throughout the year.

The ophthalmologist conducted an initial laboratory workup which included a complete blood count, fasting glucose, prothrombin time/partial thromboplastin time, protein C antigen, protein S activity, homocysteine, antithrombin III antigen, anticardiolipin panel, antinuclear antibody screen, rapid plasma reagin, and Treponema pallidum antibody. All of these lab results were noted to be within normal limits. Also conducted was a bilateral carotid ultrasound that depicted no significant stenosis or atherosclerotic plaques.

The ophthalmologist referred the patient to a retinal specialist and an internist. The retinal specialist provided regular monitoring and administered a series of intravitreal triamcinolone injections throughout the following year to reduce the macular edema present. The internal medicine physician reviewed the previous labs and ordered additional laboratory testing to include a urinalysis, complete blood count, comprehensive metabolic panel, prothrombin time/partial thromboplastin time, antinuclear antibody screen, antithrombin III antigen, factor V Leiden DNA, factor VIIIA, von Willebrand factor, factor XIIA, protein C antigen, complement protein C3 and C4, complement CH50, lupus anticoagulant battery, dilute Russell Viper venom time, immunoglobulin antibodies, cryoglobulin screen, and hepatitis B and C panel. All of these lab results were noted to be within normal limits. A computerized tomography (CT) scan of the chest and abdomen depicted minimal pleural-parenchymal densities scattered in the left peripheral lung field with a few tiny calcifications representing residua from a prior inflammatory disease. The patient denied any pulmonary symptoms and no prior CT scans were available for comparison. The internal medicine physician consulted a hematologist who reviewed the lab and CT results and offered no further diagnostic or treatment options beyond those currently being provided by the retinal specialist.

It was not until a year later that a new primary care provider noted that the patient was G6PD-deficient during routine lab screening for G6PD prior to initiating primaquine therapy for a subsequent deployment to Afghanistan. The patient's G6PD value was 0.2 IU/g Hb (reference range for normal 7.0-20.5 IU/g Hb), and he was categorized as having severe enzyme deficiency (< 10% of normal). However, he did not fulfill the full Class II criteria depicted by the World Health Organization as there was no historical evidence of intermittent hemolysis with erythrocytic stress or chronic hemolytic anemia.[2] Following a review of the patient's records, this provider hypothesized a possible connection between the patient's G6PD deficiency, his previous intake of primaquine, and the development of CRVO that ensued following his previous deployment to Afghanistan. This provider conducted a thorough literature search and discussed the case with preventive medicine specialists at the U.S. Army Center for Health Promotion and Preventive Medicine, an infectious disease specialist at Brooke Army Medical Center, and ophthalmology specialists in the Army and Navy. A similar case was not previously cited.

The patient continued routine treatment and follow-up with his ophthalmologist and the retinal specialist. At the two-year follow-up he was noted to have an uncorrected visual acuity of 20/20 OD and OS. There was no afferent pupillary defect and noncontact tonometry intraocular pressures were 15mmHg OD and 12mmHg OS. The slit lamp examination was negative for iris neovascularization OD. The OD fundoscopic exam denoted mild residual disk edema, vascular tortuosity, and macular edema with a few scattered retinal hemorrhages. The fundus was normal OS.

## Discussion

### *G6PD Deficiency*

G6PD is a critical metabolic enzyme that supports reduction and oxidation in aerobic cells such as erythrocytes. The gene for G6PD is sex linked and found on the long arm

of the X chromosome. Notable is that more than 400 million people carry a G6PD-deficient gene.[1,2,3] Although dispersed worldwide, G6PD deficiency occurs with increased frequency throughout Africa, Asia, the Middle East, and the Mediterranean region. While G6PD deficiency may provide a biological advantage through relative resistance to *Plasmodium falciparum* malaria, it has over 440 known genetic variants that result in varying degrees of enzymopathy and a wide spectrum of clinical outcomes ranging from asymptomatic to severe hemolytic reactions resulting in transfusion or death.[1,2] G6PD deficiency has conventionally been the archetype of enzymopathy hemolytic anemias and is a leading model of hemolytic anemia resulting from intracorpuscular and extracorpuscular interaction, as most of these hemolytic cases are triggered by an exogenous agent. These exogenous triggers include infections, toxins, foodstuffs (ie, fava beans), and medications (ie, antimicrobials).

Although the antimicrobial primaquine prompted the discovery of G6PD deficiency over 50 years ago,[1] primaquine continues to be an important adjunct used routinely for antimalarial therapy. As a response to frequent deployments of numerous Army personnel to malaria-endemic regions including Afghanistan, the Department of the Army directed that all deploying U.S. Army personnel would undergo G6PD deficiency screening in order to safeguard against hemolytic reactions resulting from primaquine therapy.[6] In this case report, it is uncertain how the individual described did not receive screening for G6PD deficiency prior to the initiation of primaquine therapy.

By itself, primaquine is a cause of increased levels of methemoglobin in many patients who take it, but the levels achieved seldom cause symptoms. However, pathologic methemoglobinemia and hemolytic anemia do routinely occur in G6PD-deficient individuals who consume primaquine. Primaquine is known to be associated with visual accommodation complaints, although a review of the literature does not reveal documentation of other visual disorders to include CRVO. However, the finding of increased erythrocyte aggregation and erythrocyte-endothelium interaction observed in hemolytic disease states may contribute to diffuse microvascular thrombosis in various organ systems to include the eye.[7]

*Central Retinal Vein Occlusion*

Retinal vein occlusion includes branch retinal vein occlusion and central retinal vein occlusion. Following diabetic retinopathy, retinal vein occlusion is the second most common sight-threatening retinal vascular disorder. The prevalence of CRVO in the United States has been reported to be 1 per 1000 and is slightly more common in men than in women.[5]

The majority of people diagnosed with CRVO are over the age of 50. The most common symptom of CRVO is acute and persistent monocular visual loss. Patients characteristically present with an abrupt, painless, unilateral loss of vision of variable severity. CRVO is generally categorized as ischemic or nonischemic. The hallmark fundus finding of CRVO is four-quadrant retinal hemorrhage. The more common nonischemic form has good perfusion to the retina and relatively good visual acuity on presentation. Vision may return to normal if not decreased by persistent macular edema. Nonischemic CRVO can progress to ischemic CRVO, with one-third of nonischemic cases progressing to ischemic within a year. Frequent follow-up is needed to monitor for this change. Patients can also have ischemic CRVO on initial presentation with visual acuity typically 20/400 or worse. Ischemic CRVO typically presents with more extensive retinal hemorrhage, cotton wool spots, disc edema, and often an afferent pupillary defect. Intravenous fluorescein angiogram is commonly used to help define the level of retinal non-perfusion in CRVO. Vision loss in ischemic CRVO may result from ganglion cell ischemia, macular edema, or neovascular complications with secondary glaucoma.

Although CRVO can occur without a known underlying cause, it is often associated with systemic disease (atherosclerosis, autoimmune disease, diabetes, hypertension, intravenous drug abuse, renal insufficiency, tobacco use, vasculitis) or local pathology (ocular trauma, orbital abscess, orbital tumor, glaucoma).[5,8] When CRVO occurs in younger patients it is often associated with blood dyscrasias such as coagulation disorders and hyperviscosity syndromes.

Sickle cell disease has been associated with a hypercoagulable state.[7] Given the hyperviscosity and vaso-occlusive tendencies of individuals with sickle cell crisis,[9] it is interesting that only one case of CRVO in a sickle cell patient has been reported in the literature.[10] Additionally, it is notable that in this sickle cell case report, a comorbid protein S deficiency may have contributed to the ultimate CRVO pathogenesis. Furthermore, an extensive review of the medical literature also detected only one article describing CRVO incidence in G6PD-deficient patients.[4] However, this article postulated protection against CRVO in Sardinian G6PD-deficient patients with the Mediterranean variant. The investigators in this study cited a 3.55% incidence of CRVO in their G6PD-deficient population versus a 10-15% incidence of CRVO in their general population. Not stated in this article was the risk of CRVO development in a G6PD-deficient individual with an active oxidative stressor.

Treatment of CRVO has historically been directed toward the management of the contributing or associated systemic medical problem, as few treatments have had proven efficacy in the treatment of CRVO. Treatment options include aspirin, non-steroidal anti-inflammatory drugs, plasmapheresis, anticoagulation, fibrinolytics, and systemic corticosteroids. Anti-platelet agents are frequently prescribed; however, their efficacy is controversial. Panretinal photocoagulation is used for patients experiencing neovascular complications to reduce or reverse angiogenesis and avoid the development of neovascular glaucoma.

Additional treatment options with improved efficacy have recently become available. Intravitreal triamcinolone has proven effective in reducing edema and improving vision for patients with macular edema,[11,12] and is more likely to be efficacious in patients without ischemic CRVO or diabetes. However, these patients sometimes have rebound symptoms and require continued treatment.

A new approach to treating CRVO is the use of intravitreal bevacizumab.[13] Elevated levels of vascular endothelial growth factor (VEGF) have been found in CRVO and have been positively correlated with the onset and progression

of CRVO neovascular complications.[14] The ability of VEGF blockers to decrease vascular permeability has also suggested its usefulness in treating macular edema. This therapy was successful in improving the vision of one patient with a non-ischemic CRVO from 20/200 to 20/25 eight weeks following injection. Bevacizumab also offers the advantage of not causing increases in intraocular pressure sometimes seen with intravitreal triamcinolone injections.[13]

A new option for treating ischemic CRVO may be hyperbaric oxygen therapy (HBOT).[15] There is a strong theoretical basis for HBOT to be useful in managing ischemic CRVO, and there are multiple case reports documenting success with this treatment modality. As with central retinal artery occlusion, there is likely a time window beyond which HBOT is less likely to be effective, but this time window is not well defined for CRVO.[16,17,18]

## Conclusion

G6PD-deficiency is noted to affect 2.5% of military males, with up to 12% of the African American military population.[6] Although uncertain that the CRVO experienced by the individual described in this report was a result of his primaquine therapy, this case still underscores the continued requirement for routine G6PD deficiency screening in deploying military personnel and the avoidance of all potential triggers in patients who are G6PD-deficient. G6PD-deficient individuals may suffer hemolytic reactions and other adverse reactions when exposed to oxidative stressors such as primaquine. In this case report, it may be possible that exposure to primaquine in a patient with unrecognized G6PD deficiency may contribute to the development of CRVO.

## Disclaimer

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