

Frostbite: A Novel Presentation of Glucose-6-Phosphate Dehydrogenase Deficiency?

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ABSTRACT

Acute hemolytic anemia (AHA) due to glucose 6-phosphate dehydrogenase (G6PD) deficiency has rarely been recognized as a contributor to the development of frostbite. We discuss a case of frostbite in a 32-year-old male Marine with G6PD deficiency during military training on Mount McKinley in Alaska, which eventually led to a permanent disability. In this report, the pathophysiology of G6PD deficiency, the effects of hemolytic anemia, and factors that contribute to frostbite will be discussed, as well as the clinical findings, treatment course, and the outcome of this case. The patient was evacuated and admitted to Alaska Regional Hospital. He was treated for fourth-degree frostbite, ultimately resulting in the complete or partial amputation of all toes. Although it cannot be proved that AHA occurred in this patient, this case potentially adds frostbite to the list of rare but possible clinical presentations of G6PD deficiency.

KEYWORDS: *G6PD deficiency; frostbite; acetazolamide; acute hemolytic anemia; oxidative stress; reactive oxygen species; high altitude*

Introduction

G6PD deficiency, an X-linked disease, is a common cause of AHA, affecting 200 to 400 million people worldwide.¹ This enzyme is essential in the protection of erythrocytes against oxidative stress. Reactive oxygen species are both exogenous and naturally occurring and can lead to premature cellular destruction and varying degrees of AHA. There are 187 known mutations in the *G6PD* gene. The severity of presentation is due to the subtype of G6PD deficiency and the amount of oxidative stress.² As an ever-increasing number of wilderness enthusiasts venture into the backcountry and as our military continues to operate in more extreme and austere environments, medical professionals need to be aware of the possible added risk to those with G6PD deficiency. Frostbite has not previously been described in the literature as being a complication of G6PD deficiency.

Case Presentation

A 32-year-old Hispanic, active duty, male Marine with G6PD deficiency was admitted to Alaska Regional Hospital for severe bilateral frostbite (Figure 1) that occurred while summiting Mount McKinley in Alaska (6,194 m) in May 2014. He was participating in a 14-day, military-led expedition, with a group of eight other Marines. This patient was the only frostbite casualty. He was the only individual of Hispanic origin and the only individual with G6PD deficiency. The patient reports no specific risk factors for frostbite distinct from any other members of the expedition such as uniquely wet feet or clothing or exposures. All eight members of the expedition report cough and nasal congestion. The patient reports taking two doses of acetazolamide 125mg on the day before and one dose on the morning of the summit attempt. Four of the eight Marines also took acetazolamide, at the same dose. Our patient noted dark urine, which he attributed to dehydration due to low fluid intake. He reports uncharacteristic extreme fatigue on the day of injury that was out of proportion to his previous performance compared with the other participants. He noticed no jaundice or pallor.



Figure 1
The patient's feet at 9 days after presentation.

The patient remained ambulatory and was evacuated after descending to an elevation of approximately 2500m. On hospital admission, he was started on standard frostbite protocol including sympathetic block via epidural access, dextran, and oxycodone. A technetium frostbite scan revealed impaired flow extending to the mid toe on all digits. The patient was found to have hemoglobin

of 13.2 gm/dL, hematocrit of 40.6%, and a total red blood cell (RBC) count of 4.49 million RBCs/ μ L with mean corpuscular value (MCV) of 90.4fL. Bilirubin was not measured and no peripheral smear was obtained. The patient improved throughout his hospital stay and was discharged with orthotic fracture shoes, oral analgesics, and a wheelchair. Outpatient treatment included weeks of povidine-iodine soaks, blister care, and hyperbaric oxygen treatments. In September 2014, the patient underwent amputation and surgical debridement of the dry gangrenous portions of toes 1 through 3 bilaterally and partial amputation of toes 4 and 5 bilaterally, for improved function. The surgical wounds were closed via wound vacuum and delayed coverage by plastic surgery.

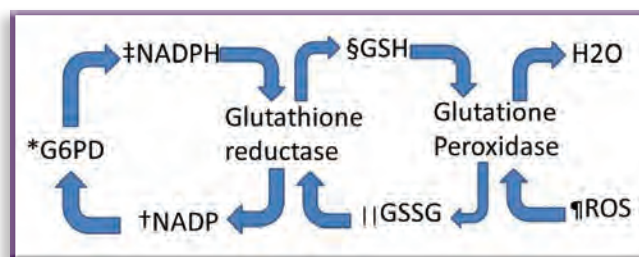
Discussion

AHA in an individual with G6PD deficiency manifests as a normocytic anemia. Anemia was not seen in this patient. This does not, however, exclude the possibility of a mild G6PD deficiency exacerbation. Given his 2 weeks in a high-altitude environment, it is expected that he have an increase in hematocrit due to dehydration and an increase in total RBC count via increased production.³ Thus, these laboratory values may represent a mild hemolysis and thus a greater degree of pathology than one would expect seeing with these values in isolation. Unfortunately, other indicators of AHA (e.g., bilirubin levels and a peripheral smear) were not obtained at Alaska Regional Hospital. The patient did exhibit dark urine and distinct fatigue, compared with his fellow expeditioners, which is out of proportion to his previous performance. Although it cannot be proved in this case, it is possible that AHA played a role in the development of frostbite in this patient with G6PD deficiency.

G6PD is an enzyme that functions in the hexose-mono-phosphate (HMP) shunt.⁴ The primary function of HMP is to indirectly protect RBCs against oxidative injury. RBCs have no other means of protection against this insult⁴ (Figure 2). Reactive oxygen species (ROS) are formed naturally within RBCs via reactions of hemoglobin with oxygen. Oxidants are also produced by many exogenous factors such as drugs, foods, herbs, and infections. Individuals with G6PD-deficient erythrocytes, when exposed to oxidative stress, lack the ability to neutralize ROS in sufficient quantities⁵ (Figure 2).

Without ample G6PD, hemoglobin becomes oxidized and will accumulate within RBCs, leading to decreased function and cell death. The accumulation of oxidized hemoglobin leads to insoluble buildup and crosslinking, causing RBCs to become rigid and making them increasingly susceptible to destruction by the macrophages in the spleen, marrow, and liver.⁵ The end product is the development of normocytic anemia with severity determined

Figure 2 Mechanism for the neutralization of ROS.



Note: *G6PD; \ddagger NADP, nicotinamide adenine dinucleotide phosphate; \ddagger NADPH, reduced nicotinamide adenine dinucleotide phosphate; \S GSH, reduced glutathione; \parallel GSSG, oxidized glutathione; and \uparrow ROS (H₂O₂ or O₂⁻).

by the degree of G6PD deficiency and the relative amount of oxidative stress.

Many substances have been identified as having the ability to cause hemolysis in G6PD-deficient RBCs. A multitude of medications, including many analgesics, antimalarials, and sulfonamides, have been recognized.^{2,4,6} A variety of infectious agents, herbs, and chemical products have been detected. Fava beans have long been known as a significant source of oxidative stress.⁷ There is evidence that high altitude alone is associated with the generation of ROS.⁸

The common presentations of acute hemolysis in G6PD deficiency are a sudden onset of jaundice, dark urine, abdominal or back pain, and all symptoms standard for anemia (i.e., pallor, fatigue, and dyspnea) with onset 2 to 4 days after the insult.² Frostbite has not previously been recognized as a possible presentation of AHA.

Acetazolamide (Diamox Sequel[®]) is a carbonic anhydrase inhibitor. It is categorized as a nonbacterial sulfonamide. Although this category of medications includes many drugs considered to not be safe in those with G6PD deficiency, there is some evidence that acetazolamide activates the enzyme G6PD and therefore may be protective against AHA in those with this disease.⁹ Because one of the effects of acetazolamide is the urinary excretion of bicarbonate, acetazolamide can directly contribute to frostbite due to dehydration.¹⁰

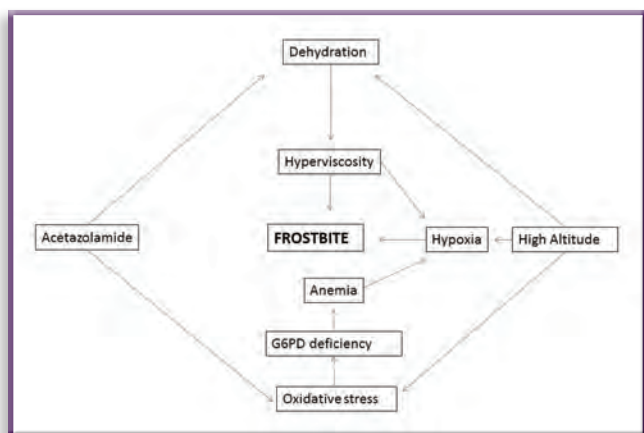
Frostbite is described as the actual freezing of tissue.¹¹ Pathological changes occur via direct cellular injury due to ice formation and indirect cellular injury from microvascular insults. These indirect processes lead to even more severe tissue damage than direct injury,¹¹ occurring via thrombosis and hypoxia.⁹ Severity varies with rate, duration, and extent of freezing as well as with a multitude of interacting individual and environmental factors. These include anemia, increasing altitude, dehydration, tobacco use, tight clothing, vasoactive medications, Raynaud disease, atherosclerosis, and others,¹¹

many of which share the common denominator of poor uptake, transport, and/or delivery of oxygen. Currently, G6PD deficiency is not included.¹¹

Conclusion

Many risk factors were present and likely working synergistically at the time this patient developed frostbite (Figure 3). G6PD deficiency is not currently recognized in medical literature as being a risk factor for frostbite.¹¹ This case proposes the mechanism that oxidative stress, from one of many possible causes, can cause AHA in those with G6PD deficiency, and this anemia can potentiate frostbite indirectly via microvascular injury (Figure 3).

Figure 3 Proposed mechanism for the factors affecting the indirect cellular injury involved in frostbite specific to this case.



More research needs to be done to determine if acetazolamide truly has the potential to protect against or induce AHA in individuals with G6PD deficiency.^{1,6,9} The diuretic effects of acetazolamide increase the risk of frostbite by directly contributing to dehydration¹⁰ (Figure 3).

Independent of the specific mechanisms discussed here, this case has identified the possibility of G6PD deficiency as a serious risk to the wilderness expeditioner. The list of causes of AHA in those with G6PD deficiency is lengthy and includes a wide variety of drugs, viruses, foods, herbs, and environments.^{2,4,6-8} AHA can be directly life threatening; however, in austere and hazardous environments, it also has the potential to increase morbidity and mortality via second-order effects. Many of the illnesses and injuries common to the wilderness environment are caused by hypoxia, worsened by hypoxia, and/or treated by supplemental oxygen. Thus, any of these will be made more severe by anemia. Due to this potential, G6PD deficiency needs to be recognized in medicine literature as a serious comorbidity that should lead to caution for these individuals during certain wilderness and high-altitude activities. Conversely, frostbite must be considered as a novel presentation of G6PD deficiency.

Disclosures

The authors have nothing to disclose.

References

1. Youngster L, Arcavi L, Schechmaster R, et al. Medications and glucose-6-phosphate dehydrogenase deficiency: an evidence-based review. *Drug Saf.* 2010;33:713–726.
2. Minucci A, Moradkhani K, Hwang MJ, et al. Glucose-6-phosphate dehydrogenase (G6PD) mutations database: review of the ‘old’ and update of the new mutations. *Blood Cells Mol Dis.* 2012;48:154–165.
3. Zubieta-Calleja GR, Paulev PE, Zubieta-Calleja L, Zubieta-Castillo G. Altitude adaptation through hematocrit changes. *J Physiol Pharmacol.* 2007;58(Suppl 5; Pt 2):811–818.
4. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet.* 2008;371:64–74.
5. Tizianello A, Pannaciulli I, Ajmar F, Salvadio E. Sites of destruction of red cells in G-6-PD deficient Caucasians and in phenylhydrazine treated patients. *Scand J Haematol.* 1968;5: 116–128.
6. Luzzatto L, Seneca E. G6PD deficiency: a classic example of pharmacogenetics with on-going clinical implications. *Br J Haematol.* 2014;164:469–480.
7. Kattamis CA, Kyriazakou M, Chaidas S. Favism: clinical and biochemical data. *J Med Genet.* 1969;6:34–41.
8. Bakonyi T, Radak Z. High altitude and free radicals. *J Sports Sci Med.* 2004;3:64–69.
9. Metin B, Erat M. Investigation of the effects of some sulfonamide derivatives on the activities of glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase and glutathione reductase from human erythrocytes. *J Enzyme Inhib Med Chem.* 2008;23:418–423.
10. Laemmle T. Acetazolamide (Diamox) may cause frostbite at extreme altitude. *Wilderness Environ Med.* 2001;12:290.
11. Imray C, Freer J. Frostbite. In: Auerbach P, editor. *Wilderness medicine.* 6th ed. Philadelphia, PA: Elsevier Mosby; 2012: 181–201.

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