Lessons for the pathogenesis of vasospasm from a patient with sickle cell disease, moyamoya disease, subarachnoid hemorrhage, and 1 month of persistent vasospasm: illustrative case

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BACKGROUND The mechanism of vasospasm post–subarachnoid hemorrhage (post-SAH) is a poorly understood yet devastating complication that can result in delayed ischemic neurological damage. High concentrations of free hemoglobin present in hemolytic conditions reduce nitric oxide (NO) availability which may disrupt vascular dynamics and contribute to the extent of vasospasm.

OBSERVATIONS The authors describe the clinical course of a sickle cell disease (SCD) patient with spontaneous SAH who suffered an abnormally long duration of vasospasm. The authors then present a focused review of the pathology of intravascular hemolysis and discuss the potential key role of intravascular hemolysis in the pathogenesis of cerebral vasospasm as illustrated in this case lesson.

LESSONS Abnormally prolonged and severe vasospasm in SCD with SAH may provide clues regarding the mechanisms of vasospasm. Intravascular hemolysis limits NO availability and may contribute to the development of vasospasm following SAH.

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KEYWORDS aneurysm; subarachnoid hemorrhage; vasospasm; hemoglobin; moyamoya; sickle cell disease

A growing body of evidence indicates that excess hemoglobin (Hb) that escapes into the plasma during intravascular hemolysis disrupts vasomotor tone and increases inflammation and thrombotic risk when compensatory mechanisms such as haptoglobin-mediated removal of Hb are overrun. For example, in children with sickle cell disease (SCD), haptoglobin is reduced with chronic hemolysis,¹ and the increased availability of Hb limits the effectiveness of the potent vasodilator nitric oxide (NO).² Because Hb reacts with NO at a 1,000-fold faster rate outside the red blood cell (RBC),³ even a small degree of hemolysis can influence vascular tone. This mechanism enhances vasoconstriction and hypertension⁴ and is thought to explain the acute hypertensive response during massive hemolysis⁵ or with Hb-based oxygen carriers that are not compartmentalized into an RBC membrane.⁶

The authors describe the case of a 17-year-old male with SCD and moyamoya disease who presented with SAH complicated by 1 month of prolonged vasospasm. We hypothesize that baseline intravascular hemolysis from this patient’s SCD predisposed him to a prolonged course of vasospasm. This case highlights a potential key mechanism by which increased free Hb limits physiological vascular regulation through NO sequestration and may suggest new avenues for vasospasm treatment.

Illustrative Case A 17-year-old male with a past medical history of SCD and moyamoya disease presented with severe headache. Head computed tomography (CT) showed subarachnoid blood in the basal cisterns (Fig. 1A). A regular-appearing 2-mm right paraceldon internal carotid artery (ICA) aneurysm was believed not to be the source of hemorrhage due to its small size, regular morphology, and paraceldon location. Hemorrhage was thought to be secondary to moyamoya pathology.
strength in the right upper extremity. He went on to make a good recovery, returning to school at 2 months. The ICA aneurysm was treated with flow diversion embolization in a delayed fashion. At last follow-up, he had a normal neurological examination and was pursuing college studies.

### Discussion

#### Timing and Severity of Vasospasm

In this report, we describe a case of SAH-associated clinical vasospasm that was unusually severe and prolonged. Although two-thirds of patients with spontaneous SAH may develop radiographic vasospasm, only one-third develop clinical vasospasm. Onset of clinical vasospasm commonly occurs on days 4–10, peaking at day 7.10,11 Treatments include hydration, blood pressure control, and endovascular treatments such as IA vasodilators and balloon angioplasty. This patient’s clinical course was complicated by his moyamoya disease, necessitating the use of IA verapamil over balloon angioplasty; however, most patients do not require IA therapy. Although vasospasm lasting longer than 14 days occurs in patients without SCD, we hypothesize that the underlying SCD pathology contributed to the unusually severe and prolonged clinical vasospasm, and this may offer clues regarding mechanisms of vasospasm.

#### Serum Hb Decreases NO and Its Vasodilatory Effects

NO, formerly known as endothelium-derived relaxing factor, is a potent endogenous vasodilator12–15 that is important for both maintaining14,16–18 and regulating14,18–21 vascular tone. Hb effectively removes NO from tissues,22 keeping it in the biological range and preventing it from increasing to pathologically toxic concentrations.23 This process can become dysregulated during states of intravascular hemolysis in SCD, where RBC lysis releases Hb into the plasma. Hb present outside the RBC binds to NO at a 1,000-fold faster rate,3 leading to rapid depletion of the vasodilator, NO, and subsequent vasoconstriction,24 which contributes to the pathogenesis of hemolytic conditions such as SCD25 and malaria.26

Although the overall concentration of Hb falls in SCD, plasma Hb increases from RBC lysis and release of Hb into the blood plasma. Plasma Hb is effective at silencing vasodilatory signals. As little as 0.01 g/dl of plasma Hb has been shown to prevent acetylcholine from dilating the rabbit aorta.27 Indeed, plasma free Hb in SCD is correlated with increased NO consumption ($R^2 = 0.92$), which limits the effectiveness of NO donor medications such as nitroprusside and nitroglycerin for these patients.25 In our patient, increased hemolysis was correlated ($p = 0.002$; $R^2 = 0.38$) with the degree of vasospasm (Fig. 3). Although this finding is anecdotal agreement, it raises the question if future vasospasm risk assessment models may find utility for tracking hemolysis in patients with concurrent hemolytic states.

#### Hb Scavenging of NO May Contribute to Vasospasm

In addition to NO consumption from intravascular Hb, Hb within the cerebrospinal fluid (CSF) may play a role in the development of vasospasm post-SAH through a similar mechanism (Fig. 4). Several theories have been proposed for the mechanism of vasospasm after SAH, though no definitive mechanism has been established. These include free radical reactions, inflammatory processes, dysregulation of neurovascular coupling, and imbalances between vasoconstrictors and vasodilators.28 What each of these have in common is involvement of the breakdown products of the SAH hematoma,
which is supported by human and animal studies demonstrating that the size of the hematoma is related to the severity of vasospasm,29,30 which is ameliorated by removal of the blood clot.31,32 Vasospasm typically occurs around day 7 after hemorrhage,10,11 which temporally coincides with the breakdown of the hematoma33 and release of RBC contents into the CSF34,35 (Fig. 4D). In fact, severe vasospasm was noted on day 7 of this patient’s hospitalization (Fig. 2). Among the potential candidates for vasospasm, Hb appears to play a pivotal role. Not only does Hb in the CSF correlate with vasospasm,34–36 it is both necessary37 and sufficient38 for vasospasms to occur.

Role of Haptoglobin in Hb Scavenging of NO in Smooth Muscle

The pathogenesis of Hb-mediated vasospasm may include the migration of Hb (Fig. 4E) because vasospasm can be prevented by restricting the migration of Hb from the CSF into the smooth muscle, where the concentration of NO contributes most to arterial tone.38 Movement of Hb from the CSF into the smooth muscle can be prevented with haptoglobin, which will ameliorate vasospasm.36,39 Haptoglobin plays a vital role in removing Hb from the plasma during states of hemolysis. Patients with SCD have lower levels of haptoglobin because it is continually being used up by a baseline chronic hemolysis.3 If endogenous haptoglobin is important in protecting against vasospasm, then a lack of haptoglobin may also be a factor in this patient’s prolonged vasospasm.

The formation of the Hb–haptoglobin complex does not change the rate of NO consumption,39 but rather the location from which NO is removed, because once the Hb–haptoglobin is formed, Hb is no longer able to penetrate the arterial wall or parenchyma38 (Fig. 4F). In agreement with this observation, previous studies of NO dynamics have also shown that the location of NO production and degradation are crucial elements of NO-mediated signaling of the cerebral vasculature.40–42 Therefore, the spatial distribution of Hb may be a critical component of understanding vasospasm using an NO–Hb mechanism.

Observations

In this study, we describe a patient with unusually prolonged and severe vasospasm after SAH complicated by intravascular hemolysis secondary to his SCD. We seek to gain insights into the mechanism of vasospasm and treatment research illustrated in this case. The patient’s underlying SCD, elevated free Hb, depleted haptoglobin, and reduced NO may explain our clinical findings and support novel insights into vasospasm mechanisms.

Lessons

Vasospasm is a poorly understood yet serious complication of SAH. The presence of free Hb in the plasma and CSF has a profound effect on vascular tone, which may be relevant in the pathogenesis of vasospasm. This observation has important implications for further spontaneous SAH vasospasm treatment and research.
We view this case as hypothesis generating, and conclusions will need to be investigated in additional patients. Intravascular hemolysis has been shown to modify vascular tone; however, its relative contribution to the development of vasospasm post-SAH has yet to be determined. Further research may focus on investigating the role of intravascular (in plasma) and extravascular (the hema
toma breaking down in the CSF) NO consumption in the develop-
ment of vasospasm post-SAH. Restricting the movement of Hb by
binding it to haptoglobin may prove therapeutic. Taken together,
these studies may deepen our understanding of SAH vasospasm and
reveal new treatment pathways.

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Conception and design: all authors. Acquisition of data: Haselden, Church. Analysis and interpretation of data: all authors. Drafting the article: Haselden. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Haselden. Statistical analysis: Haselden, Church. Study supervision: Church.

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