

Stroke in a child with hemoglobin SC disease: a case report describing use of hydroxyurea after transfusion therapy

Diana Fridlyand,¹ Caroline Wilder,¹
E. Leila Jerome Clay,¹ Bruce Gilbert,²
Betty S. Pace¹

¹Department of Pediatrics and

²Department of Radiology, Augusta University, GA, USA

Abstract

Children with hemoglobin SC (HbSC) disease suffer a significant incidence of silent cerebral infarcts but stroke is rare. A 2-year-old African American boy with HbSC disease presented with focal neurologic deficits associated with magnetic resonance imaging evidence of cerebral infarction with vascular abnormalities. After the acute episode he was treated with monthly transfusions and subsequently transitioned to hydroxyurea therapy. The benefits of hydroxyurea as a fetal hemoglobin inducer in HbSC disease, to ameliorate clinical symptoms are supported by retrospective studies. This case highlights the rare occurrence of stroke in a child with HbSC disease and the use of hydroxyurea therapy.

Introduction

Sickle cell disease (SCD) is a group of inherited blood disorders caused by either homozygous mutations in the β -globin gene producing hemoglobin SS (HbSS) or heterozygous alleles including HbS β^0 -thalassemia, HbS β^+ -thalassemia and HbSC disease. While sickle cell anemia (SCA), including HbSS and HbS β^0 -thalassemia, causes the most severe clinical phenotypes, children with HbSC and HbS β^+ -thalassemia can experience significant complications.¹ In the United States and United Kingdom, HbSC represents approximately 30% of SCD patients, and accounts for more than 50% of SCD patients in West Africa.² The phenotype of HbSC disease arises secondary to potentiation of hemoglobin S polymerization by the presence of hemoglobin C leading to cellular dehydration secondary to loss of water and potassium.³

The efficacy of hydroxyurea (HU) in reducing vaso-occlusive episodes in adults with SCA was demonstrated in the Multicenter Study of Hydroxyurea in Sickle

Cell Anemia,⁴ steering Food and Drug Administration approval. Subsequent studies showing efficacy and safety in children revolutionized care. The latest recommendation is that all children with SCA be offered HU starting at nine months of age, regardless of clinical symptoms.⁵ However, limited clinical trials make the management of children with HbSC and HbS β^+ -thalassemia less clear, although many experience a severe disease phenotype.⁶

Stroke occurs in 11% of children with sickle cell anemia, but chronic red blood cell transfusions decrease recurrence by 90%.⁷ In contrast, stroke is extremely rare in HbSC disease; however, 13.5% of children experience silent cerebral infarcts.⁸ The Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated the benefit of red cell transfusions in preventing strokes in children with Transcranial Doppler (TCD) velocities >200 mm/sec.⁹ More recently, the Transcranial Doppler with Transfusions Changing to Hydroxyurea (TWITCH) trial established the non-inferiority of substituting HU therapy for chronic transfusions in children with SCA and abnormal TCD,¹⁰ supporting its use in this population.

The most beneficial effect of HU is fetal hemoglobin (HbF) induction, which inhibits HbS polymerization.¹¹ Moreover, HU has anti-inflammatory, immune modulating, cell-signaling and gene transcription modifying effects. Consequently, we present a patient with HbSC disease with neurologic abnormality and cerebral infarction, and discuss the challenges of diagnosis and clinical management.

Case Report

History and physical exam

A 2 year old African American boy with HbSC disease was well until two years of age when he was admitted to the hospital for acute chest syndrome. A week after discharge, he was evaluated in the hematology clinic, at which point grandmother reported a week long history of *dragging his right foot*. His mother witnessed one episode of body stiffening without tonic-clonic movements and noted *starring for a few seconds* as well as *less understandable* speech. The neurology team was consulted and recommended magnetic resonance image and magnetic resonance arteriogram (MRI/MRA) studies and an electroencephalogram (EEG) after the history of a focal deficit was obtained. The MRI revealed abnormal T2 hyperintense signal within the bilateral peritrigonal white mat-

Correspondence: Betty S. Pace, Department of Pediatrics, Augusta University, 1120 15th Street, CN-4112, Augusta, GA 30912, USA.
Tel.: +1.706.721.6893 - Fax: +1.706.721.0174.
E-mail: bpace@augusta.edu

Key words: Hemoglobin SC disease, hydroxyurea, cerebral infarct, sickle cell anemia, hematology.

Acknowledgements: The authors would like to thank Judi Schweitzer for administrative assistance with data collection and the nurses in the hematology clinic and inpatient services for assisting with clinical management.

Contributions: DF designed the case report, collected data, and wrote the paper. CW reviewed the medical record, collected data on the case and contributed to writing and reviewing the paper. ELJC was involved with the diagnosis and clinical management and decision making to transition to hydroxyurea and assisted with writing and reviewing the paper. BG provided expertise for the MRI/MRA review and writing the paper. BSP supervised the overall experimental design and focus the case report and writing and editing paper.

Conflict of interest: the authors declare no potential conflict of interest.

Received for publication: 20 November 2016.

Revision received: 16 February 2017.

Accepted for publication: 17 February 2017.

This work is licensed under a Creative Commons Attribution NonCommercial 4.0 License (CC BY-NC 4.0).

©Copyright D. Fridlyand et al., 2017
Licensee PAGEPress, Italy
Pediatric Reports 2017; 9:6984
doi:10.4081/pr.2017.6984

ter due to chronic ischemic change (Figure 1), consistent clinically with an ischemic stroke. The initial MRA noted possible minimal narrowing of the right carotid terminus and the origin of the left middle cerebral artery. The EEG was normal.

Clinical management

The child was admitted to the pediatric intensive care unit for a partial exchange transfusion with a baseline HbS 48.4%, HbC 47.9% and HbF 3.7% (Table 1). Since his baseline hemoglobin was 10.6 gm/dL, blood was removed (100 mL; 7 mL/kg) and 100 mL of sickle negative packed red cells were transfused producing a post HbS 36.7%. A TCD was obtained which was normal by STOP criteria.⁹ Given the clinical history and MRI results, chronic transfusions were recommended to maintain

HbS<30% for stroke prevention. Due to an average HbS 40% and hemoglobin 11.6 gm/dL, pre-transfusion phlebotomies were performed. Coagulation studies including protein C, protein S, antithrombin III, prothrombin, Factor V Leiden, and lupus anticoagulant were normal. Echocardiogram was obtained which demonstrated a structurally normal heart. After 6 months of transfusions, a repeat MRI and MRA were performed and showed no interval change. While on transfusions symptoms resolved and his speech returned to normal, which was confirmed by joint hematology and neurology follow-up. Based on clinical improvement and studies which demonstrated clinical and laboratory efficacy of HU use in HbSC patients,¹²⁻¹⁴ the decision was made to transition the child from chronic transfusions to HU 300 mg (22.2 mg/kg/day). During therapy he had a decrease in white blood cell count from 8.2 to 6.5 cells/ μ L, absolute neutrophil count from 5576 to 2925 $\times 10^9$ /L, and platelet counts ranged from 267,000 to 154,000/mm³. Of note, total hemoglobin increased from 9.4 to 11.3 g/dL, MCV from 78.6 to 90.9 fL and HbF from 3.7% to 5.1%. He has continued to do well without reoccurrence of clinical symptoms for two years and a repeat TCD remained normal after 6 months of HU therapy.

Discussion and Conclusions

Data from the Cooperative Study of Sickle Cell Disease (CSSCD) has provided substantial information regarding the natural history of HbSC disease.⁶ The large, multi-institutional study demonstrated 0.8 pain episodes per patient-year in HbSS compared to 0.4 episodes per patient-year in HbSC.⁶ By age 3, 32% of Hb SC infants

had abnormal pocked red blood cell counts, with intermediate splenic dysfunction.⁶ The rate of osteonecrosis did not differ significantly between HbSS and HbSC patients, and the incidence of acute chest syndrome in HbSC patients was 5.2 per 100 patient years.⁶ Additionally, children with HbSS and HbSC had the highest rates of bacteremia under the age of 2 years.⁶

The coagulation workup in our case study did not show abnormalities; however, germane to our report is the role of hypercoagulation in the clinical manifestations of HbSC disease. Data in children are limited but findings of a cross-sectional observational study support increased risk of thromboembolic events in adults with HbSC disease.¹⁵ There was observed increased expression of tissue factor, thrombin-antithrombin complex and D-dimer when compared to healthy controls, but levels in HbSC patients were lower than those in SCA patients.¹⁵ The higher hemolytic activity and inflammation observed in HbSC patients were associated with retinopathy and osteonecrosis.¹⁵

Given a paucity of data regarding management of patients with HbSC disease, studies in patients with SCA have been employed in clinical decisions. Numerous clinical trials in adults and children^{16,17} have demonstrated the benefit of HU in reducing the clinical severity of SCA by decreasing dactylitis, acute chest syndrome, and hospitalization rates.¹⁷ However, stroke continued to be a common complication in SCA with significant morbidity before chronic transfusions and TCD screen were established as standard of care.⁷ The long-term complication of iron overload prompted studies to determine whether HU is an effective alternative. The Sparing Conversion to Abnormal TCD Elevation study demonstrated the efficacy of HU in

children with SCA and conditional TCD velocities (170-199 cm/sec).¹⁸ More recently, the TWITCH trial demonstrated children *without vasculopathy* on MRA could be treated with HU after a year of transfusion therapy.¹⁰

The major effect of HU is HbF induction by mechanisms including inhibition of ribonucleotide reductase and DNA synthesis leading to cell death¹⁹ and rapid maturation of erythroid progenitors;²⁰ similarly, HU has been demonstrated to increase HbF in HbSC patients.¹²⁻¹⁴ Hydroxyurea also acts as a nitric oxide (NO) donor to activate cyclic guanosine monophosphate²¹ and enhanced γ -globin gene expression by transcription factors such as cJun.²² Since NO depletion due to chronic hemolysis in SCA



Figure 1. Magnetic resonance imaging demonstrates chronic deep white matter ischemia. Standard T2 weighted imaging was performed under sedation which showed abnormal T2 hyperintense signal (arrows) within the bilateral peritrigonal white matter (left greater than right).

Table 1. Summary of laboratory and imaging tests results.

Laboratory / imaging test	Baseline	Chronic transfusions 4th months	Before start of hydroxyurea	After 1 year on hydroxyurea
HbS (%)	48.4	28.2	25.4	49.4
HbC (%)	47.9	25.8	21.7	41.8
HbF (%)	3.7	3.2	2.9	5.1
White blood cells (/ μ L)	8.2	13.5	12.9	6.5
Neutrophils ($\times 10^9$ /L)	5576	8505	6,708	2,925
Hemoglobin (gm/dL)	9.4	11.3	11.3	10.8
Platelets (mm ³)	267,000	233,000	240,000	154,000
Mean corpuscular volume (fL)	78.6	78.5	79.7	90.9
Magnetic resonance imaging	Abnormal		Unchanged	
Magnetic resonance arteriogram	Abnormal		Normal	
Computed tomography	Normal		Normal	Normal
Electroencephalogram	Normal			

contributes to the development of vasculopathy, HU reverses this effect by improving NO levels and blood flow, and decreasing endothelial activation and neutrophil adhesion to molecules such as fibronectin and intercellular adhesion molecule 1.²³ Another beneficial effect of HU is its ability to decrease the elevated white blood cell counts associated with early death, stroke and acute chest syndrome in SCA²⁴ and HU has been demonstrated to reduce white blood cell count and absolute neutrophil count in HbSC patients as well.¹² However, bone marrow suppression producing neutropenia and thrombocytopenia are limitations of HU therapy, and thrombocytopenia has led to discontinuation of therapy in HbSC patients.¹³

The role of HU therapy in HbSC patients is less clear because this population has been excluded from major clinical trials. Data from the CSSCD established a 5.6% rate for silent cerebral infarct in SCD.⁶ Using more contemporary MRI/MRA techniques, the rate ranges from 13.5-16%⁸ but overt stroke remains a rare complication. While HbSC disease generally produces a less severe clinical phenotype than SCA, our case demonstrates stroke can occur. Given the challenges of chronic red cell transfusions in this population, alternative therapy is needed. Recent single institution retrospective studies involving HbSC patients²⁵ suggest HU reduces pain crises making it a feasible option. Data from a multicenter retrospective study of several HbSC cohorts support the ability of HU to increase HbF and decrease white cell counts without severe bone marrow suppression in adults and children to produce a beneficial effect.^{12,14} Limited studies have been conducted to address treatment options for HbSC disease. Future prospective studies are required to validate HU as a treatment option for children with HbSC disease with severe clinical complications including stroke.

References

1. Ballas SK, Lief S, Benjamin LJ, et al. Definitions of the phenotypic manifestations of sickle cell disease. *Am J Hematol* 2010;85:6-13.
2. Pecker LH, Schaefer BA, Luchtman-Jones L. Knowledge insufficient: the management of haemoglobin SC disease. *Br J Haematol* 2017;176:515-26.
3. Nagel RL, Fabry ME, Steinberg MH. The paradox of hemoglobin SC disease. *Blood Rev* 2003;17:167-78.
4. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995;332:1317-22.
5. Buchanan GR, Yawn BP, Afenyi-Annan AN, et al. Evidence-based management of sickle cell disease. Expert Panel Report, 2014. US Department of Health and Human Services; National Heart, Lung, and Blood Institute. Available from: <https://www.nhlbi.nih.gov/sites/www.nhlbi.nih.gov/files/sickle-cell-disease-report.pdf>
6. Bonds DR. Three decades of innovation in the management of sickle cell disease: the road to understanding the sickle cell disease clinical phenotype. *Blood Rev* 2005;9:99-110.
7. Adams RJ, McKie VS, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial doppler ultrasonography. *N Engl J Med* 1998;339:5-11.
8. Williams KP, Fields ME, Hulbert ML. Higher-than-expected prevalence of silent cerebral infarcts in children with hemoglobin SC disease. *Blood* 2015;125:416-7.
9. Adams RJ, McKie VC, Brambilla D, et al. Stroke prevention trial in sickle cell anemia. *Control Clin Trials* 1998;19:110-29.
10. Ware RE, Davis BR, Schultz WH, et al. Hydroxycarbamide versus chronic transfusion for maintenance of transcranial doppler flow velocities in children with sickle cell anaemia-TCD With Transfusions Changing to Hydroxyurea (TWITCH): a multicentre, open-label, phase 3, non-inferiority trial. *Lancet* 2016;387:661-70.
11. Steinberg MH, Chui DHK, Dover GJ, et al. Fetal hemoglobin in sickle cell anemia: a glass half full? *Blood* 2014;123:481-5.
12. Luchtman-Jones L, Pressel S, Hilliard L, et al. Effects of hydroxyurea treatment for patients with hemoglobin SC disease. *Am J Hematol* 2016;91:238-42.
13. Yates AM, Dedeken L, Smeltzer MP, et al. Hydroxyurea treatment of children with hemoglobin SC disease. *Pediatr Blood Cancer* 2013;60:323-5.
14. Miller MK, Zimmerman SA, Schultz WH, Ware RE. Hydroxyurea therapy for pediatric patients with hemoglobin SC disease. *J Pediatr Hematol Oncol* 2001;23:306-8.
15. Colella MP, de Paula EV, Machado-Neto JA, et al. Elevated hypercoagulability markers in hemoglobin SC disease. *Haematologica* 2015;100:466-71.
16. Hankins JS, Ware RE, Rogers ZR, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood* 2005;106:2269-75.
17. Thornburg CD, Files BA, Luo Z, et al. Impact of hydroxyurea on clinical events in the BABY HUG trial. *Blood* 2012;120:4304-10.
18. Hankins JS, McCarville MB, Rankine-Mullings A, et al. Prevention of conversion to abnormal transcranial Doppler with hydroxyurea in sickle cell anemia: a phase III international randomized clinical trial. *Am J Hematol* 2015;90:1099-105.
19. Ware RE. How I use hydroxyurea to treat young patients with sickle cell anemia. *Blood* 2010;115:5300-11.
20. Ho JA, Pickens CV, Gamcsik MP, et al. In vitro induction of fetal hemoglobin in human erythroid progenitor cells. *Exp Hematol* 2003;31:586-91.
21. King SB. A role for nitric oxide in hydroxyurea-mediated fetal hemoglobin induction. *J Clin Invest* 2003;111:171-2.
22. Kodeboyina S, Balamurugan P, Liu L, Pace BS. cJun modulates Ggamma-globin gene expression via an upstream cAMP response element. *Blood Cells Mol Dis* 2010;44:7-15.
23. Canalli AA, Franco-Penteado CF, Saad ST, et al. Increased adhesive properties of neutrophils in sickle cell disease may be reversed by pharmacological nitric oxide donation. *Haematologica* 2008;93:605-60.
24. Platt OS, Brambilla DJ, Rosse WF, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-44.
25. Lebensburger JD, Patel RJ, Palabindela P, et al. Hydroxyurea decreases hospitalizations in pediatric patients with Hb SC and Hb SB+ thalassemia. *J Blood Med* 2015;15:285-90.