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

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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 and the use of hydroxyurea therapy. The benefits of hydroxyurea in 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 HbSβ +-thalassemia, HbSβ+-thalassemia and HbSC disease. While sickle cell anemia (SCA), including HbSS and HbSβ+-thalassemia, causes the most severe clinical phenotypes, children with HbSC and HbSβ+-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.3 However, limited clinical trials make the management of children with HbSC and HbSβ+-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 (TWTIXCH) 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 staring for a few seconds as well as less understandable speech. The neurology team was consulted and recommended magnetic resonance image and magnetic resonance arteriogram (MRA/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 matter 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

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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,

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/μL, absolute neutrophil count from 5576 to 2925×10^9/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 recurrence 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. 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. By age 3, 32% of Hb SC infants had abnormal pocked red blood cell counts, with intermediate splenic dysfunction. 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. Additionally, children with HbSS and HbSC had the highest rates of bacteremia under the age of 2 years.

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. 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. The higher hemolytic activity and inflammation observed in HbSC patients were associated with retinopathy and osteonecrosis.

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 have demonstrated the benefit of HU in reducing the clinical severity of SCA by decreasing dactylitis, acute chest syndrome, and hospitalization rates. 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. 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). More recently, the TWiTCH trial demonstrated children without vasculopathy on MRA could be treated with HU after a year of transfusion therapy.

The major effect of HU is HbF induction by mechanisms including inhibition of ribonucleotide reductase and DNA synthesis leading to cell death and rapid maturation of erythroid progenitors; similarly, HU has been demonstrated to increase HbF in HbSC patients. Hydroxyurea also acts as a nitric oxide (NO) donor to activate cyclic guanosine monophosphate and enhanced γ-globin gene expression by transcription factors such as cJun.

Since NO depletion due to chronic hemolysis in SCA

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**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 (μL)                 | 8.2      | 13.5                             | 12.9                        | 6.5                         |
| Neutrophils (×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                      | Normal                      |
| Electroencephalogram                   | Normal   | Normal                           | Normal                      | Normal                      |

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**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).**
Case Report

SCD.6 Using more contemporary 5.6% rate for silent cerebral infarct in has been excluded from major clinical tri-

ations of HU therapy, and thrombocytopenia bone marrow suppression producing neu-

tropenia and thrombocytopenia are limita-

tions of HU therapy, and thrombocytopenia has led to discontinuation of therapy in HbSC patients.12

The role of HU therapy in HbSC patients is less clear because this population has been excluded from major clinical tri-

als. 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.

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