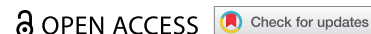


CASE REPORT



A case of S β + sickle cell disease diagnosed in adulthood following acute stroke: it's 2021, are we there yet?

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ABSTRACT

In this report, we present a 29-year-old African American female who was brought to a local emergency department after being found unresponsive by her mother. The etiology of her stroke and severe hemolysis remained unknown, despite her mother reporting the patient's history of co-inheritance of sickle cell trait and beta-thalassemia trait, and extensive workup during her prolonged hospitalization. She was diagnosed with sickle cell disease (S β + type) two years after discharge when she was referred to a sickle cell specialist for persistent anemia. Here, we also briefly review the challenges to diagnose rarer subtypes of sickle cell disease (SCD), in this case S β + type, as well as the pathophysiology and current management of stroke in SCD.

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KEYWORDS

Sickle cell disease; sickle cell beta-plus thalassemia; compound heterozygous; stroke

1. Introduction

Sickle cell disease (SCD) is an inherited hemoglobinopathy with devastating, multi-system complications when sub-optimally managed. According to the latest estimates from the Centers for Disease Control and Prevention, approximately 100,000 people in the USA live with SCD [1]. Over the past several decades, survival has improved in children with SCD by implementation of widespread newborn screening, penicillin prophylaxis, pneumococcal vaccination for encapsulated bacteria, and hydroxyurea. However, the overall life expectancy in individuals with SCD in the USA is estimated to be 43 years due to high morbidity and mortality in adulthood [2]. Cerebrovascular disease is a particularly concerning complication of SCD, as both silent cerebral infarcts and overt stroke lead to cognitive and functional deficits over time [3].

In this report, we present the case of an African American woman with SCD (S β + type), whose SCD was not diagnosed until two years after she developed acute stroke at age 29 years, requiring admission to the ICU. We briefly review here the challenges to diagnose compound heterozygous types of SCD, in this case S β + type, as well as the pathophysiology and current management of stroke in SCD.

2. Case

2.1. Initial presentation and hospital course

A 29-year-old African American female was brought to a local emergency department (ED) by her mother

after being found unresponsive at home in decorticate posture, profusely diaphoretic with urinary incontinence. While in the ED, she developed hypotension, hypothermia, and respiratory failure with an oxygen saturation of 80% and agonal respirations. She was subsequently intubated and admitted to the ICU for management of possible seizure and sepsis. The patient's mother reported that she had experienced flu-like symptoms for two weeks prior to presentation, for which she had been taking over-the-counter cold medications. Earlier on the day of admission, she had demonstrated acute confusion and later became unresponsive. During history taking, her mother also mentioned that the patient had 'sickle cell trait and beta-thalassemia trait.'

Initial laboratory workup in the ED revealed Coombs negative severe hemolytic anemia with hemoglobin 6.8 g/dL, absolute reticulocytes 0.05 tril/L, reticulocyte production index 0.79%, hematocrit 19.2%, MCV 76.5 fL, and severe thrombocytopenia with platelets 24 bil/L, for which she received packed red blood cells (PRBC) and platelet transfusions. Peripheral blood smear showed few spherocytes, few target cells, and few tear cells without schistocytes. Additional laboratory analysis revealed LDH and lactate elevated to 4385 U/L and 6.0 mMol/L, respectively, total bilirubin 1.7 mg/dL, AST 236 U/L, ALT 80 U/L, and D-dimer >21.0 mcg/mL with elevated fibrinogen. Urine drug screen was positive for amphetamines (later she denied using amphetamine but reported that she might have had passive

exposure) and marijuana, which she was consuming for chronic pain of unknown etiology.

Additional studies obtained on hospital day 1 included CT and MRI of the brain which were read as unremarkable, EEG showing diffuse slowing of brain waves without evidence of seizure, and CT scan of the chest demonstrating mild chronic interstitial lung changes bilaterally and multiple lung nodules without evidence of pulmonary embolism. CT scan of the abdomen performed on day 2 revealed high-intensity material within the gallbladder, mild hepatosplenomegaly, and 'fishmouth' deformities of the lumbar spine vertebrae. Subsequent gallbladder ultrasound demonstrated biliary sludge without evidence of discrete stones. Follow-up CT chest showed left lower lung consolidation on day 4.

Given the evidence of severe hemolysis, thrombocytopenia, and altered mental status, hematology recommended emergent empiric plasma exchange due to concern for thrombotic thrombocytopenic purpura (TTP). Empiric broad-spectrum antibiotics, fluconazole, and acyclovir were discontinued on day 5 after a negative infection workup including a negative lumbar puncture. Despite 4 days of plasma exchange treatments, there was no improvement in her clinical or laboratory status. She was therefore transferred to a tertiary care center on day 7 for higher level of care.

2.2. Tertiary care hospital course

Upon transfer, hematology discontinued plasma exchange given a normal ADAMTS13 (resulted on day 7), which ruled out TTP. Hemoglobin electrophoresis performed on day 8 was interpreted as sickle cell trait and beta-thalassemia trait (Hgb A 74.1, Hgb F 0.0,

Hgb S 22.1, Hgb A2 of 3.8, Hgb C 0.0). Haptoglobin dropped to <10 mg/dL. On day 15, total bilirubin peaked at 3.7 mg/dL, with AST and ALT reaching maximums of 634 U/L and 559 U/L, respectively, and thrombocytopenia recovered. Further laboratory investigation failed to establish the etiology of the patient's loss of consciousness and ongoing hemolysis. Folate was normal, while vitamin B12 was low at 342.2 pg/mL. Her autoimmune panel was negative, and she did not meet the Sydney Criteria for antiphospholipid syndrome. Peripheral blood flow cytometry for paroxysmal nocturnal hemoglobinuria and G6PD deficiency testing were both normal. Serology for HCV, HBV, HIV and Parvo virus was negative. TSH was also within the reference range.

A second MRI brain obtained on day 7 revealed multiple scattered microthrombi, bilateral chronic subdural hematomas, diffusion restriction in the splenium of the corpus callosum, and extramedullary hematopoiesis in the calvarium (Figure 1). Her initial MRI from the day of admission was reread by a neuroradiologist, who noted multiple lesions suggestive of a 'shower of emboli.' Echocardiogram did not show any intracardiac thrombi or septal defect and electrocardiogram confirmed sinus tachycardia. Abdominal ultrasound with duplex on day 11 revealed mild hepatomegaly (17.5 cm) with splenomegaly (13.5 cm), increased heterogeneous echogenicity of the spleen, along with mildly elevated main hepatic artery peak systolic velocity. Bone marrow biopsy obtained on day 16 demonstrated hypo-cellular marrow with extensive degenerative changes and markedly decreased trilineage hematopoietic cells, consistent with bone marrow necrosis. The patient required a total of 4 more units of PRBC during her hospitalization to maintain hemoglobin above 8 g/dL.

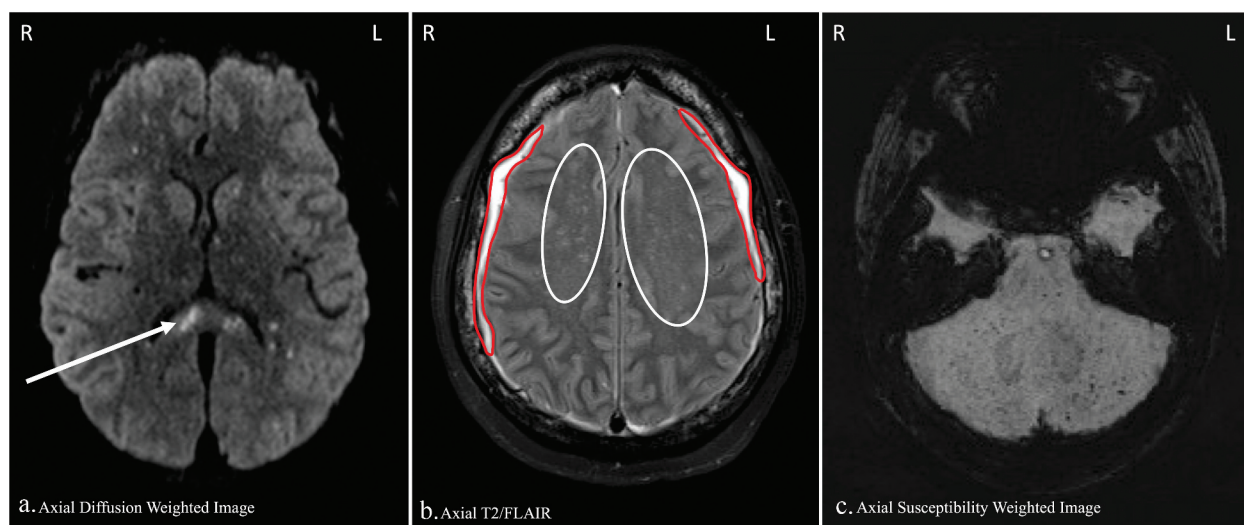


Figure 1. **A.** Axial diffusion weighted image (DWI): Multiple foci of restricted diffusion including a dominant peri-centimeter region in the right splenium of the corpus callosum (see arrow); **B.** Axial T2/FLAIR at the level of the centrum semiovale: Hyperintense foci indicative of vasogenic edema in the bilateral white matter including deep and subcortical aspects (encircled in white). Incidental bilateral cerebral convexity subdural collection that are hyperintense in signal (and intermediate intensity on T1) favoring chronic subdural hematomas (encircled in red); **C.** Axial susceptibility weighted image (SWI) at the level of the cerebellum: Numerous hypointense foci indicative of microhemorrhages throughout the cerebellum and brain stem

2.3. Hospital discharge and outpatient follow-up

Supportive care was continued and the patient's mental status gradually improved. She was subsequently extubated on day 21 of her hospital stay and discharged to an acute rehabilitation facility on day 52. Upon discharge, she was neurologically alert and responsive with globalized weakness and expressive aphasia. Approximately two years later, the patient was referred to a sickle cell clinic for persistent anemia. On further detailed questioning, she reported pain while swimming and unexplained occasional pain episodes during childhood with progressive severity for which she eventually started using marijuana. Hemoglobin electrophoresis was obtained and suggested SCD (Hgb A 20.5%, Hgb F 3.9%, Hgb A2 7.7%, Hgb S 67.9%). Further DNA testing revealed heterozygous positivity for hemoglobin S (c.20A>T) and a thalassemia trait/ β^+ mutation/pathogenic variant (c.-79A>G) in the promoter of the beta globin gene – 29 base pairs upstream of the transcription start site. DNA testing also demonstrated four alpha globin genes with duplication of the mid-portion of the alpha-2 globin gene. This confirmed the diagnosis of SCD, $S\beta^+$ type. In subsequent visits, additional workup showed avascular necrosis of the bilateral hips and left shoulder (indicative of stage III or early stage IV FICAT avascular necrosis, Figures 2 & 3). Abdominal ultrasound confirmed resolution of hepatosplenomegaly. Per patient preference, chronic transfusions were not started, and hydroxyurea was initiated instead. She demonstrated a strong response to hydroxyurea

with Hb F > 20% but developed pancytopenia at a dose of 30 mg/kg, requiring a decrease in dosage leading to decline in HbF. Therefore, she chose to add voxelotor given residual pain and low HbF and total hemoglobin interfering with her quality of life. At the time of this publication (4 years after initial stroke), she has not developed recurrent stroke and continuous physical therapy has improved her gait, musculoskeletal strength, and speech.

3. Discussion

This case presents a 29-year-old female with lifelong unrecognized sickle cell disease, $S\beta^+$ type. She presented to the emergency room with severe hemolytic anemia, acute stroke, acute respiratory failure, and alveolar hemorrhage due to thrombocytopenia secondary to hepatosplenic sequestration. This clinical presentation, along with the patient's reported personal history of sickle cell trait and thalassemia trait, pain while swimming, unexplained progressive pain, and family history of beta-thalassemia trait (mother) and sickle cell trait (father), suggests sickle cell disease (SCD). Additionally, the typical bone marrow biopsy findings, multiple-imaging reports noting osseous sequelae of SCD (e.g., 'fishmouth' deformities), and chronic interstitial lung changes on CT chest further suggest a chronic sickling process.

SCD is an autosomal recessive hemolytic anemia following Mendelian inheritance. Its complex pathophysiology is due to the presence of excess hemoglobin S (HbS), which results from the substitution of the hydrophilic glutamic acid with hydrophobic

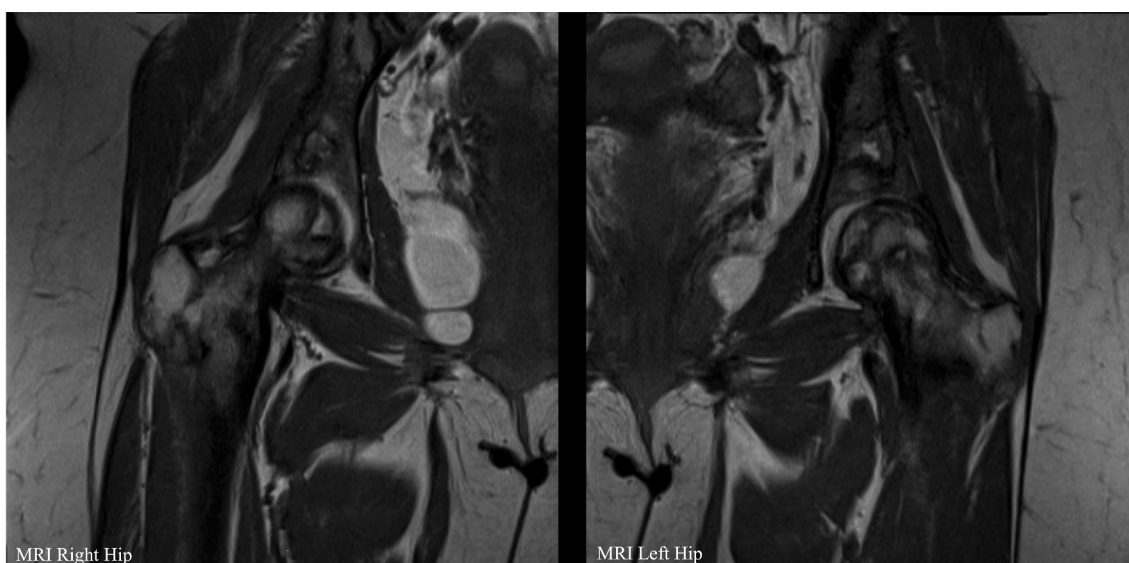


Figure 2. Coronal PD MRI of left and right hips without contrast showing serpentine low signal irregularity along the weightbearing portion of the femoral head with associated rim of edema compatible with avascular necrosis. There are extensive regions of bony infarctions involving the entire visualized bony pelvis (including the pubic body, ischial tuberosity, iliac wing and sacrum) and proximal femur/intertrochanteric region. Both studies are indicative of stage 3 and suspected early stage 4 FICAT femoral head avascular necrosis.

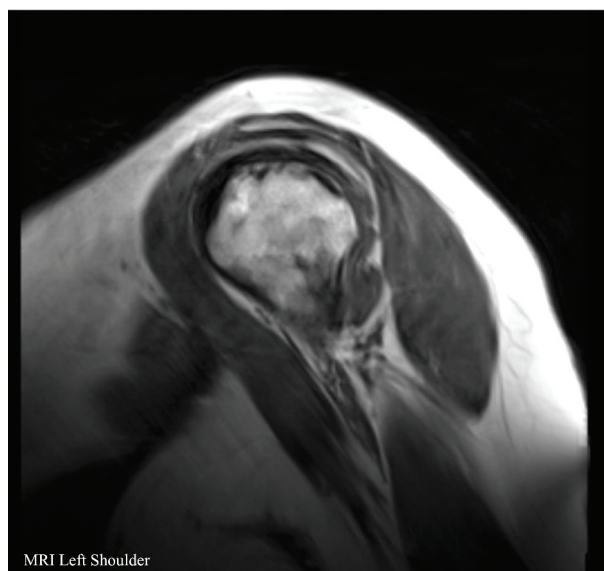


Figure 3 . MRI left shoulder demonstrating serpiginous PD hyperintense and T1 hypointense signal along the peripheral margin of the humeral head. These findings are consistent with avascular necrosis of the left humeral head.

valine in position 6 of the beta globin gene. HbS polymerizes under low oxygen tension, leading to repeated cycles of sickling that result in vaso-occlusive pain crisis and hemolysis with RBC lifespan $1/6^{\text{th}}$ that of normal RBCs [4,5]. The co-inheritance of HbS with other beta globin gene mutation variants results in several SCD subtypes. The most common genotypes are sickle cell SS (also known as sickle cell anemia) and $S\beta^0$. These subtypes frequently present with vaso-occlusive crises, hemolytic crises, or both. By contrast, $S\beta^+$ and SC are rarer genotypes and usually initially present with less severe anemia and infrequent vaso-occlusive crises in childhood. Over time, patients with these subtypes often gradually develop multiple complications such as stroke, avascular necrosis of bones requiring joint replacement, sickle cell retinopathy, and hepatosplenic sequestration [6–8]. Due to their gradual clinical progression, these rarer subtypes may be misunderstood and remain undiagnosed for years, such as in this case. A potential means of reducing the confusion may be to update the terminologies currently used by experts to name these compound heterozygous sickle cell variants. For example, using ‘ $S\beta^+$ sickle cell disease’ or ‘Sickle cell disease, $S\beta^+$ type’ instead of ‘sickle cell trait beta-thalassemia trait’ may help patients and clinicians better understand the significance of this diagnosis. In the present case, both the patient’s family and her providers knew she had co-inherited sickle and beta-thalassemia mutations but were unaware that this coinheritance is one of the several subtypes of sickle cell disease.

The result of patients’ post-transfusion hemoglobin electrophoresis often is misinterpreted as sickle cell trait and thalassemia trait. In our patient’s test, the low hemoglobin S was due to dilution of the

patient’s hemoglobin S by transfused RBCs received during her hospitalization. Her high HbA also reflected transfused RBCs rather than the patient’s own RBCs. Co-inheritance of the sickle cell mutation with another hemoglobin variant – if in the trans position – results in sickle cell disease and there is no other interpretation. The trans position can be confirmed with family testing showing that one parent has one sickle cell mutation, and the other parent carries another pathologic beta globin mutation variant. Additionally, falsely elevated HbA2 in SCD may lead to the incorrect conclusion that the patient has beta thalassemia trait [9]. The most accurate way to confirm SCD type is genetic testing, which also provides the information necessary to offer comprehensive genetic counseling. Hypochromic microcytosis in individuals with SCD in the absence of iron deficiency may reflect additional alpha or beta globin gene abnormalities. This was true for the patient in the present case, who had an MCV of 73.7 fL and MCH of 24.1 pg in the absence of iron deficiency. She also had a partial alpha duplication in addition to a beta trait mutation, which could contribute to the increased severity of her SCD.

Ischemic stroke is a well-established complication of SCD, with a recent study suggesting an incidence rate of approximately 2% in children and young adults [10]. While the existing literature suggests that the overall risk of stroke is lower among $S\beta^+$ patients, it still represents a significant source of morbidity [6–8]. This is evident in the patient described in this report, who continues to have gait problems and imbalance, expressive aphasia, and cognitive impairment requiring her mother to oversee her overall care. The increased stroke risk in SCD is attributed to several mechanisms. First, repeated

sickling episodes are thought to cause pathologic adherence of abnormal erythrocytes to the vascular endothelium, contributing to vascular injury, intimal hyperplasia, NO dysregulation, and intraluminal thrombosis [5,11,12]. These processes lead to the progressive stenosis of the cerebral arteries and the development of collateral vessels resembling moyamoya angiopathy [13,14]. Second, abnormal oxygen delivery and chronic anemia in SCD lead to decreased arterial oxygen content (CaO_2), which also contributes to stroke development [15]. Therefore, during acute severe hemolytic anemia or acute chest syndrome, cerebrovascular dilatory reserve reaches maximal capacity and cerebral blood flow cannot compensate for the acute decrease in CaO_2 , resulting in ischemia [16]. Chronic anemia and elevated cerebral blood flow may further predispose to cerebral vasculopathy due to chronic shear stress [15]. Third, 'cerebral fat embolism syndrome' in the absence of PFO, described more commonly in case reports and case series of compound heterozygous types, might be the main cause of stroke in this case [17]. Last but not least, SCD is also characterized as a hypercoagulable state, which may further elevate stroke risk [18].

It is well known that the cornerstone of primary and secondary stroke prevention in children with SCD is the use of transcranial Doppler (TCD) to identify children at risk of stroke and initiate prophylactic blood transfusions [19,20]. However, at this time there are no evidence-based, effective stroke prevention and management recommendations specific to adults with SCD, despite increased risk of stroke incidence by age [21]. Instead, it is recommended that adults with SCD receive evaluation and treatment for traditional stroke risk factors as in the general population, such as hypertension, hyperlipidemia, and atrial fibrillation. In adults with acute stroke and SCD, prompt blood transfusion is recommended, with exchange transfusion preferred to simple transfusion when possible and appropriate. According to the American Society of Hematology (ASH) 2020 guidelines, evaluation for revascularization surgery and regular blood transfusions are conditionally suggested as secondary prevention for adults with SCD and evidence of moyamoya syndrome, though very limited evidence for these recommendations exist and recommendations are extrapolated from pediatric sickle cell data [22]. Although hydroxyurea is the recommended treatment for reducing vaso-occlusive events in SCD, the data supporting its utility instead of blood transfusions for stroke prevention in children continues to evolve [22–24]. The use of hydroxyurea for stroke prevention in adults with SCD remains to be studied.

4. Conclusion

This report presents the case of a young adult with $\text{S}\beta$ + sickle cell disease whose condition was not diagnosed until after she developed an acute stroke at age 29 years requiring ICU admission. This delay occurred despite the fact she had undergone genetic testing early in her life and that she and her providers had known for years that she co-inherited the hemoglobin S and beta thalassemia (β +) mutations. Perhaps this could have been prevented by using the term ' $\text{S}\beta$ + sickle cell disease' for her diagnosis instead of 'sickle cell trait beta thalassemia trait'. This case underscores the need to establish effective educational programs to raise clinicians' awareness of the diagnosis and management of SCD and its subtypes, evidenced by the fact that all studies conducted during this patient's hospitalization provided clues towards a diagnosis of SCD. It also illustrates the fact that acute stroke and other complications of sickle cell anemia can occur in adults with compound heterozygous SCD ($\text{S}\beta$ + type in this case) if not managed properly. While these subtypes are often considered to be milder forms of the disease, this is a potentially misleading characterization. Last but not least, further research is warranted to identify effective primary and secondary stroke prevention measures for adults with SCD.

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