Case Series

Sickle Cell Disease with Cyanotic Congenital Heart Disease:

Long-Term Outcomes in 5 Children

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Sickle cell disease is a risk factor for cerebrovascular accidents in the pediatric population. This risk is compounded by hypoxemia. Cyanotic congenital heart disease can expose patients to prolonged hypoxemia. To our knowledge, the long-term outcome of patients who have combined sickle cell and cyanotic congenital heart disease has not been reported. We retrospectively reviewed patient records at our institution and identified 5 patients (3 girls and 2 boys) who had both conditions. Their outcomes were uniformly poor: 4 died (age range, 12 mo–17 yr); 3 had documented cerebrovascular accidents; and 3 developed ventricular dysfunction. The surviving patient had developmental delays. On the basis of this series, we suggest mitigating hypoxemia, and thus the risk of stroke, in patients who have sickle cell disease and cyanotic congenital heart disease. Potential therapies include chronic blood transfusions, hydroxyurea, earlier surgical correction to reduce the duration of hypoxemia, and heart or bone marrow transplantation. ***(Tex Heart Inst J 2016;43(6):509-13)***

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Congenital heart disease (CHD) has a prevalence of 0.8% in the general population and is cyanotic in approximately 15% of affected patients.[1-4] Sickle cell disease (SCD) is diagnosed in 0.27% of live births in black Americans.[5] Few data are available about the outcomes of patients who have this combination of diseases. Furthermore, patients who have either SCD or CHD have a higher risk of cerebrovascular accident (CVA). In patients who have SCD, 11% have an overt CVA before the age of 20 years,[6] and up to 37% experience a silent cerebral infarction.[7] This risk in SCD is exacerbated by hypoxemia, which promotes the sickling of erythrocytes and resultant microvascular occlusion. In one study, patients with mean nocturnal oxygen saturations below 96% had an approximate 50% risk of adverse neurologic events within the next 5 years.[8] Children with SCD and cyanotic CHD typically have saturations much lower than this before surgical intervention, and many might remain in this at-risk range after surgery. We review our experience and suggest management approaches that might improve overall outcomes in patients with SCD and cyanotic CHD.

Case Reports

After approval from our institutional review board, we identified patients in our hospital system through crosslinked diagnostic codes for the combination of SCD and CHD. We reviewed the cases of 33 patients who had presented at our institution from October 2003 through September 2014. Of these 33, 5 had SCD and cyanotic CHD (Table I).

Patient 1

Patient 1, a girl born at term, had a prenatal diagnosis of pulmonary atresia with intact ventricular septum and coronary sinusoids. At age 6 days, the patient underwent the placement of a modified Blalock-Taussig shunt and recovered uneventfully, with a postoperative oxygen saturation of 86% and a hemoglobin (Hb) level of 17.6 g/dL upon her discharge from the hospital. Both her parents had sickle cell trait. At age 3 months, she was diagnosed with sickle cell anemia (hemoglobin SS disease, Hb SS)—the most prevalent form of SCD, characterized by inheritance of the Hb S

TABLE I. Characteristics and Outcomes of the 5 Patients

Patient No.	Sex	Age at Sickle Cell Diagnosis	Hemoglobinopathy	Congenital Heart Disease	Stroke	Cardiac Systolic Dysfunction	Outcome
1	F	3 mo	Hb SS	PA + IVS	Yes	No	Alive at age 5 with developmental delays
2	F	14 mo	Hb SS	HLHS (MA + AA)	No	Yes	Died suddenly at age 18 mo
3	M	<1 mo	Hb SC	DILV + TGA + Coarc	Yes	Yes	Died at age 11 yr (end-stage CHF with AVMs and hemoptysis)
4	M	3 yr	Hb SS	TA + PA + IVS	Yes	Yes	Died at age 17 yr after 2 heart transplantations
5	F	4 mo	Hb SS	PA + VSD + MAPCAs	No	No	Died at age 12 mo of cardiac arrest after PA/VSD repair

AA = aortic atresia; AVMs = arteriovenous malformations; CHF = congestive heart failure; Coarc = aortic coarctation; DILV = double-inlet left ventricle; F = female; Hb SC = hemoglobin SC disease (sickle cell trait); Hb SS = hemoglobin SS disease (sickle cell anemia); HLHS = hypoplastic left heart syndrome; IVS = intact ventricular septum; M = male; MA = mitral atresia; MAPCAs = major aortopulmonary collateral arteries; PA = pulmonary atresia; TA = tricuspid atresia; TGA = transposition of the great arteries; VSD = ventricular septal defect

gene from both parents and consequent severe anemia. The patient had a preoperative exchange transfusion before undergoing a bidirectional Glenn procedure at 4 months of age (pre-exchange Hb level, 14.1 g/dL). Her postoperative oxygen saturation ranged from 82% to 85%. Chronic transfusion therapy, begun when she was 5 months old, was discontinued at 13 months in favor of hydroxyurea therapy. When the patient was 3.5 years old, developmental delays prompted magnetic resonance imaging, which revealed a prior CVA. As of October 2016, the 5-year-old patient remained on hydroxyurea therapy, with oxygen saturations in the mid-80% range and an Hb level of 10.7 g/dL.

Patient 2

Patient 2, a girl born at term, had a prenatal diagnosis of hypoplastic left heart syndrome. At 6 days of age, she underwent a Norwood procedure and had a postoperative oxygen saturation of 91% and an Hb level of 10.6 g/dL. When 3 months old, she underwent a bidirectional Glenn procedure (preoperative Hb level, 11.3 g/dL); her postoperative oxygen saturations were in the mid-80% range. Of note, the patient's mother had SCD; however, the patient's initial electrophoresis test—performed after a blood transfusion—indicated only sickle cell trait. Electrophoresis results at 14 months yielded the diagnosis of Hb SS disease. Severe ventricular dysfunction developed, and the patient was started on chronic transfusions. She died suddenly at home at age 18 months, of presumed cardiac arrest. The family declined an autopsy.

Patient 3

Patient 3, a boy born at term, had a prenatal diagnosis of double-inlet left ventricle with transposition of the great arteries and a hypoplastic aortic arch with coarctation of the aorta. At age 6 days, he underwent coarctation repair and placement of a pulmonary artery band; his postoperative oxygen saturations were in the low 80% range. Newborn screening yielded the diagnosis of Hb SC disease—the second most prevalent form of SCD, characterized by inheritance of the Hb S gene from one parent and the Hb C gene from the other, and anemia less severe than that in Hb SS disease. The patient underwent a bidirectional Glenn procedure at 10 months of age (preoperative Hb level, 16 g/dL) and did well initially. He presented with ventricular dysfunction at age 6 years, and cerebral magnetic resonance images revealed multiple watershed infarcts. He presented acutely 2 months later with *Escherichia coli* bacteremia, deep vein thrombosis, and a new cerebral infarction. His oxygen saturation at that time was 85%, and his Hb level was 12.5 g/dL. He was started on chronic transfusion therapy but continued to have cerebral infarctions. Because of his multisystem disease, poor vascular access, cardiac dysfunction, CVAs, and high antibody titers, he was an unsuitable candidate for Fontan completion or heart transplantation. He eventually developed pro-

gressive hypoxemia and hemoptysis secondary to pulmonary arteriovenous malformations, and he died at age 11 years.

Patient 4

Patient 4, a 7-year-old boy with tricuspid atresia and pulmonary atresia with intact ventricular septum, had initially presented at another institution. He had been diagnosed with Hb SS disease when he was 3 years old, at which age he had undergone the placement of a Blalock-Taussig shunt, followed by a bidirectional Glenn procedure and Fontan completion. The patient presented at our hospital with ventricular dysfunction, and he underwent heart transplantation. He had frequent early episodes of rejection and developed coronary graft vasculopathy, which necessitated repeat heart transplantation when he was 13 years old. During that hospitalization, he developed hemiparesis, and images revealed a CVA. Subsequently, he was maintained on chronic transfusion therapy. At 16 years of age, he again developed coronary graft vasculopathy and died at age 17.

Patient 5

Patient 5, a girl, had a postnatal diagnosis of pulmonary atresia with ventricular septal defect and major aortopulmonary collateral arteries. She had oxygen saturations in the mid-80% range and did not need neonatal intervention. Progressive hypoxemia with oxygen saturations declining to the mid-70% range prompted a Blalock-Taussig shunt procedure when she was 3 months old (preoperative Hb level, 11.2 g/dL). Abnormal newborn-screening results prompted hematologic consultation, and the diagnosis was Hb SS disease at 4 months. Her sickle Hb concentration remained below 30%. At 12 months of age, she underwent surgical repair involving unifocalization, fenestrated ventricular septal defect closure, and right ventricle-to-pulmonary artery conduit placement. Her postoperative course was complicated by cardiac arrest and necessary extracorporeal membrane oxygenation support, and she died.

Discussion

We identified 5 patients with the combination of SCD and cyanotic CHD who had been treated at our institution over 11 years. The expected outcome for patients with combined disease is more grim than that for patients who have SCD or cyanotic CHD alone. To our knowledge, no authors have reported long-term outcomes in patients with both conditions. Patients with CHD and SCD have tolerated cardiopulmonary bypass in the short term.[9,10] The longest outcome reported before our series involved the 6-month survival of a neonate who had tricuspid atresia and Hb SC disease.[11]

Three of our patients had overt cerebrovascular events—unsurprising, given that CHD and SCD are risk factors for pediatric CVA.[12,13] This risk is compounded by the higher risk of neurologic events in patients with SCD alone who are exposed to hypoxemia.[8]

Neurodevelopmental delay has been substantially associated with CHD: up to 75% of such patients display mild neurodevelopmental abnormalities.[14] Rates of severe developmental delay vary in accordance with CHD severity and any associated syndromes.[15] The overall risk of severe neurodevelopmental delay might be 5% to 10% in patients whose CHD is moderate to severe.[16] The risk of neurodevelopmental impairment in patients with both CHD and SCD supports treatment approaches that have reduced the risk of stroke in SCD patients.[7,17] Specifically, even when transcranial Doppler ultrasonographic results are normal, prophylactic blood-transfusion therapy to maintain an Hb SS level below 30% should be considered. This transfusion target lowers the risk of SCD complications and is supported by the National Heart, Lung, and Blood Institute (NHLBI) guidelines for patients with SCD and a higher risk of stroke.[18] Transfusion to raise Hb to a near-normal level should be undertaken with caution: the NHLBI guidelines recommend against an acute increase in Hb concentration of more than 10 g/dL if the sickle Hb concentration remains above 30%, because of increased blood viscosity and the associated higher risk of stroke.[6] Because of hypoxia-driven erythropoietin release, a sickle Hb concentration above 30% can be seen even in patients who receive chronic transfusions. Indeed, our Patient 3 had ongoing complications associated with an elevated sickle Hb level despite chronic transfusion therapy.

Ventricular dysfunction developed in 3 of our patients. Although ventricular dysfunction is a known complication of single-ventricle CHD, its presence in 60% of our patients is noteworthy. In a review of outcomes after superior cavopulmonary anastomosis in patients with ventricular dysfunction, only 19 of 213 patients (9%) had significant ventricular dysfunction.[19] A similar rate of ventricular dysfunction was found at the time of Fontan procedures.[20] Patients 1 and 4 in our series had pulmonary atresia with intact ventricular septum, which carries a known risk of ventricular dysfunction because of a high-pressure right ventricle and possibly coronary artery stenoses.[21] Microvascular occlusion in the coronary circulation might also contribute to impaired ventricular function. This has been reported in adults who have SCD.[22] In addition, in children who have SCD, hypoxemia has been implicated in further decreases in ventricular function.[23] Although these observations are limited by our study's small size, close attention to ventricular function in future patients is warranted.

Our series reveals opportunities to improve the care of patients who have SCD and cyanotic CHD. Timely diagnosis of SCD is crucial for appropriate observation and management, because infants with SCD can

also have life-threatening complications such as splenic sequestration or sepsis. Despite routine newborn screening, diagnosis of SCD was often delayed in our patients. In Patient 2, newborn-screening results were misinterpreted because samples had been obtained after the child received blood products during open-heart surgery. The potential for SCD should also be recognized prenatally. Particular attention should be paid to the sickle Hb carrier status of mothers with fetuses in whom cyanotic CHD has been identified.

Single-ventricle patients might benefit from Fontan completion at a younger age, which would shorten the duration of pronounced hypoxemia. Before undergoing Fontan procedures, patients with single-ventricle physiology typically have oxygen saturations in the 75%-to-85% range; postoperatively, oxygen saturations tend to rise above 90%.

Heart transplantation in a child with SCD yielded positive short-term results.[24] Bone marrow transplantation has been performed with success in children with comorbid CHD.[25,26] The latter procedure should be strongly considered, particularly when recurrent strokes are refractory to medical therapy or a matched sibling is available.[27]

In patients who have SCD and cyanotic CHD, we suggest considering therapies that shorten their exposure to hypoxemia and thus reduce the risk of adverse neurodevelopmental outcomes.

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