Pediatric sickle cell retinopathy: Correlation with clinical factors

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BACKGROUND	Sickle cell disease (SCD) occurs in 1 of every 500 African American births and 1 of every 36,000 Hispanic American births. Of children with SCD, 16.7% to 96.3% develop sickle retinopathy (SR). This study was designed to determine whether certain factors are associated with SR and whether SR is correlated with a greater incidence of other SCD manifestations.
METHODS	A retrospective analysis was performed of 258 children with SCD seen in the ophthalmology clinic at a large urban children's hospital. Of these, 54 children with SR were matched for age and sickle variant with 54 children with normal examinations. Data extracted included demographics, type of retinopathy, presence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, and history of acute chest syndrome, transfusions, pulmonary hypertension, renal disease, cerebrovascular accident, aplastic crisis, splenic sequestration, priapism, osteonecrosis, gallstones, pneumonia, leg ulcers, vaso-occlusive pain crises, and death.
RESULTS	Of the children with SR, 11 (20.3%) had active proliferative disease, 32 (56.1%) had hemoglobin SS, 18 (31.6%) had hemoglobin SC, and 4 (7.0%) had hemoglobin S-beta thalassemia. Several factors were correlated with retinopathy: pain crisis (odds ratio [OR], 5.00; $p = 0.011$), male sex (OR, 4.20, $p = 0.004$), and splenic sequestration (OR, 4.00; $p = 0.013$). G6PD deficiency was more common in patients with retinopathy, although this was not statistically significant (OR, 4.20; $p = 0.054$). No other factors, including frequency of pain crisis, were statistically significant.
CONCLUSIONS	Patients with pain crisis and splenic sequestration should be considered for early ophthalmic evaluation. Those with G6PD deficiency may also deserve early screening. By identifying patients at high risk for SR, we can refine screening protocols to safeguard patients from vision loss. (J AAPOS 2011;15:49-53)

Sickle cell disease (SCD) affects 70,000 to 100,000 people in the United States, occurring in 1 of every 500 African American births and 1 of every 36,000 Hispanic-American births.[1] According to the World Health Organization, 275,000 people worldwide have a sickle cell disorder.[2] In children with SCD, the prevalence of sickle retinopathy (SR) has been reported to be anywhere from 16.7% to 96.3%.[3-11]

Many of the complications of SCD are serious; some are life threatening. These complications include acute chest syndrome, need for transfusions, pulmonary hypertension, renal disease, cerebrovascular accident, aplastic crisis, splenic sequestration, priapism, osteonecrosis, gallstones, pneumonia, leg ulcers, vaso-occlusive pain crises, and death. The purpose of this study was to determine whether SR is associated with any of these other manifestations of SCD.

Patients and Methods

This study was conducted at a large urban children's hospital, the Children's National Medical Center in Washington, DC. The study was approved by the Institutional Review Board of Children's National Medical Center and conformed to the requirements of the United States Health Insurance Portability and Accountability Act.

A retrospective chart review was performed of patients seen during the past 10 years who are currently older than 10 years of age and have a diagnosis related to SCD, using the ICD-9 codes 282.6 (sickle cell anemia, all subtypes), 282.4 (sickle thalassemia), and V78.2 (screening for SCD or trait) and included all patients who underwent ophthalmic screening. The records of eye examinations were reviewed for nonproliferative SR (NPSR) including salmon patches, refractile or iridescent spots, and black sunbursts, and proliferative sickle retinopathy (PSR), including seafan neovascularization, vitreous hemorrhage, and tractional retinal detachment. Patients with sickle retinopathy of any type were matched for age and sickle cell type with those who had normal

Table 1. Demographics of patients with sickle retinopathy (n = 54)

Age at diagnosis	13.0 years (range 6-18 years, SD 3.1)
With nonproliferative	14.2 years (range 6-18 years, SD 1.9)
With proliferative	12.7 years (range 10-17 years, SD 3.3)
Male	38 (70.4%)
Type of SCD	
HgbSS	32 (59.3%)
HgbSC	18 (33.3%)
HgbS-beta thalassemia	4 (7.4%)
Type of retinopathy	
Nonproliferative	42 (77.8%)
Proliferative	11 (4.3%)
Youngest patient with retinopathy	Age (type of retinopathy)
Nonproliferative	
HgbSS	6 years (black sunburst)
HgbSC	6 years (gliotic seafan [inactive])
Proliferative	
HgbSS	13 years (seafan neovascularization)
HgbSC	11 years (vitreous hemorrhage)

HbgSS, hemoglobin SS; *HgbSC*, hemoglobin SC; *HgbS-beta thalassemia*, hemoglobinS-beta thalassemia; *SCD*, sickle cell disease; *SD*, standard deviation.

Table 2. Rates of retinopathy by sickle cell type

Type of sickle cell disease	Any SR, n (%)	Proliferative SR, n (%)
HgbSS (n = 186)	32 (17.2)	1 (0.54)
HgbSC (n = 55)	18 (32.7)	9 (16.4)
HgbS-beta thalassemia (n = 12)	4 (33.3)	1 (8.3)

HbgSS, hemoglobin SS; *HgbSC*, hemoglobin SC; *HgbS-beta thalassemia*, hemoglobinS-beta thalassemia; *SR*, sickle retinopathy.

Table 3. Risk ratio of associated factors and systemic manifestations

Factor	Risk ratio	95% confidence interval	*p*-value
Pain crisis	5.00	1.45-17.27	0.011
G6PD deficiency	4.50	0.97-20.83	0.054
Male	4.20	1.58-11.14	0.004
Splenic sequestration	4.00	1.34-11.97	0.013
Priapism	2.50	0.49-12.89	0.273
Aplastic anemia	2.20	0.76-6.33	0.144
Acute chest	1.86	0.74-4.66	0.187
Pneumonia	1.60	0.52-4.89	0.410
Transfusion	1.15	0.55-2.43	0.706
Gallstones	1.08	0.51-2.29	0.847
Death	1.00	0.06-15.99	1.000
Stroke	0.82	0.34-1.97	0.655
Pulmonary hypertension	0.67	0.11-3.99	0.657
Osteonecrosis	0.57	0.17-1.95	0.372

G6PD, glucose-6-phosphate dehydrogenase.

eye examinations. The matching was masked except for age and sickle cell type.

The entire medical record was reviewed on each patient. In particular, data were extracted regarding glucose-6-phosphate dehydrogenase (G6PD) deficiency, acute chest syndrome, transfusions, pulmonary hypertension, renal disease, cerebrovascular accident, aplastic crisis, splenic sequestration, priapism, osteonecrosis, gallstones, pneumonia, leg ulcers, vaso-occlusive pain crises, and death. Only clinical data, not *International Classification of Diseases*, 9th Revision, codes, was used to determine the presence or absence of these conditions. Data on treatment of SR were collected when available. These data were not always available because patients requiring treatment were transferred to retina specialists outside the medical center for further care.

The 2 groups were compared with each other for correlations between SR and any of these other factors. We implemented conditional logistic regression analysis in Stata 10.1 (StataCorp, College Station, TX) to evaluate the relationship between demographic and clinical characteristics and presence (cases) or absence (controls) of sickle cell retinopathy while accounting for case-control matching by age and type of SCD. When possible, separate analyses evaluated the strength of association between the same characteristics and proliferative sickle cell retinopathy. Associations were expressed as odds ratios (OR) $\pm$ 95% confidence intervals (CIs). We did not adjust for multiple comparisons and thus used degree of departure from 1 (no association) and failure of the 95% CI to include 1 as guidelines for hypothesis generation.

Results

A total of 643 patients were identified. Of these, 258 (40.1%) had an eye examination at our institution, which consisted of a dilated fundus examination without fluorescein angiography. Of the 258 with an eye examination, 54 (20.9%) had some type of SR, and 11 (4.3%) had PSR. Patients with SR received an average of 3.80 examinations, whereas those without SR received 2.39 examinations ($p = 0.003$). On average, patients with SR were examined 1.13 times before the examination that identified their disease; 50% of those with SR were found to have the disease on their first examination. Patients with SR were 11.67 years old at the time of their first examination; those without SR were 10.69 years old ($p = 0.230$).

The average age of patients with any retinopathy was 13.0 years (range, 6-18 years; SD 3.1). Patients with PSR were slightly older (mean, 14.18 years; range, 11-17 years; SD 1.66) than those with NPSR (mean, 12.72 years; range, 6-18 years; SD 3.29; Table 1), but the difference was not statistically significant ($p = 0.162$).

Of the 186 patients with hemoglobin (Hgb) SS, 32 (17.2%) had some type of retinopathy, and 1 (0.54%) had PSR. Of the 55 patients with hemoglobin (Hgb) SC, 18 (32.7%) had any retinopathy, and 9 (16.4%) had PSR. Of the 12 patients with HgbS-beta thalassemia, 4 (33.3%) had some type of retinopathy, and 1 (8.3%) had PSR (Table 2); 3 of these 4 patients had beta-plus thalassemia, and 1 of the patients with nonproliferative SR had beta-zero thalassemia.

Patients with PSR were referred to a retina specialist for further evaluation. Of the 11 patients with PSR, 6 (54.5%)

Table 4. Screening recommendations

Author	Age to begin examination	Frequency of examination	Type of examination
American Academy of Pediatrics[16]	10 years, especially for HgbSC	Periodic	Funduscopic examination
Babalola and Wambebe[17]	10 years	Biennial until age 20	Dilated funduscopic examination, fluorescein angiography if available
Gill and Lam[8]	9 years for HgbSC 13 years for HgbSS and HgbS-beta thalassemia	Biennial if normal	Dilated funduscopic examination, fluorescein angiography if abnormal

HgbSC, hemoglobin SC; *HbgSS*, hemoglobin SS; *HgbS-beta thalassemia*, hemoglobinS-beta thalassemia.

received laser treatment and 2 (18.2%) did not require treatment. Treatments for the other 3 (27.3%) are not known.

Of the 14 factors reviewed, 3 were found to be significantly associated with SR: pain crisis (OR 5.00; 95% CI, 1.45-17.27; $p = 0.011$); male sex (OR 4.20; 95% CI, 1.58-11.14; $p = 0.004$); and splenic sequestration (OR 4.00; 95% CI, 1.34-11.97; $p = 0.013$). In addition, G6PD deficiency showed a trend toward correlation, although it was not statistically significant (OR 4.50; 95% CI, 0.97-20.83; $p = 0.054$). No other factors, including the frequency of pain crisis, were found to be significant (Table 3). When the tests were run to compare PSR with no retinopathy, no factors were found to be significant.

Discussion

SR is a serious complication of both HgbSS and HgbSC, with a greater prevalence in SC.[12] In this study, 20.9% of patients had some type of SR and 4.3% had PSR, which is consistent with the ranges from previous studies (16.7%-96.3% for NPSR and 0%-11.1% for PSR).[3-11] If SR is untreated, 10% of eyes develop at least moderate vision loss.[13] Because patients can do very well if their disease is recognized and treated early,[14,15] it is important to screen patients appropriately (Table 4).[8,16,17]

PSR tends to develop at ages 15-19 in HgbSS and at ages 10-14 in HgbSC,[6] with two-thirds of incident cases of PSR developing at ages 15-29.[18] The youngest patient in the literature documented to have HgbSC and PSR was 7 years old.[6] In our cohort, the youngest patient who had NPSR was 6 years old, which confirmed that children younger than 10 years of age can develop SR.[6,8,19,20] Our youngest patient with HgbSC and PSR was 11 years old; the youngest with HgbSS who had PSR was 13 years of age.

One of the goals of this study was to find risk factors associated with SR with the hope that screening guidelines, including the age to start examinations, could be adjusted based on patient risk. The present study showed that SR is correlated with pain crisis (OR, 5.00) and splenic sequestration (OR, 4.00). In contrast, a prior study found that clinical events were not associated with angiographic evidence of retinal changes.[21] The lack of correlation in their study may be related to the use of fluorescein angiography, which would identify retinal findings that are likely not apparent on ophthalmoscopic examination, potentially leading to an overdiagnosis of subclinical forms of SR that may not be clinically relevant.

With a standard eye examination, Gill and Lam[8] found no correlation between retinopathy seen on dilated funduscopic examination and the presence of systemic manifestations in 263 children; however, they did not evaluate each systemic manifestation. Akgul and colleagues[22] found that pulmonary hypertension seen on echocardiography was related to retinopathy. We may have been limited in our ability to identify this association because only 25 of our 54 patients with SR (46.3%) also had an echocardiogram.

In addition to the systemic associations, we also found that retinopathy was more common in males (OR, 4.20). The authors of previous studies showed that retinal closure on fluorescein angiogram may be more common in boys,[21] but the difference was not seen after age 7.[10] Hayes and colleagues[23] showed a trend toward PSR being more common in male subjects, but it was not statistically significant. In contrast, a study of children in the Congo showed that retinal vascular tortuosity was more common in girls than boys.[11]

We found a trend toward the development of SR in patients with G6PD deficiency (OR 4.50). This relationship has not been previously elucidated. Oxidative stress caused by G6PD deficiency may aggravate the manifestations of hemolytic anemias[24]; however, the presence of G6PD deficiency does not increase the incidence of painful episodes, sepsis, anemic episodes,[25] or leg ulceration.[26] In fact, it may decrease the incidence of pain crises.[27] Several investigators have found no difference in hemoglobin levels and sickled cells in patients with SCD with and without G6PD deficiency.[26,28-30] Further study is needed to determine whether there is truly an association between G6PD deficiency and SR.

The increased risk of retinopathy in patients with pain crises, splenic sequestration, and possibly G6PD deficiency could be used to help guide screening timelines, which currently state that periodic or biennial examinations should be performed (Table 4).[8,16,17] Because patients with the aforementioned comorbidities are more likely to develop retinopathy, it may be important to screen them annually, whereas others could be examined biennially; however, our results should be confirmed in other populations before screening guidelines are changed.

Potential limitations of this study should be considered. Because this was a retrospective study, eye examinations were not standardized. We may have underestimated the number of young patients affected because they may have had SR before their first examination. It is also possible that patients could have had systemic manifestations of sickle cell that were not identified in the medical record. Patients were matched by birth date and not by age at time of examination; matching by examination age may have created a better control group. The sample size was limited by the age restrictions of our center, which only treats children. If it had been possible to follow these patients into adulthood, we would likely have found a larger number of patients with retinopathy.

We studied a large population of patients with SCD, but fewer than one-half of the patients treated for SCD in our institution were seen in the eye clinic at our medical center. It is possible that patients with more severe SCD were referred to the clinic more often, with the result that their retinopathy was identified while the retinopathy in those with less severe illness was underreported. Thus, there may be selection bias in our sample. Further selection bias may have resulted from the nature of our institution: as a large urban academic medical center, the patients may have more severe diseases than those cared for by community physicians. This bias, along with the retrospective nature of the study and the relatively small number of patients who had eye examinations, may limit the ability to generalize our results to other populations. A further limitation of this study is that multiple comparisons were made. Because no formal statistical correction was done, results can be considered hypothesis-generating. Factors associated with retinopathy were discovered that should be confirmed in prospective studies.

In conclusion, SR is an important manifestation of SCD. As pain crisis and splenic sequestration are correlated with SR, patients with these complications should be considered for early ophthalmic evaluation. In addition, the association of SR with G6PD deficiency is worthy of further study; these patients may also deserve early screening. By determining which patients are at high risk for development of SR, we can refine screening protocols to safeguard our patients from vision loss.

Acknowledgments

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