Ten-Year Review of Hospital Admissions among Children with Sick Cell Disease in Kuwait

Najwa Ali Akar^a Adekunle Adekile^{a, b}

^aDepartment of Pediatrics, Mubarak Al-Kabeer Hospital, and ^bDepartment of Pediatrics, Faculty of Medicine, Kuwait University, Kuwait

Key Words

Sickle cell disease · Hospitalization

Abstract

Objective: This study was designed to document the common causes and patterns of hospitalization among sickle cell disease (SCD) patients in Kuwait. **Subjects and Methods:** The case files of all SCD patients admitted to the hospital between 1995 and 2004 were studied. Their personal data, hemoglobin genotype, diagnosis on admission, complete blood count, treatment received, length of stay and outcome were documented. **Results:** Fifty SCD patients aged from 10 months to 14.8 years (mean: 8.7 ± 2.8 years) had 351 admissions over the 10-year period accounting for 0.6% of all admissions to the pediatric wards. The 50 patients were made up of 18 Hb SS, 28 S β^0 thal and 4 Hb SD patients. Common causes of admission were vaso-occlusive crisis: 222 (63.2%), acute splenic sequestration crisis: 32 (9.1%), hemolytic crisis: 31 (8.8%) and acute chest syndrome: 23 (6.6%). Stroke was seen in only 1 patient, and bacteriologically proven (Salmonella) acute osteomyelitis in 1 patient. There were no deaths during the study period. **Conclusions:** Vaso-occlusive crisis was the commonest cause of hospitalization among our SCD patients. Efforts should be intensified to give advice on preventive measures. The use of hydroxyurea should be encouraged in patients with frequent severe pain crises.

Copyright © 2008 S. Karger AG, Basel

Introduction

Sickle cell disease (SCD) is typically mild among Kuwaiti patients because they carry the Arabian/Indian β^S -globin gene haplotype with its associated elevated Hb F levels [1–3]. Therefore, patients tend to have infrequent crises and other complications. However, there is a subset of patients with frequent hospitalizations, especially because of recurrent vaso-occlusive crisis, which can be quite severe. They are also those that eventually have bone infarcts, including avascular necrosis of the femoral head [2, 4, 5].

Prior to 1994, there was no dedicated pediatric hematology clinic where SCD patients were counseled and followed in our hospital. Therefore, there was no organized or systematic health education to enlighten the patients and their parents or caregivers about the nature of the disease. The need for preventive measures against complications, e.g. pneumococcal vaccine and penicillin prophylaxis for infections and the increased intake of fluids (especially in hot weather) to prevent dehydration and a vaso-occlusive crisis (VOC), was not explained. Thus, there was widespread misunderstanding and ignorance about the nature of SCD among the affected families.

An earlier retrospective study of SCD admissions in the years before the clinic was established showed that vaso-occlusive crises were the commonest cause of hospitalization (60.0%) [2]. Admissions were commonest during the hottest months of the year (July and August).

We have now carried out a 10-year review of admissions, spanning the period 1995–2004, to see the prevailing pattern of admissions of our children with SCD, and to find out the impact, if any, of the hematology clinic that was established in 1994.

Subjects and Methods

Admission records in the pediatric wards, Mubarak Al-Kabeer Hospital, Kuwait, over a 10-year period (1995–2004) were reviewed. The hospital is a tertiary care center and the main teaching hospital of the Faculty of Medicine, Kuwait University. Children with SCD are monitored in the pediatric hematology clinic. At any particular time during the study period, 30–45 patients were actively monitored in the clinic. However, because of the mild nature of the disease in Kuwaiti patients, most patients are either never seen in the clinic or do not always keep their clinic appointments.

The details of all hospitalized patients with SCD (Hb genotype, diagnosis, presenting features, laboratory investigations, mode of treatment and length of stay in the hospital) were documented. Hb genotype and Hb F levels were determined in all patients either by cellulose acetate electrophoresis or cation-exchange high-performance liquid chromatography, respectively [6]. Complete blood count (CBC) was obtained by the Coulter S electronic cell counter. The frequency of admissions in individual patients was noted. The yearly and monthly distributions of overall SCD admissions and individual complications were documented (fig. 1). Data are presented as means $\pm$ SD.

Results

Over the 10-year study period, there were 57,635 admissions to the 3 general pediatric wards of the hospital. Of these, 351 (0.6%) were for SCD-related problems. Fifty SCD patients were responsible for these admissions (30 males and 20 females; mean age: 8.7 ± 2.8 years, range: 10 months to 14.8 years). The patients' Hb genotypes were 18 SS, 28 S β^0 thal and 4 SD. Their Hb F levels ranged from 10 to 41% with a mean of $22.9 \pm 7.7\%$. The diagnoses on admission were made up of VOC: 222 (63.2%), acute splenic sequestration crisis: 32 (9.1%), hemolytic crisis: 31 (8.8%), acute chest syndrome (ACS): 23 (6.6%), and others: 43 (12.3%) (table 1).

Among the VOC admissions, there were 40 patients (25 SS, 12 S β^0 thal and 3 SD genotypes). The length of hospital stay ranged from 1 to 34 days, with a mean of 3.9 ± 3.7 days. There were multiple localized pain sites in most patients. There was a total of 359 sites in all, made up of the back: 107 (29.8%), lower limbs: 105 (29.2%), upper limbs: 79 (22.0%), abdomen: 37 (10.3%), chest: 30

Fig. 1. Monthly distribution of hospital admissions for VOC.

Table 1. Breakdown of admission diagnoses

Diagnosis	n (%)
Vaso-occlusive crisis ¹	222 (63.2)
Acute splenic sequestration	32 (9.1)
Hemolytic crisis	31 (8.8)
ACS	23 (6.6)
Routine blood transfusion (preoperative or in stroke patient)	16 (4.6)
Fever for investigation	10 (2.8)
Upper respiratory tract infection	10 (2.8)
Gastroenteritis	9 (2.6)
Gastritis	5 (1.4)
Cholecystitis	1 (0.3)
Stroke	1 (0.3)

¹ Nine of these patients were eventually treated as acute osteomyelitis, based on clinical, bone scan and/or bacteriological parameters.

(8.4%), and in only 1 (0.3%) instance was the pain localized to the hands and feet, i.e. hand and foot syndrome. The common precipitating events were fever: 31 (39.7%) and physical exercise: 21 (26.9%).

The frequency of VOC admissions for the 40 patients involved is shown in figure 2. The range of number of admissions per patient over the study period was 1–17 times, with a mean of 5.6 ± 4.5 . While most patients were admitted 1–6 times, there was a subset who were admitted ≥ 10 times each. The important CBC findings in these patients are shown in table 2. Although Hb F levels are not shown in the table, the mean level in those admitted

Fig. 2. Frequency of admissions for patients with VOC.

Table 2. Hematological parameters in groups of patients

Diagnosis	Hb g/dl	WBC × 10 ⁹ /l	Platelets × 10 ⁹ /l
Vaso-occlusive crisis	9.6 ± 1.3	11.5 ± 5.8	321 ± 157
Hemolytic crisis	6.8 ± 1.5	13.1 ± 5.9	272 ± 160
ACS	7.9 ± 1.2	15.3 ± 6.7	348 ± 236
Acute sequestration crisis	5.3 ± 1.1	12.5 ± 7.0	112 ± 48

WBC = White blood cells.

≥10 times each ($20.1 \pm 2.3\%$) was not significantly different from the mean level of those with fewer admissions ($17.1 \pm 5.3\%$). Blood culture results were negative in all those tested, except in one 5-year-old SS patient in whom *Salmonella spp.* was isolated. Bone scans were performed in 33 patients who had significant localized bony tenderness and/or fever. Nine (27.3%) showed positive findings, although there was no bacteriologically proven osteomyelitis (except for the 1 patient mentioned earlier); a course of antibiotics was given in 71 instances, otherwise all patients had intravenous fluids and analgesics.

Eleven patients were admitted on 32 occasions with acute splenic sequestration crisis. Of these, 5 (45.5%) were SS, 4 (35.4%) were $S\beta^0$ thal and 2 (18.2%) were SD. There were 6 males and 5 females, aged 1.5–10.8 years, with a mean of 4.6 ± 2.3 years. The mean laboratory values on admission are shown in table 1. All the patients complained of pallor, 20 (62.5%) of abdominal pain, 13 (40.6%)

of fever, and 5 (15.6%) of bone pain. On examination, all were pale, all had splenomegaly, 18 (56.2%) were jaundiced, 14 (43.8%) had hepatomegaly and 11 (34.3%) had fever ($\geq 38^\circ\text{C}$). All received red blood cell transfusions in addition to other supportive therapy. The range of hospital stay was 1–12 days (mean: 3.2 ± 2.4 days).

Fourteen patients were admitted on 31 occasions for a hemolytic crisis. Of these, 7 were SS and 7 were $S\beta^0$ thal; there were 9 males and 5 females with a mean age of 6.4 ± 3.6 years. All presented with pallor, while 19 (61.3%) had jaundice, 14 (45.2%) had splenomegaly and 8 (25.8%) had hepatomegaly on admission. The mean CBC values for the patients on admission are given in table 1.

Fifteen patients were admitted on 23 occasions for ACS. Of these, 9 (60.0%) were SS, 4 (26.7%) were $S\beta^0$ Thal and 2 (13.3%) were SD. There were 7 (26.7%) males and 8 (53.3%) females, the mean age was 7.5 ± 3.3 years. Twenty-two (95.7%) patients presented with fever, 21 (91.3%) with a cough, 21 (91.3%) with pallor and all had radiographic lung changes, infiltrates in 16 (69.6%) and consolidation in 7 (30.4%). All were given antibiotics, 8 had top-up transfusions; none had an exchange transfusion and none had ICU (intensive-care unit) care. The mean stay in the hospital was 5.6 ± 3.3 days. Most patients were admitted only once for ACS during the study period, and 3 patients were admitted on 2, 3 and 6 occasions, respectively.

There were 43 admissions among 16 patients (7 were SS, 7 were $S\beta^0$ Thal, 2 were SD) for other diagnoses, as shown in table 1. It is noteworthy that only 1 patient, a 10-year-old female SS, was admitted with overt stroke in the study period. She was subsequently started on a chronic transfusion program, and she had a full recovery. Regular transfusions were stopped after 2 years, and hydroxyurea was started. She remains well with no recurrence, 4 years after the initial stroke.

Discussion

In a retrospective study of hospital admissions of Kuwaiti children with SCD in 1993, the most common cause of hospitalization was VOC, seen in 60.3%, followed by infections (pneumonia, cellulitis and osteomyelitis) in 19.0%, hemolytic crisis in 15.8% and hypersplenism in 5.2% [2]. Although the admissions were spread throughout the year, there was a peak in July, which is the hottest month of the year in Kuwait, and another peak in January (winter). However, at that time, SCD patients were being looked after by general pediatricians, and there was no dedicated SCD clinic where the patients were followed up.

Although the initial study had several limitations, it did show clearly that, even in our group of patients who generally have a milder clinical course, VOC is still the commonest cause of hospitalization. Secondly, admissions were commonest at the peaks of summer heat and winter cold. Indeed, VOC is the quintessential feature of SCD and is the most common cause of hospitalization in different populations [7–10]. Therefore, when a SCD clinic was eventually established in 1994, emphasis was placed on counseling and health education. In particular, the patients and their parents were informed of factors likely to trigger VOC, e.g. exposure to extremes of weather, and the need for adequate hydration in the summer months.

The results of the present study show that the most frequent cause of hospitalization is still VOC. Interestingly, however, the sharp peaks noticed in July and January in the previous study were absent. Indeed, this may indicate that the health education carried out in the clinic has been successful in preventing VOC at the critical periods of extreme weather in the country. A smaller peak is still seen in October/November, which coincides with school resumption and the onset of the flu season and cold weather.

Since only patients who have been hospitalized are generally referred to the clinic for follow-up, it is not possible to calculate the frequency of hospitalization among patients in general. However, the present study confirms our previous findings that, while the disease is quite mild in our patients, a subset is admitted repeatedly because of VOC. The patient's Hb F level is not a distinguishing factor, and we showed in previous studies that a coexistent α -thalassemia trait is also not important [2, 4]. Therefore, some other factors (probably genetic) predispose some of these patients to recurrent vaso-occlusion. There is a need to explore polymorphisms in candidate genes involved in various inflammatory pathways that may contribute to the plethora of interactions taking place between blood cells and the endothelium during the process of vaso-occlusion. Important factors in these interactions include cytokines, adhesion molecules, nitric oxide metabolites, hemostatic/coagulation factors and membrane phospholipids [11, 12].

The second commonest cause of hospitalization was anemic crisis, either related to the spleen or hemolysis. Since most of our patients have elevated Hb F levels on account of the β^S -globin gene cluster haplotypes, they tend to retain their spleen function till adolescence and adulthood. Previous studies showed that about 80% of our patients between the ages of 6 and 16 years have viable splenic tissue [13, 14]. The downside of this is that acute splenic

sequestration occurs frequently. Unsurprisingly, this accounted for 9.1% of all admissions in the present study. These patients are managed with blood transfusions, and, in recurrent cases, a splenectomy is offered [15].

ACS is a common cause of morbidity and mortality in children and adults with SCD. Quite often, patients require ICU care with ventilation and an exchange blood transfusion [16–19]. While ACS is not uncommon among our patients, it tends to be relatively mild. None of the ACS patients in the present study required exchange blood transfusions, and only 1 required ICU care. ACS was probably triggered by chest infections, especially since many were preceded by coughs and coryzal symptoms.

Bacteremia and other severe bacterial infections were relatively uncommon in this study, although reports from the US and elsewhere have emphasized the role of infections, especially pneumococemia, in the morbidity and mortality of SCD in early childhood [20, 21]. There are several factors that predispose SCD patients to overwhelming bacterial infections, the most important of which is poor splenic function [22]. However, there are several factors which appear to protect our patients from pneumococemia in the first 3 years of life when the infection is most common. Firstly, our patients' Hb F levels are usually $>30\%$ in the first 4 years of life; secondly, they do not present with SCD-related problems until aged 4–5 years; thirdly, they usually have excellent spleen function at this age [13, 14]. The administration of prophylactic penicillin, as practiced in the US and Europe, is probably unjustified in our patients.

One big challenge facing physicians looking after SCD patients is differentiating acute osteomyelitis from VOC or bone infarction. The clinical presentation, radiological and bone scan features may not be clear-cut. In the present study, many of the patients who presented with VOC had fever and localized bone tenderness and/or swelling. Bone scan findings were suggestive of osteomyelitis in 9, but only 1 patient had a positive blood culture. In such instances, it is better to err on the side of caution and treat as osteomyelitis with full coverage for *Salmonella* spp. and *S. aureus*, which are the most common bacteria responsible for osteomyelitis in SCD [23]. Increasingly, we are using MR imaging in such patients to identify those who show evidence of subperiosteal pus collection and bone marrow signal abnormalities suggestive of osteomyelitis [24, 25].

There are other complications of SCD that do not feature prominently in the morbidity pattern of our patients. There was only 1 case of stroke in the review period, and only 1 patient presented with hand and foot syndrome. There were no cases of priapism or chronic leg ulcers.

While we do see osteonecrosis, we did not have any admissions for avascular necrosis of the head of the femur. This is probably because it is not an acute problem and such patients are more likely to be admitted to the orthopedic unit.

VOC remains the most common cause of hospitalization among Kuwaiti SCD patients. Efforts should be intensified to educate patients about the triggers of this crisis, especially avoiding excessive physical exertion and extremes of weather, and the need for proper hydration. Patients who have frequent pain crises should be started on hydroxyurea, which is the recommended drug in adult SCD patients, but is also being increasingly used in chil-

dren with good results. There is anecdotal evidence that its use may indeed prevent or halt the progression of avascular necrosis of the femoral head, in addition to other benefits, and it is also relatively safe [4, 26–28].

Conclusion

VOC is the commonest cause of hospitalization among our SCD patients. Efforts should be intensified to give advice on preventive measures. The use of hydroxyurea should be encouraged in patients with frequent severe pain crises.

References

- Adekile AD, Gu LH, Baysal E, Haider MZ, Al-Fuzae L, Aboobacker KC, Al-Rashied A, Huisman THJ: Molecular characterization of α -thalassemia determinants, β -thalassemia alleles and β^S haplotypes among Kuwaiti Arabs. *Acta Haematol* 1994;92:176–181.
- Adekile AD, Haider MZ: Morbidity, β^S haplotype and α -globin gene patterns among sickle cell anemia patients in Kuwait. *Acta Haematol* 1996;96:150–154.
- Adekile AD, Al-Kandari M, Haider M, Marouf R, D'Souza M, Sukumaran J: Hemoglobin F concentration as a function of age in Kuwaiti sickle cell patients. *Med Princ Pract* 2007;16:286–290.
- Adekile AD, Gupta R, Yacoub F, Sinan T, Al-Bloushi M, Haider MZ: Avascular necrosis of the hip in Kuwaiti children with sickle cell disease: MRI images and association with α -thalassemia trait. *Acta Haematol* 2001;105:27–31.
- Marouf R, Gupta R, Al-Wazzan H, Haider MZ, Adekile AD: Avascular necrosis of the femoral head in adult Kuwaiti sickle cell disease patients. *Acta Haematol* 2003;110:11–15.
- Bissé E, Wieland H: High-performance chromatographic separation of human haemoglobins: simultaneous quantitation of foetal and glycated haemoglobins. *J Chromatogr* 1988;434:95–110.
- Brozovic M, Davies SC, Brownell AI: Acute admissions of patients with sickle cell disease who live in Britain. *Brit Med J* 1987;294:1206–1208.
- Jaiyesimi F, Pandey R, Sreekrishna Y, Zaki F, Krishnamoorthy N: Sickle cell morbidity profile in Omani children. *Ann Trop Paediatr* 2002;22:45–52.
- Izuora GI, Al-Dusari SN, Fakunle YM: Sickle cell anemia morbidity in northern Saudi Arabia. *Saudi Med J* 2003;24:269–272.
- Smith WR, Coyne P, Smith VS, Mercier B: Temperature changes, temperature extremes, and their relationship to emergency department visits and hospitalizations for sickle cell crisis. *Pain Manag Nurs* 2003;4:106–111.
- Zimmerman SA, Ware RE: Inherited DNA mutations contributing to thrombotic complications in patients with sickle cell disease. *Am J Hematol* 1998;59:267–272.
- Steinberg MH, Adewoye AH: Modifier genes and sickle cell disease. *Curr Opin Hematol* 2006;13:131–136.
- Adekile AD, Tuli M, Haider MZ, Al-Zaabi K, Mohammadi S, Owunwanne A: Influence of α -thalassemia trait on spleen function in sickle cell anemia patients with high Hb F. *Am J Hematol* 1996;53:1–5.
- Adekile AD, Owunwanne A, Al-Za'abi K, Haider MZ, Tuli M, Al-Mohannadi S: Temporal sequence of splenic dysfunction in sickle cell disease. *Am J Hematol* 2002;69:23–27.
- Adekile AD, Akar N, Ayyash K, Saldanha W, Prakash B: Indications for splenectomy among children with sickle cell disease in Kuwait. *KMJ* 2002;34:33–35.
- Gill FM, Sleeper LA, Weiner SJ, Brown AK, Bellevue R, Grover R, Pegelow CH, Vichinsky E: Clinical events in the first decade in a cohort of infants with sickle cell disease. *Blood* 1995;86:776–783.
- Sylvester KP, Patey RA, Milligan P, Rafferty GF, Broughton S, Rees D, Thein SL, Greenough A: Impact of acute chest syndrome on lung function of children with sickle cell disease. *J Pediatr* 2006;149:17–22.
- Darbari DS, Kple-Faget P, Kwagyan J, Rana S, Gordeuk VR, Castro O: Circumstances of death in adult sickle cell disease patients. *Am J Hematol* 2006;81:858–863.
- Al-Dabbous IA: Acute chest syndrome in sickle cell disease in Saudi Arab children in the Eastern Province. *Ann Saudi Med* 2002;22:167–171.
- Barrett-Connor E: Bacterial infection and sickle cell anemia: an analysis of 250 infections in 166 patients and a review of the literature. *Medicine (Baltimore)* 1971;50:97–112.
- Wong WY, Overturf GD: Infection caused by *Streptococcus pneumoniae* in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. *Clin Infect Dis* 1992;14:1124–1136.
- Pearson HA, Spencer RP, Cornelius EA: Functional asplenia in sickle anemia. *N Engl J Med* 1969;282:923–926.
- Burnett MW, Bass JW, Cook BA: Etiology of osteomyelitis complicating sickle cell disease. *Pediatrics* 1998;101:296–297.
- Wong AL, Sakamoto KM, Johnson EE: Differentiating osteomyelitis from bone infarction in sickle cell disease. *Pediatr Emerg Care* 2001;17:60–63.
- Aloui N, Nessib N, Jalel C, Ellouze S, Chahida F: Acute osteomyelitis in children: early MRI diagnosis. *J Radiol* 2004;85:403–408.
- Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ: Hydroxyurea therapy in children severely affected with sickle cell anemia. *J Pediatr* 1996;128:820–828.
- Hankins JS, Helton KJ, McCarville MB, Li CS, Wang WC, Ware RE: Preservation of spleen and brain function in children with sickle cell anemia treated with hydroxyurea. *Pediatr Blood Cancer* 2008;50:293–297.
- de Montalembert M, Brousse V, Elie C, Bernaudin F, Shi J, Landais P, French Study Group on Sickle Cell Disease: Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes. *Haematologica* 2006;91:125–128.