Clinical Factors Associated with Morbidity and Mortality in Patients Admitted with Sickle Cell Disease

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ABSTRACT

Objective: *To determine the clinical factors associated with the length of hospitalization and mortality in patients with sickle cell disease (SCD).*

Methods: *All patients with SCD admitted to the medical wards of the University Hospital of the West Indies, Jamaica, over a five-year period, January 1, 2005 to December 31, 2010, were reviewed. Data were extracted from hospital charts and comprised demographic and clinical information, investigations, interventions, duration of stay, pathological data and outcomes.*

Results: *There were 105 patients reviewed; 84% were genotype Hb SS. Females accounted for 59% and males 41%. Overall mean age was 32.5 years (SD 13.7, range 12–66 years). The mean length of hospitalization was 10.2 days (SD 10.9, range 1–84 days). The main admission diagnoses were painful crisis, acute chest syndrome, severe anaemia, sepsis, hepatic sequestration, congestive cardiac failure and renal failure. The mean values for the following laboratory investigations were: haemoglobin 7.7 g/dL (SD 2.8), total white blood cell count 21.7 × 10^9/L (SD 14.2), platelet count 320 × 10^9/L (SD 191.9), blood urea 9.8 mmol/L (SD 11.9) and serum creatinine 198 umol/L (SD 267.9). Medical interventions included: blood transfusions in 20.9%, 55% received antibiotics and 74% received narcotic analgesia. There were 40 deaths with four autopsies done. The mortality rate for SCD was 38%. There were 189 repeat SCD admissions.*

Conclusion: *Sickle cell disease still carries a high morbidity and mortality in patients admitted to hospital. Recurrent admissions are a concern, as they impact on patient's morbidity and quality of life.*

Keywords: Hospitalization, mortality, sickle cell disease

Factores Clínicos Asociados con la Morbilidad y Mortalidad en Pacientes Ingresados con la Enfermedad de Células Falciformes

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RESUMEN

Objetivo: *Determinar los factores clínicos asociados con la duración de la hospitalización y la mortalidad en pacientes con la enfermedad de células falciformes (ECF).*

Métodos: *Se hizo una revisión de todos los pacientes con ECF ingresados en las salas del Hospital Universitario de West Indies, Jamaica, durante un período de cinco años, desde el 1^{ero} de enero de 2005 al 31 de diciembre de 2010. Los datos fueron tomados de las historias clínicas, y abarcaban información demográfica y clínica, investigaciones, intervenciones, duración de la estancia, datos patológicos, y resultados.*

Resultados: *Se revisaron 105 pacientes. El 84% tenían genotipo HB SS. Las mujeres representaban el 59%, y los hombres el 41%. En general, la edad promedio fue 32.5 años (SD 13.7, con rango de 12 – 66 años). La duración promedio de hospitalización fue 10.2 días (SD 10.9, rango 1 – 84 días). Los principales diagnósticos para el ingreso fueron: crisis dolorosa, síndrome torácico agudo, anemia severa, sepsis, secuestro hepático, insuficiencia cardíaca congestiva e insuficiencia renal. Los valores promedios de las investigaciones de laboratorio fueron como sigue: hemoglobina 7.7 g/dL (SD 2.8),*

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conteo total de glóbulos blancos 21.7 × 10^9/L (SD 14.2), recuento de plaquetas 320 × 109/L (SD 191.9), urea en sangre 9.8 mmol/L (SD 11.9), y creatinina sérica 198 umol/L (SD 267.9). Las intervenciones médicas fueron como sigue: 20.9% recibieron transfusiones de sangre, 55% recibieron antibióticos, y 74% recibieron analgesia narcótica. Hubo 40 muertes con cuatro autopsias realizadas. La tasa de mortalidad por ECF fue 38%. Hubo 189 ingresos repetidos por ECF.

Conclusión: *La enfermedad de células falciformes todavía lleva una alta morbilidad y mortalidad en pacientes ingresados en el hospital. Los ingresos recurrentes son motivo de preocupación, por cuanto inciden en la morbilidad y la calidad de vida del paciente.*

Palabras claves: Hospitalización, mortalidad, enfermedad de células falciformes

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INTRODUCTION

Sickle cell disease (SCD), first reported in the western medical literature around one hundred years ago, was the first disease in which a molecular defect was identified, a mutational change in the beta-globin subunit resulting from a single nucleotide mutation in its gene (1–3). From a clinical perspective, SCD is a chronic disease with variable manifestations.

In Jamaica, homozygous S is the most severe and the commonest form of SCD, with a frequency of the sickle-cell allele of 0·055, resulting in about three per 1000 live births. The frequency of the sickle cell trait (Hb AS) in Jamaica is estimated at 10% (4). The clinical manifestations of the disease vary by age and genotype. Dactylitis and splenic sequestration are common in children under five years of age, while strokes and leg ulcerations are common during adolescence and chronic organ damage is most common in adulthood (5, 6). Within genotypes, the manifestation of the disease is highly variable (7, 8).

The wide variation in clinical expression and, hence, mortality is highlighted by two reports from Jamaica. In 1968, sixty cases of patients over 30 years of age were reported (9). This study was remarkable because the prevailing thought at the time was that survival beyond 30 years was rare. The second case series identified 102 patients who survived beyond 60 years (10). This longevity was achieved without the use of disease-modifying therapies such as chronic transfusion and hydroxyurea, and pre-dated much of the recent public health initiatives that affect survival, emphasizing the role of biological factors as disease modifiers.

A previous hospital based study in Jamaica reported that SCD was the fourth leading diagnosis of children admitted to a rural tertiary hospital in Jamaica (11). However, for adults, the situation is unclear. Sickle cell disease is a common chronic disease in Jamaica. It has a wide spectrum of clinical manifestations that can result in increased rates of hospitalization. However, the risk factors that prolong hospitalization and/or are associated with death in hospital are unclear. Further, it is unknown if some deaths are preventable. This study determined the proportion of all medical admissions to the University Hospital of the West Indies (UHWI), Jamaica, over a five-year period that was attributable to SCD and which clinical risk factors affected the length of hospital stay and mortality.

SUBJECTS AND METHODS

All patients admitted to the medical floor at the UHWI with a diagnosis code of sickle cell disease (ICD 10 D57) over a five-year period from January 1, 2005 to December 31, 2010, were identified (cases). The medical charts of these cases were retrieved and studied using a standardized data extraction instrument to obtain information from the records under the following headings: a) demographic information: age at each admission, gender and genotype, b) clinical data: diagnosis, c) investigations on admission: haemoglobin, platelet count; renal function: urea and creatinine; oxygen saturation, temperature, blood pressure, d) medical interventions (pharmacological treatment and non-pharmacological treatment, such as intravenous fluids, blood transfusions), e) duration of stay in hospital and f) outcome.

Exclusion criteria were initial admission to a non-medical ward and age less than 12 years.

The total number of admissions to the medical floors for the period was obtained from the medical records database of the UHWI.

The clinico-pathologic risk factors for length of hospitalization and death of patients with SCD were determined respectively by multivariable linear and logistics regressions. Length of stay was analysed as survival data with the event being death and the time to death being defined as the time in days from admission until the patient's death. Persons who were discharged from hospital were censored at the date of their discharge from the medical floor. Log-rank tests were conducted to determine whether the survival function differed significantly across genotypes.

RESULTS

The total number of patients admitted to the medical wards during the five-year study period from January 1, 2005 to December 31, 2010, was 21 827 including repeat admissions. This included all patients irrespective of their diagnosis. The

total number of sickle cell patients eligible for inclusion in the study was 129; however, 24 had charts classified as untraceable. The remaining 105 patients accounted for 189 admissions during the study period, yielding a sickle cell related admission rate of eight per 1000 admissions.

There were 62 females and 43 males representing 59% and 41% of the sample, respectively (Table 1). Homozygous S sickle cell disease (Hb SS) represented 84% of all SCD admissions. There was no significant difference in the gender distribution by genotype ($p = 0.98$). The mean age of the subjects admitted to hospital was 32.5 years (SD 13.7, range 12–66 years). The mean age of females was 33.2 years (SD 12.8, range 12–61 years) and of males was 31.6 years (SD 15.0, range 12–66 years). There was no significant difference in age by gender of the sample. Additionally, there were no significant differences by gender in clinical characteristic as assessed by oxygen saturation, temperature and blood pressure on admission (Table 1). Acute vaso-occlusive painful crises were the most common reason for admission, representing 22% of diagnoses. The most frequent diagnoses made by both the emergency room and the internal medicine team were painful crisis, acute chest syndrome, severe anaemia, sepsis, hepatic sequestration, congestive cardiac failure and renal failure (Table 1). However, there were no significant differences in the distribution of the diagnoses by genotype and there was no difference by gender admitted for the various diagnoses ($p = 0.2$).

The mean haemoglobin concentration was 7.7 g/dL (SD 2.8), and the mean elevated total white blood cell count was 21.7 × 10^9/L (SD 14.2). However, there was no significant difference in the mean values for haemoglobin and white blood cell counts by gender. The mean platelet count was 320 × 10^9/L (SD 191.9) and there was no significant difference by gender. The mean serum urea was 9.8 mmol/L (SD 11.9) and serum creatinine was 198 umol/L (SD 267.9). Both were elevated, as well as the liver related enzymes including aspartate transaminase, mean 88.1 IU/L (SD 136.4) and gamma-glutamyltransferase, mean 93.8 IU/L (SD 105.2). There were no significant differences by gender for these variables. Patients with homozygous S sickle cell disease had lower haemoglobin concentration, mean 6.7 g/dL (SD 2.9) *versus* 8.8 g/dL (SD 1.7) but higher platelet count, mean 374.1 × 10^9/L (SD 190.3) *versus* 266.9 × 10^9/L (SD 179.7) on admission compared with patients with other variants of the disease. There were no significant differences in serum urea, creatinine, aspartate transaminase and gamma-glutamyltransferase concentrations by genotype (Table 2). Regular blood transfusions were done in 14% of patients.

Treatment interventions in hospital included the following: 20.9% of patients (genotype SS) were transfused blood products and 56% received oxygen therapy. There were no significant differences in the proportion of homo-

Table 1: Clinical characteristics of patients

Clinical characteristics	**Female (n = 62) n (%)/mean (SD)**	**Male (n = 43) n (%)/mean (SD)**	**Total**
Genotype			
SB thal	2 (3%)	0 (0%)	2 (2%)
SB+	0 (0%)	1 (2%)	1 (1%)
SC	8 (13%)	4 (9%)	12 (11%)
SO Arab	0 (0 %)	2 (5%)	2 (2%)
SS	52 (84%)	36 (84%)	88 (84%)
Age, years	33.2 (12.8)	31.6 (15)	32.5 (13.7)
Oxygen saturation, %	94.4 (7.8)	91.9 (8.1)	93.4 (7.9)
Temperature, °F	96.9 (8.1)	98.7 (2.3)	97.6 (6.4)
Systolic blood pressure, mmHg	139.1 (127.6)	117.9 (21.3)	130.6 (99.7)
Diastolic blood pressure, mmHg	72.4 (14.5)	65.1 (14.3)	69.5 (14.8)
Admitting diagnoses			
Painful crisis	26	14	40
Gastritis	1	2	3
Heart failure	3	6	9
Urinary tract infection	3	3	6
Kidney disease	5	4	9
Renal failure	10	7	17
Pyelonephritis	6	1	7
Dehydration	7	7	14
Acute chest syndrome	11	12	23
Hepatic sequestration	9	9	18
Severe anaemia	10	7	17
Aplastic crisis	0	2	2
Sepsis	5	9	14

Table 2: Mean haematological and biochemical characteristics on admission by genotype

Haematological characteristics	Homozygous S sickle cell disease (SD)	Other sickle cell genotypes (SD)	*p*-value
Haemoglobin concentration, g/dL	6.7 (2.9)	8.8 (1.7)	0.004
White blood cell, $\times 10^9$/L	21.6 (14.2)	21.8 (14.2)	ns
Platelet count, $\times 10^9$/L	374.1 (190.3)	266.9 (179.7)	0.04
Urea concentration, mmol/L (normal: 2.5–6.7)	9.8 (12.3)	9.7 (9.4)	ns
Serum creatinine concentration, umol/L (normal: 9–124)	189.2 (260.5)	207.4 (312.9)	ns
Aspartate transaminase, IU/L (normal: 7–24)	89.9 (145.4)	76.8 (67.9)	ns
Gamma-glutamyltransferase, IU/L (normal: 5–40)	102.4 (110.2)	42.0 (44.7)	ns

ns: not significant

zygous S subjects who received these interventions compared with persons with other genotypes. Acetaminophen was the most utilized analgesic amongst all patients (65% of patients); 74% received narcotic analgesia, with pethidine as the most utilized narcotic agent (52% of patients), the other being morphine. Diclofenac (38% of patients) was the most utilized non-steroidal anti-inflammatory agent. Antibiotics were the most frequently used pharmacological agents (55% of patients). However, there were no significant differences in the types of pharmacological agents used by genotype.

The distribution of length of stay in hospital was right skewed, with the average duration of stay for the patients admitted being 10.2 days (SD 10.9) and the longest admission being 84 days. The log-rank test for equality of survivor functions showed no significant difference between the SS and non-SS genotypes ($p = 0.851$). There were 40 deaths with four autopsies recorded. Thus, the mortality proportion or rate was 38% (40/105).

DISCUSSION

Sickle cell disease is a chronic disease with variable manifestations and with an increase in morbidity and mortality compared to the general population. In the present study, in the adult patient population, recurrent admissions are a concern, as this impacts on the patient's morbidity and quality of life. Painful crisis, infection and severe anaemia appeared as the most frequent diagnoses at admission to hospital.

Acute vaso-occlusive episodes are caused by entrapment of erythrocytes and leucocytes in the micro circulation resulting in occlusion and subsequent ischaemia. Although this process requires HbS polymerization, the event that triggers the vascular obstruction by sickle erythrocytes is often inflammatory (2). In this study, homozygous SCD was associated with increased episodes of vaso-occlusive crisis and there was a resultant increase in narcotic analgesia intervention in this group when compared to the other genotypes. The patients presenting with painful crisis should be assessed with objective pain tools and treated with round the clock analgesic therapy (12). The approach to managing a painful crisis involves excluding other causes of vaso-occlusion such as infection and ensuring adequate hydration and the use of aggressive analgesia including the use of opioids (2). In this study, most patients utilized acetaminophen in addition to an opioid or non-steroidal anti-inflammatory drug for analgesia relief.

The Cooperative Study of SCD identified that the median survival was into the fifth decade, as 50% survived beyond the fifth decade. The median age at death was 42 years for males and 48 years for females, which represents a significant decrease in life expectancy compared to the general population (13). Among patients with sickle cell haemoglobin C disease, the median age at death was 60 years for males and 68 years for females (13). In a previous report from Jamaica, survival to age 60 years was associated with female gender and higher fetal haemoglobin (HbF). Elderly survivors present some features of intrinsic mildness but also manifest age-related amelioration of painful crises and falling haemoglobin levels from progressive renal damage (10).

Hydroxyurea therapy has been reported to decrease hospitalization, reduce frequency of painful crises and severity of acute chest complications. However, therapy with this agent may cause myelosuppression (2, 14). High level of HbF predicted improved survival and is probably a reliable childhood indicator of adult life expectancy (13, 15). Hydroxyurea therapy was associated with a 2.3 to 16-fold increase in the percentage of haemoglobin F and with reduced haemolysis and prolongation of red cell survival. Hydroxyurea treatment also resulted in a decrease in the percentage of irreversibly sickled cells and sickling (15). It was initially thought that recombinant human erythropoietin may also increase haemoglobin F production. However, erythropoietin, whether alone or in combination with hydroxyurea, did not show any measurable benefit (15).

In chronic transfusion therapy, the aim is to maintain a haemoglobin S concentration less than 30% by regular (monthly) exchange transfusion of red blood cells (2, 16).

Red cell transfusion is currently the most studied and accepted therapy for most acute and many chronic complications of SCD (16). This therapy has been shown to be efficacious in prevention of stroke, treatment of acute chest syndrome, perioperative transfusion management of SCD and obstetric management. Its use, however, may be associated with iron overload and allo-immunization syndromes (17). Blood transfusions were done in only 14% of patients in this study and should be considered in appropriate patients as a valuable component of early management to improve morbidity and reduce length of admission (16). The goals of management in patients with SCD include improving oxygen carrying capacity by increasing the haemoglobin level and decreasing the concentration of sickle haemoglobin (18). Blood transfusions (simple or exchange) have been shown to improve outcomes in symptomatic anaemia as well as in acute chest syndrome and stroke events (18).

In the present study, the haematological variables on admission were relatively similar between homozygous sickle cell patients and the other genotypes. However, the haemoglobin levels were notably lower in the homozygous sickle cell patients. In the Cooperative Study of SCD, a large number of patients who died had no overt chronic organ failure but died during an acute episode of pain, acute chest syndrome, or stroke. Early mortality was highest among patients whose disease was symptomatic (13). In addition, a low level of fetal haemoglobin, a low level of total haemoglobin, and an elevated baseline white cell count were associated with an increased risk of death (13). However, the steady-state leukocyte count in HbSS is higher than that in normal individuals which may blunt the utility of this measurement in the assessment of infection (19). Also, platelet counts in HbSS are often found to be above normal and show a downward trend with age; in addition, there is a progressive rise in creatinine with age (19). In patients with sickle cell anaemia older than 20 years, high rates of pain episodes tended to result in death earlier than those with low rates (20). In a previous study in Jamaica which reviewed the causes of death in patients with SCD, acute chest syndrome was the most common cause in all age groups (21).

Given that the majority of patients in the study were of genotype SS and SC with the expected complications in their clinical course, these patients should be identified at birth and monitored to benefit from targeted therapies such as blood transfusions and hydroxyurea therapy early to reduce morbidity and mortality. In the Jamaican context, the use of these disease-modifying strategies in adults is relatively low and thus clinical presentations will be dominated by the natural history of the disease. Protocols could be therefore designed to increase the utilization of disease-modifying agents early.

This hospital-based study is useful to provide information that can assist clinicians in anticipating challenging clinical conditions, inform the development of clinical management protocols to improve the quality of care as well as aid in the counselling of patients and relatives. Given the frequency of vaso-occlusive crisis as a presentation amongst all genotypes, protocols should be reviewed to ensure that appropriate analgesia in a timely fashion is offered to reduce length of stay in admitted patients. The number of patients who had autopsies done was also significantly low and post-mortem data may prove useful in guiding future management protocols. Education amongst patients must continue to sensitize them to their disease and its complications. Early health-seeking behaviour and clinical interventions should be encouraged to alter the natural history of their illness.

There were limitations in this study. A number of patient charts were missing and clinical documentation was incomplete for several patients.

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