Clinical Complications of Hemoglobinopathies in Western Saudi Arabia and the Need for Specialized Care Centers


Department of Hematology, Faculty of Medicine, King Abdulaziz University
Jeddah, Saudi Arabia

Abstract

In the absence of specialized care centers for hemoglobinopathies in Saudi Arabia, there are insufficient data on prevalence of clinical complications in this population. This is a retrospective record review about the clinical complications associated with hemoglobinopathies at King Abdulaziz University Hospital, for patients followed between January 1st 2010 through June 30th 2016. A total of 349 patients were included, with a mean age of 25.45 years, including 266 with sickle cell disease and 80 with thalassemia. Of those receiving regular transfusions, 17.5% developed alloantibodies, 16.6% tested positive for hepatitis C virus antibodies and the mean ferritin level was 2487 ng/ml. Almost half of the patients were screened for renal disease, and more than 50% were found to have proteinuria. Of 203 patients with recent echocardiograms, 15.8% had pulmonary hypertension. Thirty-one (8.9%) patients died at a mean age of 28.5 years. In conclusion, the prevalence of disease related complications is high in hemoglobinopathies. Our results reiterate the need for specialized care hemoglobinopathy centers, which can further improve patient outcomes.

Keywords

Sickle cell disease; Thalassemia; Specialized hemoglobinopathy center

Introduction

Thalassemia and sickle cell disease (SCD) are two of the most common inherited genetic disorders worldwide. It is estimated that 7% of the world population are carriers for hemoglobinopathies[1] and 300,000-500,000 children are born annually with hemoglobin disorders[2].

The global mortality rate for hemoglobin disorders is 3.4% in children less than 5 years[3]. Thalassemia and SCD can affect all organs, thus patients with these chronic conditions typically utilize a sizable fraction of health care resources and associated costs[4,5]. Improving morbidity and mortality in these patients is an urgent global need[6].
Clinical Complications of Hemoglobinopathies in Western Saudi Arabia and the Need for Specialized Care Centers
M.A. Badawi et al.

Treatment modalities for SCD and thalassemia are limited. Hydroxyurea and L-Glutamine are the two FDA-approved drugs for management of SCD[8], and transfusion is life-saving in certain clinical complications associated with the disease[9]. Transfusion is the mainstay of management of thalassemia. However, transfusion-associated complications, including alloimmunization and iron overload represent an ongoing challenge[10,11]. Furthermore, untreated iron overload is associated with risk of endocrine failure, cardiomyopathy, liver cirrhosis, hepatobiliary cancer, and early death[12-14].

In Saudi Arabia, the prevalence of SCD is up to 2.7%, and that of sickle cell trait ranges between 2% and 27%[15]. The total annual incidence of symptomatic individuals with β-thalassemia in Saudi Arabia is 0.5 per 1000, and 18.0 per 1000 for carriers[16]. Thus, hemoglobinopathies represent a significant health care burden and long-term outcomes are largely dependent on future advances in comprehensive care. Given that there are limited local and regional data on the complications and clinical outcomes of hemoglobinopathies, we report on the characteristics and clinical complications of this cohort of patients receiving care at King Abdulaziz University Hospital (KAUH), a tertiary academic medical center in Jeddah, Saudi Arabia.

Methods

King Abdulaziz University Hospital is an academic hospital with a capacity of around 600 beds. Patients with hemoglobinopathies are referred from the Makkah region and other regions within the Kingdom. In our hematology laboratory, patients with suspected hemoglobinopathies undergo routine evaluation using Sebia capillary electrophoresis instruments (Sebia, Evry Cedex, France) a method that is recognized to provide comparable results with cellulose acetate electrophoresis[17].

In this study, patients were eligible for inclusion if they were diagnosed with a hemoglobinopathy based on capillary hemoglobin electrophoresis and were followed up at KAUH from the 1st of January 2010 to the 30th of June 2016. Approval to conduct this study was obtained from KAU Research Ethics Committee, and the study was performed in accordance with the ethical standards outlined in the 1964 Declaration of Helsinki and its later amendments. Medical record numbers were retrieved through the hospital information system using relevant International Classification of Diseases-10 codes. Using a standardized data extraction sheet, we reviewed patients’ electronic and paper records. For details on pre-transfusion compatibility testing and antibody identification results, records from blood transfusion service were reviewed. Patients were excluded if an objective diagnosis was missing.

Data Collection

The following information was collected; 1) General demographics including; age, gender and nationality, 2) Relevant laboratory values, 3) Markers of end organ damage, 4) Details of hospital admissions, and 5) Transfusion history including alloantibody screening and identification, transfusion reactions and transfusion transmitted infections.

Hematological indices were expressed as the mean of the three most recent values obtained in the outpatient clinic including; hemoglobin level (Hb), hematocrit, platelet count, white blood cells count and absolute neutrophil count. Laboratory markers of hemolysis were recorded including absolute reticulocyte counts, and lactate dehydrogenase. Data reflecting end organ damage included; ferritin as a marker of iron overload, liver function, renal function, proteinuria, and pulmonary hypertension as measured by tricuspid regurgitation ≥ 2.5 m/second on echocardiogram examination. Unfortunately, the results of transverse relaxation time weighted magnetic resonance imaging (MRI T2*) studies were not accessible at the time of the analysis and therefore the related information could not be collected. Current medications, hypertension, history of stroke, history of splenectomy, history of venous thromboembolism and hospital admissions during the previous year were also recorded. Further, data on disease-specific complications such as acute chest syndrome in sickle cell disease were included.

Statistical Methodology

This study was analyzed using IBM SPSS Statistics for Windows, Version 20 (IBM Corp., Armonk, NY USA). A simple descriptive statistic was used to define the characteristics of the study variables through a form of counts and percentages for the categorical and nominal variables while continuous variables are presented by mean and standard deviations.
Clinical Complications of Hemoglobinopathies in Western Saudi Arabia and the Need for Specialized Care Centers

M.A. Badawi et al.

Results

Demographics of Patient Population

Three hundred and forty-nine patients with a mean age of 25.45 years (± 9.068) were included in the study. Of these, 185 (53%) were males and 131 (37.6%) were Saudi nationals. The remaining patients were born in 15 different countries (including Arab, African, and Asian countries). There were 266 (76.2%) SCD patients, 80 (22.9%) patients with beta-thalassemia major, and three with hemoglobin E disease. Details on characteristics of SCD and thalassemia patients are reported separately elsewhere.

Evidence of End Organ Damage

Mean ferritin level, a marker of iron overload was 2487.94 ng/ml (± 34988) (Table 1). Recent echocardiogram results (within 12 months) were available for 203 patients and showed a mean ejection fraction of 63.69% (± 8.4). Tricuspid regurgitation velocity of ≥ 2.5 m/second, reflecting pulmonary hypertension was present in 32 (15.8%) out of 203 patients. Among the 198 patients who were screened for proteinuria, 102 (51.5%) tested positive. Blood counts, liver enzymes, and renal functions are shown in Table 1.

Viral Infections

Forty-six (16.6%) patients out of 277 tested positive for Hepatitis C Virus (HCV) antibodies, and two out of 270 screened patients were found to be positive for HBsAg. All 196 patients screened for human immunodeficiency virus (HIV) antibody were negative.

None of the cases with positive testing for transfusion-transmitted infections (TTI) developed seroconversion while being treated within our center, and all presented with positive testing at time of initiation of care at KAUH.

Other Clinical Complications

Thirteen of the included patients (11 patients with SCD and 2 with thalassemia) experienced venous thrombotic events (7 deep venous thrombosis, 5 pulmonary emboli), and 46 (13.2%) patients underwent splenectomy, while 20 (5.7%) had cholecystectomy. Fourteen patients with SCD developed acute chest syndrome during the course of the disease. This is equal to 4.8% of the total number of SCD patients in this cohort. Out of 273 patients, 137 (50.2%) were admitted to KAUH once within the preceding 12 months, while 67 (24.5%) were admitted twice. The remaining 69

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Reference Range at our Center</th>
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<td>Age</td>
<td>349</td>
<td>25.45</td>
<td>9.07</td>
<td>12-15</td>
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<td>Hemoglobin (g/dl)</td>
<td>349</td>
<td>8.18</td>
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<td>12-15</td>
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<tr>
<td>Platelets (x10^9/L)</td>
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<td>White blood cell count (x10^9/L)</td>
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<td>16.44</td>
<td>25.1</td>
<td>4.5-11.5</td>
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<td>Absolute reticulocyte count (x10^9/L)</td>
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<td>93</td>
<td>108</td>
<td>25-75</td>
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<td>12.09</td>
<td>&lt;4% (age dependent)</td>
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<td>Ferritin (ng/ml)</td>
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<td>3488.7</td>
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<td>Aspartate aminotransferase (units/L)</td>
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<td>15-37</td>
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<td>Gamma glutamyl transferase (units/L)</td>
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<td>Diastolic blood pressure (mmHg)</td>
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<td>9.8</td>
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<td>Heart rate (beats per minute)</td>
<td>116</td>
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<td>11.9</td>
<td>60-100</td>
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<td>Ejection fraction (%)</td>
<td>182</td>
<td>47.33</td>
<td>27.7</td>
<td>27.7</td>
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<tr>
<td>Hospital admissions within past 12 months</td>
<td>200</td>
<td>1.44</td>
<td>1.8</td>
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</tr>
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</table>
(25.3%) were admitted more than two times, including planned admissions for regular blood transfusions.

**Mortality**

Thirty-one (8.9%) patients died at a mean age of 28.46 (±11.2%) years. Unfortunately, no further details on causes of death were collected for this study purpose. However, it is considered for future cohort study.

**Medications**

Data on current medications were available for 345 patients. Of these, 73 (21.2%) were on hydroxyurea, with a mean dose of 590 mg (range 250-1500). Thirty-nine (11.2 %) patients were on anti-hypertensive treatment and 15 (4.3%) received anti-epileptic medications. Data about utilization of iron chelation therapy could not be collected accurately from the electronic medical record.

**Transfusion and Alloimmunization Data**

Most of the patient population were group O (47.7%), followed by group A (31.1%). Sixty-one (17.5%) patients developed antibodies against red cell antigens at a mean age of 18 years. The most common alloantibody identified in isolation was anti-E. Patients received a mean of 16 packed red cell transfusions per patient (± 22.4) before developing alloantibodies. No allergic reactions were reported and only one febrile reaction was documented.

**Discussion**

The prevalence of SCD in Saudi Arabia is variable in different geographical regions\[15,16\]. Results of the mandatory Saudi Premarital Screening Program (SPSP) show that the 0.26% of applicants had SCD, 4.2% had sickle cell trait (SCT), 3.22% had thalassemia trait, while 0.07% had thalassemia disease\[18\]. Similar rates were seen six years following initiation of the SPSP\[16\]. A cross-sectional community-wide survey of schoolchildren and adolescents revealed that the rate of SCD was 24 in 100,000\[19\]. The prevalence of alpha-thalassemia gene is also high, ranging between 30-50% in various reports\[20\].

Hemoglobinopathy patients are at risk for end organ damage, either secondary to the disease itself or secondary to chronic blood transfusion. The mean ferritin level in our study is over 2000 ng/ml reflecting iron overload. For many years, desferrioxamine was the solely used iron chelating agent in our center\[21\]. Since the introduction of deferasirox and deferiprone, more patients have been prescribed these oral agents to improve compliance. Since complications of iron overload constitute major causes of death in these patients, major efforts are necessary to enhance this aspect of their care. Having access to specialized care centers would allow coordinated follow up with a multi-disciplinary team, including a clinical pharmacist, patient educators, social workers, nurses and physicians from various subspecialties. Proper imaging techniques for evaluation of iron loading (such as MRI T2*) would also be accessible to these patients in a timely manner.

In a similar manner, specialized care centers are expected to improve rates of screening and management for other complications of hemoglobinopathies. This can be achieved through regular follow up by trained coordinators, or through an electronic support system. This would be valuable in such a cohort, as rates of screening with echocardiograms and proteinuria assessment in our patients were less than 60%, despite that these tests are recommended by leading organizations\[22,23\]. The same applies to screening for TTI, as some patients in our cohort never underwent such testing.

Although the prevalence of hepatitis C antibodies in our cohort (16.6%) is higher than reported from a group of thalassemia patients in Al Hofuf (12.7%)\[24\], it is significantly lower than many reports covering the period from 1980 to 2000\[25\]. This may be explained by the improvement in blood donor selection and screening, resulting in a safer blood supply around the world.

Ensuring safety of blood is an integral part of the comprehensive management of hemoglobinopathies. Although transfusion services in Saudi Arabia are fragmented, regulatory authorities hold transfusion services in the Kingdom to high standards. Transfusion safety has been notably improved with the advent of mandatory nucleic acid testing for hepatitis B virus (HBV), HCV, and HIV. Given that patients may receive transfusions in different hospitals during the course of their disease, and in the absence of a national database for patients with hemoglobinopathies on regular transfusion, it is difficult to determine whether HCV seroconversion occurred before or after introduction of nucleic acid testing on a national level. In fact, patients with hemoglobinopathies constitute the largest
fraction of patients with HCV who have an identifiable risk factor in our institution[26].

Overall these findings highlight the need for better compliance without patient visits and more rigorous screening to allow early referrals to specialists, early initiation of therapy, and identification of associated risk factors.

A number of factors contribute to the gap in the comprehensive care of hemoglobinopathy patients. These include limited awareness of patients and caregivers, lack of psychosocial support, and the absence of a functional primary care model. This results in difficulties in accessing care from a multidisciplinary team. Poor adherence of patients to outpatient follow up appointments contributes to interruption of care. In addition, when treated in the same institution, patients with malignant diseases may be prioritized when resources (including appointments and beds) are allocated, in comparison with those suffering from conditions perceived as “benign”.

To reduce inconsistency of care, specialized hemoglobinopathy centers should be established. Previously, access to such centers was found to be associated with better survival in thalassemia patients[27], and improved compliance and quality indicators in SCD patients[28]. Specialized hemoglobinopathy centers provide comprehensive, coordinated, patient-centered care and allow smooth transition from pediatric to adult care. Furthermore, specialized staff members provide support to patients and families by addressing psychological and social needs. When compared with an “episodic” model of care, enrollment of SCD patients in comprehensive care programs was found to reduce cost, utilization of emergency department, length of hospitalization, and rate of readmission[28,29]. Quality of life outcomes were found to be poor in hemoglobinopathy patients compared to the general population[30-32]. Comprehensive care of hemoglobinopathies at specialized centers improves quality of life outcomes[33], and leads to higher patient satisfaction[34]. Furthermore, early diagnosis and implementation of preventative care at specialized hemoglobinopathy centers reduces early mortality[35].

Our data summarize some of the important clinical characteristics of patients with hemoglobinopathies in Western Saudi Arabia. Limitations of this study include some missing clinical data such as adherence to recommendations regarding vaccinations, periodic testing for TTI, and unavailability of accurate data about iron chelation and radiologic evaluation for iron loading. Mortality data are limited and do not allow for a meaningful comparison with the available literature. Nonetheless, the available findings identify opportunities for improvement of care provided to patients with hemoglobinopathies, such as providing psychosocial support and education of patients and families. Comprehensive hemoglobinopathy centers can provide support and consistent care of these chronic disorders. Furthermore, establishing a national registry of hemoglobinopathy patients would help characterize clinical outcomes of hemoglobinopathies in Saudi Arabia.

Conclusions
Patients with hemoglobinopathies should receive comprehensive patient-centered care including regular screening for organ dysfunction. Further efforts are required to implement prophylactic measures in early childhood and careful long-term follow-up in this population. Development of comprehensive hemoglobinopathy centers is encouraged to overcome inconsistencies in healthcare and provide necessary support to patients.

Conflicts of Interest
The authors declare no conflict of interest.

Disclosure
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Ethical Approval
Obtained.

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References
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M.A. Badawi et al.


المضاعفات الأكلينية لدى مرضى الأنيميا المنجلية والثلاسيمية بالمنطقة الغربية
من المملكة العربية السعودية والحاجة إلى مراكز رعاية مختصة

معا عبد الرزاق بدوي و سهير سعيد آدم و عبد الرحمن حسام الينين و أحمد عاصم جمجم و أحمد
نايف سلحي و ثنيان محمد المطيري و جليلة فيصل زاهر و سلوى إبراهيم هنادي

قسم أمراض الدم، كلية الطب، جامعة الملك عبد العزيز
جدة - المملكة العربية السعودية

المستخلص. في ظل ندرة مراكز الرعاية المختصة لمرضى أمراض الدم الوراثية بالمنطقة، تظل المعلومات المتعلقة بالمضاعفات التي تصيب هذه الفئة من المرضى غير مكتملة. في هذه المراجعة الاستعدادية تم إجراء مراجعة سجلات مرضى أمراض الدم الوراثية مستشفى جامعة الملك عبد العزيز. تم إدراج 349 مريضا في هذه الدراسة، منهم 226 مريضا بالأنيميا المنجلية و 80 مريضا بالثلاسيمية، وكان متوسط أعمارهم 25.45 عاما. من ضمن المرضى الذين كانوا يلتقيون نقل الدم بانتظام، تعرض 17.8٪ منهم للتنوع المخيف، وكان اختيار الأجسام المضادة لفيروس التهاب الكبد البولي ج موجودا في 16.2٪ منهم، بينما كان متوسط مستوى مخزون الحديد نانوجرام/ملتر. تم فحص ما يقارب من نصف أفراد العينة لأمراض الكلي، ووجد أن نصف هؤلاء يعانون من نسبة عالية من وجود بيلة بروتينية. تم إجراء مخطط صدى القلب ل 230 مريض ووجد أن 15.8٪ منهم كانوا يعانون من ارتفاع ضغط الشريان الرئوي. من ضمن كل العينة توفي 31 مريضا (8.8٪) وكان متوسط العمر لدى الوفاة 48.5 عاما. نستنتج أن نسبة المضاعفات بين المصابين بأمراض الدم الوراثية مرتفعة. تؤكد نتائجنا على أهمية توفير الرعاية الطبية في مراكز مختصة لهذه المرضى مما قد يساهم في تحسين نتائجهم.