

Clinico-Pathological Study Of Sickle Cell Anemia In Basrah

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Abstract :

Basrah is located in the world's map of geographical distribution of sickle cell anemia (SCA) that carries significant morbidity. Data on the true gene frequency, clinical spectrum of the problem and hematological and biochemical profiles of patients that could define the natural history of the problem in our country are scarce. In the present study the medical files of patients with SCA admitted to Basrah Teaching hospitals (1990-1998) were reviewed. Data on age, sex, residence, clinical presentations, mean hemoglobin level, frequency of readmissions and blood transfusions were collected.

The clinical presentation of SCA were found to be protean. The most frequent one was acute painful crisis (40%) following by aplastic crisis (10%) and hemolytic crisis (9%). Infection comprised 30% of total presentation including urinary tract infection, osteomyelitis and gastroenteritis. Splenomegaly, hepatomegaly and hypersplenism were reported in different frequencies (50%, 42% and 20% respectively). Splenic sequestration was the least common presentation (2%). The mean hemoglobin level was 7.5 ± 1.2 gm % and the total frequencies of re-admission and blood transfusion were 80-92 respectively.

It is concluded that the clinical severity of SCA in Basrah tends generally to be more severe than Mosul and Baghdad cases. Different hemoglobin haplotypes, possible interaction between sickle cell gene and other red blood cells genetic marker such as thalassemia and G₆PD deficiency and environmental factors are probable etiological for more severe clinical presentation in Basrah.

Keywords: Sick cell anemia, Clinical presentation, Basrah.

الخلاصة :

تقع البصرة ضمن خارطة العالم الجغرافية لانتشار فقر الدم المنجلي والتي تحوي نسبة أصابه مرضيه عالية له. المعلومات حول التردد الجيني الحقيقي. ان الحجم السريري للمشكلة، والمعلومات حول نتائج الدم والكيمياء السريرية للمرضى والتي من الممكن ان تعرف حجم المشكلة في بلدنا قليلة. في هذه الدراسة الملفات الطبية للمرضى المصابين بفقر الدم المنجلي والذين ادخلوا مستشفى البصرة التعليمي بين الأعوام 1990-1998 تمت دراستهم. المعلومات عن العمر، الجنس، السكن، معدل الهيموغلوبين، معدلات الدخول للمستشفى ونقل الدم تم جمعها.

المظاهر السريرية لفقر الدم المنجلي وجدت متنوعة. الأكثر شيوعا هو نوبات الألم (40%)، تتبع بنوبات (10%)، ونوبات تكسر خلايا الدم (9%). احتلت الالتهابات نسبة (30%) من مجمل الأعراض السريرية وتضمنت التهابات المجاري البولية، التهابات العظم، والتهابات المعدة والأمعاء. تضخم الطحال والكبد وفرط الطحال سجلت بنسب مختلفة (50%، 42%، 20%) وعلى التوالي. معدل مستوى الهيماكلوبين كان (7.5 ± 1.2) غم ونسبة إعادة الدخول للمستشفى وعمليات نقل الدم كانت (80%-92%) على التوالي. تم الاستنتاج ان شدة أحواله السريرية لحالات فقر الدم في البصرة تكون أكثر قوه عن مثيلاتها في الموصل وبغداد. ان مختلف الأنماط الفردانية ربما كان يمثل تفاعلات محتمله بين الجينات المنجليه والمعلومات الجينية لخلايا الدم الحمراء الأخرى مثل التلاسيميا ونقص الإنزيم (ج6 ب د) والعوامل البيئية ربما تكون أسباب محتمله لمظاهر سريرية أشد في البصرة.

Introduction:

Sickle cell disease is an inherited disorder caused by the abnormal properties conveyed to sickle cell erythrocytes by mutant sickle cell hemoglobin (Hb S) (1-3). The disease is complex, having as its cardinal features chronic hemolytic anemia and recurrent painful episodes. The illness is engendered by the interaction of the patient with this multisystem disease, the psychosocial impact of the chronic painful disorder, and the ethnic complexities of contemporary society. Traditional understandings of sickle cell disease attribute all disease features to a causative pathophysiologic cascade: an A(r)T nucleotide substitution in the sixth codon of the β globin gene; a Val(r)Glu β globin substitution on the surface of the Hb S tetramer; the reduced solubility and polymerization of deoxygenated Hb S; the impaired deformability and sickling of polymer-containing erythrocytes; and the occlusion of the microvasculature by poorly deformable red cells. The importance of these interdependent events notwithstanding, a contemporary understanding of sickle cell pathophysiology includes Sickle cell disease is an inherited disorder caused by the abnormal properties conveyed to sickle cell erythrocytes by mutant sickle cell hemoglobin (Hb S). The disease is complex, having as its cardinal features chronic hemolytic anemia and recurrent painful episodes. The illness is engendered by the interaction of the patient with this multisystem disease, the psychosocial impact of the chronic painful disorder, and the ethnic complexities of contemporary society

The clinical features of SCA reflect propensity of red cells to assume a sickled configuration when blood is oxygenated leading to a shortened red cell survival and tendency to vaso-occlusion(4). It is characterised by severe hemolysis, recurrent vaso-occlusive episodes and increase susceptibility to acute bacterial infections which lead to enhanced mortality particularly in early childhood (5,6).

Basrah is located in the world's map of geographical distribution of SCA that carries significant morbidity and mortality. The carrier frequency of HbS in Iraq is 0 – 22%(7). The objective of the present study is to highlight the clinical and hematological spectrum of patients with SCA in Basrah.

Methods :

The medical files of under patients sicklers admitted to Basrah teaching hospitals, from 1990-1998 were reviewed. The diagnosis in patients were documented by hemoglobin electrophoresis. The reviewed data were age, sex, residence, clinical presentation, mean level of hemoglobin (Hb) and frequency of re-admissions and blood transfusions. A comparison was made between our data and those reported from Mosul and Baghdad⁸.

Results :

The total Number of patients was 405 (224 males and 181 females) with a male to female ratio of 1.24:1 . Their ages at the time of the study ranged between 2 years and 49 years, with mean age of 33 ± 3.4 years .The frequency distribution of different variables in the studied sample is shown in table 1. Splenomegaly and hepatomegaly were the predominant clinical findings in the studied sample noticed in 165(40.6%) and 162 (39.6%) cases respectively. Acute painful crises were seen in 164(39.1%) cases which presented as generalized pain all over the body, back and extremities. Infections were found in 122 (30%) cases, manifested mainly as urinary tract infections (UTI), osteomyelitis and gastroenteritis. Hypersplenism, aplastic and hemolytic crises (fig.1) were noticed in 81(20%), 40(10%) and 36 (9%) cases respectively. Splenic sequestration was the least common presentation seen in 8(2%) case. However, dactylitis and acute syndrome were not

reported. The mean hemoglobin level in the studied sample was 7.5 ± 1.2 g/dl. The total number of re-admission and blood transfusion were 152 and 181 respectively.

Discussion :

Traditional understandings of sickle cell disease attribute all disease features to a causative pathophysiologic cascade: an A(r)T nucleotide substitution in the sixth codon of the β globin gene; a Val(r)Glu β globin substitution on the surface of the Hb S tetramer; the reduced solubility and polymerization of deoxygenated Hb S; the impaired deformability and sickling of polymer-containing erythrocytes; and the occlusion of the microvasculature by poorly deformable red cells. The importance of these interdependent events notwithstanding, a contemporary understanding of sickle cell pathophysiology includes many polymerization-independent mechanisms(1-5) Fig2 .

The present study revealed that SCA is commonly associated with crisis and infection. Acute painful crisis, which is an emergency state and needs immediate management was the most common form of emergency presentation in Basrah (55.6%) Mosul (35.6%) and Baghdad (39%) studies. The main site involve in the Basrah cases were generalized all over the body, back and extremities; nearly similar to the Iraqi patterns.

Acute painful crisis was reported in much higher figure in the Senegalese sicklers that possibly reflects different hemoglobin haplotypes distribution(10).

Aplastic and hemolytic crisis were reported in nearly similar percentages (10%) (9%) respectively, in the Basrah study compared to that of Mosul (11.7% and 11.7% respectively) and Baghdad studies (7.4% and 7% respectively).

Infection represented the second leading case of hospitalization after crises in Basrah, Mosul and Baghdad studies (30%, 14.8% and 6% respectively), while Urinary tract infection (UTI), osteomyelitis and gastroenteritis were predominant in the Baghdad series while pneumonia, UTI and typhoid fever were preponderant in the our series. Osteomyelitis and septic arthritis were reported in the Mosul study. Altered splenic function and deficient levels of serum opsonins, of the alternate complement pathway, in sicklers are significant factors leading to their increase susceptibility to meningitis, sepsis and other serious infections mainly caused by pneumococci and H.influenza. Moreover they have increased susceptibility to Salmonella osteomyelitis partly because of bone necrosis(5,10,12).

Splenomegaly and hepatomegaly were reported in a higher frequency in our study (50% and 40% respectively) than other Iraqi study. The spleen is commonly enlarged during the first decade of life, but then undergoes atrophy due to repeated attack of vaso-occlusion and infarction leading to siderofibrotic nodules (autosplenectomy) that renders sicklers at risk of catching serious infection(5,12,13). Persistent splenomegaly beyond this period can lead to increase morbidity and mortality from chronic hypersplenism and acute splenic sequestration and acute splenic sequestration(14). Hepatic involvement in SCA was reported to range from mild with normal liver function to severe liver disease(15).

Hypersplenism and splenic sequestration were reported in higher frequencies in our study (20% and 2% respectively) than other Iraqi study (17.6 and 6% respectively). Splenic sequestration was recorded in a remarkable percentage (10%) in India reflecting possibly altered hemoglobin haplotype pattern(16).

Dactylitis was reported in 1.5% study sample compare to what was reported in the Mosul (11.7%). Dactylitis together with severe anemia and leucocytosis that appear in the first two years of life can predict the possibility of severe SCA later in life(17). In acute chest syndrome was not noticed in all the three studies though it was started in a considerable frequency (21.8%) in Jamaica representing the second leading cause of admission following the painful crisis(18). A recent observation that the acute chest syndrome may be grossly under diagnosed by doctors implies that

chest radiograph should be performed routinely in the management of any febrile child with SCA(19).

The mean hemoglobin levels in the Baghdad, Mosul and Basrah studies were $(8.9 \pm 1.13, 7.7 \pm 1.95$ and $7.5 \pm 1.2)$ gm/dl respectively implying a worst hemoglobin profile in the Basrah cases.

The total number of re-admission and blood transfusions in our study was more (152 and 181 respectively) than the Mosul study (116 and 104 respectively) denoting variation in health resources, methods of diagnosis and treatment and possibility more frequent complications in the Basrah cases. For patients with disabling chronic pain, ischemic organ damage (acute chest priapism) or stroke, or in preparation for major surgery, blood transfusion of normal RBCs can provide symptomatic relief and prevent further ischemic complications. Packed RBCs transfusion are specifically for acute splenic sequestration and aplastic episodes(5,12).

The clinical spectrum of SCA in Basrah appeared to be of more sever than Mosul and Baghdad spectrum. The geographical location of Basrah in the south implying the presence of more than one hemoglobin haplotype together with possible complex interaction of sickle cell gene with other RBC genetic marker such as G₆PD deficiency and thalassemia and environmental factors are probable etiologies for worse disease tolerance in Basrah(20-23).

Decreased life expectancy is one of the original correlates of sickle cell disease. In contrast with the mean life-expectancy of 14.3 years posited by Diggs in 1973, the current survival is 42 years for men and 45 years for women with sickle cell anemia(24-30). This improved survival is more the result of better general medical care than of specific antisickling therapy. The effect of prophylactic penicillin therapy on preventing mortality from *S. pneumoniae* bacteremia is now influencing survival.

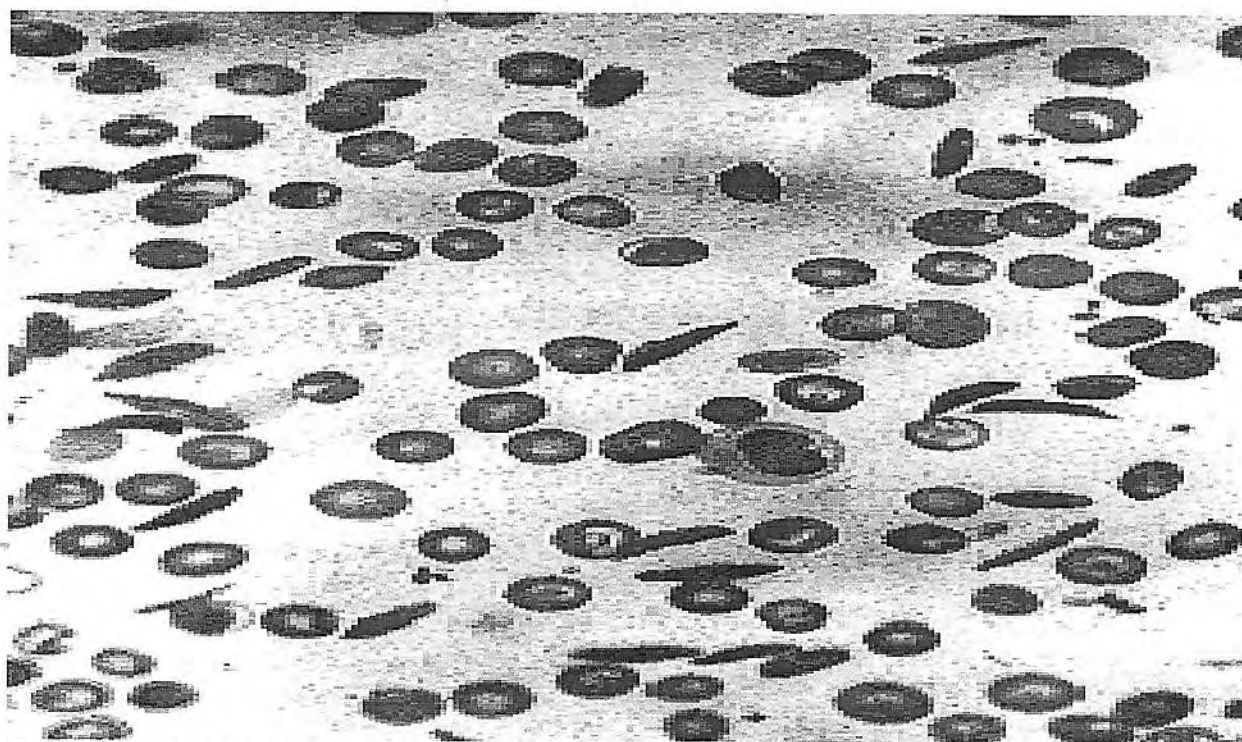
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Table 1: frequency distribution of deferent variables in the studied sample (n=202).

<i>Variable</i>	<i>Value</i>
Splenomegaly	202(50%)
Hepatomegaly	170 (42%)
Acute painful crisis	162(40)
Infection	122(30%)
Hypersplenism	81(20)
Aplastic crisis	40(10)
Hemolytic crisis	36(9)
Splenic sequestration	8(2%)
Mean hemoglobin level	7.5(1.2%)
Dactylitis	6(1.5%)
Total number of re-admissions	152
Total number of blood transfusions	181

**Fig.1. A peripheral blood smear showing the "peculiar elongated forms of the red corpuscles in a case of hemolytic crises.**

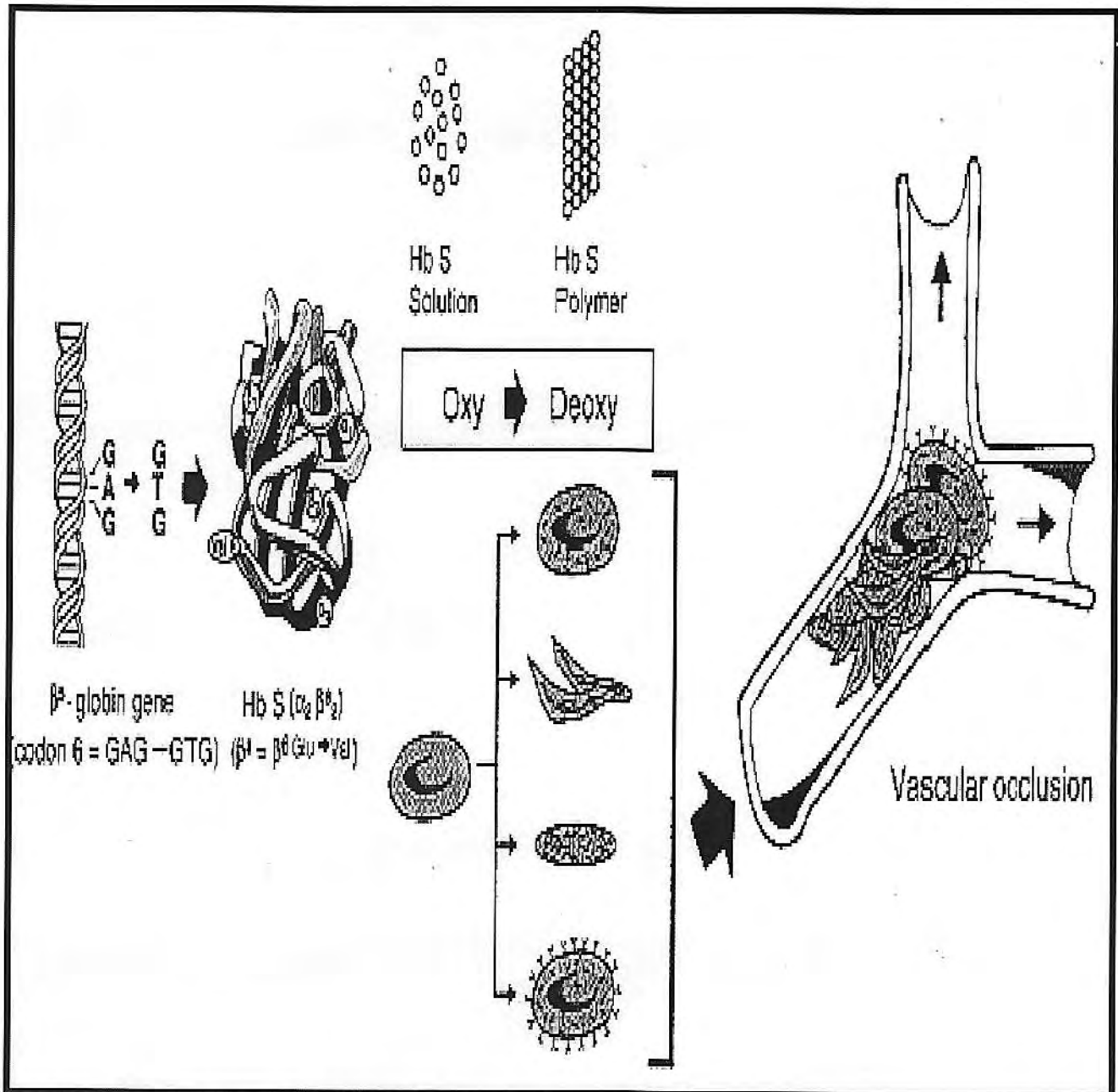


Fig. 2. Schematic view of the pathophysiology of sickle cell disease.

The double-stranded DNA molecule on the left represents a β -globin gene in which a GAG $\rightarrow$ GTG substitution in the sixth codon has created the sickle cell gene. The product of this gene is the β^A -globin variant in which valine is substituted for glutamic acid as the sixth amino acid. The mutant hemoglobin tetramer $\alpha_2\beta^S_2$ is Hb S, which loses solubility and polymerizes when deprived of oxygen. Upon deoxygenation most sickle cells accumulate polymer and lose deformability; some cells sickle; a fraction of cells become dehydrated, irreversibly sickled, and poorly deformable; and a few cells retain or accrue cytoadherence molecules on their surface. Dehydrated and highly adherent cells also may be generated by polymerization-independent processes. Vaso-occlusion, shown on the right, is initiated by adherent cells sticking to the vascular endothelium, thereby creating a nidus that traps rigid cells and facilitates polymerization.