Clinical Course of Patients With Sickle Cell Anemia and Co-inherited Hematological Disorders: Experience at a Tertiary Hematological Centre

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Abstract To study the clinical course of patients with sickle cell anemia and coinherited hematological disorders. Retrospective analysis of clinical data of patients enrolled at our hospital over last 7 years was performed. Eighty four patients of symptomatic sickling disorders were registered during this period, comprising of HbSS (n = 49), HbS- β thalassemia (n = 28), HbS-HbD disease (n = 5), HbS- β thalassemia with G6PD deficiency (n = 1) and HbS-hemophilia A (n = 1). Among HbS- β thalassemia, 18% suffered from occasional pain crises and 27% required occasional blood transfusion. 40% patients with HbS-HbD disease required occasional blood transfusions, one patient was transfusion dependent, while none suffered from crisis episodes. Patient with HbS- β thalassemia with G6PD deficiency had increased transfusion requirement during first 3 years of life, which decreased after that. Patient with HbS and severe hemophilia A had only one episode of severe bleeding, suffered from 1 crisis episode. In conclusion, HbA reduces severity of HbS in HbS- β + thalassemia. HbS-HbD disease can manifest as a transfusion dependent illness. HbSS reduces severity of G6PD deficiency after first few years of life. HbS and hemophilia coinheritance ameliorates symptoms of hemophilia.

Keywords Sickle cell anemia · Hemoglobinopathies · Hematological disorders

Introduction

Sickle cell anemia is one of the commonest hemoglobinopathy worldwide. Possession of a single HbS gene (AS state) results in the asymptomatic sickle cell trait, while homozygous HbSS disease is often a severe condition leading to rapid red cell hemolysis and sickling of red blood cells leading to blockage of flow in blood vessels with painful and often serious complications [1]. The varied clinical features occur because of vaso-occlusive crisis, hemolytic crisis or aplastic crisis. Clinical course varies among patients; some may have major problems during their lifetime requiring multiple hospitalizations while others may have less severe course. Several hematological disorders have interaction with sickle cell anemia and can affect the clinical course of the illness. There is a dearth of literature on clinical course of patients with these symptomatic sickling disorders.

Aim

This study was performed to observe the clinical course and impact of coexistent hemoglobinopathies and other hematological disorders on patients with symptomatic sickling disorders at our centre.

Methods

Retrospective analysis of medical records of patients diagnosed over a period of 7 years was performed (2011–2017). All these patients were diagnosed as symptomatic sickling disorders by sickling test and high performance liquid chromatography (HPLC). Parental studies

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were done to identify double and compound heterozygotes. Medical records were analysed for age and mode of presentation, clinical features, transfusion requirements, crises episodes and other complications during follow up.

Results

Out of 84 patients with symptomatic sickling disorders, 49 patients were HbSS homozygous, 28 patients had HbS- β thalassemia, 5 patients had HbS-HbD disease, 1 patient suffered from HbS- β thalassemia with G6PD deficiency and 1 patient had HbSS with hemophilia. Details of the cases are mentioned in Table 1.

Discussion

The substitution of valine for glutamic acid on the surface of the variant β -globin chain allows HbS to polymerise when deoxygenated—the primary event in all sickle cell pathology. The polymer is a rope-like fibre that aligns with others to form a bundle, distorting the red cell into characteristic sickled forms [2]. Polymerisation is dependent on intra-erythrocytic HbS concentration, the degree of hemoglobin deoxygenation, pH and the intracellular concentration of HbF. It is a highly complex process that results in the formation of gelled, aggregated HbS tetramers. The kinetics of HbS polymerization can be explained by double-nucleation mechanism. The result of this double nucleation mechanism is a measurable “delay time”, the time between initiation of polymerization and exponential rise in polymer formation.

HbA and HbF have a profound, dose related effect in which delay time is increased and the HbS polymer content in cells is decreased. The effect of HbF is considerably greater than the effect of HbA. HbA and HbF also increase the solubility of HbS, with HbF being more effective than HbA [2].

Platt et al. [3] showed that increment in HbF above 4% was associated with reduced pain crises and HbF levels greater than 9% were associated with decreased mortality. This effect of HbF on HbS polymerization has been utilized in the role of hydroxyurea and other agents that increase HbF. Hydroxyurea has shown efficacy in increasing HbF levels and consequently reducing the number of painful crises, acute chest syndrome, transfusions, and hospitalizations [4].

HbS- β Thalassemia

The clinical severity of patients heterozygous for HbS and β -thalassemia depends on the output of the thalassemic β

gene. Cases with HbS- β thalassemia can be either HbS- β^+ thalassemia or HbS- β^0 thalassemia. In HbS- β^+ thalassemia, there is 20–30% of HbA, which increases the delay time and reduces polymerization of HbS, thereby reducing sickling. Thus, these patients have a milder clinical course. Whereas in HbS- β^0 thalassemia, there is complete absence of HbA. These patients suffer from a severe clinical course, similar to those with HbSS disease [2]. In our cohort, all patients had HbS- β^+ thalassemia and had a mild clinical course.

HbS-HbD Disease

HbD^{Punjab} variant is derived from a point mutation in the first base of codon 121 (GAA → CAA) with the substitution of glutamine for glutamic acid (Glu > Gln) in the β -globin chain. It is prevalent in Punjab region, Northwest India, with an estimated frequency of 2.0%. HbA-HbD^{Punjab} (HbD trait) presents no clinical or hematological alterations. Homozygous HbDD, the rarest form of inheritance, is not commonly symptomatic, but occasionally individuals can develop mild to moderate hemolytic anemia [5].

Patel et al. [6] observed greater vulnerability for red cell lysis in HbS-HbD^{Punjab} patients than with the HbSS state. They also noted reduction in the incidence of vaso-occlusion and frequency of blood transfusions in these patients using low dose hydroxyurea. Clinical severity of HbS-HbD^{Punjab} could be related to the fact that HbD favors polymerization of HbS [7].

At our hospital, three patients required blood transfusions and one patient was transfusion dependent. None of the patients suffered from any episode of crisis. This finding could be due to their recent diagnosis and relatively short period of follow up of these patients.

HbS- β Thalassemia With G6PD Deficiency

Both HbS and G6PD deficiency confer partial protection against malaria and have therefore been selected in geographic areas where malaria is endemic [8]. The prevalences of both diseases are highest in sub-Saharan Africa, Arabian Peninsula, and central India [9].

Benkerrou et al. [10] showed that G6PD deficiency in babies with HbSS could worsen the chronic anemia, increase the risk of acute clinical events, and increase blood transfusion requirements during the first 2 years of life. The deleterious effects of concomitant G6PD deficiency tended to lessen after 2 years of age. One hypothesis could be that the decline in fetal haemoglobin levels leads to increased sickle cell hemolysis and reduced red cell life span [10, 13, 14]. Thus, with time, older HbSS patients have relatively younger red cells, which would have higher

Table 1 Description of cases

Disease association	HbS- β thalassemia	HbS-HbD disease	HbS- β thalassemia with G6PD deficiency	HbSS with hemophilia
No. of patients	28 (11 on follow up)	5	1	1
Male:female ratio	18:10	3:2	1 (male)	1 (male)
Period of follow-up	10 months to 6 years	6 months to 1.5 years	14 years	13 years
Presentation	Anemia, hepatosplenomegaly	Age at presentation: 8 months to 6 years	At 13 months: fever, jaundice, hemoglobinuria and hepatosplenomegaly. Investigations revealed vivax malaria, routine evaluation revealed G6PD deficiency. Peripheral smear suggestive of sickle cells, hence confirmed on HPLC	Known case of Hemophilia A, presented with fever, chest pain, anemia at 7 years of age
Treatment received	Special vaccines, Hydroxyurea, folic acid supplementation, penicillin prophylaxis	> Anemia with hepatosplenomegaly (3/5) > Recurrent jaundice for 2 years starting at 6 years of age (1/5) > Incidental finding of anemia with mild splenomegaly (1/5)	Special vaccines, Hydroxyurea, folic acid supplementation, penicillin prophylaxis	Special vaccines, Hydroxyurea, folic acid supplementation, penicillin prophylaxis
No. of crisis episodes	2/11 (18%) suffered from 1 and 2 episodes of pain crisis each	Nil	Four episodes of pain crisis, 2 each at 4 years and 8 years of age, 1 episode of hemolytic crisis at 8 years and 2 episodes of sequestration crisis at 10 years and 11 years of age	One episodes of dactylitis at 9 years of age
Blood transfusion requirements	3/11 patients (27%) required occasional blood transfusions. However, none of them were transfusion dependent	3/5 patients required blood transfusions; of these two patients required occasional transfusions, one patient was transfusion dependent	Required regular transfusions every 2–3 months till 3 years of age. Later on, blood transfusion requirements decreased to 1–2 times per year	Once—at diagnosis
Other complications	None			One episode of joint swelling, requiring factor VIII transfusion at the age of 6 years

G6PD activity and would therefore be less susceptible to oxidative stress exposure.

Another study by Baffour et al. [11] found significant difference between the hemoglobin concentration of patients having G6PD deficiency and those with normal G6PD activity. Simporé et al. [12] however, did not detect a significant difference for counts of erythrocytes, leucocytes and reticulocytes, hemoglobin level and annual vaso-occlusive attacks between persons with HbSS having G6PD deficiency and those with normal G6PD activity. They concluded that G6PD deficiency does not seem to increase the severity of HbSS.

In our patient, G6PD deficiency worsened anemia and increased transfusion requirements in first few years of life. Afterwards, patient continued to have a relatively severe course with multiple crises. However, transfusion requirements decreased in the later years.

HbSS with Hemophilia

Hemophilia A is an X-linked recessive bleeding disorder due to deficiency in anti-hemophilic factor A (factor VIII). Coexistence of HbSS and hemophilia is an uncommon association and it is rarely described in literature. Glenn

et al. [15] reported the concurrence of hemophilia A and HbSS in a 30-year-old black male. The second case was a combination of HbSS and hemophilia B, it was described in a 15-year-old African-American male [16]. Another case was a coinheritance of HbS β -thalassemia and hemophilia A in a 19-year-old male in India [17]. Maataoui et al. [18] reported the case of two brothers from Morocco with concomitant sickle cell trait and major haemophilia A.

HbSS is a hypercoagulable state due to platelet activation and generation of intravascular thrombi. Low plasma levels of protein S, protein C, and antithrombin; elevated plasma levels of thrombin-antithrombin (TAT) complexes, prothrombin fragment 1 + 2 (F1 + 2), D-dimer complexes, and circulating antiphospholipid antibodies; platelet activation during vaso-occlusive crises; abnormal external exposure of phosphatidylserine (PS) and adherence of sickle erythrocytes to the vascular endothelium; reduced nitric oxide levels in the presence of hemolytic anemia; and increased tissue factor expression have been detected in HbSS patients. All these factors lead to a prothrombotic state in patients with HbSS [19].

In our patient, although the patient had severe hemophilia, significant bleeding complications did not occur. In the rare event of co-existence of HbSS with haemophilia, it is hypothesized that a balance occurs between the prothrombotic and hemorrhagic tendencies respectively, thus reducing the bleeding episodes and its complications.

In conclusion, HbA reduces severity of HbS in HbS- β^+ thalassemia. HbD increases polymerization of HbS and HbS-HbD manifests like HbSS disease. HbS-HbD disease can manifest as a transfusion dependent illness. HbS reduces severity of G6PD deficiency after first few years of life. HbSS and hemophilia coinheritance ameliorates symptoms of hemophilia.

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