International Journal of Medicine and Medical Science Research Vol. 2(1), pp. 001-006, February 2014
Available online at http://academeresearchjournals.org/journal/ijmmsr
ISSN 2331-1819 ©2014 Academe Research Journals

Full Length Research Paper

Hematological indicators of priapism in sickle cell disease in rural India

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Accepted 11 February, 2014

The sickle cell disorder is a common disabling disease that profoundly affects human morbidity, mortality and quality of life. Priapism in sickle cell disease is a condition that causes sustained, painful, and unwanted erection of the penis in boys or men without any sexual stimulation. Sickled cells are short lived and can cause vaso-occlusive crisis in affected persons. A few case reports have shown the rare occurrence of priapism in sickle cell disease in India. This hospital based study showed around 2.97% prevalence of priapism in cases suffering from sickle cell disease in a tertiary hospital at Jabalpur in Madhya Pradesh of Central India. The present study reports the lower fetal hemoglobin (mean, 8.5%) in two of the three cases, and elevated serum bilirubin level (mean, 4.4 mg/dl) and higher platelet (mean, 351.7 m/mm3) and reticulocyte (mean, 8.7%) counts of all patients studied with priapism in sickle cell disease, indicating erythropoietic imbalance. It is a common practice in India that any problem related to sex or sex organs is intentionally not disclosed (kept secret) to elderly family members because of shyness or psycho-social implications or due to a stigma attached to it. It is rarely brought to the notice of a medical doctor. This is due to utter lack of sex education that results in deteriorated health complications in rural areas of the state. Priapism in sickle cell disease is a pathological condition of penile erection and recovery of erectile function is dependent on prompt counseling and urgent intervention. Priapism should be considered as a medical and surgical emergency and efforts should be made to educate both professionals and vulnerable population as well.

Key words: Priapism, sickle cell disease, prevalence, sex education, ischemic, stuttering.

INTRODUCTION

Sickle cell anemia is a common disabling disorder profoundly affecting human morbidity, mortality and quality of life. The sickle cell disease (SCD) is an autosomal recessively inherited condition caused by a point mutation in the β-globin gene, resulting in the substitution of valine for glutamic acid at position 6 of the β-globin chain ($Glu^{6}Val$). This mutation results in the abnormal sickle hemoglobin (HbS) which is when deoxygenated, polymerizes damaging the sickle erythrocyte. Sickling is dependent on multiple variables including hemoglobin concentration and hydration status, pH and degree of deoxygenation. Sickling is more common in vascular beds with low-flow states including the splenic sinusoids, the bone marrow, and the penile corpora during an erection, or in any inflamed tissue. The combined influence of these factors can result in a vicious cycle of inflammation, hypoxia, and acidosis resulting in increased sickling, vessel occlusion, and ischemia. Priapism is a patho-physiologically sustained, painful, and unwanted erection of the penis due to either increased arterial inflow (that is, high flow) or more commonly, the failure of venous outflow (that is, low flow) resulting in blood trapping within the erectile bodies. Although uncommon in the general population, priapism was recognized as a serious complication of the SCD as early as 1934 (Obendorf, 1934). Since then, many researchers have estimated its incidence/prevalence including various treatment choices in different populations.

The penile erection normally occurs in response to

physical or psychological stimulation. This stimulation causes certain blood vessels to relax and expand, increasing blood flow to spongy tissues in the penis. Blood vessels, that control the flow of blood out of the penis, contract and result in trapping of blood. Consequently, the blood-filled penis becomes erect. After stimulation ends, the blood flows out, and the penis returns to its non-rigid (flaccid) state or detumescence. Priapism probably results from abnormalities of the blood vessels and nerves that cause blood to become trapped in the erectile tissue (corpora cavernosa) of the penis. Thus, priapism occurs when some part of this system - the blood, blood vessels or nerves - changes normal blood flow. Subsequently, an unwanted erection persists. There are several factors that can contribute to priapism or to erectile dysfunction or impotence.

The average allele frequency of the sickle cell disorder has been observed to be 4.3% in India (Balgir, 1996). The prevalence has been recorded to be high among some tribes, castes, other backward castes as well as among some general caste people of central India (Balgir, 2011a). Sickle cell anemia, one of the most common causes of priapism, is an inherited disorder characterized by abnormally shaped red blood cells. These abnormally shaped cells can block the flow of blood and cause priapism.

Considering the embarrassing nature of the problem and the dire consequences to erectile function, it is important to inform patients, parents, and health providers about the relationship of SCD to prolonged painful erections. Ideally, patients at high risk for the development of such episodes would be identified early to increase education of the risks of prolonged priapism and to institute potential prophylactic strategies. Increased awareness of the signs of priapism and educational need for early treatment may be the best way to prevent long term sequelae.

The occurrence of priapism since time immemorial is not uncommon in India. It is widely encountered all over the country (Kar et al., 1986; Balgir, 2007). It is a common practice in India that any problem related to sex or sex organs is intentionally kept hidden because of shyness or psycho-social implications or due to a stigma attached to it. It is not common to bring to the notice of elderly members of the family or to a medical doctor. Further, there is utter lack of sex education in India, resulting in deterioration of health related complications. The case of priapism especially its occurrence in sickle cell disease is one of such examples. This article emphasizes the need of imparting sex education to rural masses especially associated with the sickle cell disease in India.

MATERIALS AND METHODS

This study was a part of a major research project undertaken on ‘Reproductive Outcome in Carrier Couples of Hemoglobinopathies in a Tertiary Hospital in Central India.’ Ethical approval of this project was obtained from the Human Ethical Committee, Regional Medical Research Centre for Tribals (RMRCT), under Indian Council of Medical Research, Jabalpur. A total of 1,279 subjects suspected to have anemia and/or hemoglobinopathies referred from a tertiary hospital, Netaji Subhash Chandra Bose Medical College and Hospital, Jabalpur in Central India were screened for different hemoglobinopathies during the period from March 2010 to December 2012.

About 2-3 ml of peripheral blood was intravenously taken under aseptical conditions of disposable syringes and needles using disodium salt of ethylene diamine tetra acetic acid (EDTA) as anticoagulant from each individual after taking informed/written consent and was free of blood transfusion at least one month prior to screening for hemoglobinopathies. Blood samples were transported to laboratory at RMRCT, Jabalpur under wet-cold conditions for analysis. All the adopted procedures and techniques standardized in the laboratory were followed for diagnosis as described elsewhere (Balgir, 2011a, b; Dacie and Lewis, 1991). Hematological indices were measured using $MS_5$9 Hematological Analyzer (Melet and Schloesing Laboratories, Cergy-Pontoise Cedex, France). Laboratory investigations were carried out following standard procedures. For quality control, results were cross-checked periodically. Some blood samples of doubtful cases were further subjected to confirmation by hemoglobin variant analysis (Bio-Rad Diagnostics Group, Hercules, California, USA). Family studies were carried out to confirm the diagnosis of sickle cell disease and differentiate it from sickle cell-β-thalassemia/hemoglobin D disease, whenever it was felt necessary.

RESULTS AND DISCUSSION

The first reported case of priapism in patient with homozygous sickle cell disease was presented to the New York Society for Clinical Psychiatry as a ‘castration fear complex’ in 1932 (Obendorf 1934), although Diggs and Ching (1934) were the pioneer to recognize the association with sickle cell disease. Subsequently, the priapism was recognized as a complication of sickle cell disease in various reports and reviews (Hasen and Raines, 1962). Of the precipitating factors, the priapism may follow sexual intercourse (Krauss and Fitzpatrick, 1961), masturbation (Karayalcin et al., 1972), and alcohol ingestion (Conrad et al., 1980), and drugs (Kassim et al., 2000). Other causes of priapism already reported are: spontaneous nocturnal erections, night dreaming, night stuttering attacks, which cease during painful crises, but resume after resolution of the pains.

In the present hospital based study, out of the total of 1,279 subjects screened, 101 (7.9%) had homozygous sickle cell disease. Three of these (2.97%) presented priapism. These patients belong to adjoining rural areas

Table 1. A comparative study of hematological parameters and other features in cases with priapism in sickle cell disease in Madhya Pradesh, India.

Salient features	Normal range	Patient-1	Patient-2	Patient-3	Patient*	Patient*
Caste	-	Katiya (Scheduled Caste)	Gond (Scheduled Tribe)	Jharia (Scheduled Caste)	-	-
District	-	Balaghat	Jabalpur	Narsinghpur	-	-
Age (in years)	-	24	22	23	24	23
Hb (g/dl)	12-18	9.7	9.9	6.9	7.8	12.2
RBC(m/mm3)	4-5.9	4.5	3.9	2.1	-	-
MCV (fl)	83-98	76.9	78.2	100.5	80	82
HCT (%)	35-54	34.7	30.5	20.3	-	-
MCH (pg)	25-33	21.5	25.3	34.1	-	-
MCHC (g/dl)	28-40	28.0	32.4	33.9	31	30
RDW (%)	8-15.5	14.0	13.8	13.8	-	-
WBC(m/mm3)	3-14	5.1	11.7	4.6	-	-
PLT (m/mm3)	150-450	309	391	355	-	-
Hb F (%)	<2.0	16.4	6.3	2.7	5.8	22.8
Reticulocyte count (%)	3-5	6.9	9.5	9.7	26	11.5
Total serum bilirubin	1-2.5 mg/dl	5.4 mg/dl	3.5 mg/dl	4.2 mg/dl	3.4 mg/dl	2.5 mg/dl
Type of priapism	-	Ischemic	Stuttering	Ischemic	-	-
Treatment	-	Penis blood aspiration	Phenylephrine (Medication)	Glucose drip and hydration	-	-
Red cell morphology	-	Hypochromia	Microcytosis, Normochromia	Macrocytosis, Hemolytic Anemia	-	-

of Jabalpur town in Central India. A summary of most relevant hematological findings and other features of three cases of priapism are presented in Table 1.

A comparison of hematological characteristic features in patients with and without a history of priapism revealed that the priapism group has lower fetal hemoglobin levels and higher platelet counts (Emond et al., 1980). The results of the present study also support these findings. The Indian sickle cell disease patients, in general, present with higher level of fetal hemoglobin as high as 37% (Balgir 1995), but under abnormal situation, it may be reduced to lower level. Other studies have also shown associated risk for priapism in hemolytic diseases. Lactate dehydrogenase (LDH), bilirubin and reticulocyte count were all elevated in men with SCD who experienced priapism compared with men with SCD who had rarely experienced an episode of priapism (Nolan et al., 2005). The findings of the present study are consistent with those of previous studies (Emond et al., 1980; Kar and Dash, 2000; Nolan et al., 2005) that reported lower fetal hemoglobin (mean, 8.5%) in two of the three cases, elevated serum bilirubin level (mean, 4.4 mg/dl), and higher platelet (mean, 351.7 m/mm3) and reticulocyte (mean, 8.7%) counts of patients with priapism in sickle cell disease, indicating erythropoietic imbalance.

Sickle cell anemia is the most common cause of priapism in boys. There is a wide age range of onset of priapism but involvement in childhood under the age of 18 years is common in sickle cell disease (Winter and McDowell, 1988). Priapism appears to be rare among Indian and Eastern Province of Saudi Arabians, even when they are directly asked (Al-Awamy et al., 1985; Kar et al., 1986; Padmos et al., 1991). Priapism is an uncommon condition that needs immediate medical attention. Prompt treatment for priapism is usually needed to prevent tissue

Table 1. Cont'd

Clinical features	-	Pallor, Abdominal and Joint pains, H/o jaundice, Hepatomegaly (3-4cm), Splenomegaly (5-6 cm), Occasional epistaxis, Retarded growth and development, Premature cataract, H/o Blood trans-fusion, Painful priapism, Pains during urination, Bended Penis.	Pallor, Abdominal pains, Body ache, Bony or joint pains	Fatigue, Pallor, H/o Jaundice, Joint pains, Splenomegaly (3-5 cm)	Asymptom atic with fever, Abdominal pains, Severe painful erection	Enlarged swollen and soft penis

*Data from: Dash and Kar (2000).

damage that results in the inability of the penis to become or stay erect with sexual arousal (erectile dysfunction). Priapism is most common in boys between ages 5 and 10 years old and in men from ages 20 to 50 years (Serjeant and Serjeant, 2001). In this study's series, the age of patients was 22, 23 and 24 years.

Priapism is a full or partial erection that persists more than 4 h. There are three kinds of priapism: ischemic priapism (veno-occlusive, low flow), stuttering priapism (recurrent ischemic priapism), and non-ischemic priapism (arterial, high flow). Ischemic priapism is a vaso-occlusive complication of SCD. It is a urologic emergency that when untreated it can result in corporal fibrosis and erectile dysfunction. If one has an erection lasting more than four hours, one needs emergency care. The emergency room doctor will determine first whether one has ischemic priapism or non-ischemic priapism. This is necessary because the treatment for each is different, and treatment for ischemic priapism needs to be done as soon as possible. The answers to questions, a physical examination and a blood test are usually enough to determine what type of priapism one has. One will undergo additional tests to determine the underlying cause of priapism, which may need to be treated, usually in a nonemergency setting. Ischemic priapism - the result of blood not being able to exit the penis - is an emergency situation that requires immediate treatment.

The vascular mechanism of priapism in sickle cell disease is predominantly ischemic type or low flow. The occlusion of the outflow vessels from the corpora cavernosa is most likely by sickled cells. The aspiration of the static reservoirs of the corpora yields a thick, dark-red, viscous fluid (Rosokoff and Brodie, 1946; Gillenwater et al., 1968) consisting of sickled cells (Diggs, 1965). Priapism in homozygous sickle cell disease is of low-flow ischemic type, although high-flow priapism occurs and one case was treated by selective embolization of the cavernous and dorsal penile arteries (Ramos et al., 1995). The mechanism of high-flow priapism in sickle cell disease is still unclear.

Priapism in sickle cell disease typically affects only the corpora cavernosa and spares the corpus spongiosum. Two different patterns are observed: stuttering and major attacks (Emond et al., 1980; Fowler et al., 1991). Stuttering attacks are typically brief (< 3 h), nocturnal, recurrent, and are associated with normal intervening sexual function. They may act as a prodrome and are found to proceed to major attacks. Stuttering attacks may cause a loss of sleep and daytime

sleepiness. Relief from stuttering episodes is most commonly sought by gentle exercise such as walking or cycling, ice or cold water directly applied to the penis, drinking cold water, passing urine, or by taking cold showers (Emond et al., 1980; Fowler et al., 1991).

Major attacks usually exceed 24 h, do not recur, and are generally followed by impotence, although the prognosis is better in patients aged less than 15 years (Emond et al., 1980; Sharpsteen et al., 1993; Chakrabarty et al., 1996). Prompt recognition and appropriate treatment of a priapism episode in males with sickle cell disease is critical as the end result of prolonged and/or repeated episodes of priapism can be ischemia and fibrosis in the corpus cavernosa of the penis, potentially leading to impaired sexual function and impotence. They are characterized by extremely severe penis pain which may persist for several days. Pain may also occur in the lower abdomen and perianal region, and may be associated with dysuria (Erman and Bloomberg, 1960; Fowler et al., 1991), acute urinary retention (Sawan and Cawley, 1947; Grace and Winter, 1968; Seeler, 1973; Noe et al., 1981), penile and/or scrotal edema (Arduino, 1954; Baron and Leiter, 1978) and a large, boggy, tender prostate (Nolan et al., 2005). After a major attack, further episodes of either stuttering or major forms are mostly unusual.

Thus, the priapism in sickle cell disease is under reported in India due to several confounding factors although it is an emergency condition and needs immediate attention, medication, relief and treatment.

Conclusions

Priapism in sickle cell disease is a pathological condition of penile erection that persists beyond four hours or is unrelated to sexual stimulation. Clinically and pathologically, two subtypes are seen - the high flow (non-ischemic) variety and the low flow (ischemic) priapism. The low flow type is more dangerous as these patients are susceptible to greater complications and the long term recovery of erectile function is dependent on prompt and urgent intervention. The present study reports the lower fetal hemoglobin, elevated serum bilirubin level, and higher platelet and reticulocyte counts of patients with priapism in sickle cell disease. As such, priapism should be considered as a medical and surgical emergency. Moreover, the priapism in sickle cell disease is not uncommon in India but under reported due to poverty, ignorance, shyness, and psycho-social factors.

ACKNOWLEDGEMENTS

The author is grateful to Dr. V. M. Katoch, Secretary, Department of Health Research, Government of India, and Director General, Indian Council of Medical Research, New Delhi for the permission and provision of the necessary research facilities. He is also grateful to the patients for their kind cooperation in the study.

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