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## ORIGINAL ARTICLE

## Priapism, an Emerging Complication in $\beta$ -Thalassemia Intermedia Patients

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### Abstract

The increase in survival rate of  $\beta$ -thalassemia ( $\beta$ -thal) patients allowed for the appearance and manifestation of several complications in almost every organ system. Priapism in  $\beta$ -thal patients is rarely reported in the literature. We herein report and investigate the occurrence of two cases of priapism in two young patients with  $\beta$ -thal intermedia ( $\beta$ -TI). The potential mechanisms are due to either a cellular mechanism involving a thrombus obstructing the efferent venules of the corpora cavernosa leading to priapism, or a recently elucidated functional mechanism that causes alteration of nitric oxide (NO) response of the penis, ultimately causing priapism. This should incite clinicians for a close follow-up and monitoring of high risk patients who are susceptible to developing priapism.

### Keywords

$\beta$ -Thalassemia intermedia ( $\beta$ -TI), hypercoagulability, nitric oxide (NO), priapism

### History

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Priapism is a urological emergency that is defined as a persistent penile erection that lasts more than 4 hours. Hematological factors account for 20.0% of the causes of priapism (1) and include hyperviscosity syndromes, amyloidosis, sickle cell disease and hypercoagulable status. The thalassemia spectrum is wide, on the one hand comprising  $\beta$ -thalassemia ( $\beta$ -thal) minor that consists of a mild hypochromic microcytic anemia with no obvious clinical manifestations, while on the other hand,  $\beta$ -thal major ( $\beta$ -TM), characterized in patients who present in their first years of life with profound anemia and regular transfusion requirements for survival (2). Despite the considerable knowledge gained from research about  $\beta$ -thal intermedia ( $\beta$ -TI) in the past few years, diagnosis remains to be made on clinical grounds.

The wide clinical spectrum of  $\beta$ -TI entails a wide range of clinical presentations. Some patients remain asymptomatic for most of their lives with hemoglobin (Hb) levels ranging between 7.0 and 10.0 g/dL, while others will present during their childhood years and require transfusions for normal sustained growth (3). The hallmarks of  $\beta$ -TI are ineffective

erythropoiesis, chronic hemolytic anemia and iron overload, which in turn causes clinical complications affecting almost every organ system (4). We herein describe two  $\beta$ -TI patients who suffered from recurrent episodes of long term stuttering priapism.

We investigate two young patients with  $\beta$ -TI who developed long lasting stuttering priapism (patient A is 30 years old and patient B is 35 years old). They both underwent splenectomy, and are mainly transfusion independent. Both patients were on deferasirox (DFX) therapy. They both had a medical history consisting of symptomatic gallstones that required cholecystectomy. Patient B developed extramedullary hematopoiesis and osteoporosis, while patient A had no evidence of extramedullary hematopoiesis and osteoporosis as well as no leg ulcers, pulmonary hypertension, thromboembolic events, abnormal liver enzymes or endocrinopathies; these latter complications were also not present in patient B. The patients reported a 1-month history of recurrent painful episodes of long lasting stuttering priapism occurring at night and lasting around 3–5 hours each. They were unrelated to sexual intercourse, use of over the counter (or illicit drugs), or any trauma to the genital, pelvic or perineal areas, and did not require any corpora blood aspiration or sympathomimetic agents irrigation. A urological consultation was requested and did not show any structural abnormalities. The laboratory data are shown in Table 1. Patient A was started on Actifed (which contains phenylephrine, an  $\alpha$ 1 adrenergic receptor agonist) 60 mg daily at bedtime, while patient B started receiving 3 drops of the  $\beta$  blocker, cloridrate propanolol daily.

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Table 1. Patients' characteristics.

Parameters	Patient 1 Ref. 5	Patient 2 Ref. 9	Patient 3 Ref. 6	Patient 4 Ref. 7	Patient 5 Ref. 8	Patient 6 Ref. 10	Patient 7 Ref. 11	Patient A This Study	Patient B This Study
Sex-Age	M-15	M-25	M-28	M-40	M-19	M-15	M-32	M-30	M-35
Diagnosis	$\beta$ -TI	Hb H disease	$\beta$ -TI	$\beta$ -TI	$\beta$ -TI	$\beta$ -TM	Hb E/ $\beta$ -thal Compound	$\beta$ -TI	$\beta$ -TI
$\beta$ Mutations	NA	NA	NA	NA	NA	NA	heterozygote for IVS-I-5(G>C)/ codon 26(G>A)	IVS-I-6(T>C)/ IVS-II-1(G>A)	Codon 39(C>T)/ IVS-I-6(T>C)
Hb Electrophoresis (%)	Hb F: 70.0	Hb H: 85.0	Hb F: 85.0	NA	NA	Hb A: 34.8 Hb A <sub>2</sub> : 2.6 Hb F: 62.6	Hb E + A <sub>2</sub> : 46.2 Hb F: 42.2 Hb A: 6.7 Hb S, Hb C, Hb D-Punjab: 0.0 Unidentified peak at 4.6	Hb F: 61.3 Hb A: 35.2 Hb A <sub>2</sub> : 3.5	Hb F: 63.0 Hb A: 33.3 Hb A <sub>2</sub> : 3.7
Transfusion (yes/no)/ frequency	Yes irregular	Yes chronic transfusions for 5 years	Yes sporadic	Yes irregular	Yes irregular	Yes regular until 5 years ago	No	No	Yes sporadic (three times during surgery)
Hb (g/dL)	10.2	11.9	10.0	10.0	NA	10.0	10.6	9.2	7.0
Serum ferritin (ng/mL)	NA	NA	NA	1200.0	NA	696.0	NA	3158.0	750.0
LJC (mg/g dry weight)	NA	NA	NA	NA	NA	NA	NA	12.9	7.24
Chelation therapy (yes/no)	No	No	No	Yes	No	No	No	No	Yes
Splenectomized (yes/no)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Medication	None	None	None	Anti platelet, not specified	None	None	None	Folic acid	HU, DFX, cholecalciferol, folic acid

$\beta$ -TI:  $\beta$ -thal intermedia;  $\beta$ -TM:  $\beta$ -thal major; NA: not available; Hb S (HBB: c.20A>T), Hb C (HBB: c.19G>A), Hb D-Punjab (HBB: c.364G>C); Hb: hemoglobin; LJC: liver iron concentration; HU: hydroxyurea; DFX: deferasorix.

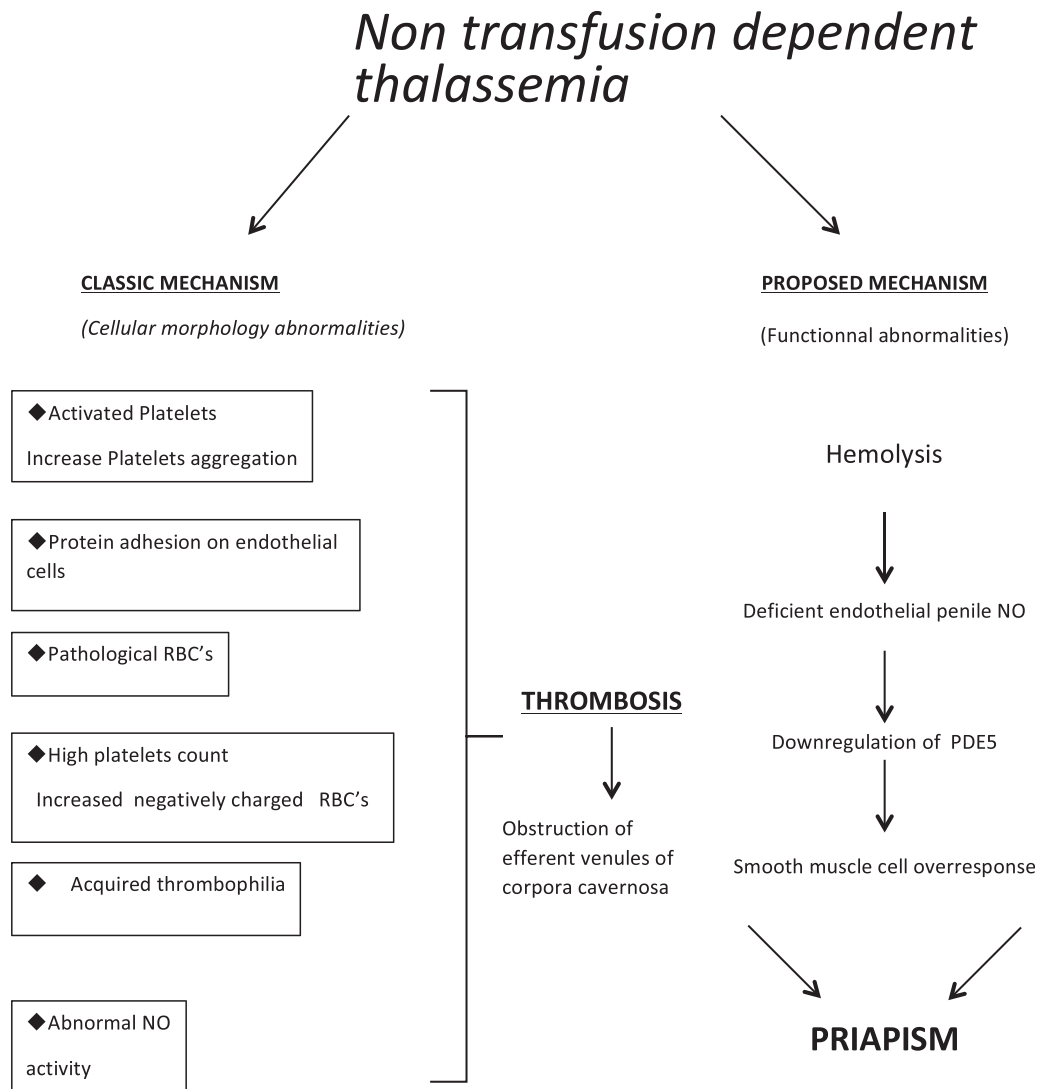


Figure 1. Potential mechanisms of priapism. Nitric oxide (NO), Phosphodiesterase type 5 inhibitor (PDE5i), Red blood cell (RBC).

Improvement was obvious for both patients, as patient B stopped his treatment. However, patient A recently developed a new episode of priapism. He was thus switched from Actifed to propanolol 40 mg daily at bedtime. Patient A was followed once a week, while patient B once every month, and they both did not report any episode of priapism on normal erection.

A handful of cases of priapism due to thalassemia (5–11) have been reported in the past three decades. The absence of predisposing factors and lack of underlying history makes a causal relationship between priapism and  $\beta$ -TI in our patients likely. Elevation of blood viscosity demonstrated by the elevated nucleated red blood count (NRBC) and thrombocytosis, as well as intravascular stasis in  $\beta$ -TI patients can obstruct the efferent venules of the corpora cavernosa that will promote sludging within the corpora, causing fibrosis and damage to the erectile mechanism (4).

Priapism is a rare variety of thromboembolic disease. The elevated NRBC and platelet count in our splenectomized patients make them more prone to developing a thromboembolic event (TEE). Furthermore, high NRBC and platelet counts as well as transfusion naïvety are associated with earlier development of TEE following splenectomy (12). It is

worth noting that splenectomized  $\beta$ -TI patients have significantly higher rates of complications compared to non splenectomized  $\beta$ -TI patients. They are more susceptible to thrombosis due to the presence of high platelet count and aggregation after splenectomy, and to the increased number of red blood cells (RBCs), with negatively charged membranes carrying a thrombogenic potential (13).

Hypercoagulability in non transfusion-dependent thalassemia (NTDT) is multifactorial, as it has been attributed to abnormalities in platelets and deformed RBCs. There are also several factors that are believed to be involved in thromboembolic events in this group of patients (14–17). Our patients, being splenectomized, having an elevated NRBC and platelet count, as well as being mainly transfusion naïve, are considered high risk patients and could have been developing intravascular thrombosis causing obstruction of the efferent venules of the corpora cavernosa leading to priapism. A plausible mechanism that leads to the occurrence of priapism is demonstrated in Figure 1.

Transfusion could be initiated, as transfusion therapy was shown to be protective against thrombotic events (13). Additionally, low doses of hydroxyurea (HU) not only

induces fetal Hb (Hb F), but may also improve the risk of thrombotic events through effects on phosphatidylserine externalization in the RBC (18). Therefore, iron chelation therapy, a transfusion regimen, Hb F inducers, as well as long term follow-up, are all appropriate in order to ensure less clinical comorbidities and priapism recurrence.

Recently, the validity of the mechanism of priapism consisting of venous occlusion of the corpora cavernosa has been debated (19). It has been suggested that the mechanism of priapism involves phosphodiesterase type 5 inhibitors (PDE5i) down regulation, which results from abnormal nitric oxide (NO) activity in the penis altering molecular determinants of the erectile response (8). Nitric oxide hemostasis is disturbed in the hemolytic state of  $\beta$ -thal; this will consume NO, leading to vasoconstriction (14). The mechanism of recurrent priapism as explained by Tzortiz *et al.* (8) is illustrated in Figure 1.

According to Olujohungbe *et al.* (20), pharmacological management of priapism in sickle cell disease may consist of adrenergic system effectors, hormonal analogues or smooth muscle regulators. A cohort observational study on the use of etilefrine (an  $\alpha$  adrenergic agonist) for the management of priapism in sickle cell disease showed that 72.0% of these patients reported a good clinical response (21). On the other hand, it is worth mentioning that there was no large randomized clinical trials highlighting the medical management of priapism in sickle cell disease or thalassaemic patients. Thus, hematologists and urologists should consider a treatment regimen based on each clinical scenario.

## Conclusions

The development of priapism in  $\beta$ -TI patients is scarce in the literature and no long-term follow-ups have been reported. Splenectomized patients are known to be at higher risk of complications compared to non splenectomized patients. Priapism can be added to the list of complications. Physicians' awareness as well as patients' education are essential to incite proper clinical management and monitoring of this emerging manifestation.

## Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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