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Testosterone Replacement Therapy in Adolescents With Sickle Cell Disease Reverses Hypogonadism Without Promoting Priapism: A Case Report

Belinda F. Morrison [a,*], Wendy Madden [b], Stephanie Clato-Day [c], Leslie Gabay [c]

[a] Department of Surgery, University of the West Indies, Mona, Kingston 7, Jamaica
[b] Sickle Cell Unit, University of the West Indies, Mona, Kingston 7, Jamaica
[c] Department of Paediatrics, University of the West Indies, Mona, Kingston 7, Jamaica

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ABSTRACT

Delayed puberty secondary to hypogonadism is commonly seen in sickle cell disease (SCD), affecting normal growth and development. The condition is rarely treated in SCD for fear of inducing priapism episodes. We present a case report of an Afro-Jamaican adolescent male at 16 years of age who presented with symptoms of delayed puberty as well as frequent stuttering priapism episodes. Endocrinological assessment revealed low serum total testosterone levels. Treatment was commenced monthly with testosterone enanthate which resulted in improved symptoms of delayed puberty, improvement in anthropometric parameters while apparently ameliorating priapism episodes.

Introduction

Delayed puberty in boys is defined as the absence of testicular development at an age 2–2.5 SD later than the population mean, which is traditionally 14 years.[1] It may be classified as hypogonadotropic hypogonadism, hypergonadotropic hypogonadism or constitutional delay in puberty. Delayed puberty results in a delay in the attainment of secondary sexual characteristics, pubertal growth spurt and skeletal maturation. It may negatively affect the psychosocial development of the affected boy.

Delayed puberty has been previously described in males with sickle cell disease (SCD). In several cases of delayed puberty, treatment with androgens may be initiated to improve psychosocial effects. However this is not commonly practiced in SCD, as it is thought that androgen administration is a risk factor for priapism. Priapism which occurs in approximately 42% of males with the SCD has a mean age of onset of 13 years.[2] However, the association of priapism in hypogonadal males with SCD receiving testosterone replacement therapy (TRT) has only been reported in the literature twice. Furthermore the safety of TRT in adults with SCD has been reported.[3]

Non-treatment of hypogonadism in SCD presents challenges to the adolescent. We report a case of an adolescent male with SCD who had hypogonadism as well as frequent stuttering priapism episodes and was treated successfully with TRT.

Case presentation

A 14 year old Afro-Jamaican male with homozygous SCD was referred to the Urology clinic at the Sickle Cell Unit, University of the West Indies, Jamaica in July 2013. He reported a history of stuttering priapism since age 8 years, occurring initially with a frequency of 3 nocturnal episodes weekly which progressed to 7 episodes weekly. He reported two prior major episodes of priapism which required penile aspiration. His mother reported concerns that since age 9 years he appeared small for his age.

On examination he was noted to have a small stature (weight and height were below the third centile) and features in keeping with delayed puberty. His stretched penile length was 11.5 cm. His testes were ~10 mls in volume bilaterally.

He was referred to the pediatric endrocrine clinic. Serum early morning total testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and cortisol were requested. Early morning total testosterone was 1.7 nmol/L (50 ng/dl), LH was 2.4 IU/L and FSH was 2.6 IU/L. Early morning and afternoon cortisol were 182 nmol/L (normal range: 138–689.8 nmol/l) and 75 nmol/L

* Corresponding author. Fax: +1 876 9704302.
E-mail address: bfmorrison11@hotmail.com (B.F. Morrison).

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Table 1
Total testosterone levels (ng/dl) and priapism frequency

	Total testosterone levels (ng/dl)	Monthly priapism frequency (*n*)
Baseline	50	28
At 11 months of testosterone replacement therapy	210	0

(55.2–331.1 nmol/l). Radiological assessment of bone age corresponded to an age of 10 years.

He was diagnosed with a delayed puberty and was commenced on testosterone enanthate 50 mg intramuscularly every 4 weeks and increased by 25 mg every 4 months. Serum testosterone increased to 7.3 nmol/L (210 ng/dL) after 11 months of TRT (Table 1). Improvements in anthropometric measures were noted during TRT, with increase in height and stretched penile length. Within 3 months of TRT, he noted a single major priapism episode occurring approximately 1 week after TRT injection, requiring penile aspiration. He however noted an overall reduction in the frequency of stuttering episodes with no priapism episodes noted in the last 12 months of treatment. He has reported preservation of normal sleep-related erections.

Discussion

TRT was able to successfully resolve delayed puberty. Though there is no current guideline in management of adolescent males with hypogonadism, there are successful reports of reversal of delayed puberty after receiving short or long-term androgen therapy.[1] TRT shows benefit in improving bone mass, body composition and improving psychological distress in males with delayed puberty.

Reduced testosterone levels are seen in 29% of males with SCD.[3] The etiology is unknown with reports suggesting a mechanism of primary hypogonadism due to possible testicular infarcts or secondary hypogonadism due to pituitary or hypothalamic dysfunction. A recent study with a mouse model of SCD designed to determine the mechanism of testosterone deficiency revealed reduced serum and intratesticular testosterone levels in SCD versus wild type mice. In addition LH levels were elevated confirming a primary cause of hypogonadism. The proposed mechanism was impairment in the Leydig cell steroidogenic pathway secondary to increased oxidative stress and NADPH oxidase activation in the SCD testis.[4] There is variation in the severity of endocrine abnormalities in SCD which directly correlates with the severity of the hemoglobinopathy. Other determinants of delayed puberty in SCD include nutritional factors and high resting energy expenditure.

Androgens play an important role in early penile development. Suppression of neonatal androgen levels results in reduced expression of corpora cavernosal phosphodiesterase type 5 (PDE5) enzymes, which terminate nitric oxide (NO)-induced cGMP-mediated cavernosal smooth muscle relaxation, as well as loss of cavernosal smooth muscle cells ultimately leading to disorders of penile function. Nitric oxide synthase (NOS) synthesizes NO, a vital molecule in the physiology of erections. The expression of NOS is regulated by androgens, with androgen withdrawal reducing levels of NOS and testosterone replacement increasing its levels. The pathophysiology of priapism in SCD has been linked to abnormal NOS activity/reduced NO bioavailability in the penis. Transgenic sickle-cell mice have reductions in penile NO/cGMP signaling leading to deficient PDE5 function and uncontrolled erectile responses.[5] The dysregulation of the NO/NOS system in SCD results in disorders of penile tumescence and detumescence resulting in priapism. It is believed that this abnormal molecular signaling in SCD is worsened by hypogonadism.[3] We therefore suggest that TRT may improve rather than worsen priapism episodes in SCD since it reverses the molecular abnormalities involving the NO/c GMP/PDE5 system.[3]

In summary, we report on a case of hypogonadism in adolescents with SCD where TRT improved delayed puberty. We are aware of the limitation of the modest follow-up period. Appropriate duration of therapy for these adolescents is undetermined. We believe our findings support consideration of TRT in these patients and also warrant further controlled studies on the benefit of androgens in males with SCD.

Conclusion

The report represents a case of hypogonadism in SCD where TRT improved delayed puberty without worsening priapism.

Conflicts of interest

The authors have no conflict of interest.

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