EDITORIAL WILEY

Oral testosterone undecanoate is an effective treatment for micropenis therapy

5α-reductase deficiency (5α-red def) is an autosomal recessive condition caused by a homozygous mutation in the 5α-red type 2 gene (*5α-R2*). The condition is very rare, it only affects males and is characterized by a broad spectrum of presentations most apparent in the external male genitalia. The condition was first described in 1974 in the Dominican Republic,[1-3] it occurs however in many parts of the world. The current series of 90 male patients from China with 5α-red def is one of the largest series described to date.[4]

A variety of mutations in the *5α-R2* gene responsible for this condition have been identified in all five exons. Some are single point mutations, while other affect multiple exons. In the large kindred in New Guinea, the entire gene on chromosome 2 is deleted.[5-10]

Despite the generalized defect in 5α-reduction of steroids, the only significant manifestation that has been shown to date is the defective reduction of testosterone to dihydrotestosterone (DHT) which normally is approximately 10% of the daily testosterone production in males.

Individuals have ambiguous genitalia with a clitoral like phallus, severely bifid scrotum, and pseudovaginal perineoscrotal hypospadias (this defect was most likely already described by Lenz W in 1960 in Germany. He could not verify the diagnosis because steroid hormone level could not be measured then).

Many of these patients are thought to be girls and are unambiguously reared as females from birth. However, at puberty there is an increase in muscle mass, a deepening of the voice, and a significant growth of the phallus that in some patients becomes a functional penis. The third degree hypospadias needs to be repaired surgically and herein the problem lies: the phallic structure needs to be enlarged therapeutically with androgens before surgery to facilitate a successful surgical intervention. The penis has to be enlarged in infancy prior to surgery which should be performed as it was done in the report by Liu et al[4] where most patients were between 1 and 2 years of age.

Despite having been reared as female, the vast majority of patients with 5α-red def change their gender role from female to male at puberty.[5] In the Dominican Republic, the age at change in gender role ranged from 14 to 24 years, with an average age of 16. The gender change has been documented in many countries. It appears that the influence of androgens, mainly testosterone, on the brain when present in utero, in the immediate postnatal period, and again at puberty outweighs socio-cultural influences in the development of male gender identity and gender role.[5] This genetic defect in steroid hormone metabolism emphasizes the importance of androgens in the function and in the establishment of a male gender identity and gender role.

At puberty, there is masculinization but no beard growth, the prostate remains small, and there is no temporal recession of the hairline. Libido is preserved and these individuals are capable of erections and ejaculations.

5α-red def is to date the first and so far the only steroid hormone metabolism disorder that figures predominantly in the current novel by the American author Jeffrey Eugenides, published in 2002 in the U.S. The book is the coming of age story of a Greek intersex individual growing up in the U.S. who is suffering from 5α-red def. The much lauded book which received the prestigious Pulitzer Prize in the U.S. in 2002[11] will soon become a major TV movie and is currently being filmed in the U.S.

Enlargement of the phallus, to assist with the successful repair of infants with severe hypospadias characteristic with this defect, can be achieved with DHT cream. Enhancing phallic growth can facilitate corrective surgery. In China, DHT preparations as a cream are not available. Innovatively, Liu et al[4] report in this manuscript the successful use of oral testosterone undecanoate to enhance phallic growth.

Oral testosterone undecanoate can produce a normal

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plasma testosterone level in hypogonadal male adults and in prepubertal boys. As Behre et al[12] have shown it is well tolerated via injection. Liu et al[4] observed no harmful effects have been described even after three courses of oral therapy lasting a total of 90 days. Analysis of bone age advancement during this therapy did not lead to accelerated bone maturation. At completion of therapy, which lasted in some patients up to 90 days, Liu et al[4] document an increase in penile length from 1.9 ± 0.6 cm to 3.2 ± 0.4 cm. Penile length increased to the target length facilitating urological surgery for hypospadias repair in these infants with 5α-red def.

Thus, oral testosterone undecanoate treatment may be utilized as an efficacious and safe alternative for micropenis therapy in countries where topical DHT gel is not available.

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CONFLICT OF INTEREST

None.

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