CLINICAL VIGNETTE

Severely Depressed Testosterone in a 20-Year-Old Male

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A 20-year-old male with no significant past medical history presents to endocrinology with one week of testicular pain and low testosterone level. He was in his usual state of health until a week prior to presentation when he had sudden onset of sharp, bilateral testicular pain. He denies testicular trauma, dysuria, penile discharge, penile lesions, fever, or chills.

Evaluation by a urologist was concerning for epididymitis and the patient was started on ciprofloxacin. Laboratory evaluation was notable for a very low testosterone level of 20 ng/dl which prompted referral to endocrinology. The patient was afebrile with somewhat improved testicular pain. Physical examination showed 15 ml bilateral testes which were non-tender, without mass lesions. Laboratory testing included luteinizing hormone (LH) of 3.2 IU/ml, follicle-stimulating hormone (FSH) of 4.1 mIU/ml, total testosterone of 30 ng/dl and a normal prolactin level of 15 ng/ml.

The patient was accompanied by his father and denied use of anabolic steroids or street drugs. He does not take any prescriptiton medications.

Due to the inappropriately normal gonadotropin levels, MRI pituitary was ordered which showed a normal pituitary gland with no mass lesions or other pathology. The patient continued to have testicular pain which prompted testicular ultrasound and a new urology referral. The testicular ultrasound showed no torsion and urology started intratesticular lidocaine injections for pain relief. During the course of treatment, he revealed that he had been using recreation fentanyl. He was counseled to stop and subsequently enrolled in an opioid detoxification program.

Follow-up testing 3 months after stopping fentanyl showed a normal total testosterone of 435 ng/dl and complete resolution of his testicular pain.

Discussion

Hypogonadism is a syndrome resulting from sub-physiological production of testosterone and/or sperm from the testes due to a disruption of the hypothalamic-pituitary-testicular axis.[1] Primary hypogonadism is defined as impairment at the testicular level resulting in low serum testosterone, decreased spermatogenesis, and elevated gonadotropins.[1] In contrast, dysfunction of the hypothalamus-pituitary axis is defined as secondary hypogonadism and results in low serum testosterone, decreased spermatogenesis, and low or inappropriately normal gonadotropin levels.[1]

The diagnosis of hypogonadism is made when there are signs and symptoms of low testosterone and at least two morning fasting (>8 hours) testosterone levels below the normal range.[1] As the normal range for testosterone varies between different assays, the Endocrine Society proposed a lower range of 264 ng/dL or 9.2 nmol/L.[1] Testosterone deficiency can manifest as: reduced libido, decreased sexual activity, erectile dysfunction including decreased spontaneous erections, infertility, gynecomastia, hot flushes, sweats, osteopenia and osteoporosis.[1] Non-specific symptoms including fatigue, reduced muscle mass, depressed mood, poor concentration and memory. Increased BMI, and increased body fat are also common.[1]

Population studies over the past 50 years have shown a persistent decrease in testosterone levels[2,3] and sperm count.[4] Theories regarding the reason for the decrease include increased population visceral fat, changes in lifestyle and behaviors, environmental pollution, and increase in endocrine-disrupting compounds in the environment.[5] Unhealthy behaviors leading to reduced testosterone levels and/or reduced sperm production include alcohol abuse, tobacco use, excessive caffeine intake, illicit drug intake, opioid use, and inappropriate use of anabolic steroids.[6] In particular, opioid induced androgen deficiency (OPIAD) is a recognized syndrome that is characterized by low testosterone, decreased libido, reduced muscle mass, fatigue, and osteopenia.[7]

The mechanism by which opioids decrease testosterone levels is through inhibition of the pulsatile secretion of gonadotropin-releasing hormone (GnRH) leading to decreased luteinizing hormone (LH) secretion and testosterone production.[8,9] Opioids also increase prolactin secretion which can further cause central inhibition of testosterone secretion.[9] Opioids have a more modest effect on FSH levels [8] but studies in opium-addicted men show a high incidence of oligozoospermia, lower antioxidant activity, and higher sperm DNA fragmentation than non-opioid using age-matched males.[10]

Opioid use is on the rise in the United States with annual opioid overdose deaths up to 47,000.[11] With the rise in opioid use, opioid-induced androgen deficiency has also risen dramatically in the past 10-15 years. In one study, up to 85% of heroin addicts and 81% of patients on methadone reported sexual dysfunction. Of the commonly used opioids, fentanyl, methadone,

and oxycodone were associated with higher odds of androgen deficiency compared to hydrocodone.[12]

Treatment of OPIAD depends on the feasibility of stopping opioid use. In cases where opioid use must be continued, such as for the treatment of chronic pain, testosterone replacement therapy has been shown to improve libido, reduce pain perception, improve muscle mass, and improve bone mass.[13-15]

Opioid induced androgen deficiency is a recognized cause of hypogonadism. In cases of unexplained hypogonadism, a careful opioid history should be obtained. Treatment with testosterone replacement should be consider in cases where opioids cannot be stopped.

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