CLINICAL VIGNETTE

Hypogonadism in an Adult Male Lacking Secondary Sex Characteristics: A Tale of Two "K Syndromes"

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Case

A 29-year-old man without significant medical history presented with concerns about Klinefelter Syndrome based on his online research. Since birth, he had lacked a sense of smell, which had always been attributed to allergies and his genitalia had never grown. He felt that his chest and extremities were bigger than normal, a problem that started around age 12. He has no facial or leg hair, and minimal hair in the axillary, arm, and groin areas. The patient recalled a growth spurt around age 18-20, and reported his height and weight had been increasing over the last 2 years. He also reported newer symptoms of fatigue, lack of muscles, and no sexual desire. He did not have spontaneous morning erections. He had no children and had never tried to conceive. He denied headaches, vision changes, nipple discharge, bowel changes, snoring, head trauma, or groin trauma. He had no kidney/liver/thyroid disease; use of opiates, marijuana, anabolic steroids, hormone-blocking therapies, or herbal supplements. No radiation or surgery; sleep apnea; or mood disorders. There was no family history of infertility or hormone issues.

On exam, the patient's vital signs were 36.3 C (97.4 F), HR 53, BP 122/76, height 72 inches, 207 pounds, BMI 28.07 kg/m2, with arm span of 77.5 inches. He had minimal muscle bulk in his extremities. Other than fine, light-colored hair above his upper lip, he had no facial hair or stubble. He had fine, light-colored hair on his arms and legs. He had excess bilateral fatty breast tissue in addition to mild bilateral gynecomastia. His right testicle was firm and 2-3 mL (Tanner stage I) and his left testicle could not be located. Penis and pubic hair growth were Tanner stage I. The remainder of his exam was normal.

Based on his history and exam findings, testosterone deficiency (hypogonadism) was suspected. The patient did not have medical insurance at his first visit, so initial testing was limited judiciously. Morning testosterone was low, 10 ng/dL (250-1,100), luteinizing hormone (LH) <0.1 mIU/mL (1.5-9.3), and follicle stimulating hormone (FSH) 1.0 mIU/mL (1.6-8.0). His karyotype was normal male 46,XY. He returned for lab review after obtaining medical insurance. Additional morning testing included normal basic metabolic panel, normal thyroid stimulating hormone (TSH), free thyroxine (T4), adrenocorticotropic hormone (ACTH), cortisol, prolactin, insulin-like growth factor-1 (IGF-1), ferritin, and iron. Estradiol levels were low, within the standard male reference range. Pituitary MRI showed a tiny Rathke's cleft cyst without suprasellar extension without other pituitary pathology.

The patient started testosterone replacement therapy for hypogonadism with weekly 100 mg intramuscular injections. He returned after 2 months of testosterone replacement therapy (TRT). He reported new spontaneous morning erections, hair growth on his stomach and legs, with light hair growth above his upper lip and on his chin, larger facial skin pores, acne on his back, deepening of his voice, and mild bilateral nipple sensitivity. He was pleased with the changes. Repeat laboratory testing included increased testosterone levels to 616 ng/dL (300-1,080), with free testosterone 159 pg/mL (47-244) and bioavailable testosterone 421 ng/dL (131-682). Hemoglobin, hematocrit, and PSA levels were within normal limits and he continued on the same testosterone replacement therapy.

Discussion

The patient had presented with concerns about hypogonadism, which was confirmed, due to Klinefelter Syndrome, which was not confirmed. Klinefelter Syndrome is a consequence of aneuploidy, with 80-90% of affected males having a 47,XXY karyotype. The other 10-20% have 48,XXXY or 48,XXYY karyotypes, abnormal X chromosomes, or mosaicisms.[1] This patient had a normal male karyotype of 46,XY. The prevalence of Klinefelter Syndrome is 0.1-0.2% in newborn males, 3-4% in infertile men, and 5-12% in patients with azoospermia, with overall male prevalence of 1:500 to 1:1000.[1-3] The additional X chromosome(s) and testosterone deficiency are responsible for symptoms and signs that include small firm testes, gynecomastia, decreased facial and body hair, tall stature, broad hips, fatigue, infertility/azoospermia, erectile dysfunction, absent/reduced libido, osteoporosis, metabolic syndrome, type 2 diabetes, insulin resistance, increased cardiovascular disease risk, venous thromboembolism, and cognitive, mood, and behavioral difficulties.[1-3] Klinefelter Syndrome is a cause of primary hypogonadism,[4] consistent with dysfunction at the level of the gonads. In contrast, dysfunction at the level of the hypothalamus or pituitary gland is termed hypogonadotropic or secondary hypogonadism.

Diagnosis of Klinefelter Syndrome is made by karyotype analysis, confirming the extra X chromosome(s), in addition to low testosterone levels and high LH and FSH levels.[1] The median age of diagnosis is 27 years old.[2] Treatment includes TRT to improve hypogonadal symptoms and facilitate the development of secondary sex characteristics, as well as advanced reproductive technology in those desiring to conceive.[2,3]

Another "K syndrome," Kallman Syndrome, may be more consistent with this patient's presentation, with his minimal secondary sex characteristics, anosmia, and normal male karyotype 46,XY. Kallman Syndrome is a type of secondary hypogonadism with anosmia. A less severe form called normosmic idiopathic hypogonadotropic hypogonadism (nIHH) is also reported.[5] This is seen in both males and females, characterized by delayed or absent puberty, anosmia or severe hyposmia, infertility, and in a smaller number of cases, cleft lip/palate, hearing issues, unilateral renal agenesis, dental agenesis, and syndactyly, polydactyly, or camptodactyly.[6] Genetic mutations alter gonadotropin release hormone (GnRH) neuronal development or their functioning during embryogenesis, thereby affecting GnRH and gonadotropin and sex hormone production.[5] Kallman Syndrome has autosomal dominant, autosomal recessive, or X-linked inheritance,[6] and is responsible for two-thirds of congenital secondary hypogonadism cases.[7]

Diagnosis of Kallman Syndrome is clinical, based on history, examination, labs, and imaging. GnRH stimulation testing and genetic counseling and testing can also be helpful, as Kallman Syndrome is associated with mutations in multiple genes, including *CHD7*, *DUSP6*, *FEZF1*, *FGF17*, *FGF8*, *FGFR1*, *FLRT3*, *GLCE*, *HS6ST1*, *KAL1*, *IL17RD*, *NSMF*, *PROK2*, *PROKR2*, *SEMA3A*, *SEMA3E*, *SOX10*, *SPRY4*, *TUBB3*, and *WDR11*.[5,6,8,9] Treatment of Kallman Syndrome includes appropriate hormone replacement therapy (estradiol and progesterone in females, testosterone in males), GnRH, and/or gonadotropins (LH, FSH, human chorionic gonadotropin (hCG)) to help with testicular function, secondary sex characteristic development, sperm production, and fertility.[6]

Klinefelter Syndrome and Kallman Syndrome are both causes of hypogonadism with overlapping treatment modalities to improve hypogonadal symptoms, fertility, and quality of life. However, they have different underlying etiologies - Klinefelter Syndrome is a cause of primary hypogonadism most commonly due to a 47,XXY genotype, whereas Kallman Syndrome is a cause of secondary hypogonadism due to genetic mutations affecting GnRH neuronal development. Diagnosis, treatment, and management of hypogonadism may benefit from a multidisciplinary team approach.

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