SEXUAL MEDICINE REVIEWS REVIEW

Klinefelter Syndrome. The Effects of Early Androgen Therapy on Competence and Behavioral Phenotype

Ryan Flannigan, MD,[1] Premal Patel, MD,[2] and Darius A. Paduch, MD, PhD[1,3]

ABSTRACT

Introduction: Klinefelter syndrome (KS) is the result of sex chromosome aneuploidy most often characterized as 47,XXY. The typical features of KS include tall stature, gynecomastia, small firm testicles, hypergonadotropic hypogonadism, and infertility. However, abnormalities in neurodevelopment, cognition, and social and behavioral functioning also can be present. The abnormalities in neurodevelopment are believed to be due in part to androgen deficiency during early development and puberty.

Aim: To discuss the role of androgens in normal adolescent development; discuss the cognitive, behavioral, and social functioning of children with KS; evaluate the evidence for early androgen therapy in men with KS; and discuss management strategies in the development of boys with KS.

Methods: A systematic review of early androgen therapy and KS was performed using PubMed-Medline and Scopus databases. Relevant articles commenting on social, behavioral, cognitive, and physical outcomes among infants, children, and adolescents were included for reporting and discussion.

Main Outcome Measures: Social and behavior functioning; cognitive outcomes; adverse effects associated with androgen therapy.

Results: 3 retrospective articles and 2 randomized controlled trials addressing early androgen therapy in boys with KS were reviewed. These studies showed an improvement in several aspects of social and cognitive functioning based on validated questionnaires. Treatment strategies, potential negative effects, and limitations of the literature on early androgen therapy in boys with KS are discussed.

Conclusion: Our findings indicate that early androgen supplementation in children with KS combined with specific educational, family, and social support improves behavioral functioning. The optimal timing of hormonal therapy might require prospective studies, but based on our data and review of the literature, the benefit of early hormonal and therapeutic intervention in KS is very encouraging. **Flannigan R, Patel P, Paduch DA. Klinefelter Syndrome. The Effects of Early Androgen Therapy on Competence and Behavioral Phenotype. Sex Med Rev 2018;X:XXX–XXX.**

Key Words: Klinefelter Syndrome; 47,XXY; Testosterone; Neurodevelopment; Behavioral Phenotype; Androgen

INTRODUCTION

Klinefelter syndrome (KS) refers to the genetic diagnosis of an X chromosome polyploidy with at least 1 additional X chromosome present and a clinical phenotype of tall stature, small testicles, androgen deficiency, infertility, and gynecomastia. The syndrome was 1st described by Klinefelter et al,[1] when they reported on a series of 9 men in 1942; these men were found to have azoospermia, small hard testicles, limited hair growth to the face and body, and gynecomastia. However, it wasn't until 1959 when patients presented with this phenotype and were found to have an additional X chromosome.[2] KS has since become the most common genetic X chromosome abnormality. KS is identified in 0.1% to 0.2% of newborn boys and is the most common genetic cause of male infertility, with an incidence of 3% to 4% in infertile men, attributed to oligozoospermia in 0.6% and azoospermia in 10% to 12%.[3–6] Most diagnoses of KS are made through prenatal diagnosis in mothers older than 35 years.

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[1]Department of Urology, Weill Cornell Medicine, New York, NY, USA;

[2]Division of Urology, Department of Surgery, University of Manitoba, Winnipeg, MB, Canada;

[3]Consulting Research Services, Inc, North Bergen, NJ, USA

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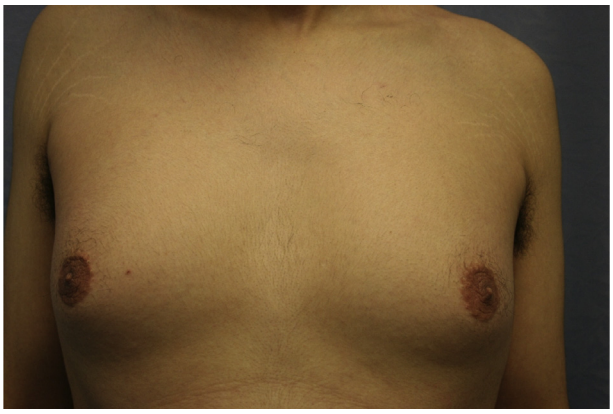

Figure 1. Gynecomastia in a man with Klinefelter syndrome.

Genetics of KS

In KS, non-dysjunction of the sex chromosomes results in at least 1 additional X chromosome. 80% to 90% of men with KS have a 47,XXY karyotype. Several variant karyotypes also have been described such as 47,iXq,Y, 48,XXYY, and 48,XXXY or mosaicisms 47,XXY and 46,XY. In these cases, non-dysjunction occurs most frequently during meiosis I in oogenesis (50%) and spermatogenesis (40%) or in meiosis II during oogenesis (10%).[7] Rarely, non-disjunction occurs in early embryogenesis (3%).[2] It is important to discuss with the patient and parents that it is the Y chromosome that determines the sex of an individual; hence, regardless of the number of X chromosomes, boys and men with KS are phenotypically male. Genes derived from the X chromosome are predominantly expressed in the brain, testes, and ovaries. Most of the genetic material on 1 X chromosome in women undergoes inactivation; hence, in 46,XX female and 46,XY male individuals, there is only 1 functional X chromosome. Inactivation of additional X chromosomes occurs by epigenetic regulation through non-coding RNAs called XIST, which is expressed on the X chromosome to be inactivated.[8] Unfortunately, the process of X chromosome inactivation is promiscuous and not complete; hence, the entire additional X chromosome is not always inactivated.[9] It is believed that the variability in X chromosome inactivation, and approximately 15% of X chromosome genes escaping silencing, could be responsible for the phenotypic variability observed in KS.

Clinical Phenotype and Endocrinology of KS

The clinical manifestation has been further characterized since its initial inception. The clinical phenotype classically includes tall stature, gynecomastia (Figure 1), gynoid hips, sparsity of body hair, firm hypotrophic testes (<4 mL; Figure 2), hypergonadotropic hypogonadism, infertility, and a propensity toward obesity.[2] Infertility is typically associated with progressive hyalinization, fibrosis, Leydig cell hyperplasia, and depletion of germ cells among the seminiferous tubules. This typically results in Sertoli cell only syndrome and is believed to worsen immediately after puberty.[10] This most often results in azoospermia and requires surgical sperm retrieval by microdissection testicular sperm extraction. Boys with KS also might have abnormal physical features including a small or micropenis, truncal hypotonia (68%), joint laxity (50%), hand tremors in children after 5 years of age (20−50%), clinodactyly or curved 5th digit (26%), pectus excavatum, delayed puberty (50%), gynecomastia (30%), mirror movements (40%), infantile cherubic faces, and disproportionately long limbs. Other clinical features include developmental abnormalities in speech with decreased phoneme repertoire (50−75%), age-appropriate language comprehension (80%), delayed auditory memory (50−80%), enhanced visual memory (50−80%), normal IQ within 10 to 15 points of siblings (80%), reading deficiencies or dyslexia (50%), delayed balance skill acquisition (50−80%), sensory differences, pseudo-torticollis (20%), developmental dyspraxia (50−80%), and psychosocial functioning.[11−13] The behavioral profile of boys with KS consists of poor self-esteem, shyness, increased anxiety, depression, and social difficulties.[12−14] Because of androgen deficiency in infants and boys with KS, they can exhibit, albeit less commonly, features of under-virilization such as micropenis, bifid scrotum, cryptorchidism, and hypospadias.[15] During adolescence 62% of boys can maintain serum testosterone (T) levels higher than 10 nmol/L through hypergonadotropic compensation, and most will enter puberty.[16] However, relative androgen deficiency is progressive in most men in later stages of life; men with KS are at risk of sequelae of androgen deficiency such as osteoporosis, low libido, and erectile dysfunction (ED). It appears that ED is likely the result of androgen deficiency and not linked to the syndrome itself, because 1 study reported a comparable rate of ED in 40 men with KS compared with age- and T-matched controls[17]; similarly, a study of 53 men with KS had a comparable rate of ED as 75 age-matched controls with a rate of 18.9% but significantly lower sexual desire.[18] The severity of ED in young

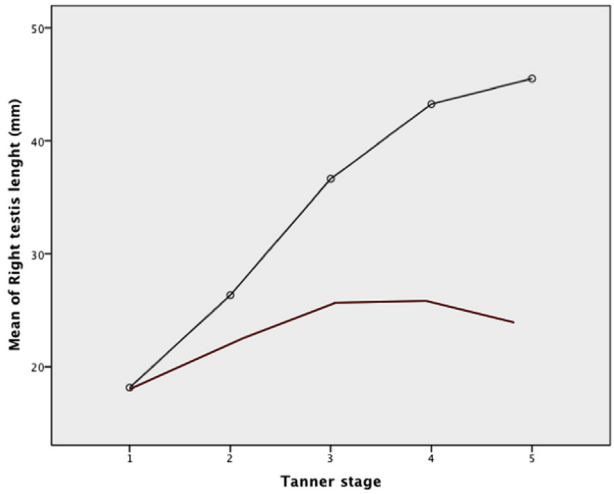

Figure 2. Tanner stage vs mean right testis length (millimeters). Gray line represents testicular growth during puberty in a normal boy. Red line represents decreased trajectory of testicular growth during puberty in a boy with Klinefelter syndrome and decreased final testis length by the end of puberty compared with boys without Klinefelter syndrome.