PEER REVIEWED

Klinefelter's syndrome

The most overlooked cause of androgen deficiency

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Klinefelter's syndrome (KS) 47,XXY, the most common cause of noniatrogenic hypogonadism in men, is associated with significant morbidity, mortality and psychosocial disadvantage yet most cases escape detection lifelong. Because early diagnosis may improve patient outcomes, doctors should consider KS in children with speech or motor delay, learning disabilities or psychobehavioural problems; in adults a simple testicular examination will ensure this important syndrome is not overlooked.

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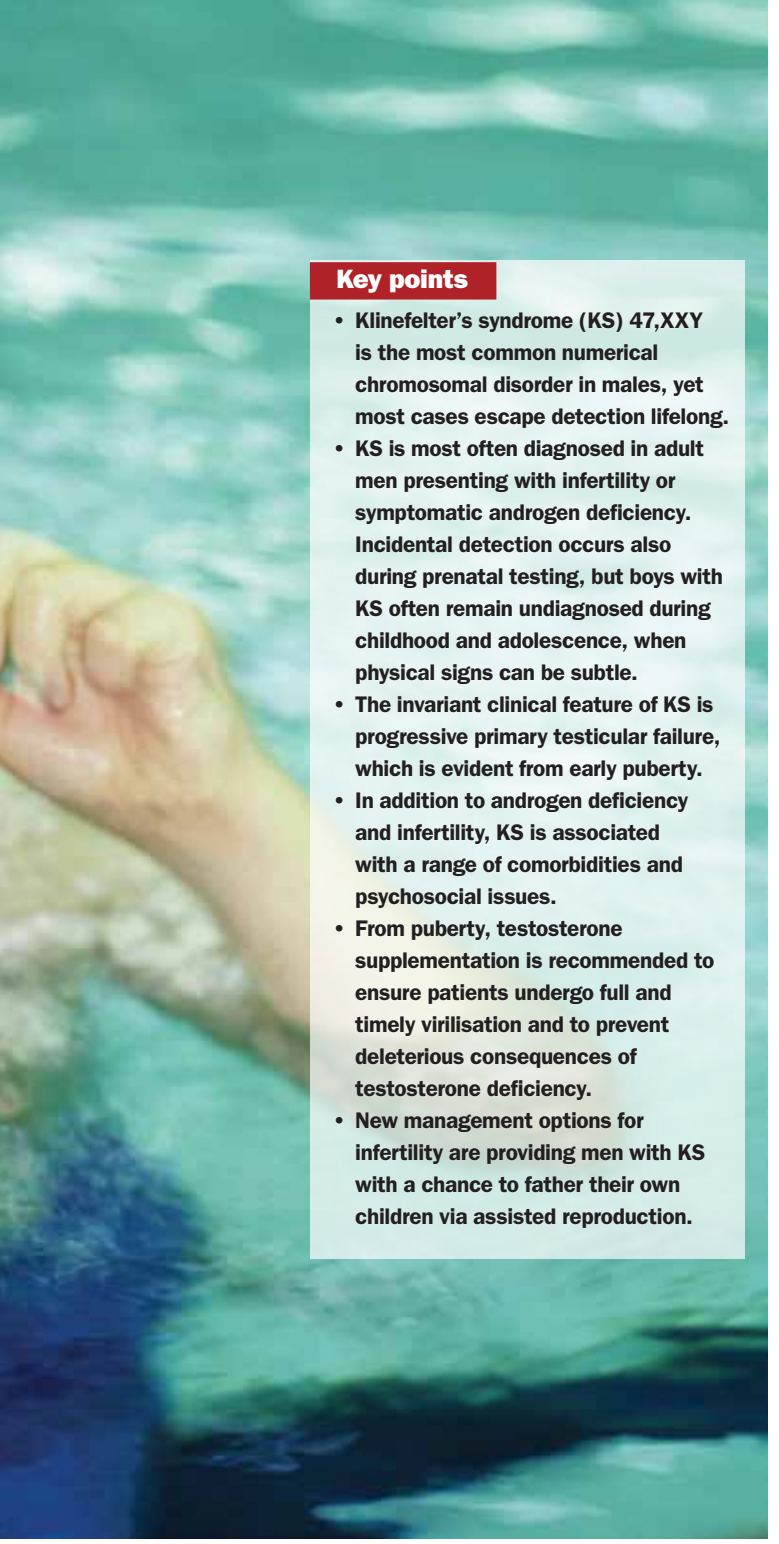
Klinefelter's syndrome (KS) 47,XXY is the most common numerical chromosomal disorder in males, affecting around one in 450 males in Australia.[1] The hallmarks of the syndrome – small firm testes, gynaecomastia and hypogonadism – were described more than 70 years ago, yet today about 50% of males with KS in Australia remain undiagnosed during their lifetime.[1] These rates are similar to those in a large European population dataset, which reported a prevalence of one in 660 and roughly a 30% lifetime diagnosis estimate.[2]

KS is not only associated with androgen deficiency and infertility but also with a range of comorbidities and psychosocial issues, and



Key points

- **Klinefelter's syndrome (KS) 47,XXY is the most common numerical chromosomal disorder in males, yet most cases escape detection lifelong.**
- **KS is most often diagnosed in adult men presenting with infertility or symptomatic androgen deficiency. Incidental detection occurs also during prenatal testing, but boys with KS often remain undiagnosed during childhood and adolescence, when physical signs can be subtle.**
- **The invariant clinical feature of KS is progressive primary testicular failure, which is evident from early puberty.**
- **In addition to androgen deficiency and infertility, KS is associated with a range of comorbidities and psychosocial issues.**
- **From puberty, testosterone supplementation is recommended to ensure patients undergo full and timely virilisation and to prevent deleterious consequences of testosterone deficiency.**
- **New management options for infertility are providing men with KS with a chance to father their own children via assisted reproduction.**

life expectancy is modestly reduced by 2.1 years.[3] Early recognition and intervention, including androgen replacement, lifestyle modification and counselling, may improve health outcomes of affected individuals.

This article aims to increase awareness and knowledge about diagnosis and management of KS to improve detection and facilitate optimal multidisciplinary treatment.

Pathophysiology

The extra X chromosome in KS originates with an equal chance from the mother or father and is transcriptionally inactivated, as is the second X chromosome in females. However, the inactivation is believed to be incomplete, such that some genes on the extra X chromosome are overexpressed. This gene dosage effect determines the KS features (Figure 1).[1,2,4-6] The invariant clinical feature is progressive primary testicular failure, evident from early puberty, with rising serum luteinising hormone (LH) and follicle stimulating hormone (FSH) and falling testosterone levels. Although the timing of pubertal onset is usually normal, pubertal progression may be incomplete and the patient remains incompletely virilised (see 'Clinical picture' below). Germ cell loss is initiated after birth and accelerates around puberty, with most seminiferous tubules ending up germ cell-free with a hyalinised appearance and containing only Sertoli cells. As testicular size is mainly determined by the spermatogenic compartment, patients with KS always have very small testes from puberty onwards and are almost always azoospermic.

Clinical picture

The original description of 'classic KS' has led to the widely held assumption that all KS cases are clinically obvious. This is untrue; the only reliable feature is small testes, whereas other features are variable (see Figure 1) and may easily be overlooked.

Incidental detection during prenatal testing is one pathway of recognition, but boys with KS often remain undiagnosed during childhood and adolescence, when physical signs are subtle or don't trigger consideration of KS. Such signs include undescended testicles, a taller stature and longer legs than genetically expected, higher rates of nonfamilial central obesity,[7] slightly smaller testes and, rarely, micropenis. However, neurocognitive disorders, such as speech and motor delays, learning disabilities, attention deficit disorders and psychobehavioural problems, are often clues to the syndrome.[4]

KS is most often diagnosed in adult men presenting with infertility or symptomatic androgen deficiency. A physical examination at this stage will reveal small and firm testicles. Men with KS are often taller than expected relative to their parents/siblings but from a population perspective are not always tall. They have long legs relative to truncal length with narrow shoulders and broad hips (Figure 2).[8] Features of testosterone deficiency become increasingly evident after puberty (Figures 1 and 2) and include gynaecomastia, decreased beard and pubic hair growth, reduced libido, and erectile dysfunction in 70% of patients by the age of 25 years.[9] Muscle strength and physical fitness are substantially reduced. Osteopenia (occurring in 40% of cases) and osteoporosis (in 10%) are more common and fracture risk and mortality from fractures are increased.[10,11]

Body composition

Compared with the general population, patients with KS have an increase in total body and truncal fat and a decrease in lean body mass. BMI may be normal despite abdominal obesity, which is due to decreased muscle mass and with poor musculature often visible. Consequently, nearly 50% of patients with KS fulfil the diagnostic criteria for the metabolic syndrome.

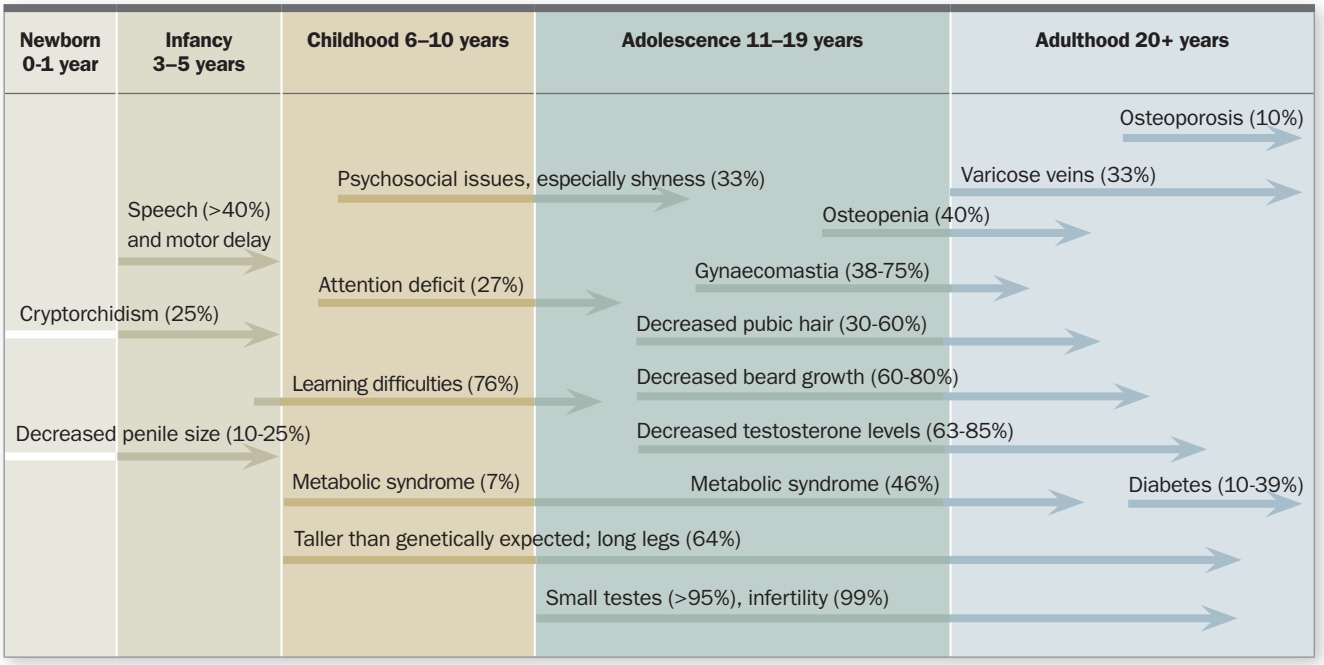


Figure 1. Potential clinical features of Klinefelter's syndrome according to age (estimated frequencies).*

* Adapted from Herlihy, et al 2011; Groth, et al 2013; Nahata, et al 2013; Abdel Razic, et al 2012; and Lanfranco, et al 2004.[1,2,4-6]

1. Main comorbidities of Klinefelter's syndrome

Metabolic disorders: metabolic syndrome, type 2 diabetes

Circulatory disorders: varicose veins, deep venous thrombosis and pulmonary embolism

Autoimmune diseases: lupus erythematosus, type 1 diabetes

Malignancies: breast cancer, mediastinal germ cell tumours, lung cancer, non-Hodgkin lymphoma

Psychiatric diseases: depression, schizophrenia, attention deficit disorders

Neurological diseases: tremor, epilepsy

Other associated morbidities

The incidence of type 2 diabetes is increased in patients with KS; however, type 1 diabetes is also more common, as are other autoimmune diseases such as systemic lupus erythematosus. Varicose veins, deep venous thrombosis and pulmonary embolism are also more common in those with KS, as are certain malignancies, although they rare in absolute terms. Box 1 summarises some of the morbidities associated with KS.

Cognitive and psychosocial aspects

The overall intellectual capacity of patients with KS is usually within the normal range but below that of siblings, and the standard distribution of IQ scores of patients with KS is shifted to the left compared with controls.[12] Patients with KS generally have reduced verbal intelligence and problems with memory and planning. Some patients have problems in identifying and verbalising emotions, feel different from their peers and consider themselves more introspective and insecure.[7,13] Problems arising from these deficits may result in behavioural problems such as aggressive outbursts. In addition, an increased prevalence of depression, attention deficit disorders, substance abuse and schizophrenia is seen.

Characteristically, patients with KS do not achieve the professional level of their own family and, compared with age-matched controls, they have fewer partners, have a lower income and retire earlier.[2,12] Although reported in small studies, an increased crime rate was not confirmed when the socioeconomic status was taken into account.[14]

Confirming the diagnosis

A diagnosis of KS will be driven by a physical examination revealing small firm testicles of less than 4 mL, as assessed with a Prader orchidometer, along with other signs of androgen deficiency (see 'Clinical picture' above). At least one genitoscrotal examination as early as possible during adult life should be part of the healthcare plan for every man so that the diagnosis will not be overlooked. The diagnosis is confirmed on karyotyping. Laboratory findings will reveal low or low-normal testosterone levels with increased gonadotrophin levels (LH and FSH) from puberty onwards.

When fertility is in question, a semen analysis will likely reveal azoospermia, as determined by examination of the sediment of centrifuged semen using WHO methodology.

Given the high rate of the metabolic syndrome in patients with

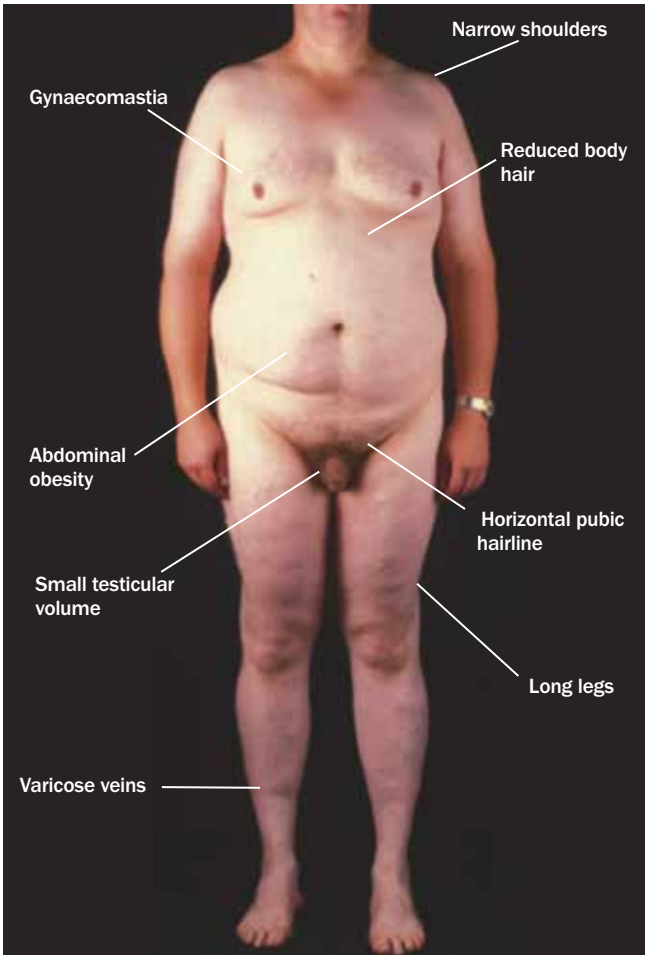


Figure 2. A 30-year-old man with Klinefelter's syndrome.
Reproduced with permission from Professor Nieschlag (reference 8).

2. Initial assessment of Klinefelter's syndrome and management issues*[2,21]

History
Educational/employment, psychosocial aspects
Wellbeing, energy level, sexual activity, libido

Physical examination
Height, weight, waist circumference, blood pressure, gynaecomastia, testis volumes, varicose veins

Tests
Confirmatory chromosomal analyses: karyotype or microarray
Testosterone, LH, FSH levels
Fasting glucose, HbA_{1c}, lipid levels
Haematocrit/haemoglobin
Prostate specific antigen level (in those 45 years or older)
Semen analysis
Bone density and vitamin D level (if osteopenia or osteoporosis present)

Management in conjunction with specialist(s)
Information provision
Discussion of fertility: referral to specialist
Androgen replacement therapy
Gynaecomastia: specialist referral to discuss medical treatment *vs* plastic surgery
Consideration of referral to psychologist
Lifestyle interventions

Abbreviations: HbA_{1c} = glycosylated haemoglobin; FSH = follicle stimulating hormone; LH = luteinising hormone.

* Modified from Groth, et al 2013 and Andrology Australia, Clinical Summary guide 10.[2,22]

KS, routine evaluation of fasting glucose and lipid levels is appropriate.

Management

Management of KS depends on the developmental stage of the patient at diagnosis. Clear information and counselling for patients (and parents) at diagnosis is crucial, as the knowledge regarding the extra X chromosome, poor virilisation and infertility can impact on the patient's self-image. On the other hand, many adult patients are relieved that an explanation has been provided for their life experiences.

Improved counselling of prospective parents has markedly decreased the rate of elective termination of pregnancy following a prenatal diagnosis of KS.[15] Management of cryptorchidism and micropenis involves specialist referral. During childhood, there is a focus on healthy exercise and nutrition, physiotherapy and/or speech therapy and educational assistance. From puberty, testosterone supplementation is recommended to ensure patients undergo full and timely virilisation and to prevent deleterious consequences of testosterone deficiency. There are no placebo-controlled studies supporting this practice, but nonrandomised studies have shown that it results in better physical and psychosocial outcomes.[2,16,17] Before testosterone replacement is commenced, discussion of future fertility is essential (see below). There are no specific guidelines for testosterone supplementation in KS, but treatment, particularly in adolescents, needs to be titrated for individual needs and warrants referral of patients to a specialist.

Testosterone replacement options include transdermal, injectable and oral testosterone preparations, as for any cause of androgen deficiency.[18]

Testosterone gel or solution provides physiological replacement but requires careful daily application and carries a risk of interpersonal transfer and suboptimal compliance over the lifetime treatment required. Testosterone patches are suitable but can cause skin irritation in 30% of patients.[19] A testosterone cream is available but is not listed on the PBS.

A convenient injectable formulation for adult patients is

long-lasting testosterone undecanoate, which is injected on average once every three months. Testosterone enanthate and another injectable solution containing several different testosterone esters require dosing every two to three weeks, result in fluctuating testosterone levels and are often less well tolerated by men,[20] but they are used in low doses to induce delayed or failed puberty.

Oral testosterone undecanoate has unreliable absorption,[21] and subcutaneous implants may no longer be available .

Monitoring of testosterone replacement therapy focuses on the clinical response, trough levels of serum testosterone and safety parameters such as the haematocrit, as polycythemia should be avoided due to the increased thromboembolic risk in KS.

Men with KS are relatively protected from prostate cancer, but discussion about prostate health is appropriate in middle-aged and older men.

Box 2 lists some of the management issues in patients with KS.[2,22]

Infertility

Specialist referral is required for patients with KS to discuss the complex issue of infertility. Management options for infertility have changed radically with the advent of intracytoplasmic sperm injection (ICSI). Most patients with KS are azoospermic but a few spermatozoa are present in the semen of 8.4% of affected patients.[6] Patients who wish to be able to father their own child (be they adolescent or adult) should be encouraged to provide a semen sample before the initiation of testosterone therapy and to consider sperm cryopreservation, because androgen therapy will suppress gonadotrophin levels as well as any residual sperm production and spermatogenesis decreases with age.

Patients with azoospermia undergoing testicular sperm extraction will have sperm recovered in 40 to 57% of cases, depending on the technique used.[23] Success rates from ICSI in men with KS are similar to those in men with other types of severe infertility. Remarkably, most sperm in men with KS have a normal chromosome complement and their offspring will not have KS. Nonetheless, international experience is still limited and preimplantation or prenatal testing is often advised.

Other options for patients with KS wishing to have a family are the use of donor sperm or adoption.

Other issues

A predisposition to chronic diseases in men with KS directs the need for lifestyle modification and related treatment. For patients who have painful gynaecomastia, off-label use of tamoxifen (at a dosage of 20 mg daily for three months, prescribed by a specialist) might be beneficial, whereas those with long-lasting cosmetic concerns may require a mastectomy by an experienced breast surgeon.

Summary

Unless genetic screening programs are implemented, patients with KS will rely on the clinical skills of the health professionals involved in their management to reach an early diagnosis and multidisciplinary treatment to improve their overall physical, psychological and social outcomes. The clinical key to diagnosis is testicular examination confirmed by karyotyping. At least one genitoscrotal examination as early as possible during adult life should be part of the healthcare plan for every man. Patients with KS are no longer invariably infertile and have a chance to father their own children via assisted reproduction. **ET**

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A list of references is included in the website version of this article (www.medicinetoday.com.au).

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