Klinefelter syndrome: a general practice perspective

Elyssia Bourke
Amy Herlihy
Pamela Snow
Sylvia Metcalfe
David Amor

Background

Klinefelter syndrome (KS) is a common genetic condition affecting one in 450 men, but is only diagnosed in fewer than half of those affected.

Objective

To increase awareness among general practitioners of their role in the diagnosis and management of KS.

Discussion

KS has a highly varied phenotype comprising a range of physical and psychosocial features and comorbidities. For patients diagnosed with KS, a range of management strategies can be used to improve health outcomes and quality of life.

Keywords

Klinefelter syndrome; genetics; men's health

Klinefelter syndrome (KS) is a common genetic condition, affecting one in 450 men.[1] KS is caused by the presence, in men, of one or more supernumerary X chromosomes. Most men with KS have a 47,XXY karyotype;[2–3] however 20% have a variant form, which most commonly is the presence of higher numbers of X chromosomes (eg. 48,XXXY), or mosaicism for two or more cell populations (eg. 46,XY/47,XXY).[2–3] Men with a mosaic picture typically present with a less severe phenotype than men with a 47,XXY karyotype.[4–5] Conversely, the presence of higher numbers of X chromosomes (eg. 48,XXXY) results in a more severe phenotype and more pronounced learning difficulties.[4–5]

KS was first described in 1942 and defined by a clinical phenotype comprising tall stature with a feminine body type, gynaecomastia, small testes and infertility.[6] More recent studies have demonstrated a broader phenotypic spectrum of KS with no single presentation.[5–9] The physical characteristics, psychosocial difficulties and comorbidities shown by individuals with KS are highly varied, and this should be borne in mind when assessing an individual for the presence of KS.[7–10] Most men with KS have a degree of androgen deficiency, to which a number of clinical features can be attributed.[4] Men with KS are typically azoospermic and therefore are unable to conceive naturally.[11]

Currently, KS is significantly under-diagnosed: only 39% of men with KS receive a diagnosis postnatally.[1] Even for those who are diagnosed, only 10% will receive their diagnosis before puberty.[5] This can be attributed to the difficulty in diagnosing KS, due to the heterogeneous phenotypic presentation and the lack of awareness of KS.[10,12]

General practitioners can play a major part in improving health outcomes for men with KS through improved detection amongst their male patients. Ongoing care and management can then be provided in the general practice setting and through the use of appropriate referral pathways.

When to consider a diagnosis of KS

KS can be diagnosed at any age. Clinical features suggestive of KS are listed in *Table 1*, and clinical suspicion should be raised whenever two or more of these features are present. Currently, KS is diagnosed most commonly at one of four stages of life:

1. during the prenatal period when diagnosis of KS at amniocentesis or chorionic villus sampling is usually an incidental finding
2. in male children with a developmental delay and/or learning difficulties
3. in young adult men with incomplete virilisation after puberty
4. in men of reproductive age presenting with azoospermia (absent sperm).

Once the diagnosis of KS is suspected, it is easily confirmed by a simple chromosome test.

Comorbidities associated with KS

KS is associated with an increased risk of a variety of comorbidities, resulting in life expectancy being reduced by 2–6 years, compared with 46,XY men.[13] These comorbidities and their relative risks in men with KS are detailed in *Table 2*. Although some of these comorbidities can be attributed to androgen deficiency, for many, the reason for the increased relative risk is not known.

Management in general practice

Although no cure exists for KS, there are a number of treatment and management options that can have a positive impact on the quality of life for men with KS. For most management options, the earlier they are instigated, the greater the benefit.[11]

Testosterone replacement therapy (TRT) has been used with great success in men with KS. TRT can alleviate many of the features associated with KS, leading to improved mood, lessened fatigue, increased libido, heightened concentration, enhanced muscle strength and optimised bone mineral density.[14] TRT has also been shown to prevent or alleviate many of the comorbidities associated with KS and to have a positive effect on general health and quality of life.[3,14] However, it is important to note that TRT does not improve fertility in men with KS. When considering whether or not to use TRT, it is important to view serum testosterone and luteinizing hormone (LH) levels in combination, as it has been demonstrated that in the presence of raised LH levels, even men with normal serum testosterone levels will benefit from TRT.[15] All men with KS should be referred to an endocrinologist for assessment and consideration of TRT, which is now available as implants, patches, gels, oral tablets and intramuscular injections.

It is important to make men with KS aware of the fertility options available to them. Until recently, men with KS were considered to be infertile, with sperm donation being the primary option for achieving fatherhood; however with the recent developments of *in vitro* fertilisation (IVF), some men with KS have been able to biologically father a child.[16] In about 50% of men with KS who undergo testicular sperm extraction (TESE), sperm can be recovered from the testes;[16] however, the success of the retrieval, and therefore live birth, is highly dependent on age. A progressive decline in successful retrieval rates has been demonstrated with increasing age; therefore men with KS should consider TESE as early as possible.[17] For those men from whom

Table 1. Possible features of Klinefelter syndrome

	Physical	Psychosocial
Postnatal period	• Micropenis • Cryptorchidism • Hypospadias • Simian palm crease (Note: most individuals with KS will show no physical features during the postnatal period.)	• Anxious • Easily upset • Introverted personality type (shy, passive) • Quiet baby • Easily fatigued
Childhood	• Low muscle tone and resulting comorbidities (eg. chronic constipation, sleep apnoea, abnormal posturing) • Increased relative height ± long arms and legs • Delayed developmental milestones	• Lower verbal IQ and delays in reaching early language milestones • Language and learning problems including difficulties reading; expressive and receptive language problems, global speech delay • Difficulty socialising with others, fewer friends than other children • Body image issues • Depressed mood
Puberty	• Small firm testes • Poor virilisation including lack of facial, pubic and underarm hair • Gynaecomastia • Truncal obesity • Sexual dysfunction	• Body image issues • Depressed mood
Adulthood	• Infertility • Fatigue • Low libido	• The continuation of a number of the features above is possible

Table 2. Comorbidities associated with Klinefelter syndrome

Comorbidity	Relative risk
• Cancer (all types) • Breast • Mediastinal	1.3[24] 19.2[25] 14.1[9]
• Metabolic syndrome • Type II diabetes • Obesity	5.0[26,27] 3.7[14] 3.4[14]
• Endocrine diseases (all types) • Hypothyroidism	3.2[9] 27.4[9]
• Venous thromboembolic disease • Pulmonary embolism	5.3[9,28] 3.6[9]
• Osteoporosis • Fractures	5.7[7,29] 1.4[9]
• Anaemia	3.2[9]
• Systemic lupus erythematosis (SLE)	14.0[30]
• Asthma	3.3[9]
• Epilepsy	4.3[9]
• Psychiatric disturbance • Depression • Psychosis	1.5[31] 7.6[32] 5.0[9]

sperm is recovered, pregnancy rates are around 20–25% per IVF cycle.[18] Males with KS who have received an early diagnosis should be referred to a fertility specialist as an adolescent, or if a diagnosis is determined later than this stage of life, a referral should be offered at the time of diagnosis.[19] Most offspring of men with KS have normal chromosomes; however, there is some evidence of an increased risk of chromosome abnormalities in general, and so prenatal diagnosis should be considered if pregnancy is achieved.

General practitioners have a role in monitoring men with KS for comorbidities, which are outlined in *Table 2*. A full blood examination, thyroid function test, cholesterol and fasting blood glucose levels should be performed every two years. In addition, DEXA scans can be considered because of the increased risk of osteoporosis.[20] Men with KS may also benefit from allied health support. Although reliant on a case-by-case assessment, educational support, speech therapy, and physical and occupational therapy can be useful management strategies that can provide improved outcomes.[21,22]

Referral to a clinical geneticist should be considered, particularly for Men who have questions about the genetics of KS. Referral to a psychiatrist should also be considered where psychiatric comorbidities exist. Some KS men may also wish to be referred to a plastic surgeon for cosmetic bilateral mastectomy or liposuction.

Finally, all men with KS, and their parents if appropriate, should be offered the opportunity to be linked in with KS support groups. Support groups have been demonstrated to relieve some of the anxiety associated with a new diagnosis and the uncertainties surrounding prognosis.[23] Individuals with KS can also be offered fact sheets available from the Andrology Australia website, which provides useful information about KS, including treatment and management options.

Key points

- KS is a common genetic condition affecting one in 450 men, but it is only diagnosed in 40% of men.
- KS has a broad phenotype, but some of the common features are increased height, small firm testes, azoospermia, symptoms of androgen deficiency, as well as difficulties with language, learning and psychosocial function.
- Treatment and management strategies exist for KS and can provide good outcomes for these individuals, especially when initiated early.

Authors

Elyssia Bourke BMedSce (Hons), Medical Student, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, and Department of Clinical Genetics, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC. lissiebourke@gmail.com

Amy Herlihy BSc, MGC, PhD, MD Candidate, Faculty of Medicine, Nursing and Health Sciences, The University of Melbourne, and Department of Public Health Genetics, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC

Pamela Snow, PhD, FSPAA, MAPS, is Associate Professor, School of Psychology & Psychiatry, Bendigo Regional Clinical School, Monash University, Bendigo, VIC

Sylvia Metcalfe BSc, PhD, Head of Genetics Education and Health Research Unit, Murdoch Children's Research Institute; and Professor of Medical Genetics, Department of Paediatrics, The University of Melbourne, VIC

David Amor FRACP, PhD, Practising Clinical Geneticist, Royal Children's Hospital, TAS and Melbourne IVF; Director, Victorial Clinical Genetics Service; and Associate Professor, Faculty of Medicine, Nursing and Health Sciences, The University of Melbourne, VIC

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correspondence **afp@racgp.org.au**