International Journal of Andrology
international journal of andrology ISSN 0105-6263

LETTER TO THE EDITOR

Thinking outside the square: considering gender in Klinefelter syndrome and 47, XXY

A common genetic condition affecting males, Klinefelter syndrome (KS), is often described as 'The Forgotten Syndrome'. Although the prevalence of KS has been estimated to be as high as 1 in 450 (Herlihy *et al.*, in press.), between 50 and 70% of males are never diagnosed (Bojesen *et al.*, 2003). Klinefelter *et al.*, 1942 first described KS as a syndrome in males, characterized by tall stature with eunuchoidal body proportions, gynaecomastia, small testes, hypogonadism, azoospermia and increased FSH levels (Klinefelter *et al.*, 1942). The cause of this syndrome was identified 17 years later as an additional X chromosome in males, resulting in a 47, XXY karyotype (Jacobs & Strong, 1959). Since then, there have been many advances in research concerning the biomedical aspects of KS, in addition to the cognitive and neuropsychological features, providing a greater understanding of the variety of behavioural, learning and psychological difficulties that may be present (Bojesen & Gravholt, 2007).

We recently completed a study examining the psychosocial impact of KS (Herlihy *et al.*, unpublished data). The recruitment material called for adult males diagnosed with KS at any age, but now aged 18 years and older. Our inclusion criterion was any individual who had a karyotype consisting of more than one X chromosome and a single Y chromosome (e.g. XXY, XXXY), including mosaic variations (e.g. XY/XXY) and those with XX testicular disorder of sex development, but excluding those with a female cell line (e.g. XX/XXY). This seemed at the time to be a clearly defined subpopulation; however, it soon became apparent that things were not so straightforward.

Over the course of our recruitment period, from November 2008 to December 2009, a number of inquiries came through, some from clinicians, but mostly from the support group Organisation Intersex International Australia Ltd. Were we just looking for male XXY participants? Or were we also interested in XXY participants who were female, intersex, or at least did not identify as male? This initially caused some concern amongst the research team – we certainly had not intended to exclude anyone with XXY chromosomes, regardless of their gender identity, and we had lacked awareness of the possibility of this occurring, by assuming that all XXY individuals are male.

However, none of the health professionals involved in the planning of this study had encountered this before and so it had not been raised as a possibility. In addition, there was, and still is, very limited evidence in the literature regarding the prevalence of non-male individuals amongst those with an XXY karyotype. The information that is available usually concerns an XXY karyotype found in conjunction with an additional genetic variation, such as a mutation in the androgen receptor gene (Girardin *et al.*, 2009). Follow-up studies of XXY individuals diagnosed through newborn screening surveys would suggest that almost all of these babies will be phenotypically male and identify as male. However, although probably only a small minority, individuals with XXY who do not identify as male do indeed exist, and a number of intersex organizations report more than a handful of female or non-male identifying people who have an XXY karyotype. Ultimately, it remains unknown what proportion of individuals born with XXY will identify as female, intersex or other. This caused us to consider carefully the definition of KS and of XXY, not only within our own research but also in terms of healthcare provision for these individuals.

In our experience, both in research and in clinical practice, the two terms – KS and XXY – are almost always used interchangeably. Yet, the study inquiries that we received highlighted an interesting issue: Should there be a distinction between XXY and KS? Males diagnosed with KS will generally have an XXY karyotype, or variation thereof. However, perhaps not everyone with a XXY karyotype should be diagnosed with KS. KS defines characteristics that are only unusual if found in a male. Common symptoms, such as low testosterone and breast development, are not unexpected features (or symptoms) if identified in a female. Therefore, for an individual with an XXY karyotype who does not identify as male, KS may not be a suitable diagnosis.

This line of thinking may even be extended to individuals who identify as male, but whose concept of masculinity may not align with that of their health professional or societal norms. For example, take two individuals with an XXY karyotype, one who clearly identifies as male, the other who does not identify as female, but who views their breast development as a part of who they are, not as a symptom. In these examples, KS is an appropriate diagnosis for the first individual, but may not be for the second.

To provide patients with the most appropriate care and treatment, it is important to understand these potential differences amongst those diagnosed with an XXY karyotype. The role of testosterone replacement therapy in KS

has numerous benefits, both medical and psychosocial (Simpson *et al.*, 2003). For some men, especially those who have not fully virilized in puberty, it can be a life-altering treatment. However, the reality is that it may not work for everyone, and especially for those individuals who may not consider themselves female, but do not wish to be more 'male' either. Whilst it may be argued that choosing not to have testosterone treatment could have a number of negative long-term medical consequences (Bojesen & Gravholt, 2007; Maggi *et al.*, 2007), this may not be the most important consideration for those who feel they are being medicated to change them into a person whom they do not feel themselves to be.

This situation is unlikely to present major problems for fertility specialists, who usually see men in heterosexual relationships seeking reproductive advice. However, it is possible that not all individuals, especially those who are diagnosed outside this context, will identify with typical notions of gender, sexual identity and therefore, masculinity (Noble, 2003).

As awareness of KS and other sex chromosome variations grows, it may become more important that these distinctions are clear, and that the spectrum of possible human variation is reflected in the medical information available to families and the general public. There are two reasons for this: the first is so that people with XXY who do not identify as male are not considered 'weird', and so that informed decision-making regarding the most appropriate treatment regime for them is encouraged. The second reason is that men with KS are not constantly struggling to dispute beliefs that they are intersex, or half female, which is a common message amongst media reports, and can be a source of uncertainty, stress and shame for these men (Herlihy *et al.*, unpublished data).

Ultimately, we decided that the goal of our research was to look at KS as a genetic condition affecting males, and not just the karyotype XXY, which may manifest in different ways for a small number of people. With little evidence in the literature to guide clinicians as to the gender profiles of people with XXY, the best practice is to approach each patient with an open mind (Gillam *et al.*, 2010). However, this issue begs further exploration: Should individuals with an XXY karyotype who do not identify as male be considered to have KS? In addition, how should individuals with an XXY karyotype who do identify as male, but do not wish to become more masculine, be informed of the possible consequences of lifelong testosterone deficiency, whilst maintaining respect for the patient's choice? This is an area of endocrinology that would benefit from further discussion and collation of clinical experience. Research into the range of karyotypes and their possible corresponding phenotypes, in addition to the current difficulties experienced by these people, would be beneficial.

Source of funding and disclosure statement

A. S. Herlihy is supported by funding from the National Health and Medical Research Council of Australia. L. Gillam is supported by funding from the Royal Children's Hospital Foundation. The authors have nothing to disclose.

A. S. Herlihy†‡§ and L. Gillam*¶***
**Murdoch Childrens Research Institute, Parkville, Vic., Australia, †Department of Obstetrics & Gynaecology, Monash University, Clayton, Vic., Australia, ‡Andrology Australia, Clayton, Vic., Australia, §Prince Henry's Institute of Medical Research, Clayton, Vic., Australia, ¶Centre for Health & Society, The University of Melbourne, Parkville, Vic., Australia and **Royal Children's Hospital, Parkville, Vic., Australia*
E-mail: amy.herlihy@mcri.edu.au

References

Bojesen A & Gravholt CH. (2007) Klinefelter syndrome in clinical practice. *Nat Clin Pract Urol* 4, 192–204.

Bojesen A, Juul S & Gravholt CH. (2003) Prenatal and postnatal prevalence of Klinefelter syndrome: a national registry study. *J Clin Endocrinol Metab* 88, 622–626.

Gillam L, Hewitt J & Warne G. (2010) Ethical principles for the management of infants with disorders of sex development. *Horm Res Paediatr* 2010; doi: 10.1159/000316940.

Girardin CM, Deal C, Lemyre E, Paquette J, Lumbroso R, Beitel LK, Trifiro MA & Van Vliet G. (2009) Molecular studies of a patient with complete androgen insensitivity and a 47, XXY karyotype. *J Pediatr* 155, 439–443.

Herlihy AS, McLachlan R, Cock M & Halliday J. (2010) The prevalence and diagnosis rates of Klinefelter syndrome: an Australian comparison. In press.

Jacobs PA & Strong JA. (1959) A case of human intersexuality having a possible XXY sex-determining mechanism. *Nature* 183, 302–303.

Klinefelter H, Reifenstein E & Albright F. (1942) Syndrome characterized by gynecomastia, aspermatogenesis without a-leydigsm and increased secretion of follicle-stimulating hormone. *J Clin Endocrinol Metab* 2, 8.

Maggi M, Schulman C, Quinton R, Langham S & Uhl-Hochgraeber K. (2007) The burden of testosterone deficiency syndrome in adult men: economic and quality-of-life impact. *J Sex Med* 4, 1056–1069.

Noble M (2003) Representations of Klinefelter Syndrome (revised 2010). Accessible from http://oiiaustralia.com/media/articles/representations-klinefelter-syndrome/.

Simpson JL, De La Cruz F, Swerdloff RS, Samango-Sprouse C, Skakkebaek NE, Graham JM Jr *et al.* (2003) Klinefelter syndrome: expanding the phenotype and identifying new research directions. *Genet Med* 5, 460–468.

doi: 10.1111/j.1365-2605.2010.01132.x