SSBP Syndrome Sheets

47,XXY (Klinefelter Syndrome)

First description and alternative names

“Klinefelter Syndrome” or “Klinefelter’s Syndrome,” sometimes abbreviated as KS, was first described by Dr. Harry Klinefelter in 1942 as an endocrine disorder characterized by small testes, hypogonadism, gynecomastia, and increased levels of follicle-stimulating hormone (FSH). Patricia Jacobs determined in 1959 that the clinical phenotype was due to a 47,XXY genotype (rather than the neurotypical 46,XY).

Genetics and molecular biology

47,XXY (KS) is a chromosomal variation in males in which one extra X chromosome is present, resulting in an XXY karyotype. 47,XXY (KS) is not inherited. The additional X chromosome arises from non-disjunction either during germ-cell development or in early embryonic cell divisions. Approximately 50% of non-disjunctions appear to be of maternal origin (Iitsuka et al., 2000). The cause of the non- disjunction is not known. Some cases of 47,XXY (KS) may have 46,XY/47,XXY mosaicism, which is when some of the cells have the 46,XY karyotype and some have the 47,XXY karyotype. Mosaic 47,XXY occurs because of an error in the division of the sex chromosomes in the zygote after fertilization. Mosaicism is not associated consistently with milder presentation in neurodevelopment. Although the higher the presence of mosaicism of 46, XY, the more likely of a milder presentation developmentally.

Incidence/prevalence

47,XXY (KS) is the most common sex chromosome disorder and is currently estimated to affect approximately 1: 400 to 650 males. 47,XXY (KS) is an underdiagnosed condition, as only 25% of all cases are detected in their lifetime. Of those diagnosed, it is estimated that less than 10% of cases were diagnosed before puberty (Bojesen & Gravholt, 2007). However, diagnosis of 47,XXY (KS) through prenatal detection may be increasing through advances in prenatal screening such as non-invasive prenatal screening (NIPS) with confirmatory prenatal (amniocentesis or chorionic villus sampling) or postnatal (chromosomal microarray or chromosome karyotype) testing. A chromosomal microarray (CMA) test consists of a blood sample or oral cheek (buccal) swab. Cheek swabs are an easy and painless way to detect chromosomal abnormalities to provide a definitive diagnosis.

Physical features and natural history

Although 47,XXY (KS)is associated with a characteristic pattern of physical differences, the degree to which an individual is affected may vary. Males with 47,XXY (KS) have been

traditionally described as tall, with narrow shoulders, broad hips, sparse body hair, gynecomastia, small testes, and androgen deficiency. However, with testosterone replacement many physical features such as sparse body hair and gynecomastia may be mitigated. Post-pubertal males may manifest infertility, gynecomastia, lack of complete pubertal virilization, testicular failure, azoospermia and elevated gonadotropin levels, with decreased 17-ketosteroid levels. Studies investigating the efficacy of targeted administration of male hormones (androgens), such as testosterone enanthate, in boys with 47,XXY (KS) have shown hormone replacement to alleviate feminization effects that may have occurred due to insufficient testosterone levels, while also promoting the development of secondary male sexual characteristics. During adulthood, boys with 47,XXY (KS) are also at increased risk of low energy, low libido, osteoporosis, thromboembolic disease, obesity, and diabetes mellitus when hormonal levels, health and well-being are not well managed. Recently, studies have demonstrated the positive effect of testosterone treatment on the well-being and neurocognitive profiles of boys with 47,XXY (KS) (Samango-Sprouse et al., 2013; 2018). Testosterone treatment in boys with 47,XXY has also been shown to decrease anxiety and increase motor proficiency (Samango-Sprouse et al. 2013; 2015).

Behavioural and mental health characteristics

Individuals with 47,XXY (KS) may be at increased risk for behavioral problems and psychiatric disorders. Behavioral problems are variable in incidence—although the child with a prenatal diagnosis presents with fewer problems and often has no behavioral issues (Ross et al., 2012; Samango- Sprouse et al., 2013; 2015). Additionally, boys receiving early hormonal treatment in infancy or early childhood have fewer behavioral problems than the untreated child or the child postnatally diagnosed (Samango-Sprouse et al., 2015, 2021). School-aged children frequently show problems with anxiety, mood dysregulation, self-esteem, and socialization. Socialization problems frequently relate to social avoidance, secondary to generalized anxiety, and they may become more pronounced during adolescence especially without appropriate hormonal treatment and support. Some of these problems may be exacerbated from frustration stemming from a relatively depressed expressive ability as compared to receptive skills (Simpson et al., 2003; van Rijn et al., 2006). Testosterone replacement therapy may minimize these neurodevelopmental dysfunctions, specifically early hormonal treatment (Ross et al., 2014; Samango-Sprouse et al., 2011, 2013, 2015, 2018, 2021).

Neuropsychological characteristics

Emerging neuroimaging technology has increased and improved our understanding of the relationship among brain development, neurocognition, and behavioral outcome—especially in boys with 47,XXY (KS) (Giedd et al., 2007). Studies on boys with 47,XXY (KS) utilizing these neuroimaging techniques have revealed reduced total brain volumes that are specifically seen in the frontal, caudate, and temporal (especially left) regions of the brain (Giedd et al., 2007). Abnormalities in frontal and caudate brain MRIs are similar to those seen in MRIs of boys with ADHD, and indicative of the executive dysfunction seen in boys with 47,XXY (KS) (Giedd et al.,

2007; van Rijn and Swaab, 2015). The temporal lobes are associated with language capacities involving reading, social language, and processing of spoken information—all of which are notably challenged in untreated males with 47,XXY (KS) (Shen et al., 2004; Savic, 2012). Abnormalities in the caudate nucleus are believed to adversely affect speech and language, as well as manifest as dyspraxia and oral motor dysfunction that may be found in 47,XXY (KS) boys (Giedd et al., 2007). The gray matter density in the insula region of the brain in these boys is also decreased, which is linked to social and emotional processing issues (Nagai et al., 2007). The parietal lobe, however, is relatively unaffected when measured by cortical thickness and volume (Giedd et al., 2007). The preservation of this region is evident in the enhanced spatial cognitive skills in males with 47,XXY (KS) (Samango-Sprouse and Law, 2001; Savic, 2012). Many 47,XXY (KS) males have normal or above average cognitive capacity with typically higher nonverbal IQs than verbal IQs . These neuroanatomical findings in 47,XXY (KS) boys have revealed several salient characteristics that are morphologically different from neurotypically developing peers. Several studies, however, have suggested that more normalized brain development is possible through the utilization of hormonal treatment (Patwardhan et al., 2000; Samango-Sprouse et al., 2015). Patwardhan et al. (2000) compared two groups of 47,XXY (KS) individuals (one receiving hormonal treatment therapy versus no treatment) and found that temporal gray matter was preserved in the treated group, but diminished in the untreated group. Further studies are warranted to confirm these findings and investigate whether other abnormal brain areas, as described above, show similar normalization after hormonal treatment therapy.

Available guidelines for behavioural assessments/treatment/management

Once the individual or fetus is diagnosed with 47,XXY (KS), it is important to seek consultation with medical and health care professionals who are familiar with 47,XXY (KS) for recommendations regarding resources, appropriate biological and neurodevelopmental therapies, as well as medications for ADHD or anxiety (Samango-Sprouse & Gropman, 2016). Early interventional therapies (e.g. physical, occupational, and speech therapies) are recommended when discrepancies or deficits are identified throughout early childhood to enhance neurodevelopmental outcomes. Physical therapy is indicated when there is hypotonia, motor delay, and/or poor coordination and is most effective between 4 and 18 months in order to develop independent ambulation skills. Occupational therapy should be considered for the boys with decreased muscle tone in the trunk or upper body, because these deficits will affect handwriting, posture, attention, and eventual school success. This type of evaluation may be most beneficial between 4 and 6 years of age and typically is needed for 12 months. Additionally, 95% of identified boys with 47,XXY (KS) have reading disorders, which makes many aspects of learning challenging if not properly addressed. Specific speech and language therapies should address speech delays with motor planning deficits, language formulation abnormalities and syntactical delays. Speech therapy should focus on eliminating oral motor weakness and dysfunction through a sensorimotor approach. If there is history of early feeding difficulties with challenges in latching onto the breast or challenges to transitioning to table foods, then an evaluation for tongue and lip ties should be considered. Because of decreased muscle tonus and androgen deficiency, an active and healthy lifestyle should be encouraged from infancy through adulthood. Androgen replacement therapy can improve bone density, increase muscle mass

and strength, produce more masculine body contour, and decrease body fat. Infants with 47,XXY (KS) experience the neurotypical “mini-puberty” in which testosterone levels surge in the first 6 months of life, though at a significantly reduced rate (Forest et al., 1974, Lahlou et al., 2004). Early hormonal treatment (EHT) may mitigate these testosterone levels and keep these infants on an appropriate neurodevelopmental track (Davis et al., 2019, Samango-Sprouse et al., 2020, 2021). Testosterone can produce adequate pubertal maturation with increased body hair, penile enlargement, and male distribution of facial and body hair.

Useful websites/associations for further information

The Association for X and Y Chromosome Variations AXYS
https://genetic.org/variations/about-47xxy/

●The Focus Foundation
https://thefocusfoundation.org/x-y-chromosomal-variations/xxy/

● Genetics Home Reference
https://ghr.nlm.nih.gov/condition/klinefelter-syndrome

Genetic and Rare Diseases (GARD) Information Center
https://rarediseases.info.nih.gov/diseases/11920/47-xxy

● Klinefelter’s Syndrome Association UK
http://www.ksa-uk.co.uk/

● National Organization for Rare Disorders
https://rarediseases.org/rare-diseases/klinefelter-syndrome/

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