Short stature, cubitus varus, foot deformity and intellectual disability with sexual infantilism: clinical clues to 49,XXXXY variant of Klinefelter syndrome

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DESCRIPTION

A boy in his early adolescence was referred for delayed development of sexual characters. He was born of a non-consanguineous union, and had delayed developmental milestones. He had received elementary school education only, and his IQ was 52. Clinical examination of this mid-teenager revealed the following: height: 150 cm; weight: 41 kg; arm span: 152 cm; lower segment: 82 cm; upper segment: 68 cm. He had facial asymmetry, gynaecomastia, bilateral cubitus varus and bilateral clubfoot with pes planus (figure 1). The epididymides were well formed and the testes were 'shotty' with a volume of 1 mL (figure 1). The auxological parameters ('long-legged', difference between arm span and height of less than 5 cm) and the testicular appearance led to a working diagnosis of Klinefelter syndrome (KS). However, short stature (height less than third percentile, height SD score: −3.1) was not consistent with the clinical diagnosis of KS. Hormonal evaluation was suggestive of hypergonadotropic hypogonadism (testosterone: 9.67 ng/dL, follicle-stimulating hormone: 76.52 IU/L, luteinising hormone: 56.81 IU/L); however, the karyotype revealed 49,XXXXY pattern (figure 2). The boy was treated with monthly injection of testosterone esters and referred for rehabilitation therapy.

KS is the most common form of sex chromosome aneuploidy, and the leading aetiology of primary male hypogonadism with an estimated prevalence of about 1: 2500; however, the condition often remains undiagnosed. The principal karyotype obtained from peripheral blood leucocyte in KS is 47,XXY (90%) and majority of the remaining 10% have 47,XXY/46,XY mosaicism. Rarely, they have more than one extra X (or Y) chromosome (48,XXXY, 48,XXYY, 49,XXXXY). The 49,XXXXY variant is rare with an incidence of 1 in 85 000–100 000 live births. Because of shared features of tall stature, long legs, gynaecomastia, small 'shotty' testes and hypergonadotropic hypogonadism, they are considered as variants of KS. Some of the non-gonadal features are relatively more common in these patients compared with classic KS.

Interestingly, unlike other variants of KS, 49,XXXXY individuals often have short stature due to extreme overdosage of sex chromosomes genes, which was evident in this patient.[1]

KS with an extra X (or Y) chromosome often demonstrates one or more of the following dysmorphic features: hypertelorism, epicanthal folds, upslanting palpebral fissures, hooded eyelids, cleft palate, fifth-digit clinodactyly, short nail beds, pes planus, joint hyperextensibility, prominent elbows with cubitus varus, radioulnar synostosis, hip dysplasia, clubfoot, congenital heart defects and kidney dysplasia. In addition, inguinal hernia, cryptorchidism, cognitive impairment and psychological disorders are more frequent in 48,XXYY or 48,XXXY compared with 47,XXY. The prevalence is even higher in 49,XXXXY.[1] Intellectual disability is almost universal in 49,XXXXY with speech delay, learning difficulties (100%), intellectual impairment (>95%) and a mean full scale IQ of 20–60 (verbal IQ<performance IQ).

The carrying angle is the acute angle formed between the median axis of arm and the median axis of forearm, with the latter held in full extension and supination. Carrying angle, being greater in females than in males, is considered a sexually dimorphic secondary sexual characteristics to accommodate the broader pelvis in women. However, some studies reported no significant difference in carrying angle between males and females in any age group. Some found that the angle is greater in non-dominant arm than in dominant arm and is inversely related to the height of the person, while others documented the reverse.[2] Short stature homeobox-containing (SHOX) gene is thought to play an important role in the formation of carrying angle. The SHOX gene is located in the pseudo-autosomal region 1 (PAR1), situated at the end of the short arms of both the X and Y chromosomes (Xp22.3 and Yp11.3), and like other

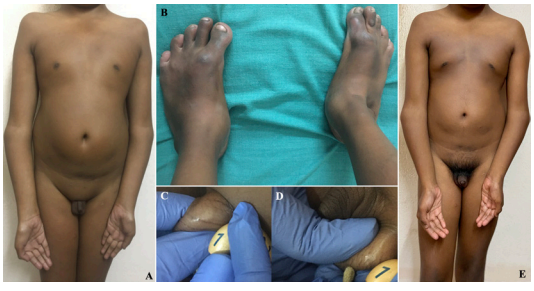

Figure 1 (A) Clinical picture showing bilateral cubitus varus and lack of pubic hairs; (B) clubfoot and flat foot; (C,D) small testes having a volume of 1 mL; (E) appearance of pubic hairs with testosterone supplementation.

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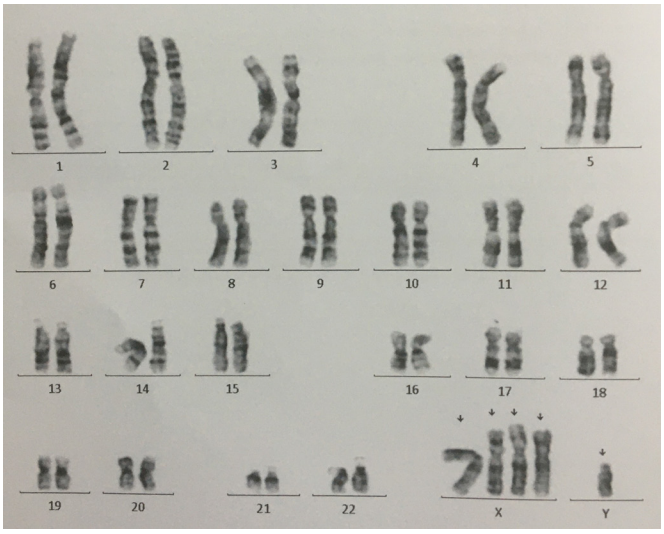

Figure 2 Peripheral G-banded karyotype showing 49,XXXXY pattern.

genes in PAR1, escapes X-inactivation. SHOX is expressed in the developing limbs and pharyngeal arches in human embryos, and likely regulates differentiation and proliferation of chondrocytes. Increased carrying angle or cubitus valgus is seen in about 70%–85% cases of Leri-Weill dyschondrosteosis and Turner's syndrome, conditions characterised by SHOX deletions/mutations and SHOX haploinsufficiency, respectively. Cubitus rectus or cubitus varus, conditions characterised by decreased carrying angle, is seen in 48,XXXY, 48,XXYY, 49,XXXXY syndromes, possibly due to SHOX overdose.[3] Presence of cubitus rectus or cubitus varus in absence of radioulnar synostosis is a strong indicator of overdosage of sex chromosomes and the degree of carrying angle is inversely related to the number of sex chromosomes.[4] The angle is increased (cubitus valgus) in 45,XO, normal in 47,XXY, absent (cubitus rectus) in 48,XXXY or 48,XXYY, and inverted (cubitus varus) in 49,XXXXY individual.

In addition to cognitive impairment and developmental delay, reduced expressive language abilities often predispose such individuals to behavioural dysfunction, occupational skills and difficulties in daily living. Early testosterone supplementation is associated with a positive impact on language deficits.[5] Thus, comprehensive clinical assessment and multidisciplinary management involving physical therapists, speech therapists, occupational therapists, psychologists and endocrinologists at an early age are essential for favourable long-term outcome of the syndrome.

Learning points

- The 49,XXXXY variant is a rare variant of Klinefelter syndrome with prominent facial dysmorphism, distinctive skeletal abnormalities (cubitus varus, clubfoot, flat foot) and pronounced cognitive, behavioural and intellectual disabilities. Unlike other variants of Klinefelter syndrome, 49,XXXXY is often short.
- The carrying angle is inversely proportional to the number of sex chromosomes, high in monosomy and absent or inverted in presence of additional sex chromosomes. Cubitus varus in patients with suspected Klinefelter syndrome is an important clinical clue for underlying short stature homeobox-containing gene overdosage due to extra X (or Y) chromosome.
- Early diagnosis of such tetrasomy and pentasomy sex chromosome aneuploidy is important as they often require additional evaluation and multidisciplinary approach in addition to sex steroid therapy.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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