Near absent carrying angles: a clinical clue to underlying SHOX overdosage

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DESCRIPTION

A 17-year-old right-handed boy with childhood onset seizure disorder presented to us with new onset diabetes mellitus. Clinical examination revealed tall stature (height: 181.2 cm, mid-parental height: 166.4 cm), normal body mass index (20.1 kg/m^2), normal waist circumference (83.5 cm) without acanthosis. The upper segment (85.2 cm):lower segment (96 cm) ratio was 0.89 and the difference between arm span (185.3 cm) and height was 4.1 cm. He had normal stretched penile length, small firm testes (left: 4 mL, right: 3 mL), Tanner stage 3 pubic hairs without gynaecomastia. He appeared to have no carrying angles, subsequently goniometry revealed grossly reduced carrying angles (right: 1° , left: 2°) (figures 1 and 2). The relevant investigations have been summarised in table 1.

Psychological testing with Binet Kamat Intelligence Test and The Vineland Social Maturity Scale revealed mild intellectual disability (intelligent quotient: 63) with 50% intellectual impairment along with deficit in social adaptive functioning. G-banded karyotype from peripheral blood leucocytes documented 48, XXYY pattern (figure 3).

Carrying angle, the acute angle between the median axes of arm and a fully extended and supinated forearm is typically greater in females

Figure 2 Measurement of carrying angles with a goniometer. The angle measured 1° in right elbow (A) and 2° in left elbow (B).

compared with males. The relatively higher angle in females may be explained teleologically to accommodate the wider gynaecoid pelvis. This sexual dimorphism though not universal in prepubertal children, usually increases in girls post puberty; hence, carrying angle may be considered as a secondary sex characteristic of the females. The underlying reason(s), however, is unexplained and a number of postulations have been put forward. Height and forearm length have been found to be inversely related with carrying angle and females by virtue of their shorter height and forearm length have greater carrying angle. Some studies noticed no real sex differences and concluded that such apparent differences may be explained by increased joint laxity in females, permitting a greater degree

Figure 1 Clinical photograph showing absent carrying angles, normal penile length and Tanner stage 3 pubic hairs.

Table 1 Summary of relevant work-up

Parameters	Patient's value	Reference range
Fasting plasma glucose	245	<100 mg/dL
2 hour postmeal plasma glucose	389	<140 mg/dL
Glycated haemoglobin (HbA1c)	10.6	<5.6%
Triglyceride	347	<150 mg/dL
High density lipoprotein cholesterol	21	>40 mg/dL
Testosterone (09:00)	132.9	295–545 ng/dL
Leutinsing hormone (pooled)	19.63	1.5–9.3 mIU/mL
Follicle stimulating hormone (pooled)	29.9	1.4–18.1 mIU/mL
Ultrasonography of abdomen	Fatty liver	
Seminogram	Azoospermia

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Figure 3 48, XXYY pattern in G-banded karyotype.

of extension. The carrying angle may be asymmetric as some studies have noticed greater carrying angle in dominant arm, while others came up with the reverse finding. The observed mean carrying angle in males varies in different studies and values ranging from 4.55° to 19.4° have been reported. Short stature homeobox-containing gene (SHOX) is also believed to play a role in the formation of carrying angle. SHOX resides in the pseudoautosomal region 1, situated in short arms of both the X and Y chromosomes (Xp22.3 and Yp11.3), escapes X inactivation and encodes a transcription factor exclusively expressed in the developing limbs and pharyngeal arch of the developing embryo. 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.¹

Cubitus varus is a condition when the carrying angle is decreased and complete loss of angulation is called cubitus rectus. Excess SHOX is expected to be associated with cubitus varus as encountered in conditions like 49,XXXXY, 48,XXYY and 48,XXYY syndromes.² Radioulnar synostosis leading to limited supination/pronation is another elbow abnormality associated with 48,XXYY syndrome, which however was absent in this boy.

The above listed conditions mimic classical 47, XXY Klinefelter syndrome (KS) in many aspects and principles of management also do not differ much. An association between KS and type 2 diabetes has long been recognised due to increased adiposity secondary to hypogonadism. Similarly, boys with 48,XXYY karyotype are also vulnerable to metabolic syndrome and type 2 diabetes. Increased propensity for autoimmunity is also associated with increased risk of type 1 diabetes in both these conditions as well. Fertility can be achieved in some cases

of KS if viable sperms are able to be retrieved.³ Unfortunately however, a severe delay in diagnosis, underdiagnosis or nondiagnosis is quite common in KS. Testosterone supplementation in KS needs to be initiated at the beginning of puberty, as follicle stimulating hormone and leutinising hormone start to rise, to secure sufficient increase in bone mineral density (BMD) and muscle bulk to prevent subsequent osteoporosis. So, it suffices to state that early diagnosis of such related syndromes is of utmost

Learning points

- ▶ 48,XXYY syndrome with an incidence between one in 17 000 and 50 000 live births shares many features with classical 47, XXY Klinefelter syndrome (incidence one in 1000 live births) like tall stature, small firm testes and hypergonadotrophic hypogonadism. However, facial dysmorphism, skeletal abnormalities like cubitus rectus/varus and more pronounced cognitive, behavioural and intellectual disabilities are important distinctive features.
- ▶ Cubitus rectus or cubitus varus is a skeletal marker of short stature homeobox-containing gene overdosage and an important clinical clue to the underlying diagnosis particularly in peri-pubertal individuals with no/minimal hypogonadal symptoms.
- ▶ Early diagnosis of syndromes such as 48,XXYY is important to help address the learning and behavioural difficulties, to ensure appropriate testosterone and medical management and to guide discussions of current research related to possible fertility interventions.

importance and the role of vigilant clinical examination can not be overemphasised.

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