Exceptional Association Between Klinefelter Syndrome and Growth Hormone Deficiency

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ABSTRACT

Klinefelter syndrome (KS) is characterized in adults by the combination of a tall stature, small testes, gynecomastia, and azoospermia. This case is described in a North African population of the Mediterranean region of North Africa. We report the case of a male 16 years old, of Arab ethnic origin, and diagnosed with this syndrome, who had a small height in relation to a growth hormone (GH) deficiency and a history of absence seizures (generalized myoclonic epilepsy). The patient's size was < -2.8 standard deviation (SD) with weight < -3 SD. GH deficiency was isolated and confirmed by two dynamic tests (insulin — hypoglycemia tolerance test and clonidine) with normal hypothalamic magnetic resonance imaging (MRI). GH supplementation using recombinant GH was advocated, while gonadotropin treatment was deferred.

Small size in children or adolescents should not eliminate the diagnosis of Klinefelter syndrome — on the contrary, the presence of any associated sign (brain maturation, delay in puberty, aggressiveness) should encourage one to request a karyotype for the diagnosis and appropriate care of any case of KS that can be associated with GH deficiency, or which is in a variant form (isochromosome Xq, 49,XXXXY).

Key words: Growth hormone (GH) deficiency, Klinefelter syndrome (KS), short stature

In 1942 Klinefelter, Albright, and Reifenstein described Klinefelter syndrome (KS) as the association of small firm testes with hyalinized seminiferous tubules, gynecomastia, elevated gonadotropins, and azoospermia.^[1] Seventeen years later in 1959 Jacobs related this syndrome to the presence of an extra X chromosome with a 47,XXY karyotype.

It is one of the most common chromosomal aberrations with a prevalence of about 1/660 male births,^[2] thus representing the most common genetic cause of hypogonadism and male infertility, with 11% of patients with azoospermia presenting a case of KS.^[3]

Although tall stature is very characteristic of KS, some cases associated with small size have been described.^[4-12]

We report an unusual case of KS with small stature secondary to growth hormone (GH) deficiency. This case is described from within a North African population of the Mediterranean region of North Africa.

The patient was a young male, eldest of three siblings; with history of infertility in his paternal uncle; child of a consanguineous marriage with uneventful gestation, normal delivery, and good postbirth adaptation, imprecise size at birth, and no delayed psychomotor acquisitions.

The patient had a history of gastroesophageal reflux, and asthma that responded to treatment after the age of 7 years. The parents were consulted after onset of aggressiveness and absence seizures in the patient around the age of 16, associated with persistent stunted growth.

On physical examination, the patient weighed 31 kg [< -3

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standard deviation (SD)], had a height of 1.54 m (<-2.8 SD on presumed growth curve), presenting macroskelia with bitrochanteric diameter greater than biacromial diameter without midline defects.

The patient showed signs of puberty (Tanner stage II), with intrascrotal testes measuring 2.5 cm $\times$ 1.5 cm for the right and 2.3 cm $\times$ 1.5 cm for the left testis; penis length of 6.5 cm $\times$ 2 cm; urinary meatus in place; hair Tanner stage III-IV, axillary hair less developed; painful stage II bilateral gynecomastia without galactorrhea or nodule or even axillary lymphadenopathy. In addition, the patient showed no clinical signs of hypercorticism or thyroid dysfunction. Physical examination, especially cardiovascular lumbar and neurologic, were unremarkable.

Faced with the clinical presentation mentioned above, laboratory investigations were performed to ascertain the cause of persistent stunted growth. The results were as follows.

The bone age was estimated at 10 years (6-year differential with calendar age); malabsorption test, celiac disease serology, thyroid function tests as well 8 AM blood cortisol level showed normal results.

Insulin-like growth factor-1 (IGF1) was decreased to 156 ug/L while normal rates are comprised between 188 and 510; GH deficiency was confirmed by two dynamic tests: The insulin tolerance was test and found lower than 3.33 ng/ml and clonidine demonstrated a peak at 0.166 ng/mL.

Magnetic resonance imaging (MRI) did not reveal pituitary gland hypoplasia or any associated hypothalamic malformation.

The exploration of the gonadotropic axis highlighted high gonadotropin levels with normal testosterone: follicle-stimulating hormone (FSH) 16.57 mIU/mL (Tanner stage 0.4-2.8) (age: 0.6-4.8 years); luteinizing hormone (LH): 3.60 mIU/mL (Tanner 0.4-1.9) (age: 0.9-2); testosterone: 5.3 ng/mL (Tanner 0.2-3) (age: 1.2-7); estradiol: 11 pg/mL (ages 6-27); and prolactin: 14.37 ng/L (age: 1-17).

Thus, our patient had isolated GH deficiency with normal pituitary glands on MRI and high gonadotropin levels, which led us to request a karyotype. KS was retained with 47,XXY.

As for the seizures, no cerebral malformation was discovered on MRI.

With respect to the patient's small size, GH supplementation was recommended, and due to the inherent fertility prognosis the patient was sent to a specialized center for cryopreservation and storage of spermatogonia before beginning androgen therapy.

The diagnosis is particularly easy to make in young adults with the conditions of large size, gynecomastia, and small testes that are suggestive of KS, which could otherwise prove more difficult before puberty.^[4]

This diagnosis should be considered in a child presenting with severe character disorders, psychiatric antecedents, or major mental retardation impeding schooling. The discovery of a micropenis and severe testicular atrophy contrasting with age or cryptorchidism also constitutes revealing indices.

At puberty, attention can be drawn to the possibility of this syndrome in the presence of gynecomastia or less developed testes, which may even be atrophic.^[5]

The large-size phenotype may not be present: several cases of KS have been reported in the literature with small stature, yet its pathophysiological mechanism remains unclear.^[10]

Pepin-Donat *et al.* reported a case of a stunted growth and delayed neuromotor acquisitions in a 15-month-old infant presenting with dysmorphic syndrome with associated microcephaly, round facies, narrow and inwardly inclined palpebral fissures, wide nasal bridge, long eyelashes, hyperlaxity, small penis, and cryptorchidism. The additional tests, i.e., GH, thyroid function, and bone age tests were normal, while the karyotype was 49,XXXXY/48,XXXY (80%/20%).^[6] This syndrome, called Schmid-Fraccaro syndrome, is associated with: small size, intellectual deficit [average intelligence quotient (IQ): 25-50, maximum 80-90; disproportion between verbal IQ which is very low and normal IQ performance], thin skull, hypertelorism, prognathism, abnormal sacral vertebrae, vertebral body squaring, scoliosis, thin sternum, and hypoplasia of the rib cage.^[6]

Richer *et al.* reported a case of a 30-year-old male patient, with children, with height lower of 5 cm compared to his father presenting with gynecomastia, small testes, and normal androgen levels. Karyotype analysis demonstrated the aneuploidy 47,Xi(Xq)Y.^[7]

Other cases were described that were associated with GH deficiency, as in the Ramesh *et al.* report of a case of KS in a 3-year-old infant with a micropenis, for which the etiological exploration revealed isolated GH deficiency secondary to an anterior pituitary gland hypoplasia.^[8]

Rossodivita *et al.*^[9] and Bahillo-Curieses *et al.*^[10] also reported a case of KS in a child aged 8 years with cryptorchidism and small stature and another case of KS associated with delayed puberty relating to idiopathic GH deficiency, respectively.

A similar combination (KS + GH deficiency) was also described by Ben-Skowronek *et al.*^[11] and Tori *et al.*^[12] with a yet-unknown underlying mechanism.

Our case clearly illustrates another case of this unusual association of small size with KS, related to GH deficiency, normal MRI, and aneuploidy 47,XXY karyotype.^[13]

Finally, small size in children or adolescents should no longer rule out the diagnosis of KS. Instead, the presence of any associated signs (mental retardation, delayed puberty,

aggressiveness) should urge one to request a karyotype as it allows the diagnosis and appropriate management of KS, which can be associated with GH deficiency, or which may be present in other variant forms (isochromosome Xq, 49,XXXXY). Additionally, further studies would be needed to explain these associations.

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Conflicts of interest

There are no conflicts of interest.

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