CASE REPORT

Klinefelter syndrome with low gonadotropin levels

Kripa Elizabeth Cherian, Felix K Jebasingh, Nitin Kapoor, Thomas Vizhalil Paul

Department of Endocrinology, Christian Medical College, Vellore, Tamil Nadu, India

Correspondence to
Professor Thomas Vizhalil Paul, thomasvpaul@yahoo.com

Accepted 11 December 2015

SUMMARY

Klinefelter syndrome is usually characterised by the presence of a eunuchoid body habitus and testes that are usually small and firm, with low testosterone, and elevated luteinising hormone and follicle-stimulating hormone levels, consistent with hypergonadotropic hypogonadism. Low levels of gonadotropins in karyotypically proven cases are not expected, they are extremely rare occurrences. We report a case of a patient who was diagnosed to have Klinefelter syndrome (47 XXY) with low gonadotropin levels. The rest of his anterior pituitary hormonal profile was normal with no lesions in the pituitary gland on imaging. He was continued on androgen replacement therapy.

BACKGROUND

Klinefelter syndrome (KS) is a common cause for hypergonadotropic hypogonadism. Finding low gonadotropin levels is very rare in KS. In these individuals, an associated pituitary pathology has to be excluded. Karyotyping in our individual was 47 XXY. Evaluation of anterior pituitary revealed normal levels of all hormones except for low gonadotropin levels and normal sella on imaging.

CASE PRESENTATION

A 40-year-old businessman presented to our endocrine clinic, with bilateral gynaecomastia and poor development of secondary sexual characters. He was elsewhere earlier diagnosed to have KS at the age of 31 years (follicle-stimulating hormone (FSH) of 55 μIU/mL with a karyotyping showing 47 XXY pattern), and was initiated on testosterone replacement therapy. He had been irregular with androgen replacement and had not been on treatment for the past 6 months. There was no history of anosmia and he had no visual disturbances. On examination, the patient had eunuchoid body proportions with poorly developed secondary sexual characteristics along with a testicular volume of 2 mL bilaterally and testes with a firm consistency. His optic fundi and fields were within normal limits. He had no dysmorphic features. A diagnosis of KS was again considered.

INVESTIGATIONS

The patient was found to have unusually low levels of luteinising hormone (LH) <0.1 mIU/mL and FSH 0.1 mIU/mL on two different occasions, with

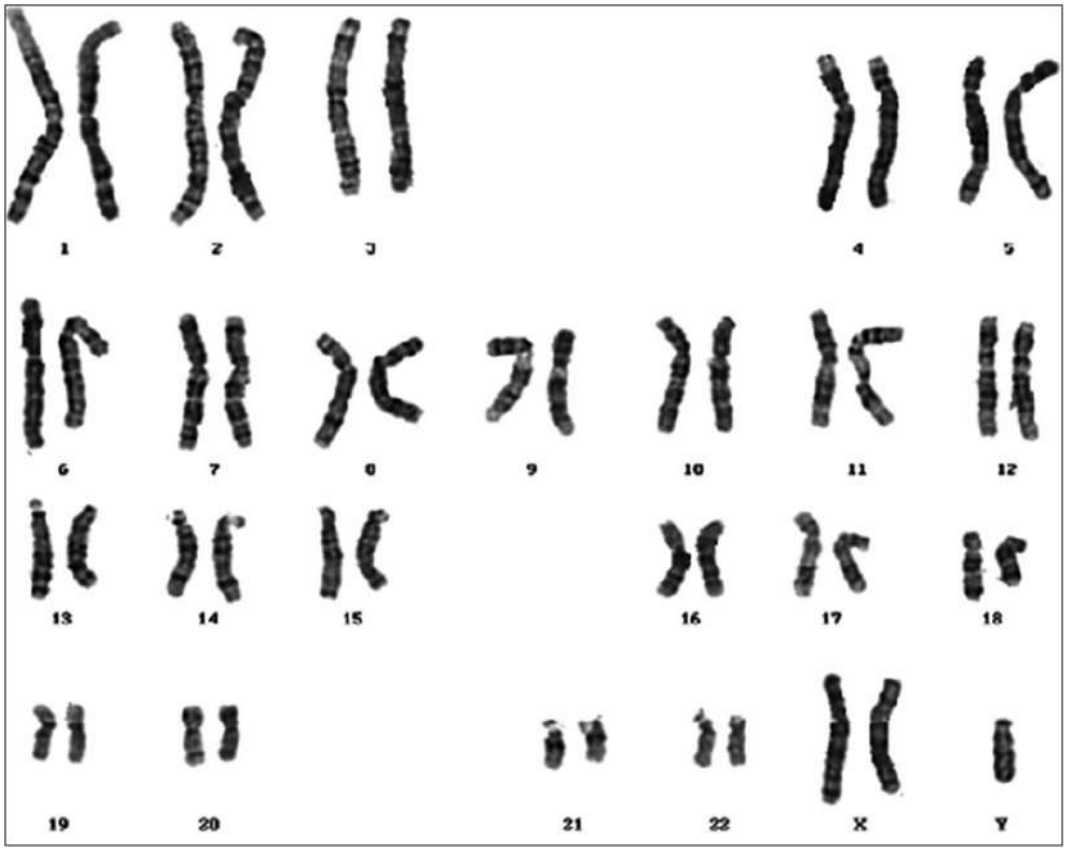

Figure 1 Peripheral blood karyotyping showing a 47 XXY pattern.

To cite: Cherian KE, Jebasingh FK, Kapoor N, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-213333

a very low testosterone level—<20 ng/dL (normal: 270–1040). Peripheral karyotyping revealed a 47 XXY pattern (figure 1).

DIFFERENTIAL DIAGNOSIS

In order to rule out the possibility of associated hypogonadotropic hypogonadism, further testing of other hormonal axes was carried out, which were as follows: 8:00 cortisol 19 µg/dL (normal: 7–28), thyroid-stimulating hormone 1.3 mIU/L (normal: 0.4–4.2), prolactin 5.7 ng/mL (normal: 2–18), thyroxine (T4) 7.6 µg/dL (normal: 4.4–12.5), free T4 1.1 ng/dL (normal: 0.8–1.8) and human chorionic gonadotropin below 5 mIU/mL (normal: <5). This was followed up with MRI of the pituitary, which was normal (figure 2). Repeat karyotyping confirmed a 47 XXY pattern. The patient was initiated on testosterone replacement therapy.

TREATMENT

This patient had hypergonadotropic hypogonadism, needing long-term replacement of androgens for the development and maintenance of secondary sexual characters.

OUTCOME AND FOLLOW-UP

The patient was referred for a surgery consultation for his gynaecomastia and was scheduled for a follow-up visit with us after 6 months.

DISCUSSION

KS was originally described by Klinefelter *et al*[1], who reported nine adult males with gynaecomastia, small and firm testes, azoospermia and elevation of serum FSH. KS is characterised by a tall stature, gynaecomastia, small testes and androgen deficiency. Many of these characteristics can be attributed to a genetically determined primary gonadal defect characterised by the XXY karyotype. In adults with KS, the testes are small due to hyalinisation of the seminiferous tubules, serum testosterone levels are in the low normal range, and serum gonadotropin levels are subsequently elevated.[2]

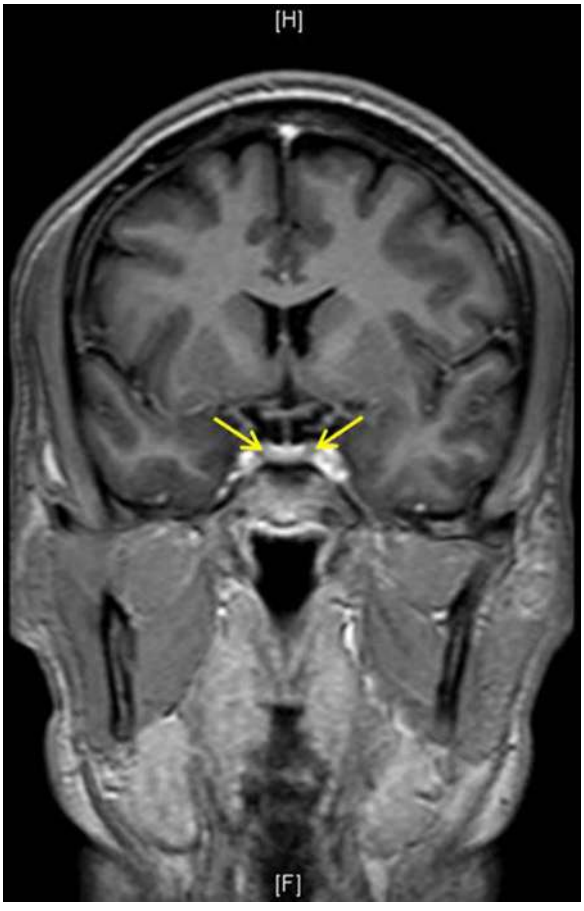

Figure 2 MRI of the brain showing a normal pituitary.

Precise regulation at the level of the hypothalamus, pituitary and gonads is required for normal sexual maturation. The episodic stimulation by hypothalamic gonadotropin releasing hormone (GnRH) drives the pulsatile release of LH, which in turn causes testosterone secretion by the Leydig cells. LH secretion is under tight negative feedback control by testosterone, which is chiefly at the level of the hypothalamus. As a result, low serum testosterone is accompanied by a compensatory increase in LH concentrations.[3 4] The regulation of pituitary FSH release is under the influence of GnRH, testosterone, estradiol (E_2) and inhibin B concentrations.[5]

Serum FSH and LH are increased uniformly in men with KS, thus indicating Leydig cell and seminiferous tubule dysfunction. Mean serum testosterone levels are reduced, but as many as one-third of patients have total testosterone levels within the low normal range.

The case scenarios depicted above describe the rare association of KS with paradoxically low levels of LH and FSH. Similar cases have been reported in the past. Advani *et al*[6] reported two cases of KS with non-elevated levels of LH and FSH. It is postulated that chronic stimulation of the gonadotropes results in exhausting of the LH and FSH, leading to low serum levels. As this can potentially confound the clinical picture further, evaluation of pituitary hormonal axes and imaging of the brain may be undertaken to exclude other organic causes. As mentioned in the first case scenario, an exhaustive work up carried out in our patient made it possible to rule out other possibilities and further established the prospect that chronic hyperstimulation had indeed led to an exhaustion of pituitary gonadotropins, manifesting as low serum levels of FSH and LH.

The exact reason for low levels of gonadotropins has not been elucidated. It has been postulated that diabetes mellitus can cause changes in the microvasculature at the hypothalamo-pituitary axis.[7] However, the occurrence of an isolated gonadotropin deficiency with the other pituitary hormonal axes being normal does not seem to justify this. It is possible that the condition of our patient represents a variant of KS, with a reduction in the release of LH and FSH occurring secondary to prolonged hypersecretion and exhaustion of the pituitary gonadotropins.

Learning points

- In men, Klinefelter syndrome is a common cause for hypergonadotrophic hypogonadism with a common karyotype of 47 XXY.
- A low gonadotropin level in Klinefelter syndrome is rare where there is associated pituitary pathology.
- Individuals with Klinefelter syndrome will need long-term androgen replacement therapy for the development and maintenance of secondary sexual characteristics.

Acknowledgements The authors would like to thank Banu Sanker for secretarial help.

Contributors KEC and FKJ wrote the manuscript. NK and TVP reviewed the manuscript. KEC, FKJ, NK and TVP approved the final manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Klinefelter HF, Reifenstein EC, Albright F. Syndrome characterized by gynecomastia, aspermatogenesis without A-Leydigism, and increased excretion of follicle-stimulating hormone. *J Clin Endocrinol Metab* 1942;2:615–27.
2 Lanfranco F, Kamischke A, Zitzmann M, *et al*. Klinefelter' syndrome. *Lancet* 2004;364:273–83.
3 Paulsen CA, Gordon DL, Carpenter RW, *et al*. Klinefelter syndrome and its variants: a hormonal and chromosomal study. *Recent Prog Horm Res* 1968;24:321–63.
4 Veldhuis JD, Straume M, Iranmanesh A, *et al*. Secretory process regularity monitors neuroendocrine feedback and feed forward signaling strength in humans. *Am J Physiol Regul Integr Comp Physiol* 2001;280:R721–9.
5 Andersson AM, Petersen JH, Jorgensen N, *et al*. Serum inhibin B and follicle-stimulating hormone levels as tools in the evaluation of infertile men: significance of adequate reference values from proven fertile men. *J Clin Endocrinol Metab* 2004;89:2873–9.
6 Advani SK, Chadha MD, Khan NM. Klinefelter syndrome with unelevated serum gonadotropin levels (a case report). *J Postgrad Med* 1991;37:171.
7 Carter JN, Wiseman DG, Lee HB. Klinefelter syndrome with hypogonadotrophic hypogonadism. *Br Med J* 1977;1:212.