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46, XX Male Disorder of Sexual Development

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Abstract

Presentation

A 47-year-old male was referred to endocrinology with a 9-year history of primary hypogonadism. Baseline testosterone was 4.3 nmol/L (RR 8-30) with an elevated follicle stimulating hormone (17.5 IU/L) and luteinizing hormone (15.2 mIU/ml). He had a short stature with bilateral small pre-pubertal testicles.

Diagnosis

Karyotyping showed 46 XX, making a diagnosis of 46, XX male disorder of sexual development. Fluorescence in situ hybridization analysis identified the presence of a translocated sex-determining region Y gene.

Treatment

Testosterone replacement therapy (testogel). Monitoring blood markers affected by testosterone therapy and metabolic risk factors.

Conclusion

Primary hypogonadism in males can be divided into congenital and acquired causes. 46, XX male disorder of sexual development is a rare congenital cause, with an incidence of approximately 1 in 20,000 newborn males. This case report highlights the value of karyotyping in the workup for primary hypogonadism.

Introduction

46, XX male disorder of sexual development is a very rare congenital cause of primary hypogonadism, with an incidence of approximately 1 in 20,000 newborn males [1]. Having been initially described in 1964[2], approximately 150 cases had been reported worldwide by 1996[3]. Since then, only over 100 cases are estimated to have been reported globally between 1996 and 2006[4].

The features include a 46 XX karyotype, normal or ambiguous external genitalia, azoospermia and absence of mullerian structures[5]. The vast majority of males (85%) present after puberty with small testes, gynecomastia and infertility, with only approximately 15% presenting with ambiguous external genitalia at birth [5].

Case Report

A 47-year-old male was referred with a history of hypogonadism. History taking revealed he presented to his General Practitioner 9 years previously with sweating, loss of libido, weight gain but denied erectile dysfunction. He has never desired fertility. Baseline hormone profile showed a morning testosterone of 4.3 nmol/L (RR 8-30) with an elevated follicle stimulating hormone (17.5 IU/L) and luteinizing hormone (15.2 mIU/ml). He was commenced on transdermal testosterone (testogel) by his General Practitioner. On treatment, he is shaving, has a normal libido and is sexually active. Past medical history included an undescended testicle and depression. He has no relevant family history.

On review, he was normotensive, height 155cm (less than 3rd percentile) and body mass index 38.8 Kg/m^2. He had no hypogonadal features on treatment or a phenotype characteristic of Klinefelter's syndrome (eunachoid habitus or glandular gynecosmastia). He had bilateral small testicles, less than 4 mls. Ultrasound confirmed atrophic testes. Penile development is normal.

A blood sample was sent for karyotyping. This revealed a 46 XX karyotype. Fluorescence in situ hybridization (FISH) analysis identified the presence of the sex-determining region Y (SRY) gene and its location on the distal region of the short arm of one X chromosome.

Discussion

This is a very rare case of primary hypogonadism. While there are known familial cases, the majority of 46 XX male karyotypes are not inherited [5]. The SRY gene is the major determinant of gender and is responsible for the differentiation of the bipotential gonad into testis [6]. The vast majority of male cases, approximately 80%, are SRY positive[5], as was this patient. Such males generally do not present until after puberty as it is only then that testosterone deficiency becomes apparent[4,7]. In most cases, there is translocation of the Y chromosome to the X chromosome during paternal meiosis [6].

The clinical features of 46 XX males can overlap with Klinefelter syndrome (47 XXY karyotype). Both conditions can present with small testes, hypogonadism and gynecomastia[5]. However, an important distinguishing factor is height [4]. Males with 46 XX karyotype tend to be significantly shorter and have a greater incidence of maldescended testes than males with Klinefelter's syndrome [4,8].

Disorders of sexual development are associated with a heightened risk of malignancy, particularly germ cell tumours and testicular carcinoma in-situ[9]. This is linked to genetic material located on the Y chromosome and to undescended testes[9].

Management of males with 46 XX karyotype involves testosterone replacement with regular monitoring of serum testosterone level, haematocrit, liver profile, prostate specific antigen and bone mineral density.

In conclusion, 46 XX male disorder of sexual development is a differential in the workup for primary hypogonadism and should be considered, especially with a history of maldescended testes and short stature [4].

Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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