Achondroplasia with SRY-positive 46, XX disorder of sex development: an extremely rare association

Yang Timothy Du¹, Angus Rutter² and Jui T Ho¹

¹Department of Diabetes and Endocrinology, Flinders Medical Centre, Bedford Park, South Australia, Australia and ²School of Medicine, Flinders University, Bedford Park, South Australia, Australia

Summary

A 40-year-old man with achondroplasia presented with symptoms of hypogonadism, low libido and gynaecomastia. He was found to have hypergonadotropic hypogonadism, and karyotype and fluorescent in situ hybridisation analysis showed SRY-positive 46, XX disorder of sex development (DSD). He was tested to have the common activating mutation of the FGFR3 gene implicated in achondroplasia, indicating that he had the two rare conditions independently, with an extremely low incidence of 1 in 400 million. This, to the best of our knowledge, is the first report of an individual having these two rare conditions concurrently. This case highlights that individuals with achondroplasia should have normal sexual development, and in those presenting with incomplete sexual maturation or symptoms of hypogonadism should prompt further evaluation. We also propose a plausible link between achondroplasia and 46, XX DSD through the intricate interactions between the SRY, SOX9 and FGFR9 gene pathways.

Background

To our knowledge, this is the first report of an extremely rare association of achondroplasia and 46, XX SRY-positive testicular disorder of sex development (DSD) diagnosed in adulthood. This man presented relatively late at the age of 40 years with symptoms of hypogonadism and small testes, which he had always attributed to complications of achondroplasia. When he was investigated for causes of hypogonadism, the diagnosis of DSD was made, allowing appropriate management, counselling and patient satisfaction in understanding his condition.

Case presentation

A 40-year-old man with achondroplasia was referred to the endocrine service for assessment of painful left gynaecomastia, low libido, poor energy levels and irritable mood.

He was the second child of healthy parents of normal height who were in their late 20s at the time of conception. There was no history of consanguinity and no family history of dwarfism. He has severe bony and neurological complications from craniocervical stenosis and syringomyelia, requiring ventriculoperitoneal shunt.

Learning points:

• The SOX9 and FGF9 genes, which are upregulated by the SRY gene, are important in both sex determination in the embryo, as well as endochondral bone growth.
• Patients with achondroplasia should have normal sexual development and function in the absence of other confounding factors.
•Patients with achondroplasia who present with symptoms and signs of abnormal sexual development and/or hypogonadism should be appropriately investigated for other causes.

Correspondence

Correspondence should be addressed to Y T Du
Email yang.timothy.du@gmail.com
insertion for hydrocephalus at age 4 years and multiple neurosurgical interventions over the years. He suffers from chronic back pain and mobilises with a walking aid. He also has obstructive sleep apnoea treated with continuous positive airways pressure therapy and underwent a sleeve gastrectomy for obesity in 2014. Other past medical history included an episode of renal colic in 2006 and childhood mumps.

Apart from psychomotor delays in infancy as he failed to walk until age 2 years, he has normal intelligence and underwent puberty at the age of 14 years. He became sexually active at age 20 years, but not for the past 5 years as he was embarrassed by the size of his genitalia and physical appearance.

His medications include Buprenorphine patch 10mg weekly, Pregabalin 300mg BD, cholecalciferol 25 µg daily and a multivitamin supplement. He had no prior exposure to glucocorticoids or androgen therapy.

On examination, he was 127 cm tall and weighed 70 kg (BMI 41 kg/m²). He had disproportionate short stature with rhizomelic shortening, macrocephaly with frontal bossing, midface hypoplasia, lumbar hyperlordosis and a trident hand configuration (Fig. 1). He had a generalised paucity of body hair and exhibited poor secondary sexual characteristics – Tanner's stage III with sparse pubic hair, bilaterally descended small testes (1 mL volume) and a penile length of 5 cm without hypospadias. His visual field examination was normal. There was tender left gynaecomastia with no masses on palpation.

**Investigation**

Hormone analysis revealed hypergonadotropic hypogonadism (LH 39 U/L, FSH 36 U/L and testosterone 8.4 nmol/L). The rest of his anterior pituitary hormonal profiles were normal. There was no evidence of haemochromatosis, nor evidence of Müllerian structures on pelvic ultrasound. Cytogenetic analysis revealed 46, XX karyotype with a small amount of Y chromosomal material at the end of one of the X chromosomes (Fig. 2). Fluorescent in situ hybridisation (FISH) identified a sex-determining region Y (SRY) gene translocation onto one X chromosome (Fig. 3).

**Treatment**

The diagnosis of SRY-positive 46, XX testicular DSD would explain his male phenotype and diminished secondary sexual characteristics. Testosterone replacement was commenced, initially with topical testosterone, which resulted in supraphysiologic levels and later to oral testosterone capsules with good symptom resolution. Referral to the genetics clinic was made to discuss the implications of DSD on his fertility. He underwent genetic testing for achondroplasia, which confirmed that he was positive for the c.1138G>A (G380R) mutation in the FGFR3 gene (Fig. 4). Given his short stature, he also underwent multiplex ligation-dependent probe amplification sequencing for the short stature homeobox (SHOX) gene, usually located on each of the sex chromosomes in the

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psuedoautosomal region (1) to determine if he has a concurrent deletion of this gene. No deletion of the SHOX gene was found. Further testing was not pursued as he did not desire reproduction.

**Outcome and follow-up**

Counselling and education about his condition has allowed him to better understand his previous symptoms of hypogonadism and physical attributes, including small testes. He had been aware of these for most of his life and perplexed by them, but, in part, was too embarrassed to seek earlier medical attention and ‘kept it quiet a lot of the time’. Understanding his DSD has given him satisfaction, and ongoing treatment with oral testosterone capsules has provided him with good symptom resolution.

A year after diagnosis, this man continues to attend regular follow-up in the endocrine clinic. He is aware of the need for ongoing surveillance for breast and germ cell cancer and continues to enjoy an improved quality of life from testosterone replacement therapy.

**Discussion**

The 46, XX DSD occurs rarely, with an incidence of 1 in 20 000 births (2). Most cases are sporadic, though familial cases have been reported (3). The majority of cases (90%) are SRY positive, caused by translocation of part of the Y chromosome, including the SRY gene, to the X chromosome due to recombination during paternal meiosis (3). These patients usually have male external genitalia and normal virilisation, hence, are not usually diagnosed before puberty, after which they may present with infertility, hypogonadism, gynaecomastia and/or small testes. They generally have a shorter than average stature, normal cognitive development and do not have evidence of Müllerian structures (3). Laboratory findings include hypergonadotropic hypogonadism, azoospermia and a 46, XX karyotype. The small testes, azoospermia and hypogonadism are largely due to the lack of a Y chromosome (despite translocation of the SRY gene), which contains relatively few genes but several that are required for spermatogenesis and testosterone production. SRY-negative cases (10%) often have ambiguous genitalia and poor virilisation, and hence, would usually be diagnosed at or soon after birth (3). In our case, the patient presented relatively late at the age of 40 years with symptoms of hypogonadism, which may have been masked for many years by his chronic opioid use for his debilitating pain from neurological complications of achondroplasia. He also never wondered about his height, which was shorter than the average male with achondroplasia (131 cm) or small testes and hence did not seek medical attention till much later in life.
The **SRY** gene is usually located on the Y chromosome and is one of the most important foundation genes of sex determination in the embryo \(^2\). Factors involved in the early development of the bipotential gonad are shown in Fig. 4. At about 6 weeks of gestation, the **SRY** gene initiates male sex determination by downstream regulation of sex-determining factors, including encoding a unique testis determining factor that activates a testis-forming pathway and facilitates activation of the **SRY**-like HMG Box 9 (**SOX9**) gene, critical for development of the early testes \(^4\). Expression of genes including **WT1**, **CBX2**, **MAP3K4** and **GATA4** is important in **SRY** activation \(^5\) \((\text{Fig. 5})\).

Once **SOX9** expression is upregulated in the developing testes, it then upregulates and forms a positive feed-forward loop with fibroblast growth factor 9 (**FGF9**), enhancing gonadal development and sexual differentiation in the male direction and blocks upregulation of the WNT4/β-catenin pathway and hence inhibiting any possible development in the female direction. The production of anti-Müllerian hormone (AMH) by Sertoli cells and androgens by Leydig cells further induces male sexual differentiation in a dose- and time-dependent manner \(^4\).

Important factors involved in ovarian differentiation are also shown in Fig. 5. By week 6, in the absence of a **SRY** gene, the WNT4/β-catenin pathway is activated in the setting of increased expression of **DAX1** and **RSPO1**, prompting gonadal development and sexual differentiation in the female direction, at the same time blocking **SOX9** and **FGF9**, inhibiting any possible development in the male direction \(^4\).

Achondroplasia is the commonest bone dysplasia in humans, affects males and females equally with an incidence of 1 in 20,000 and is almost invariably due to an activating mutation in the fibroblast growth factor receptor 3 (**FGFR3**) gene \(^6\). It is an autosomal dominant condition, though 80% of cases, including this one, is due to a *de novo* mutation \(^6\). In the absence of other confounding conditions, subjects with achondroplasia have normal cognitive and sexual development – the latter of this important for clinicians to remember. Testicular and penile size should be normal in males with achondroplasia, as these are not affected by impaired endochondral bone growth \(^7\). In our case, the presentation of small testes and symptoms of hypogonadism should prompt investigation for other causes of hypogonadism.
SOX9 is a well-established activator and up-regulator of both endochondral bone growth could be seen. The upregulation of SOX9 produces the achondroplasia phenotype (Fig. 6), even without a concurrent activating FGFR3 mutation.

In conclusion, we report the first case of achondroplasia in a patient with SRY-positive 46, XX DSD. Though the two conditions appear to have occurred independently in this case, there remains a possibility that they may be linked via SRY, SOX9 and FGF9 gene overexpression. Sexual development should be normal in individuals with achondroplasia, hence symptoms or signs concerning for abnormal sexual development should be appropriately investigated.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this case report.

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Patient consent
Written informed consent has been obtained from the patient for publication of this article and accompanying images.

Author contribution statement
Y T D, A R and J H were involved in the conception, drafting and critical review of this case report.

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