

10. Nichols J, Warren JC, Mantz FA. ACTH-like excretion from carcinoma of the ovary: the clinical effect of m,p'-DDD. *J Am Med Assoc.* 1962;182:713–8.

Maria D. Ballesteros-Pomar*, Alfonso Vidal-Casariago

Sección de Endocrinología y Nutrición, Complejo Asistencial Universitario de León, Spain

* Corresponding author.

E-mail addresses: Mdballesteros@telefonica.net,
dballesteros@saludcastillayleon.es
(M.D. Ballesteros-Pomar).

21 March 2014 18 April 2014

Sexual differentiation anomalies. XX male syndrome[☆]



Anomalías de la diferenciación sexual. Síndrome del varón XX

The XX male syndrome was first described in 1964 by De la Chapelle, who called it "sex inversion in women". This author reported patients with male phenotype and psychosexual identification in whom the gonad was of the testicular type and who had no microscopic or gross evidence of ovarian tissue and karyotype 46,XX.¹

Frequency of this syndrome is very low (1/20,000 live newborns). It is called the XX male syndrome, and is currently classified within sex differentiation abnormalities, a group of conditions where a defect occurs in normal fetal development of genetic sex, gonadal sex and/or external genitalia.²

The XX male syndrome consists of a discordance between a male phenotype and a female karyotype. During sex differentiation occurring between the fifth and seventh weeks of embryonic development, anti-müllerian hormone (AMH) is sufficient in these patients to inhibit development of müllerian structures, with complete differentiation of wolffian derivatives and adequate masculinization of external genitalia. Spermatogenesis is highly deficient or absent, and patients are therefore infertile. However, Leydig cells have a variable development, and produce sufficient androgens to ensure marked post-pubertal virilization.³

Most patients have normal male phenotype, but hypospadias, cryptorchidism, and ambiguous genitalia have been reported in 10–15% of cases. Diagnosis is made at pubertal age, when the most common clinical and laboratory signs occur: gynecomastia, hypogonadism, shorter penile length, and infertility due to oligospermia or azoospermia. Height is usually normal, and well as psychomotor development and intellectual capacity.⁴

As regards management after diagnosis, regular monitoring, closer in puberty, is done, and repair surgery and psychological support is offered.

We report the case of a one month-old infant who was referred for balanic hypospadias, a supernumerary first

finger, and agenesis of the second finger in both hands. Physical examination was otherwise normal. As was genital examination, which revealed a well developed scrotum containing testes 2 mL in volume and a 2.9 cm long penis (P50 for age) of normal thickness and with erectile capacity. The infant had no remarkable family and personal history. Because of the described physical abnormalities, karyotype was requested and was reported to be 46, XX, with no detection of the SRY gene by FISH (46, XX; SRY(–)). Hormone tests performed included AMH, testosterone precursors (5-DHT; 17-OH progesterone; 17-OH pregnenolone), LH, and FSH; basal serum levels were normal for males. Ultrasonography and abdominal and pelvic MRI were also normal for a male. Abnormal sex differentiation consisting of a XX male syndrome with no SRY detection was diagnosed. Genetic study should be elaborated on at this point.

The XX male syndrome is a very uncommon condition (1–9 cases per 1,000,000 males) difficult to diagnose before puberty or adult age due to the scarcity or absence of physical manifestations. It may be suspected in a newborn with perineal hypospadias and cryptorchidism. Our case was diagnosed by chance when karyotyping was requested due to abnormalities seen in both fingers, plus hypospadias.

Clinical suspicion is based on physical examination and is supported by hormone testing. Diagnosis of certainty is genetic, based on the finding of the karyotype 46, XX.

During sex differentiation, genetic sex determines gonadal sex from the sixth month of pregnancy. The undifferentiated gonad spontaneously tends to female sex. Masculinization starts by the action of the testicular development factor (TDF), encoded by the SRY gene, which will lead to differentiation of the seminiferous cord that contains pre-Sertoli cells (secreting AMH) and spermatogonia. AMH causes disappearance of müllerian ducts (and the resultant absence of Fallopian ducts, uterus, and vagina), while androgens secreted by Leydig cells will determine differentiation of Wolffian ducts into epididymis, deferent ducts, and seminal vesicles. Decreased testicular testosterone production in cases with hypogonadism causes in some patients abnormalities in the external genitalia.

AMH production by Sertoli cells in testes remains high during infancy, but decreases to low levels during puberty and adult life. In recent years, AMH measurement is widely used to assess testicular presence and function in boys with hermaphroditic conditions or ambiguous genitalia.⁵

The sex-determining region Y (SRY) gene, critical for male sex differentiation, is located in the short arm of

[☆] Please cite this article as: Moreno Balsera M, Romero Pérez MM, Bermúdez de la Vega JA. Anomalías de la diferenciación sexual. Síndrome del varón XX. *Endocrinol Nutr.* 2014;61:438–439.

chromosome Y. In most cases of XX male syndrome, translocation occurs in meiosis between chromosomes X and Y, and the SRY gene is located in chromosome X. However, this gene is not identified in other cases, in which several hypotheses have been proposed to explain male sex differentiation. This has been attributed to mutations in some of the more than 50 genes involved, in addition to sex chromosomes, in sex differentiation, or to Klinefelter syndrome (47, XXY) with subsequent loss of chromosome Y when virilization has already started.⁶

The SOX9 gene is a transcription factor essential for sexual and skeletal development, and its impairment may cause from bone changes alone to a combination of sex differentiation and skeletal abnormalities. Rearrangements have been reported in the SOX9 region, including duplication in the Xq 26 region, or balanced translocations *t*(17:20) (q24.3;q11.2) and *t*(7:17) (p13;q24), which have been associated to sex reversal and skeletal changes.^{7,8} The SOX3 gene shares the same functions as the SRY gene. Mutations causing changes or overexpression of this gene may induce male sex differentiation in individuals with 46, XX chromosomal endowment.⁹

Treatment of the XX male syndrome consists of repair surgery for gynecomastia, hypospadias, and cryptorchidism by testicular descent and orchiopexy, and even testicular prostheses. Prenatal diagnosis of these abnormalities is increasingly common.¹⁰

References

- De la Chapelle A. Analytic review: nature and origin of males with XX sex chromosomes. *Am J Hum Genet.* 1972;24:71–105.
- Audí Parera L, Gracia Bouthelie R, Castaño González L, Carrascosa Lezcana A, Barreiro Conde J, Bermúdez de la Vega JA, et al. Anomalías de la diferenciación sexual; protocolos diagnósticos-terapéuticos de la Asociación Española de Pediatría, 1; 2011. p. 1–12.
- Nistal M, García-Fernández E, Mariño-Enríquez A, Serrano A, Regadera J, González-Peramato P. Diagnostic value of the gonadal biopsy in the disorders of sex development. *Actas Urol Esp.* 2007;31:1056–75.
- Abusheikha N, Lass A, Brinsden P. XX males without SRY gene and with infertility. *Hum Reprod.* 2001;16:717–8.
- Audí L, Vicens-Calvet E. Desarrollo y diferenciación sexual normal. In: Argente Oliver J, Carrascosa Lezcana A, Gracia Bouthelie R, Rodríguez Hierro F, editors. *Tratado de Endocrinología Pediátrica y de la Adolescencia*. 2.ª ed. Madrid: DOYMA; 2000. p. 775–96.
- Pozo Román J, Argente Oliver J. Trastornos del desarrollo sexual. In: Pallardo Sánchez LF, Lucas Morante T, Marazuela Azpiroz M, Rovira Loscos A, editors. *Endocrinología clínica*. 2.ª ed. Madrid: Díaz de Santos; 2010. p. 176–89.
- Fonseca AC, Bonaldi A, Bertola DR, Kim CA, Otto PA, Vianna-Morgante AM. The clinical impact of chromosomal rearrangements with breakpoints upstream of the SOX9 gene: two novel de novo balanced translocations associated with acampomelic campomelic dysplasia. *BMC Med Genet.* 2013;14:50.
- Cox JJ, Willatt L, Homfray T, Woods CG. A SOX9 duplication and familial 46, XX developmental testicular disorder. *N Engl J Med.* 2011;364:91–3.
- Sutton E, Hughes J, White S, Sekido R, Tan J, Arboleda V, et al. Identification of SOX3 as an XX male sex reversal gene in mice and humans. *J Clin Invest.* 2011;121:328–41.
- Margarit E, Soler A, Carrió A, Oliva R, Costa D, Vendrell T, et al. Molecular, cytogenetic, and clinical characterisation of six XX males including one prenatal diagnosis. *J Med Genet.* 1998;35:727–30.

Macarena Moreno Balsera*, María del Mar Romero Pérez, José Antonio Bermúdez de la Vega

Servicio de Endocrinología Pediátrica, Unidad de Gestión Clínica de Pediatría, Hospital Virgen Macarena, Sevilla, Spain

*Corresponding author.

E-mail address: macarena_mb@hotmail.com (M. Moreno Balsera).

Ketoacidosis as a debut to type 1B diabetes mellitus in a patient with Turner's syndrome[☆]



Cetoacidosis como inicio de diabetes mellitus tipo 1 B en una paciente con síndrome de Turner

In Turner syndrome (TS), mortality is three times higher as compared to the population with a normal karyotype.

This is partly explained by the increasing incidence of diabetes mellitus (DM) and cardiovascular diseases.¹ There is an increased risk of developing both type 2 DM (relative risk, 4.4) and type 1 DM (DM1) (relative risk, 11.6) as compared to the general population.² Development of frank DM during childhood is however exceptional, and is usually more commonly associated to treatment with GH or sex hormones.^{2,3}

The unusual case of a two-year-old patient with DM1 of a non-autoimmune origin in whom TS was diagnosed is reported. Few patients with TS in whom DM1 has developed in childhood have been reported,^{3–6} and this is the youngest known.

Our patient was a Roumanian girl aged 2 years and 4 months with polyuria, polydipsia, and weight stagnation for the past two weeks. She weighed 8.100 kg (–3.6 SDS) and measured 77.5 cm in height (–3.8 SDS). The patient had a unique phenotype, with anteverted, low-set

[☆] Please cite this article as: Navarro Moreno C, Cañabate Reche F, Vicente Pintor A, Vela Enríquez F, Benavides Román MR. Cetoacidosis como inicio de diabetes mellitus tipo 1 B en una paciente con síndrome de Turner. *Endocrinol Nutr.* 2014;61:439–441.