

10. Kyritsis AP. Management of primary intracranial germ cell tumors. *J Neurooncol.* 2010;96:143–9.

Víctor González-Sánchez^a, Oscar Moreno-Pérez^a,
Ruth Sánchez-Ortiga^a, Elena Gastaldo Simeón^b,
Antonio Miguel Picó Alfonso^{a,*}

^a *Endocrinology and Nutrition Department, Hospital General Universitario de Alicante, Alicante, España*
^b *Paediatric Endocrinology Department, Hospital de la Ribera, Alzira, España*

* Corresponding author.

E-mail address: pico_ant@gva.es (A.M. Picó Alfonso).

Complete androgen insensitivity syndrome with persistent müllerian remnants. A case report[☆]

Síndrome de insensibilidad completa a andrógenos con persistencia de restos mullerianos. Descripción de un caso

Sex differentiation is a process that starts early during embryogenesis. In males, the SRY gene, located in the short arm of chromosome Y, encodes for the testis-determining factor, which causes the gonad to differentiate into testis. Testicular androgen synthesis by Leydig cells starts from the eighth week of development. It is initially stimulated by placental chorionic gonadotropin (HCG), and subsequently by luteinizing hormone (LH). Fetal gonadotropins stimulate the testicular production of antimüllerian hormone (AMH), which stimulates the regression of müllerian ducts in males. Testosterone, whose action starts in the ninth week once the androgen receptor (AR) is present, allows for the stabilization of wolffian ducts and their differentiation into epididymis, deferent duct, and seminal vesicles. The conversion of testosterone into its most active metabolite, dehydrotestosterone (DHT), allows for the growth of the genital tubercle to form the penis and ventral raphe closure, so forming the penile urethra and scrotal raphe (Fig. 1).

Complete androgen insensitivity syndrome (CAIS) is an XY sexual development disorder where AR function loss exists. CAIS occurs in subjects with the 46 XY karyotype with external genitalia of the female phenotype.

We report the case of a term newborn delivered after a physiological pregnancy. She was the first daughter of healthy, non-consanguineous parents. Birth weight was 3420 g and birth length 50 cm, while the Apgar score was 9–10. Physical examination disclosed normal external female genitalia and two 1-mm masses in both inguinal canals, which led to inguinal hernia being suspected. Abdominal ultrasound examination revealed a persistent peritoneo-vaginal process in both inguinal regions with herniation of abdominal contents and two homogeneous ovoid formations 1 cm in diameter with Doppler flow inside, with no follicles suggesting gonads. At two days of life, LH and follicle-stimulating hormone (FSH) levels were less than 0.1 IU/L (reference values (RV): 0.02–7.0 mIU/L), testosterone was 1.45 nmol/L (RV: 0.42–0.72 nmol/L), and the

estradiol level was <73.4 pmol/L (markedly elevated values were to be expected).

Based on the suspected presence of gonads in the inguinal canal, the patient underwent surgery on her third day of life. Intraoperative vaginoscopy showed no uterine cervix. A gonadal biopsy revealed a fragment of testicular parenchyma consisting of solid cords with Sertoli cells and spermatogonia. Leydig cells were not identified. Left gonad biopsy showed a high number of spermatogonia, a hydatid with a cystic aspect, and many tubular structures consistent with epididymis. A duct consistent with a müllerian remnant was found in the vicinity (Fig. 2). Both testes were replaced into the abdomen.

The karyotype was 46 XY. The molecular study of the AR gene found a base change in exon 5, an arginine by glutamine replacement at codon 752 (R752X). This mutation had previously been reported in the literature in a patient with CAIS,¹ and therefore confirmed the diagnosis. The molecular study of the mother was positive for the same mutation, but she had no phenotypic changes.

CAIS is an X-linked autosomal recessive disease caused by a mutation in AR that may be inherited (70%) or occur de novo (30%). The gene is located in the chromosomal region Xq11-12 and consists of eight exons encoding for a 919 amino acid protein. It has four functional domains: NTD (N-terminal transactivation domain), encoded in exon 1; DBD (DNA binding domain), encoded in exons 2 and 3; a hinge region; and LBD (ligand binding domain), encoded by exons 4–8.² AR is located in cell cytoplasm bound to protein, and upon ligand binding translocates to the nucleus, where it is bound to DNA. The same mutation may cause different phenotypes in the same affected family.³

Prevalence is estimated at 2–5/100,000.⁴ Clinically, CAIS occurs in individuals with karyotype 46 XY and normal external female genitalia, blind-ending vagina, and intra-abdominal testes. Leydig cells secrete testosterone in adequate amounts for a male of that age, which is normally converted into dehydrotestosterone (DHT) through 5- α reductase, but the effect of DHT is virtually nil because of the presence of non-functioning AR. AMH production by Sertoli cells and the synthesis of its receptor AMHR2 is not affected by AR impairment. This allows for a normal action of AMH during the embryonic period, explaining the regression of müllerian structures (upper third of vagina, uterus, and ovaries) in patients with CAIS.

CAIS should be suspected in two instances: firstly, in a phenotypically female newborn with bilateral inguinal hernia, because this is uncommon in females. One to 25% of these lesions correspond to CAIS.⁵ The second presentation form occurs in a female adolescent with adequate breast development and a little or no pubic and/or axillary hair

[☆] Please cite this article as: Grob F, et al. Síndrome de insensibilidad completa a andrógenos con persistencia de restos mullerianos. Descripción de un caso. *Endocrinol Nutr.* 2013;60:216–8.

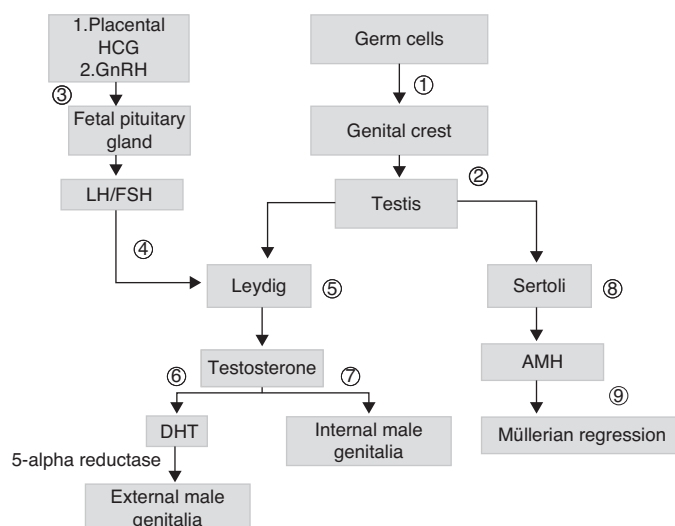


Figure 1 Scheme of embryonic sexual development: germ cells migrate to genital crests (1), form primary sex cords originating testes (2). Leydig cells are stimulated by placental chorionic gonadotropin (HCG) and later by luteinizing hormone (LH) (4), which depends on the gonadotropin releasing hormone (GnHRH) secreted by fetal hypothalamus (3), which stimulates the production of gonadotropins. These stimulate the production of androgens (7) and antimüllerian hormone (AMH) (8), which allows for the regression of müllerian ducts (9). The testosterone initially secreted (7) allows for the development of internal male genitalia. The conversion of testosterone into dehydrotestosterone (DHT) allows for the formation of external male genitalia (6).

and with primary amenorrhea, in whom the absence of an uterus and ovaries is shown.

LH and testosterone are normal or in the upper limit during the first three months of life. In patients with preserved gonads, reactivation of the hypothalamic-pituitary axis during puberty induces Leydig cell activity, increasing intratesticular androgens and allowing for the arrest of Sertoli cell proliferation. AMH production is maintained due to AR insensitivity in the nucleus of Sertoli cells.⁶ Testosterone and LH remain elevated due to andro-

gen resistance at hypothalamic-pituitary level. Testosterone is aromatized peripherally to estrogens, which explains the normal female breast development seen in these cases.⁷ Gonad preservation until puberty appears to be safe, because the risk of gonadoblastoma or other tumors only increases subsequently.⁸

The presence of müllerian remnants has sporadically been reported and has no clinical consequences. Various hypotheses have been suggested regarding their persistence, including (1) the presence of defects in AMH secretion or function, (2) the absence of a müllerian tissue response to the action of AMH due to the presence of high estrogen levels (secondary to peripheral testosterone conversion), or (3) early testicular descent, which places müllerian structures outside the range of action of AMH during embryogenesis.⁹ These hypotheses were evaluated in a 20-week fetus with prenatal diagnosis of CAIS and the presence of müllerian remnants. Three events were seen: first, increased AMH expression by Sertoli cells; second, decreased expression of peritubular mesenchymal cells positive for the AMH receptor (AMHR2); and third, Leydig cell hyperplasia. These findings suggest a new hypothesis with regard to AMH action during the embryonic period, based on prenatal resistance to AMH.¹⁰

In conclusion, the presence of minor müllerian structures in cases of CAIS may be more common than previously reported, but this should not affect diagnosis, and does not modify either its course or its treatment.

Acknowledgement

We thank Dr. Alejandro Martínez-Aguayo for his critical review of the manuscript.

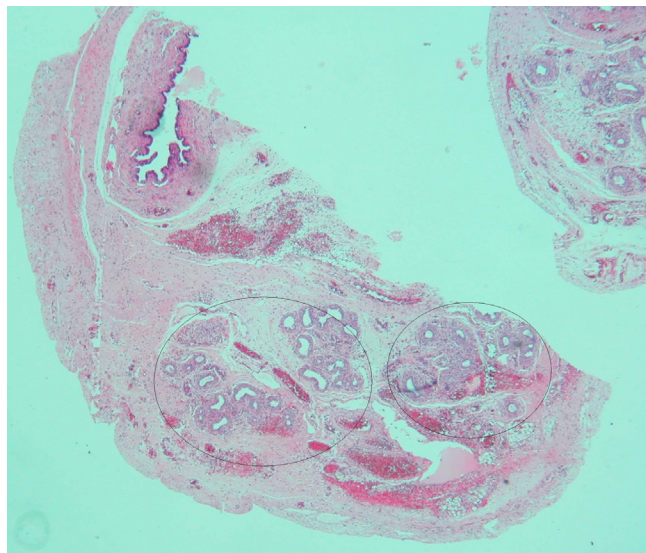


Figure 2 Testicular biopsy showing images (in black circles) which could correspond to müllerian remnants.

References

1. Cabral DF, Maciel-Guerra AT, Hackel C. Mutations of androgen receptor gene in Brazilian patients with male pseudohermaphroditism. *Braz J Med Biol Res.* 1998;31:775–8.
2. Galani A, Kitsiou-Tzeli S, Sofokleous C, Kanavakis E, Kalpini-Mavrou A. Androgen insensitivity syndrome: clinical features and molecular defects. *Hormones (Athens).* 2008;7:217–29.
3. Gottlieb B, Beitel LK, Trifiro MA. Variable expressivity and mutation databases: the androgen receptor gene mutations database. *Hum Mutat.* 2001;17:382–8.
4. Boehmer AL, Brinkmann O, Bruggenwirth H, van Assendelft C, Otten BJ, Verleun-Mooijman MC, et al. Genotype versus phenotype in families with androgen insensitivity syndrome. *J Clin Endocrinol Metab.* 2001;86:4151–60.
5. Deeb A, Hughes IA. Inguinal hernia in female infants: a cue to check the sex chromosomes? *BJU Internat.* 2005;96:401–3.
6. Grinspon RP, Rey RA. Anti-mullerian hormone and sertoli cell function in paediatric male hypogonadism. *Horm Res Paediatr.* 2010;73:81–92.
7. Ahmed SF, Cheng A, Hughes IA. Assessment of the gonadotrophin–gonadal axis in androgen insensitivity syndrome. *Arch Dis Childhood.* 1999;80:324–9.
8. Hannema SE, Scott IS, Rajpert-De Meyts E, Skakkebaek NE, Coleman N, Hughes IA. Testicular development in the complete androgen insensitivity syndrome. *J Pathol.* 2006;208:518–27.
9. Nichols JL, Bieber EJ, Gell JS. Case of sisters with complete androgen insensitivity syndrome and discordant Mullerian remnants. *Fertility Sterility.* 2009;91, 932e15–e18.
10. Corbetta S, Muzza M, Avagliano L, Bulfamante G, Gaetti L, Eller-Vainicher C, et al. Gonadal structures in a fetus with complete androgen insensitivity syndrome and persistent Mullerian derivatives: comparison with normal fetal development. *Fertility Sterility.* 2011;95, 1119e9–14e.

Francisca Grob^a, Mario Varela^b, José Domingo Arce^c, Virginia Martínez^d, Hernán García Bruce^{a,*}

^a *División de Pediatría, Unidad de Endocrinología Pediátrica, Pontificia Universidad Católica de Chile, Santiago, Chile*

^b *Departamento de Cirugía Pediátrica, Clínica Santa María, Santiago, Chile*

^c *Departamento de Radiología Pediátrica, Clínica Santa María, Santiago, Chile*

^d *Departamento de Anatomía Patológica, Clínica Santa María, Santiago, Chile*

* Corresponding author.

E-mail address: hgarciaab@gmail.com (H. García Bruce).

Boucher–Neuhäuser syndrome[☆]

Síndrome de Boucher-Neuhäuser

Boucher–Neuhäuser syndrome (BNS) is a clinical condition characterized by the triad of hypogonadotropic hypogonadism, cerebellar ataxia, and retinochoroidal degeneration.^{1,2} BNS is difficult to diagnose in its early stages because the triad components occur at different times in the lives of patients with a wide variability in the few subjects reported to date.³

We report the case of a 26-year-old male patient from the state of Merida (Venezuela) with no family history of consanguinity or significant diseases in his parents or siblings. The patient was referred to the endocrinology unit due to an absence of secondary sexual characteristics, in addition to bilateral visual acuity decrease from 16 years of age and unstable gait from 20 years of age.

A physical examination revealed a body weight of 57 kg, a height of 160.0 cm, an arm span of 165.7 cm, a body mass index of 22.2 kg/cm², eunuchoid habitus, acute voice, bilateral gynecomastia, bilateral horizontal nystagmus with rapid phase to the right, corrected visual acuities in counting fingers at 50 cm in the right eye and 20/80 in the left eye, intraocular pressure of 12 mmHg in both eyes, Tanner II pubic hair, a 4 cm-long penis, and right and left testes of 2 and 3 mL respectively (Prader orchidometer), both in hypoplastic scrotal sacs. Neurological examination revealed ataxic gait, truncal ataxia mainly on the right, dystonic posture, dysidiadochokinesia, dysmetria, hypotonia,

and global hyperreflexia. No changes were found in superficial or deep sensitivity, nor anosmia or cardiovascular changes.

Eye fundus examination showed in both eyes a pale optic disk, retinal vessels with mild tortuosity and retinochoroidal dystrophy characterized by diffuse atrophy of the retinal pigment epithelium, with pigment deposition toward the periphery and visualization of choroidal vessels. Fluorescein angiography showed in both eyes a preserved vascular tree with diffuse atrophy of the retinal pigment epithelium and hyperfluorescent areas with dye accumulation. Optical coherence tomography revealed retinal thinning with changes in the outer layers and thickened and irregular pigmented epithelium, mainly in the fovea, which affected the choriocapillaris (Fig. 1).

Laboratory tests showed no hematological changes; however, neutrophil hypersegmentation was seen in peripheral blood smears. Blood chemistry tests showed normal values of blood glucose, kidney function, calcium, and phosphorus. Other test results included: follicle-stimulating hormone (FSH), 0.5 mIU/mL (normal range [NR], 0.7–11); luteinizing hormone (LH), 0.3 mIU/mL (NR, 0.8–7.6); total testosterone, 0.9 ng/mL (NR, 2.45–18); prolactin, 8.4 ng/mL (NR in males, 0–15); thyrotropin, 1.2 mIU/mL (NR, 0.3–4.2); free thyroxine, 0.9 ng/dL (NR, 0.8–2). Plasma levels of LH and FSH did not increase 30, 60, and 90 min after intravenous administration of 100 µg of gonadotropin-releasing hormone (GnRH).

In 50 metaphases analyzed, the karyotype was 46, XY; X-rays of the left hand and wrist revealed a bone age of 16 according to the Greulich and Pyle atlas. Magnetic resonance imaging of the brain showed increased amplitude and depth of both cerebellar hemispheres consistent with cerebellar atrophy (Fig. 2). Bone densitometry showed a bone

[☆] Please cite this article as: Lima-Martínez MM, et al. Síndrome de Boucher-Neuhäuser. *Endocrinol Nutr.* 2013;60:218–20.