

Case report



PERFORMING GONADECTOMY IN A 15-YEAR-OLD BULGARIAN GIRL WITH COMPLETE ANDROGEN INSENSITIVITY SYNDROME: A CASE REPORT

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ABSTRACT:

Complete Androgen Insensitivity Syndrome (CAIS) is a rare genetic Disorder of Sex Development linked to the X chromosome. It occurs due to mutations—either from mother inheritance or arising spontaneously—in the androgen receptor (AR) gene, located in the Xq11-q12 region.

Individuals with CAIS have a 46, XY karyotype, meaning they are genetically male. However, due to a complete inability of their body’s tissues to respond to androgens, they develop female external genitalia. Internally, they have fully formed but undescended testes and their bodies do not develop male reproductive structures. Diagnosis typically involves genetic testing, hormone analysis, and imaging to assess the presence of testes.

This is a case report of a 15-year-old female-looking Bulgarian patient with primary amenorrhea who underwent prophylactic gonadectomy after ultrasound examination and MRI was performed. From the performed imaging studies, Sertoli cell adenoma was suspected. Histological findings were rudimentary testicles with the presence of paratesticular cysts (more prominent on the left). Rudimentary Fallopian tubes were also present. The patient’s karyotype was 46, XY without any evidence of aberrations.

A precise algorithm should be established for diagnosis, treatment and prevention for patients with CAIS, in order to improve the quality of life and prognosis. The key, in our opinion, is the multidisciplinary approach and the creation of specialized centers for children with rare genetic disorders.

Keywords: Complete androgen insensitivity syndrome (CAIS), Sertoli cell adenoma, hormonal replacement therapy, persistence of Fallopian tubes in CAIS,

INTRODUCTION:

Androgen Insensitivity Syndrome (AIS) is a genetic Disorder of Sex Development caused by mutations in the androgen receptor (AR) gene, located in the Xq11-q12 region of the X chromosome. This disorder results in varying degrees of resistance to androgens, classified as mild (MAIS), partial (PAIS), or complete (CAIS). It occurs due to maternally inherited or spontaneous mutations affecting the androgen receptor. CAIS is characterized by a female phenotype in individuals with a 46, XY karyotype. Diagnosis is based on the presence of female external genitalia despite the individual being genetically male, with fully developed but undescended testes and a complete inability of target tissues to respond to androgens [1, 2, 3]. More than 95% of CAIS cases are linked to AR gene mutations [4]. The prevalence of the condition ranges from 1 in 20,400 to 1 in 99,100 among male individuals [5].

During fetal development, individuals with CAIS form primordial testes in the abdomen by the seventh week of gestation due to the presence of the SRY gene, which initiates testosterone production. However, because of the AR gene mutation, testosterone has no effect on target cells [6,7]. As a result, male genitalia do not develop apart from the testes. Internal female reproductive structures, such as the uterus, cervix, and upper vagina, are also absent due to the production of anti-Müllerian hormone (AMH). However, the lower part of the vagina is present, though typically shorter than usual and ending in a blind pouch [8,9].

In infancy and before puberty, CAIS may be detected incidentally through ultrasound examination performed for unrelated reasons, or it may present with inguinal hernias due to undescended testes. In individuals who reach puberty, the most common complaint is the absence of menarche or primary amenorrhea. Puberty tends to occur later than in unaffected females and progresses more slowly, but breast development and female fat distribution still take place due to the conversion of testosterone into estradiol via peripheral aromatization [10].

The timing and necessity of gonadectomy in indi-

viduals with CAIS remain a topic of debate. Because CAIS is associated with an increased risk of testicular germ cell tumors (TGCT), some experts advocate for the removal of the gonads as prevention against testicular cancer. However, delaying gonadectomy until after puberty allows for spontaneous pubertal development due to estradiol production from the retained testes. Testicular germ cell tumors account for 1–1.5% of all cancers in the general male population and are the most common malignancies among males aged 15–40 [11]. Cryptorchidism is a known risk factor, and while the incidence is low in childhood and adolescence, individuals with CAIS who retain their testes beyond puberty have an estimated 5% risk of developing malignant tumors [12, 13]. The most commonly associated tumors include seminomas and gonadoblastomas, though other forms, such as choriocarcinomas, teratomas, embryonal tumors, adenomas, and Leydig or Sertoli cell tumors, have also been reported [14, 15].

Despite the low overall risk of invasive cancer in CAIS, early detection of suspicious lesions is crucial. However, both germ cell neoplasia in situ (GCNIS) and seminomas generally do not produce detectable serum markers like β -HCG and α -FP, making early diagnosis more challenging. Therefore, if imaging findings may be indicative of disease, such as the presence of mass, development of cysts, calcifications, unexplained abdominal lymphadenopathy, or asymmetric change in size encountered on ultrasound, then MRI should be performed to further delineate the characteristics. If MRI is consistent with ultrasound findings, diagnostic laparoscopy might not be warranted. If there are abnormal imaging findings, laparoscopy for direct visualization with possible biopsy might be considered. At any point, if the gonads appear abnormal intraoperatively, biopsy should be considered and/or gonadectomy of the affected gonad(s) should be performed [12, 15, 16].

MATERIALS AND METHODS:

The patient was evaluated using a diagnostic protocol that included clinical, hormonal, sonographic, MRI, and cytogenetic examinations. The patient and her parents were counselled by the team concerning the different treatment modalities, and contrary to the assigned gender, gonadectomy was offered to them. A bilateral gonadectomy was performed, and the gonads were submitted for histopathological examination.

CASE PRESENTATION:

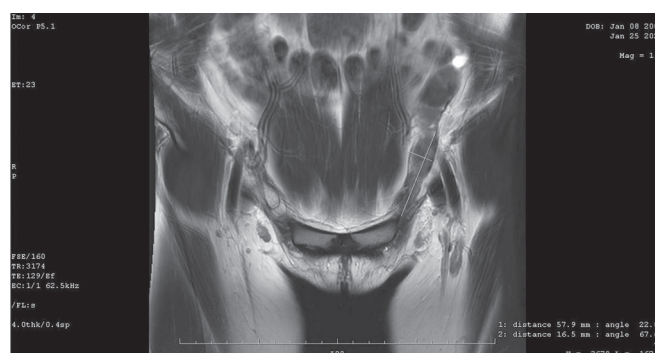
A 15-year-old female-looking patient was presented with primary amenorrhea. The girl was born from first normal pregnancy with a weight of 3800 g and a length of 52 cm. She has had a smooth neonatal period. Medical history included: due to paroxysmal tachycardia lasting up to 10 minutes at the age of 10, mitral valve prolapse 1st degree has been diagnosed. The therapy that has been prescribed was with beta blocker - Metoprolol tartrate 25 mg

daily. The family history of the patient included a father with Thyroid carcinoma, a mother with Arterial hypertension and a sister with pubertas praecox (Precocious puberty).

Clinical examination found normal intellectual function and feminine habitus (weight 53.5 kg, height 173.5 cm) and voice, with development of breasts at Tanner stage V. Pubic and axillary hairs were absent – Tanner stage I. A 2 cm long vaginal stump with a blind end was found during the gynecological exam. Secondary sexual characteristics have been developed by the age of 9.

Ultrasonographic investigation confirmed the uterine agenesis and identified the gonads at the entrance of the pelvis. The right gonad measured 33/29 mm, while the left one measured 26/15 mm in its visible part. Both gonads were with heteroechogenic structure, the lower pole of the left one could not be traced. There was a significant difference in the sizes of the two gonads. (fig. 1.)

Fig. 1. Ultrasonographic investigation confirmed the uterine agenesis and identified the gonads at the entrance of the pelvis. The right gonad measured 26.6/15.5 mm, while the left one measured 30/28 mm in its visible part. Both gonads had heteroechogenic structure, and the lower pole of the left one could not be traced.



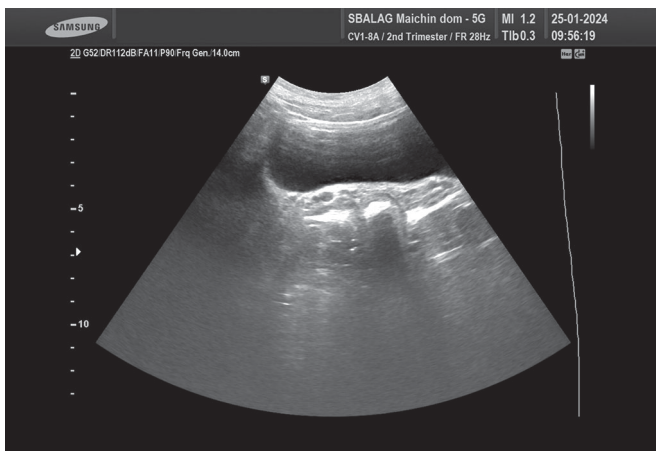
Routine investigations like hemogram, blood sugar, urea, and serum creatinine were within normal limits. Hormone estimation showed: the serum testosterone level (22.6 nmol/L) exceeded the typical normal values for female patients (2.3 nmol/L), but it corresponded to the normal rates for boys of the same age. The serum levels of Luteinizing hormone (LH) (42.1 IU/L; normal values: 2.4–8.3 IU/L) Follicle-stimulating hormone (FSH) (6.9 mIU/ml), estradiol <73 pmol/L, prolactin 297 mIU/L, SHBG 51.7 nmol/L (18–114 nmol/L), AFP 0.773 μ g/L, B-CHG <1.0 mIU/L.

From the Cytogenetic analysis of cultured lymphocytes from venous blood, a karyotype 46, XY was established in all analyzed metaphases. No systemic numerical or structural abnormalities were identified. From the additionally performed segregation analysis, a hemizygous carrier of the genetic variant was found c.1738T>G (p.Cys580Gly) in the AR gene, consistent with CAIS.

A decision was made to perform an MRI due to the difficulties in performing a US examination and the signifi-

cant difference in the size of the two gonads. From the performed multiparametric MRI of the small pelvis, the uterus and ovaries were not visualized. In the left iliac fossa, adjacent to the pelvic wall on the left, an oval soft-tissue lesion was visualized. The presence of restriction of the diffusion of water molecules is suspicious for testicular tissue. MRI data on paratesticular cysts adjacent to its upper pole. In the structure of the finding, an oval hypointense lesion with approximately axial dimensions of 11/9 mm was visualized on T2 images. The caudal finding was traced ventrally from the external iliac vessels, entering in the direction of the left inguinal canal. The described testicular tissue had maximum coronal dimensions of 102.5/22 mm. Identical vestigial tissue was also visualized adjacent to the pelvic wall on the right, and small peritesticular cysts are present at the periphery. The finding did not reach the inguinal canal and had a maximum size of 47/16 mm. No pathologically enlarged mentase and inguinal lymph nodes were visualized bilaterally, as well as no pathological lesions were visualized in the scanned bones. (Fig. 2.)

Fig. 2. MRI data on paratesticular cysts adjacent to its upper pole. In the structure of the finding, an oval hypointense lesion with approximately axial dimensions of 11/9 mm was visualized on T2 images. The caudal finding was traced ventrally from the external iliac vessels, entering in the direction of the left inguinal canal.



Conclusion of presented MRI: The described soft tissue findings in the pelvis corresponded to rudimentary testicles, with the presence of paratesticular cysts (more prominent on the left). The described hypointense lesion in the left testis was suspicious for Sertoli cell adenoma.

The patient was hospitalized, and after the whole necessary clinical and paraclinical examinations were done, a bilateral gonadectomy was performed by a multidisciplinary team of gynecologists and urologists.

A thorough conversation was held with the parents and the patient, and the results of the tests were explained to them. The risks associated with the patient's current condition were explained, as well as the options for surgical treatment and follow-up therapy. The parents decided to remove both gonads.

Due to the described MRI finding, it was decided a bilateral gonadectomy with a retroperitoneal approach to be performed. The left testicle was sent for express histopathological examination (Gefrir) (Fig. 3), and the result was: Left gonad 6/3/2 cm, multinodular, homogeneous; cysts up to 1 cm on the surface.

Fig. 3. Left gonad 6/3/2 cm, multinodular, homogeneous after the surgical removal.



Histological result: structure of prepubertal testis (Morris syndrome); cystic structures were lined with cylindrical ciliated epithelium. The result of the final histopathological examination was: Right gonad - 3/2.5/1.5 cm, Left gonad - 6/3/2 cm, multinodular, homogeneous; cysts up to 1 cm on the surface. Both gonads had a multinodular testis structure represented by atrophic tubules and intertubular stroma with Leydig cell hyperplasia. Focal marked fibrosis. In both gonads - the presence of cysts lined with single-row cylindrical ciliated epithelium (morphologically, they resemble malformed fallopian tubes with peritubal cysts) Mesonephric remnants. (Figs. 4, 5, 6.)

Fig. 4. Histological result: Both gonads had a multinodular testis structure represented by atrophic tubules and intertubular stroma with Leydig cell hyperplasia.

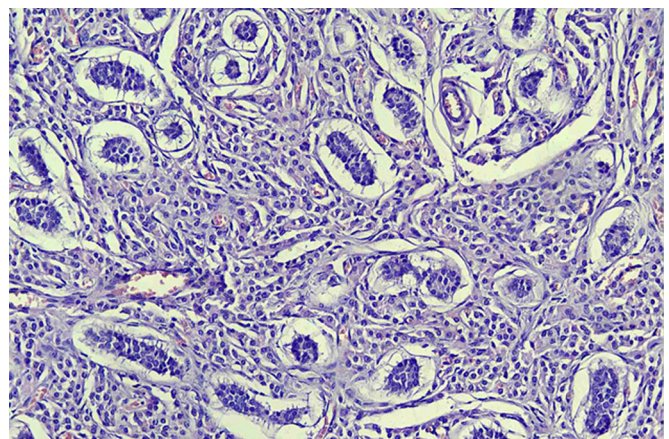


Fig. 5. Focal marked fibrosis in both gonads

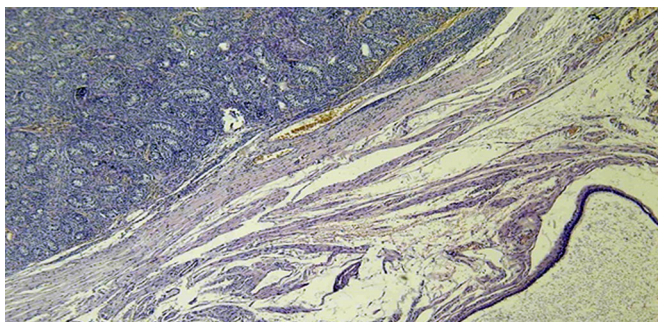
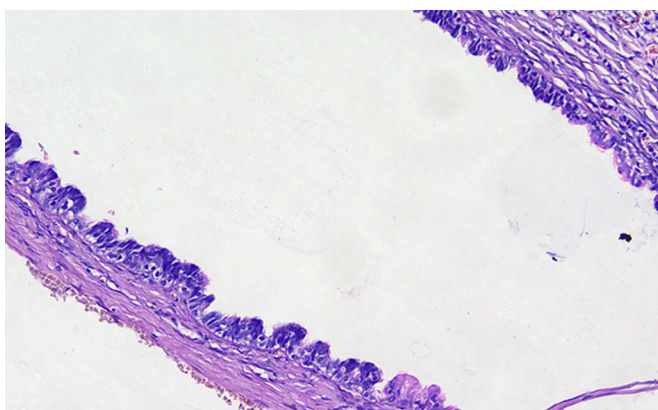


Fig 6. In both gonads, there was a presence of cysts lined with single-row cylindrical ciliated epithelium (morphologically, they resemble malformed fallopian tubes with peritubal cysts) Mesonephric remnants.



RESULTS:

Despite the suspicion of Sertoli cell adenoma on MRI, the histological result showed a prepubertal testicular structure in our patient with CAIS. Gonadectomy was performed after the full development of the secondary sexual characteristics of the patient to avoid the risk of malignancy. Hormonal replacement therapy with estrogens was administered. Additional treatment for this patient includes vaginal dilation because of a blind-ending vagina (2 cm) with Frank's method – gradually increasing the size of the dilator for 30 minutes a day over a period of 4-6 months.

DISCUSSION:

This current case report describes the typical diagnosis and medical treatment process that is followed in a representative patient with CAIS. Individuals with CAIS present with typical female external genitalia despite having a 46, XY karyotype and undescended testes due to a complete lack of response to androgens. This is a rare genetic disorder, with an estimated prevalence ranging from 1:20,400 to 1:99,100 among those assigned male at birth [4, 5].

The pathogenesis of CAIS is caused by the mutation of the androgen receptor (AR) gene located in the Xq11–12 region [1-3, 8]. Mutations in the androgen receptor gene (AR) are found in most individuals with CAIS but in fewer individuals with PAIS [6]. In our case, the diagnosis was

made after karyotyping with a proven 46 XY karyotype in a female phenotype. After Cytogenetic segregation analysis was performed, a hemizygous carrier of the genetic variant was found c.1738T>G (p.Cys580Gly) in the AR gene, consistent with CAIS.

Primary amenorrhea is presented because normal production of anti-mullerian hormone (AMH) by the testis impeded uterus, cervix and proximal vagina development. A shortened, blind-ending vagina is observed in almost all patients. The vaginal measurement varied from 2.5 to 8 cm in CAIS and 1.5 – 4 cm in PAIS. Pubic and axillary hair are sparse or absent [1, 4, 9]. Androgen insensitivity syndrome accounts for about 10% of all cases of primary amenorrhea (the leading symptom in the manifestation of this syndrome). This is the third most common cause after gonadal dysgenesis and congenital absence of the vagina [7]. Our patient's main complaint was the lack of menarche – primary amenorrhea without any other subjective complaints. After the physical examination, it was found – a blind-ended vagina – 2 cm long, absence of pubic and axillary hair and breast development Tanner V stage.

During adolescence, individuals with CAIS typically exhibit normal height growth, with a growth peak occurring around the age of twelve. In the absence of an increase in estradiol production, epiphyseal closure may be delayed, allowing for a longer growth period. Individuals with CAIS are generally taller than the average female population. Our patient's high was 173.5 cm, an average height for Bulgarian girls of the same age, 164 cm [9].

The expected hormone profile in patients with CAIS includes elevated luteinizing hormone (LH) levels above the normal reference range, while follicle-stimulating hormone (FSH) levels generally remain within normal ranges, likely due to gonadal inhibin regulation. Basal testosterone levels are usually within the normal male range but significantly higher compared to female ranges. Estradiol serum levels fall within the normal male range but are considered low when referenced to female levels [9, 15]. In our case, as it was expected, the serum testosterone level was 22.6 nmol/L. It exceeded the typical normal values for female patients (2.3 nmol/L), but it corresponded to the normal rates for boys of the same age. The serum levels of LH were 42.1 IU/L (normal values: 2.4–8.3 IU/L), and FSH was 6.9 mIU/ml, estradiol <73 pmol/L.

In terms of whether and when to remove the gonads, the probability of gonadal tumors in patients with CAIS is higher than that of normal men. Studies showed that the occurrence of gonadal tumors in patients with CAIS is related to age. The estimated risk of gonadal malignancy is 14% (range 0% and 22%) in adults with CAIS. [10,12,16] Because of the low rate of gonadal malignancy during and before puberty and the benefits of gonadal preservation, most experts recommend gonadectomy as early as possible after puberty [1]. On the other hand, there is literature evidence suggesting a 5% chance of developing malignant tumors in patients with CAIS retaining their testicles through puberty [11,13]. In our case, we performed gonadectomy at age of 15 after a written informed consent was obtained from the patient's parents. This decision was in-

duced by the presence of doubt about the Sertoli cell adenoma in the left testis from the MRI examination.

For women who wish to keep their gonads, it is proposed a regular (bi-)annual screening program comprising gonadal imaging by US or MRT, depending on the size and localization of the gonad, determination of tumor markers (alpha-fetoprotein, beta-HCG, LDH, and optionally PLAP in non-smokers), and endocrine evaluation (LH, FSH, testosterone, and inhibin B). Again, it has to be stressed that no specific and sensitive parameters exist for early detection of (pre-)malignant changes in the gonads, so in other high-risk populations (e.g., for ovarian cancer), early gonadectomy is still recommended. [2, 12, 15]. Our patient's serum levels of AFP 0.773ig/L, B-CHG <1.0 mIU/L were in the normal range.

After gonadectomy, hormonal replacement therapy with estrogens is initiated, as endometrial protection is unnecessary because of the absence of a uterus. There is no consensus on the optimal hormone replacement therapy dosage in these individuals. In addition, monitoring bone mineral density is essential since a higher risk of low bone mineral deficiency is reported, although a great risk of fractures has not been demonstrated. For this reason and to promote overall psycho-physical well-being, some have suggested replacement therapy with androgens, but this remains a topic of debate. Maintaining vitamin D levels and dietary calcium balance, with possible supplements, is recommended [2, 9]. In our case TTS with conjugated estrogens was chosen, with an additional intake of vitamin D and Calcium.

CONCLUSIONS:

In summary, CAIS is a rare genetic disorder that is connected with an increased risk of neoplastic processes, although the incidence is lower compared to other disorders in Sex Development (DSD). The greater percentage of diagnosed testicular neoplastic processes are non-invasive, with a low likelihood of progressing into more aggressive forms. However, the histological, epidemiological, and prognostic characteristics of testicular cancer in CAIS support the option of postponing gonadectomy until after puberty. In patients whose gonads appear normal without features suggestive of disease, continued monitoring with annual imaging should be pursued. Tumor serum markers in germ cell tumors have not shown to be fully effective as a guidance tool or provide benefit in determining risk for malignancy.

Work should be done in the direction of creating algorithms for diagnosis, treatment and prevention, both for patients with CAIS and other rare diseases, in order to improve the quality of life and prognosis of these patients. The key, in our opinion, is the multidisciplinary approach and the creation of specialized centers for children with rare genetic disorders.

Ethical Guidelines: A written informed consent was obtained from the patient's parents, with the understanding that there would be no recognition or compensation provided and that all their data would be kept completely anonymous for the publication of this case report and any accompanying images.

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