Complete Androgen Insensitivity Syndrome

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Opening

In this chapter, the clinical features, diagnosis, and treatment of complete androgen insensitivity syndrome (CAIS) are presented. CAIS is a rare disease belonging to the disorders of sex development (DSD), which is a cause for primary amenorrhea in women. CAIS is caused by various mutations in the androgen receptor (AR) gene

Definition of the Disease

Complete androgen insensitivity syndrome (CAIS) can be defined as hormone resistance to androgens resulting in a female phenotype in an individual with a normal male 46,XY karyotype and testes producing age-appropriate normal concentrations of androgens (testosterone) (46,XY DSD). It can also be categorized as a form of sex reversal, since a female phenotype develops despite a normal male karyotype. Previously, the term male pseudohermaphroditism was also used for describing such syndromes where the affected individual has testes, but female external genitalia or a complete female phenotype like in CAIS is present.

Other forms of AIS (androgen insensitivity) include mild AIS (MAIS) and partial AIS (PAIS). The etiopathogenesis is related to mutations in the X-linked androgen receptor gene. This syndrome was described by John Morris in 1953 based on 82 cases. He named this syndrome "testicular feminization syndrome." It reflected the observation that testes in these patients produced a hormone that had a feminizing effect on the body. At present, it is understood that it results from the subsequent aromatization of testosterone into estrogen. In the past, other names to describe this syndrome were also used, namely, Morris' syndrome and Goldberg-Maxwell syndrome. After the understanding of the underlying molecular pathogenesis (defects in the androgen receptor) of this syndrome, the currently accepted name is androgen insensitivity syndrome. Complete AIS is rare and occurs in as many as 1 in 20,000 live births. About two-thirds of CAIS are inherited from the mother as an X-linked recessive trait, and one-third present as de novo, sporadic mutations. Patients with CAIS are infertile.

Case Presentation

A 44-year-old Caucasian female was referred to the Department of Gynecological Endocrinology, Poznan University of Medical Sciences, due to primary amenorrhea. It is rare to diagnose primary amenorrhea in a patient at this age. Nevertheless, she had never requested diagnostic examinations before admission. She did not have any relevant past medical or family history.

What relevant clinical characteristics were found during the examination of the patient?

The patient had normal breast development (Tanner stage 5) and poor pubic hair (Tanner stage 1). She had no axillary hair. Her weight on admission was 98 kg, her height was 164 cm, and her BMI was 36.5 kg/m^2. Gynecological examination and transvaginal ultrasound revealed a blind-ended hypoplastic vagina with 3 cm of depth and the complete lack of uterus and ovaries. External genitalia were completely female. Urography revealed no abnormalities of the urinary tract.

Which clinical characteristics are the most important for CAIS diagnosis?

The diagnosis, which is typically made in an adolescent or young adult woman, is based upon a constellation of clinical and biochemical findings, including the following:

- Female phenotype with normal breast development
- Primary amenorrhea
- Little or no axillary or pubic hair
- Absent uterus, but testes present
- Blind vaginal pouch on examination

Which hormones should be measured?

The most important hormonal parameter measured in a case of suspicion of CAIS is testosterone (T). In CAIS patients, serum testosterone concentrations are either within or above the normal range for males. Luteinizing hormone (LH) concentrations are inappropriately elevated due to the fallout of negative feedback by T via the AR. Levels of follicle stimulating hormone (FSH) and inhibin can be normal, as the secretion of FSH is predominantly regulated by inhibins produced by testicular cells and is therefore less influenced by androgen insensitivity.

What were the hormonal results of our patient?

Serum LH, FSH, and total testosterone concentration were significantly elevated, while estradiol serum concentration was considerably low for a female. The other hormonal results were within normal limits (Table 43.1). Taking into consideration the described results, androgen insensitivity syndrome was suspected.

What additional diagnostic tests should be undertaken?

In CAIS, the testes may be located in the abdomen or in the inguinal region due to the lack of androgen action. It has been established that androgens mediate the inguinoscrotal phase of testis descent to ensure that the testes are in the scrotum at or soon after birth in humans. The site and size of the testes can be determined by ultrasonography or magnetic resonance imaging (MRI).

Table 43.1 Hormonal profile of patient on admission to hospital

	Hormonal results at diagnosis	Reference values for females
FSH [mIU/mL]	45.26	3.50–12.50[a]
LH [mIU/mL]	69.11	2.40–12.60[a]
Estradiol [pg/mL]	22.10	12.50–166.0[a]
Testosterone [ng/mL]	6.12	0.06–0.82
DHEAS [µmol/L]	4.54	1.65–9.15
TSH [µIU/mL]	1.45	0.27–4.20
FT4 [ng/dL]	0.98	0.93–1.70
Insulin [mIU/mL]	6.89	2.60–24.90

[a]Normal ranges for the follicular phase of the menstrual cycle

What was the result of diagnostic imaging in our patient?

A small pelvis MRI was performed that confirmed the absence of a uterus and ovaries; moreover, an adequately developed distal vagina was also noted. MRI did not reveal any additional pathology or masses within the pelvis. Because of the strong suspicion of AIS, we performed examinations focused on a search for testes. An ultrasound of the inguinal canals was then performed, which revealed the presence of two oval, homogenously echogenic structures bilaterally below the superficial inguinal rings (right 43 × 24 × 21 mm, left 29 × 21 × 20 mm). A follow-up contrast-enhanced pelvic MRI was performed to visualize the inguinal canals. Two homogenous contrast-enhancing solid mass lesions were confirmed bilaterally in the distal canals. It was determined that these lesions most likely corresponded to the

undescended testes. On the basis of these clinical findings, biochemical parameters, and diagnostic imaging, the patient was referred for surgery. She underwent surgical excision of both inguinal masses.

What was the histopathological result of the excised masses?

The seminiferous tubules located in the excised gonads contained only Sertoli cells. There were numerous Leydig cells in the stroma. Within the right gonad, a nodule composed of hypoplastic seminiferous tubules with immature Sertoli and Leydig cells was present (Sertoli-Leydig hamartoma). The whole microscopic image corresponded to the clinical diagnosis of androgen insensitivity syndrome.

Why was gonadectomy needed?

Prophylactic gonadectomy has been performed because of the risk for developing gonadal malignancy, mostly germ cell tumors (gonadoblastoma or dysgerminoma). The risk is low below the age of 25 years and tumor formation is most frequent between 30 and 50 years of age. An estimated average of 5% CAIS patients develop gonadal tumors.

Is genetic testing necessary for establishing the diagnosis?

The AR is coded by a single-copy gene on the X chromosome. A diagnosis of CAIS can be confirmed by sequencing the coding region of this gene. Loss-of-function mutations in the coding sequence of the AR can be found in most women with CAIS.

What was the result of genetic testing in our patient?

Chromosomal analysis (using GTG banding) confirmed a 46,XY karyotype. We have sequenced the coding AR region. A novel single base substitution from cytosine to thymine at position 66,942,710 was identified that predicted pathological effect in the Mutation Taster web application (► http://www.mutationtaster.org/).

What was the follow-up of our patient?

The patient is leading a well-adjusted life as a woman and is a fully functioning member of society. After surgical removal of both testes, she was administered hormone replacement therapy (HRT). Due to the lack of a uterus, monotherapy with estradiol 2 mg per os daily was started. Serum FSH and estradiol concentrations were measured at 1 year follow-up after surgery (◘ Table 43.2). To this day, the patient remains under our control and her health condition remains stable.

What kind of other causes of primary amenorrhea should be mentioned?

◘ **Table 43.2** Hormonal profile of patient 1 year after surgery on hormonal replacement therapy (HRT)

	After surgery; on HRT	Reference values for females
FSH [mIU/mL]	21.30	3.50–12.50[a]
LH [mIU/mL]	10.40	2.40–12.60[a]
Estradiol [pg/mL]	73.10	12.50–166.0[a]
Testosterone [ng/mL]	0.23	0.06–0.82
DHEAS [µmol/L]	9.90	1.65–9.15
TSH [µIU/mL]	1.40	0.27–4.20
FT4 [ng/dL]	1.09	0.93–1.70
Insulin [mIU/mL]	7.45	2.60–24.90
AMH [ng/mL]	<0.01	

[a]Normal ranges for the follicular phase of the menstrual cycle

- *Turner syndrome* is the most common cause of primary amenorrhea in women and it is discussed in ► Chap. 40.

- *Pure Gonadal Dysgenesis (Swyer syndrome)*

- Patients with Swyer syndrome, another syndrome of sex reversal, also referred to as pure gonadal dysgenesis (karyotype 46,XY), are clinically characterized by a delay in puberty, normal or increased height, and primary amenorrhea. They only have a streak gonad and there is a lack of the prenatal synthesis of AMH (anti-Müllerian hormone) and testosterone, leading to the preservation of the Müllerian structures (uterus, fallopian tubes, upper third of the vagina) and the atresia of the Wolffian duct. It is a very rare syndrome (estimated prevalence 1:80,000–100,000) and has been related to mutations in a number of different genes. In the perineal area, transition of the urogenital sinus into the urethra and the lower two-thirds of the vagina occurs, as well as formation of the clitoris from the genital tubercle and the development of the labia majora from urogenital swelling. As a result, the external genitals are female. Laboratory investigations show hypergonadotropic (primary) hypogonadism, with high serum concentrations of FSH, LH, and low serum concentrations of estradiol and AMH. The presence of a Y chromosome may be a risk factor for the development of tumors, such as gonadoblastoma and dysgerminoma within the gonadal tissue with a prevalence of 14–45%. Management of those patients is based on the preventive excision of streak gonads and long-term hormone replacement therapy.

- *Mayer-Rokitansky-Küster-Hauser Syndrome (MRKH syndrome)*

- Patients with Mayer-Rokitansky-Küster-Hauser syndrome lacks a uterus and a vagina due to the absence of Müllerian duct development. They have normal female gonads, normal female phenotype with pubic and axillary hair, normal breast development, and internal female genitalia. Their karyotype is 46,XX and the serum concentrations of FSH, LH, AMH, and estradiol are within the normal range. In 2015, the first live births were reported after uterus transplantation in women with MRKH syndrome.

- *Kallmann syndrome* is a hereditary form of hypogonadotropic hypogonadism associated with anosmia/hyposmia that is discussed in ► Chap. 7.

- *Enzyme Deficiencies*

- Deficiency of 5-α reductase or other enzymes (cholesterol side chain cleavage enzyme – gene *CYP11A1*, 3ß-hydroxysteroid dehydrogenase 2 – gene *HSD3B2*, 17α-hydroxylase/17,20-lyase – gene *CYP17A1* (► Chap. 35), StAR – gene *StAR*) can also lead to sexual ambiguity and must be differentiated in particular from partial AIS (PAIS) and mild AIS (MAIS).

- **Is androgen insensitivity syndrome always characterized by a female phenotype?**

- The clinical presentation of androgen insensitivity is associated with the degree of tissue resistance to the biological actions of androgens. Complete androgen insensitivity syndrome (CAIS) results in a female phenotype. Affected women (including some models and actresses) are taller than the average.

- Partial androgen insensitivity syndrome (PAIS) includes phenotypes of various degrees of masculinization in relation to AR mutations resulting in different responsiveness of external genitalia to androgens. Patients with PAIS may have both male and female physical characteristics (DSD). Typical phenotypes are associated with micropenis, severe hypospadias, and bifid scrotum. Sequencing of the AR gene is necessary to confirm the diagnosis of PAIS and to distinguish the syndrome from

other causes of undermasculinization such as partial gonadal dysgenesis, mutations of the luteinizing hormone receptor, enzyme deficiencies, or Klinefelter syndrome (▶ Chap. 42).

Mild androgen insensitivity syndrome (MAIS) also results from a mutation of the androgen receptor gene but is not associated with genital anomalies and therefore is infrequently reported. MAIS can present in men as infertility and gynecomastia. There is a form of MAIS related to Kennedy's disease that is characterized by the weakness and wasting of bulbar, facial, and limb muscles (bulbar and spinal muscular atrophy). Kennedy's disease is caused by a trinucleotide repeat expansion in the AR gene.

What kind of treatment options can be envisaged for patients?

Management of complete androgen insensitivity syndrome includes gonadectomy and subsequent hormone replacement and creation of a functional vagina. Genetic counseling and psychological care should also be provided. The primary treatment is laparoscopic gonadectomy because of a risk of gonadal malignancy, mostly germ cell tumors (gonadoblastoma or dysgerminoma). Choosing the right time for a gonadectomy is also very important from the psychological point of view. Most AIS guidelines recommend to perform gonadectomy only after the sexual characteristics are fully developed or the patient is over 16 years of age with full breast development. Other authors suggest to perform a gonadal biopsy as soon as AIS is diagnosed and propose prepubertal gonadectomy if precancerous lesions or in situ carcinomas are found. Estrogen replacement is needed to induce puberty or to maintain secondary sex characteristics. HRT is not only necessary for the development of sexual characteristics but is also a preventive option that affects later complications, such as osteoporosis and cardiovascular disease. Bone mineral density can be significantly lower in patients with CAIS that can also be improved by the administration of estrogens. Progesterone is not indicated due to the absence of a uterus. Some women suffering from CAIS prefer to take supplementary testosterone too after gonadectomy as it might improve their overall well-being including sexual desire.

Is there any adjuvant therapy that should be considered?

Psychological care and support seem to be crucial for parents and especially for children diagnosed with CAIS. Making the diagnosis affects the life of the whole family. Parents have to decide the gender their child should be raised in. Children with CAIS are mostly brought up as females. The struggle is greater with children with PAIS. Children may later need complex psychological support, especially if the gender their parents decide upon does not match their gender identity.

Tips

The reader is advised to read the chapter on Turner syndrome (▶ Chap. 40) and also the chapter on Kallmann syndrome (▶ Chap. 7) as a prototype of hypogonadotropic hypogonadism.

Take Home Messages

- Androgen insensitivity syndrome (AIS), resulting from androgen receptor dysfunction, is an important cause of disorders of sex development (DSD).
- AIS phenotypes include complete, partial, and mild forms that are associated with various degrees of residual androgen receptor activity.
- In the complete androgen insensitivity syndrome (CAIS), a female phenotype is found in a patient with a male 46,XY karyotype and testes associated with an

age-appropriate normal male concentration of testosterone.
- Imaging tests in CAIS can reveal a short vagina, absence of the uterus, or the presence of Müllerian or Wolffian duct remnants. The gonads in CAIS are invariably testes that can be located within the abdomen or labia but are most frequently found in the inguinal canals.
- Management of CAIS includes gonadectomy because of the risk of gonadal tumors in later life and hormone replacement therapy after the operation.
- Psychosocial support is central to the multidisciplinary approach for the management of androgen insensitivity syndrome.

Suggested Reading

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