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46 XY, Female. Complete androgen insensitivity syndrome: a case report

Anna Grądzik [1], Anna Gorajek [2], Małgorzata Kudan [2], Aleksandra Osiejewska [1], Karolina Mikut [3]

1. University Clinical Center, Medical University of Warsaw, 02-097, Warsaw, Poland
2. Central Clinical Hospital of the Ministry of Interior and Administration, 02-507, Warsaw, Poland
3. Collegium Medicum Nicolaus Copernicus University, 85-067, Toruń, Poland

Corresponding author: Anna Grądzik, anna.gradzik123@gmail.com

ORCID ID and e-mail:
Anna Grądzik: https://orcid.org/0000-0002-8457-5172; anna.gradzik123@gmail.com
Anna Gorajek: https://orcid.org/0000-0002-8043-2246; agorajek@vp.pl
Małgorzata Kudan: https://orcid.org/0000-0001-6463-6735; malgorzata.kudan@gmail.com
Aleksandra Osiejewska: https://orcid.org/0000-0002-1729-9905; aleksandraosiejewska@gmail.com
Karolina Mikut: https://orcid.org/0000-0001-7022-581X; karolina.mikut@gmail.com

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Abstract

Introduction: Androgen insensitivity syndrome (AIS) is an inherited disorder of sexual development caused by mutations in the androgen receptor encoding gene.

Case report: A female patient born in 1984, at the age of 17, was diagnosed with complete androgen insensitivity syndrome, during the diagnosis of primary amenorrhea. She was assigned grade 7 in the Quigley scale. Cytogenetic analysis showed a 46 XY karyotype. Gynecological examination revealed a blind ending vagina and a lack of uterus. Physical examination revealed normal breast development and scanty pubic and axillary hair. The patient kept seeing herself as a woman. At the age of 18, the patient underwent laparoscopic gonadectomy. After the procedure, the patient was under medical supervision and was taking orally 1 mg of estradiol daily. At the age of 24 patient was diagnosed with. The patient received sodium alendronate and ibandronic acid. The level of FSH was 35.50 mlU / ml and LH was 13.05 mlU/ml.

Discussion: Quigley grades 6 and 7 correspond to complete androgen insensitivity. The genitals are completely feminized and newborns at birth are assigned as females. The diagnosis is usually established during the diagnostics of primary amenorrhea. CAIS is associated with high risks of gonad carcinogenesis and therefore a gonadectomy must be performed. Hormone replacement therapy (HRT) is required after gonadectomy in order to maintain secondary sexual characteristics. Due to the high risk of osteoporosis patient requires calcium and vitamin D supplementation and bone density control. The prognosis is good, and gonadectomy and HRT usually give satisfactory long-term results.

Introduction:

Androgen insensitivity syndrome (AIS) is an inherited, congenital disorder of sexual development caused by mutations in the androgen receptor encoding gene. This gene is located on chromosome X (loci Xq11-q12)[1] and has a X-linked recessive inheritance. AIS has three types, complete AIS (CAIS), partial AIS (PAIS), and mild AIS (MAIS) [2][3]. The Quigley scale enables to classify the patient based on the phenotype of external reproductive organs. The frequency of the prevalence of CAIS and PAIS is 2-5/ 100 00 of every person with XY karyotype, and mild AIS is much rarer. [4]

The effects of androgen appear only after it binds to its protein androgen receptor, protein AR. Mutations within this gene lead to a vast range of male genital development disorders. On the one hand there are people with complete androgen insensitivity, who are presenting a proper development of mammary glands and external reproductive organs and on the other there are people with a full male phenotype, however undervirilaized or infertile. [2] During the

embryological development of a 46 XY karyotype foetus, in the presence of SRY gene on chromosome Y, the development of testes begins, and with it the testosterone production. This hormone is responsible for enhancing the development of external reproductive organs. Additionally, anti-Müllerian hormone (AMH) is released, leading to the inhibition of the development of paramesonephric duct (from this tube the fallopian tube, uterus and the upper part of the vagina originates).[5] In patients with CAIS there is a lack of testosterone cell stimulation, regardless of its high concentration, and this leads to a female development of external reproductive organs. However, the production of AMH is not disturbed, which is the cause of the inhibition paramesonephric ducts. Estrogens, produced by the testes and by the peripheral aromatization of androgens [6], leads to the development of external reproductive organs: a blind-ending vagina (lower part of vagina) and female mammary glands.

Below we present a case report of a patient with complete androgen insensitivity syndrome, who was assigned stage 7 in the Quigley scale.

Case report:

Our patient born in 1984, weighing 68 kg and measuring 171 cm. At the age of 17 years old, during the diagnostics of primary amenorrhoea, complete androgen insensitivity syndrome was diagnosed. Cytogenetic evaluation revealed a 46 XY karyotype, even though the patient thought of herself as a woman. No specific mutation of the androgen receptor was determined, due to the family's refusal of genetic testing. Gynecological examination revealed a blind ending vagina and a lack of uterus, which was confirmed with USG and laparoscopy. Physical examination revealed normal breast development, 3/4 in Tanner scale, and scanty pubic and axillary hair, 1/2 in Tanner scale. The patient has seen herself as a woman.

At the age of 18, she underwent a bilateral laparoscopic gonadectomy. Before the surgery, the testosterone level was 5.6 ng/ml, and after 0.6 ng/ml (N: 0.11-0.78 ng/ml). Macroscopic evaluation of the removed gonads showed testicle tissue. One gonad had a 4 cm in diameter cyst and 2 cm lumps. Microscopic evaluation revealed a tubular stroma padded out with Sertoli cells and some aggregations of Leydig cells on both gonads, which led to a suspicion of tubular adenoma. After the procedure, the patient stayed under medical supervision and has been administered 1 mg of estradiol daily.

At the age of 24, the patient was diagnosed with osteoporosis. T-SCORE was -2.6 SD, osteocalcin level was at 26 ug/dl(N), calcium level was at 9.1 mg/dl (N) and phosphates 3.7mg/dl (N). However, in 2012 T-SCORE dropped down to -2.76 SD and Z-SCORE was at -2.92. In consequence she started receiving alendronate sodium and ibandronic acid.

During the follow-up examination at the age of 34, the patient was diagnosed with type 2 diabetes (OGTT 6,2 mmol/l- after 2 hours 15,1 mmol/l) and treatment with metformin was started. The level of the follicle-stimulating hormone (FSH) was 35.50 mlU/ml, and the luteinising hormone (LH) level was 13.05 mlU/ml. Because of the persistent high levels of alanine aminotransferase 55.2 U/l (N: 0-33U/l) the patient is under hepatological supervision; infection of HBV and HCV was excluded.

Discussion:

Quigley grades 6 and 7 are indicated when the reproductive organs are completely feminized, corresponding to complete androgen insensitivity syndrome, and always a female sex is assigned at birth [7]. The characteristics of CAIS are lack of pubic and axillary hair, normal breast development due to the peripheral conversion of testosterone to estradiol during puberty and a blind ending vagina. As a result of such features, CAIS is very rarely identified in the neonatal stage. Most of the cases, like our patient, are diagnosed during puberty, during the diagnostics of primary amenorrhoea. In a handful number of cases CAIS is diagnosed prenatally on the grounds of incompatibility of the genetic gender determined during amniocentesis and the structure of the external genitalia visible during the USG, resulting in mapping the karyotype in order to differentiate CAIS from other genetic disorders. [8]

During physical examination in such patients a short vagina and a lack of uterus is detected. Thanks to imaging techniques (USG, CT, MRI) the lack of uterus and ovaries and the presence of the testicles is confirmed. [9] In about 2/3 CAIS patients the testicles are situated near the inguinal canal or the vulva, and in 15% they are placed in the peritoneal cavity. The diagnosis of CAIS requires elimination the abnormally located testicles, due to the increased risk of neoplastic changes.[10] Laparoscopic method is preferred, because of the minimal invasiveness and accompanying low mortality rate. [8]

The most common gonadal tumours are seminomas, rarer gonadoblastomas, choriocarcinomas, teratomas or Sertoli cells tumours. The risk of developing a malignant tumour in CAIS,

increases with the age of the patient – from 3.6% at the age of 25 to 33% after the age of 50. The incidence of tumours in CAIS is 0.8% to 2%. [8] Our patient underwent at the age of 18 a gonadectomy, and during the histopathological examination a suspicion of tubular adenoma was raised. Postponement of this surgical procedure until the patient reaches the age of puberty, enables a spontaneous adolescence thanks to the aromatization of testosterone, while at the same time being a safe solution, as a result of the low risk of developing a malignant tumour. Additionally, the patients can take an active part in the decision-making process. [9] After the gonadectomy it is crucial to implement an estrogen substitution therapy in order to maintain the secondary sexual characteristics and the proper proportions of the body, to prevent the decrease of bone density and to ensure a proper psychosocial development and well-being. Patients with CAIS take mainly estrogens orally, rarely percutaneously. The treatment begins with low doses, which are systematically increased, whilst observing the bone age. In women with CAIS by cause of uterus agenesis, progesterone substitution therapy is not recommended.[8]

The described patient was diagnosed with osteoporosis (T-SCORE -2.96 SD), which may be connected to the decline of bone density in patients with CAIS, and what's more with the irregular administration of hormonal replacement therapy. For CAIS patient's vitamin D and calcium supplementation, a regular physical activity, and regular controls of bone density and of BMI is endorsed. [10][11]

It is crucial to provide psychological care for the patients and their families, even at an early stage of the diagnosis. Most patients, like ours, identifies themselves as women. However, knowing they are genetically male and that they are infertile, can be extremely difficult for them. Therefore, a thorough psychological assessment and psychiatric intervention leads to a considerable extent to the reduction of associated stress and to the improvement of their well-being.

Conclusion:

To summarise, complete androgen insensitivity syndrome, although occurring rarely, is a very stressful disorder for the patient and for their families. The prognosis is generally good, especially when diagnosed early. Gonadectomy and hormonal replacement therapy give satisfactory short- and long-term results. A continuing observation of the patients is vital in order to avoid the longstanding consequences of bone demineralization, the negative side-effects of hormonal therapy and to ensure the psychological comfort of our patients. [12] An

interdisciplinary team of surgeons, gynaecologists, and psychiatrists and their tight cooperation is crucial for the correct treatment of complete androgen insensitivity syndrome.

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