Case Report

https://doi.org/10.23934/2223-9022-2023-12-2-327-332

Clinical Case of the Complete Form of Androgen Insensitivity Syndrome (AIS)

MM. Damirov, I.V. Anchabadze ✉, A.A. Medvedev, M.A. Eremenko

Department of Acute Gynecological Diseases
N.V. Sklifosovsky Research Institute for Emergency Medicine
3, Bolshaya Sukharevskaya Sq., 129090, Moscow, Russian Federation

✉ **Contacts:** Irina V. Anchabadze, Candidate of Medical Sciences, Senior Lecturer, Educational Department, N.V. Sklifosovsky Research Institute for Emergency Medicine.
Email: anchabadzeiv@sklif.mos.ru

ABSTRACT The article presents a clinical observation of an extremely rare in gynecological practice androgen insensitivity syndrome (AIS). The authors give data on the pathogenesis of the disease, modern classification and terminology of various forms of this pathology. The phenotypic manifestations of the disease, the results of clinical and instrumental studies and surgical treatment are described.

The results of the study show the possibility of clinical diagnosis of AIS and timely surgical treatment of patients with this pathology, due to the high risk of gonadal malignancy.

Keywords: androgen insensitivity syndrome, testicular feminization syndrome, Morris syndrome, disorder of sex development, gonadectomy, hormone replacement therapy

For citation Damirov MM, Anchabadze IV, Medvedev AA, Eremenko MA. Clinical Case of the Complete Form of Androgen Insensitivity Syndrome (AIS). *Russian Sklifosovsky Journal of Emergency Medical Care.* 2023;12(2):327–332. https://doi.org/10.23934/2223-9022-2023-12-2-327-332 (in Russ.)

Conflict of interest Authors declare lack of the conflicts of interests

Acknowledgments, sponsorship The study has no sponsorship

Affiliations

Mikhail M. Damirov	Professor, Doctor of Medical Sciences, Head, Department of Acute Gynecological Diseases, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-6289-8141, damirov@inbox.ru; 35%, validation of critical intellectual content of the manuscript, editing the final version of the text
Irina V. Anchabadze	Candidate of Medical Sciences, Senior Lecturer, Educational Department, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0009-0005-9336-2768, anchabadzeiv@sklif.mos.ru; 30%, article concept and design, data systematization, text writing
Alexander A. Medvedev	Chief, Department of Acute Gynecological Diseases, N.V. Sklifosovsky Research Institute for Emergency Medicine; https://orcid.org/0000-0001-7159-7287, medvedevaa@sklif.mos.ru; 25%, practical part of the research, preparation and performance of surgical treatment, participation in text writing
Maria A. Eremenko	Clinical Intern, N.V. Sklifosovsky Research Institute for Emergency Medicine; maryyeremenko@bk.ru; 10%, search and selection of publications in databases, participation in the surgery and postoperative follow-up

17β-HSD-17beta-hydroxysteroid dehydrogenase
AIS - androgen insensitivity syndrome
AMH - anti-mullerian hormone
HRT - hormone replacement therapy
LH - luteinizing hormone
MRI - magnetic resonance imaging
POR - P450 oxidoreductase
SDD - sex differentiation disorder
StAR - steroidogenic acute regulatory protein

Sex differentiation disorder (SDD) is a condition associated with the clinical and biochemical manifestations of a discrepancy between the genetic, gonadal and phenotypic sex of the child. Previously, the term "hermaphroditism" was used to describe this condition. Until recently, the classification of hermaphroditism was mainly guided by the patient's karyotype. Thus, with a 46XX karyotype, the condition was regarded as female hermaphroditism, with a 46XY karyotype, as male hermaphroditism, and if gonads of both sexes were detected in one patient, it was considered as true hermaphroditism. However, in recent years, this classification has ceased to satisfy doctors in clinical practice. On the one hand, the widespread use of the term "hermaphroditism" outside of medical circles has led to a breach of patient confidentiality as a result of misinterpretation of the diagnosis in the patients' environment. This inevitably exacerbated the patients' psychological discomfort, causing social

problems for both them and their relatives. On the other hand, to date, the mechanisms of development of this group of diseases have been accurately elucidated, which makes it possible to establish an accurate nosological diagnosis from the standpoint of the etiopathogenesis of the disease. In this regard, in 2006, the classification of hermaphroditism was revised at the International Meeting of Pediatric Endocrinology [1]. It was proposed to replace both the term “hermaphroditism” itself and the indication in the diagnosis of gender, that is, male or female hermaphroditism [2]. The use of the term "sex differentiation disorder" (SDD) was recommended (Table 1) [3]. It is noted that SDD is a congenital condition caused by chromosomal, gonadal and somatic disorders of sex development.

Table 1

Classification of disorders of sex development [4]

Chromosomal SDD	46 XY SDD	46 XX SDD
45 X (Shereshevsky–Turner syndrome and its variant)	Testicular dysgenesis syndrome: — pure testicular dysgenesis — mixed testicular dysgenesis — • gonadal regression syndrome (rudimentary testes syndrome)	Ovarian dysgenesis: — gonadal dysgenesis — testicular SDD — ovotesticular SDD
47, XXY (Klinefelter syndrome and its variants) 45, X/46, XY 46, XX/46, XY (mixed ovotesticular form of SDD)	Disorders of androgen biosynthesis: — 17-β-HSD deficiency — 5α-reductase deficiency — StAR deficiency — androgen insensitivity syndrome - complete and incomplete forms — LH deficiency — Anti-Müllerian hormone (AMH) or AMH receptor defect	Excess androgens: — 21-hydroxylase deficiency — 11β-hydroxylase deficiency — POR deficiency — fetoplacental SDD (aromatase deficiency) — maternal SDD (luteoma, medications)

Notes: SDD - sex differentiation disorder; LH - luteinizing hormone; HSD - 17beta-hydroxysteroid dehydrogenase; StAR - Steroidogenic acute regulatory protein; POR - Protein oxidoreductase

One of the variant of XY SDDs is androgen insensitivity syndrome (AIS), complete and partial types. This disease was first described by E. Steglehner in 1817, who, during the autopsy of a 23-year-old woman, found male gonads, while the uterus and appendages were absent. Much later, the American obstetrician-gynecologist F. Morris most fully studied this disease and in 1953 proposed the term "testicular feminization" [5]. It should be noted that this pathology is quite rare. According to various sources, this disease occurs with an incidence of 1:10,000–1:65,000 in genetic males [6]. Such variability in incidence is explained by the fact that many cases of the disease remain clinically unrecognized. According to the National Medical Research Center for Endocrinology, AIS is diagnosed in only 5% of all SDD forms [7, 8].

Complete AIS (synonyms: Morris syndrome, testicular feminization syndrome, testicular feminization syndrome, false male hermaphroditism) is a genetic disease in which there is a defect in the androgen receptor gene localized on the short arm of the X chromosome (Xq11–12) [9]. This disease is of X-linked recessive inheritance and often has a family history [10, 11].

The leading role in the pathogenesis of the disease is associated with the lack of tissue sensitivity to androgens (testosterone, dihydrotestosterone). During embryogenesis, under the influence of the Y chromosome, the gonad differentiates to testes which secrete testosterone and a substance that inhibits the Müllerian ducts. But, despite the normal level of testosterone in the blood, it does not affect those tissues from which the male genital organs would normally form. At the same time, the secretion of estrogens is preserved by the adrenal glands and partially by the gonads, and as a result of this effect, a female phenotype is formed in the fetus of the genetic and gonadal male [12].

In patients with the incomplete form of androgen insensitivity, the body's reactivity to androgens is partially preserved. Therefore, in the structure of the external genital organs, signs of masculinization are noticeable - a hypertrophied clitoris, a funnel-shaped vestibule of the vagina; vaginal aplasia is often found [7]. For the purpose of psycho-emotional and sexual adaptation, surgical correction of the vagina is indicated for patients with partial AIS.

An outstanding contribution to the research of this anomaly of the genital organs’ development, as well as in the improvement of the methods of surgical treatment for the diagnosed disorders was made by Professor M.S. Alexandrov, the first Head of the Department of Acute Gynecological Diseases of the N.V. Sklifosovsky Research

Institute for Emergency Medicine. It should be noted that his doctoral dissertation M.S. Alexandrov defended at the intersection of surgical specialties (surgery and gynecology), and it was devoted to solving an extremely complex problem - the surgical formation of the artificial vagina from the sigmoid intestine (1943). Based on the results of his dissertation work and the performance of similar surgeries on many patients, in 1955 he published the monograph "Formation of an artificial vagina from the sigmoid intestine" [13].

Unlike other types of SDD (testicular dysgenesis syndrome, true hermaphroditism, congenital dysfunction of adrenal cortex, etc.), in case of AIS there are no female internal genital organs (uterus, fallopian tubes, ovaries), which is a fundamental distinguishing feature and greatly facilitates the formulation of the correct clinical diagnosis. A comprehensive examination of such patients, along with clinical and gynecological evaluations, includes genetic counseling, karyotyping, determination of sex hormone level in the blood serum, as well as instrumental research methods (ultrasound of the pelvic organs, magnetic resonance imaging – MRI – of pelvic organs).

It should be noted that for a long time this disease may not be diagnosed, and only complaints about the absence of menstruation (primary amenorrhea) force the child's parents to consult the obstetrician-gynecologist. According to modern concepts, in the gonads of patients with AIS located in an atypical place and conditions (the temperature in the abdominal cavity is higher than in the scrotum by about 3.0–3.5 ° C), as a result of constant exposure to elevated temperature, spermatogenesis and testosterone production stop and, most importantly, the risk of malignancy significantly increases. It has been shown that testicular gonadoblastoma in such cases occurs in 20–50% of cases [14–16]. In this regard, it is recommended to remove the gonads after the completion of the pubertal period of the girl's life and her constitutional formation. The treatment consists in surgical gonadectomy and hormone replacement therapy (HRT) in the future, since after the removal of the gonads there is a risk of developing severe osteoporosis [17, 18].

We present our own clinical observation of a patient with complete AIS.

Patient N., aged 41, was admitted to the N.V. Sklifosovsky Research Institute for Emergency Medicine with complaints of pain in the lower abdomen. From the anamnesis it was established that at birth, according to the somatic sex, she was identified as a female newborn, and grew up and was brought up in the family as a girl. The diagnosis was first made at the age of 17, when the patient went to the obstetrician-gynecologist with complaints about the absence of menstruation. During comprehensive examination at the National Medical Research Center for Endocrinology, a 46 XY karyotype was identified and the diagnosis was made: "Androgen insensitivity syndrome (Morris syndrome)". In the period from 1997 to 2019, the patient was observed on an outpatient basis by an obstetrician-gynecologist, repeatedly underwent pelvic ultrasound, but categorically refused surgical treatment. In the last two years, the patient began to be disturbed by pulling pains in the lower abdomen and frequent urination; and during dynamic ultrasound, a growth of dysgenetic gonads was noted.

When talking with the patient - self-awareness, sex-role behavior and psychosocial orientation are female (married, raising a foster child). General physical examination: female phenotype, hypersthenic physique, height 180 cm, weight 140 kg, body mass index -43.2, which corresponds to class 3 obesity. The mammary glands are developed correctly, soft-elastic on palpation. Axial and pubic hair growth is scanty (Fig. 1).

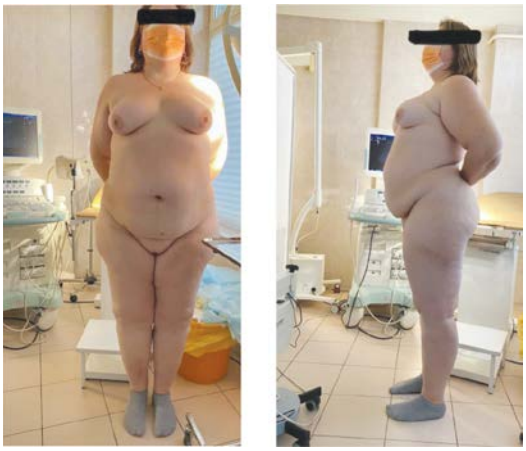


Fig. 1. Objective examination

Vaginal examination: the external genitalia fully correspond to the female phenotype, the length of the vagina measured by a probe is 8 cm. When viewed using Cusco vaginal speculum, the vagina is narrow, ends blindly, the cervix is not visualized.

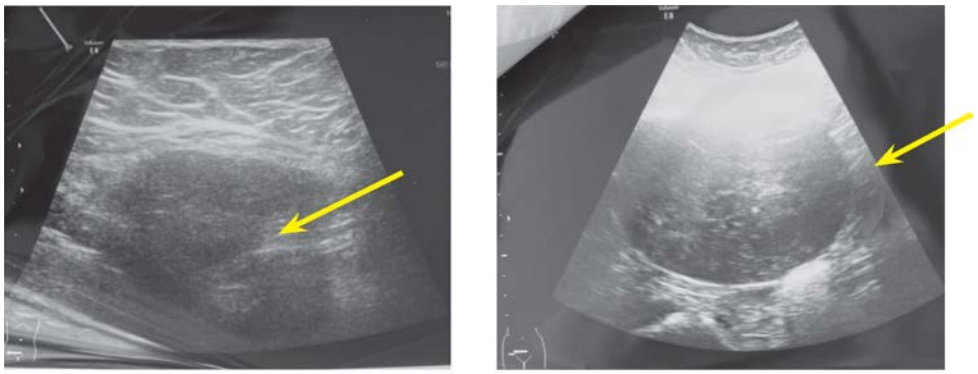
The patient underwent a complete clinical, laboratory, and instrumental examination. A hormone blood test (Table 2) revealed a decrease in the level of testosterone and an increase in the content of gonad-stimulating hormones, which probably enhances the patient's feminization.

Table 2

Hormone level test

Indicator	Result	Reference values
Testosterone	3.260	in men over 14 years old - 5.76-28.14 nmol / l; in women over 10 years old - 0.45–3.75 nmol / l
Progesterone	0.46	in men <0.47 nmol/l; in women by cycle phases: follicular - 0.181-2.84 nmol / l, ovulatory - 0.385-38.1 nmol / l, luteal - 5.82-75.9 nmol / l
Luteinizing hormone (LH)	33.70	in men - 1.37-13.58 mU / ml; in women by cycle phases: follicular 2.4–12.6 mIU/ml, ovulatory — 14–96 mIU/ml, luteal — 1–11.4 mIU/ml, postmenopausal — 7.7–59 mIU/ml)
Follicle-stimulating hormone (FSH)	24.20	in men - 1.5-12.4 mIU / ml; in women by cycle phases: follicular - 3.5-12.5 mIU / ml, ovulatory - 4.7-21.5 mIU / ml, luteal - 1.7-7.7 mIU / ml, postmenopausal - 25.8 -134.8 mIU/ml

During pelvic ultrasound (Fig. 2), the uterus and appendages are not visualized. On the right, in the region of the internal inguinal ring, the right gonad is determined (Fig. 2A). On the left in the small pelvis, a formation is visualized, the left gonad (Fig. 2Б). No free fluid was found in the pelvic cavity.



A B

Fig. 2. Ultrasound examination of the pelvic organs; A — right gonad (arrow), oval in shape, 5.0×7.0 cm in size, with clear contours, moderately decreased echogenicity; B — left gonad (arrow), a mass measuring 17×10×16 cm, with clear contours, moderately decreased echogenicity, with calcification

The patient underwent MRI of the pelvic organs, which revealed that the pelvic cavity is occupied by a volumetric soft tissue formation that deforms the left side wall of the bladder. The right gonad was determined in the right inguinal canal (Fig. 3).

In order to clarify the state of calcium and phosphate metabolism, X-ray densitometry of the lumbar spine and left hip joint was performed. The bone mineral density of the lumbar vertebrae and the proximal left femur was within the expected age norm.

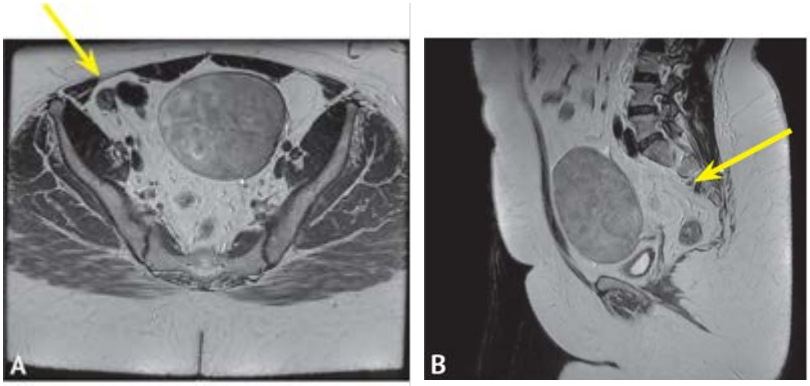


Fig. 3. Magnetic resonance imaging of the pelvic organs; A — right gonad (arrow), oval, 7×3×3 cm in size, heterogeneous structure, with clear contours; B — left gonad (arrow), 17×18×19 cm in size, with clear, uneven contours, heterogeneous structure, with calcified inclusions

After receiving the results of additional examination, the patient underwent surgery in the amount of laparoscopic bilateral gonadectomy. Intraoperatively, during the revision of the pelvic organs, it was found that the entire small pelvis was occupied by a volumetric formation - the left gonad (Fig. 4A). The right gonad was visualized in the region of the internal inguinal ring on the right (Fig. 4Б).

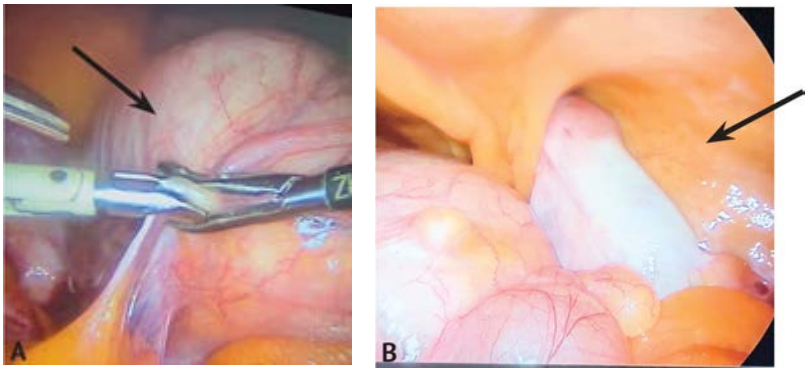


Fig. 4. Laparoscopy: A — left gonad (arrow), 20×20 cm in size, dense consistency, on a wide base, comes from the left abdominal inguinal ring; B — right gonad (arrow), up to 7 cm in size, ovoid in shape, whitish color, dense consistency

The postoperative period was uneventful, the patient was discharged in a satisfactory condition on the 3rd day after surgery. Histological examination results: intermediate androblastoma without signs of malignancy.

CONCLUSION

The presented clinical observation of the patient with complete androgen insensitivity syndrome is a rather rare nosology in gynecological practice. Diagnosis of this disease is not always timely, since the first complaints most often appear at the beginning of puberty and constitutional formation. The described clinical case clearly demonstrates the phenotypic manifestations of the disease as a result of androgen resistance of the organism, and also confirms the possibility of full-fledged auto-identification in accordance with the passport sex, psycho-emotional and social adaptation of those patients. Given the high risk of malignancy of dysgenetic gonads, there is no doubt the need for timely laparoscopic gonadectomy followed by hormone replacement therapy.

REFERENCES

1. *Clinical guidelines for the management of disorders of sex development in childhood*. Consortium on the Management of Disorders of Sex Differentiation. Intersex Society of North America; 2006. Available at: https://www.researchgate.net/publication/320867625_Clinical_Guidelines_for_the_Management_of_Disorders_of_Sex_Development_in_Childhood [Accessed June 07, 2022].
2. Dreger AD, Chase C, Sousa A, Gruppuso PA, Frader J. Changing the nomenclature/taxonomy for intersex: a scientific and clinical rationale. *J Pediatr Endocrinol Metab*. 2005;18(8):729–733. PMID: 16200837 https://doi.org/10.1515/jpem.2005.18.8.729\

3. Lee PA, Houk CP, Ahmed SF, Hughes IA; International Consensus Conference on Intersex organized by the Lawson Wilkins Pediatric Endocrine Society and the European Society for Paediatric Endocrinology. Consensus statement on management of intersex disorders. International Consensus Conference on Intersex. *Pediatrics*. 2006;118(2):e488–500. PMID: 16882788 https://doi.org/10.1542/peds.2006-0738
4. Hughes IA, Houk C, Ahmed SF, Lee PA; LWPES Consensus Group; ESPE Consensus Group. Consensus statement on management of intersex disorders. *Arch Dis Child*. 2006;91(7):554–563. PMID: 16624884 https://doi.org/10.1136/adc.2006.098319
5. Morris JM. The syndrome of testiculare feminization in male pseudophermadoites. *Am J Obstet Gynecol*. 1953;65(6):1192–1211. https://doi.org/10.1016/0002-9378(53)90359-7
6. Chen H. *Atlas of Genetic Diagnosis and Counseling.* 2nd ed. New York: Springer, 2012. https://doi.org/10.1007/978-1-4614-1037-9
7. Agadzhanova EM, Aīrapetian ÉM. Nepolnaya forma sindroma testikulyarnoy feminizatsii (opisanie sluchaya i obzor literatury). *Russian Journal of Human Reproduction*. 2007;13(5):68–73. (In Russ.)
8. Vikhlyaeva EM. (ed.) *Rukovodstvo po endokrinnoy ginekologii*. 3rd ed., exp. Moscow: MIA Publ.; 2006. (In Russ.)
9. Pishchulin AA, Yarovaya IS, Tyul'pakov AN, Manchenko OV. K voprosu o khirurgicheskoy taktike pri sindrome testikulyarnoy feminizatsii. *Russian Journal of Human Reproduction*. 1999;(5):43–46. (In Russ.)
10. Yen SSC, Jaffe RB. *Reproductive Endocrinology*. Philadelphia: Saunders, 1986. [Rus. ed.: Yen SSK., Dzhaffe RB. (eds.) *Reproduktivnaya endokrinologiya*. Vol.1. Moscow: Meditsina Publ.; 1998].
11. Gîngu C, Dick A, Pătrăşcoiu S, Domnişor L, Mihai M, Hârza M, et al. Testicular feminization: complete androgen insensitivity syndrome. Discussions based on a case report. *Rom J Morphol Embryol*. 2014;55(1):177–181. PMID: 24715185
12. Zhukovskiy MA, Lebedev NB, Semicheva TV, Chkheidze LV, Khaysman AE. Testikulyarnaya feminizatsiya. In: Zhukovskiy MA (ed.) *Narusheniya polovogo razvitiya*. Moscow: Meditsina Publ.; 1989. Ch. 9. (In Russ.)
13. Aleksandrov MS. *Obrazovanie iskusstvennogo vlagalishcha iz sigmovidnoy kishki*. Moscow: Medgiz Publ.; 1955. (In Russ.)
14. Cassio A, Cacciari E, D'Errico A, Balsamo A, Grigioni FW, Pascucci MG, et al. Incidence of intratubular germ cell neoplasia in androgen insensitivity syndrome. *Acta Endocrinol (Copenh)*. 1990;123(4):416–422. PMID: 2173324 https://doi.org/10.1530/acta.0.1230416
15. Manuel M, Katayama KP, Jones HW Jr. The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. *Am J Obstet Gynecol*. 1976;124(3):293–300. PMID: 1247071 https://doi.org/10.1016/0002-9378(76)90160-5
16. Müller J, Skakkebaek NE. Testicular carcinoma in situ in children with the androgen insensitivity (testicular feminisation) syndrome. *Br Med J (Clin Res Ed)*. 1984;288(6428):1419–1420. PMID: 6426583 https://doi.org/10.1136/bmj.288.6428.1419-a
17. Litvinov VV. Sindrom testikulyarnoy feminizatsii: 12 let nablyudeniy. *Tavricheskiy mediko-biologicheskiy vestnik*. 2011;14(3–2):238–239. (In Russ.).
18. Bisceglia M, Margo G, Ben Dor D. Familian complete androgen insensitivity syndrome (Morris syndrome or testicular feminization syndrome) in 2 sisters. *Adv Anat Pathol*. 2008;15(2):113–117. PMID: 18418092 https://doi.org/10.1097/PAP.0b013e318166aa3b

Received on 23.06.2022
Review completed on 28.03.2023
Accepted on 28.03.2023