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Complete Androgen Insensitivity Syndrome: Review of Four Cases

Case Report

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Abstract: Background: The Detection of the Complete Androgen Insensitivity Syndrome is not simple since diagnostic can start from different points, depending on clinical features. Case Presentation: Four cases of complete androgen insensitivity syndrome are presented through diagnostic modalities and therapeutic approaches. The initial reasons for investigation were as follows: prenatal amniocentesis being in conflict with the postnatal phenotype, secondary clinical finding, testicle finding during hernia repair, and post pubertal primary amenorrhea. Complete chromosomal, hormonal and ultrasonographical investigations were performed in all patients. Laparoscopy or open inguinal approaches were performed for gonadectomy in all patients, and the microscopic finding was testicular tissue without malignancy. Conclusion: Complete Androgen Insensitivity Syndrome is a type of male pseudohermaphroditism that could be diagnosed as early as in pre-adult age, before any malignant changes appear, and early enough to reach the correct therapy in time.

Keywords: *Androgen Insensitivity Syndrome • Male Pseudohermaphroditism • Amenorrhea • Hernia*
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1. Introduction

Androgen Insensitivity Syndrome (AIS) is an inherited form of male pseudohermaphroditism (MPH) when phenotypically normal women have a male karyotype (46,XY) and negative sex chromatin. This is an X-linked recessive disorder characterized by varying degrees of feminization secondary to androgen receptor insensitivity and can be present as complete androgen insensitivity syndrome (CAIS), mild androgen insensitivity syndrome (MAIS), or as partial androgen insensitivity syndrome (PAIS). Patients with CAIS have normal external female genitalia, variable depth of vagina, and adequate breast development, but uterus is not present and also axillary and pubic hairs are scarce or absent [1-3]. Testes may be located in the abdomen, inguinal canal or labia and before puberty may have normal histological appearance [4].

2. Case presentation:

Case 1.

A one year old child was admitted with suspicion of sexual non-differentiation: amniocentesis was performed

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at the 16th week of pregnancy which resulted in the discovery that the mother carried a chromosomal normal 46,XY fetus. After ordinary delivery the mother was informed that she had given birth to a healthy female newborn. The confusion was resolved by repeating the newborn karyotype analysis and the result was normal male 46,XY karyotype. Hormonal investigation revealed increased testosterone level after gonadotropine test. On ultrasound the uterus was absent. The infant had bilateral hernia and underwent bilateral herniorrhaphy at the age of 2 when male gonads were found and removed. The microscopic finding confirmed testicular tissue. The parents were suggested periodical follow up by pediatric endocrinologist, pediatricians and psychologist until the patient's adult age when hormonal therapy would be planned.

Case 2.

A seven year old girl was admitted for elective operation of bilateral inguinal hernia. Hernias were visible on both sides, and gonads were palpable. Physical examination revealed normal female external genitalia. During the surgical procedure gonads / testicle were noticed in hernia sacs bilaterally. The specimen of both gonad tissues were taken for histology, and gonads were left "in situ". Pathohistology results confirmed the presence of testicular tissue in both specimens. In postoperative period the karyotype analysis showed 46,XY. The uterus was not detected by ultrasonography. The parents refused any further investigation, so there is no follow up of this case in the last 8 years.

Case 3.

A girl of seventeen was admitted at the Institute for primary amenorrhea. When was at the age of twelve she underwent bilateral herniorrhaphies without any specific remarks.

Physical examination revealed normal female breast development and normal female external genitalia but no hairs were found in axillary (Figure 1) and pubic region. Cytogenetic report showed 46,XY karyotype. Hormonal analysis showed high elevation of testosterone after gonadotropine stimulation. Ultrasonography revealed no uterus. The vagina length was 46 mm measured both by ultrasonography and sondage. An expert team of pediatric urologist, juvenile gynecologist, pediatric endocrinologist, clinical genetics and psychologist were involved in consultation with parents and patient, presenting them the future prospects. Following the expert team conclusions the patient underwent laparoscopic bilateral gonadectomy. The microscopic histopathology

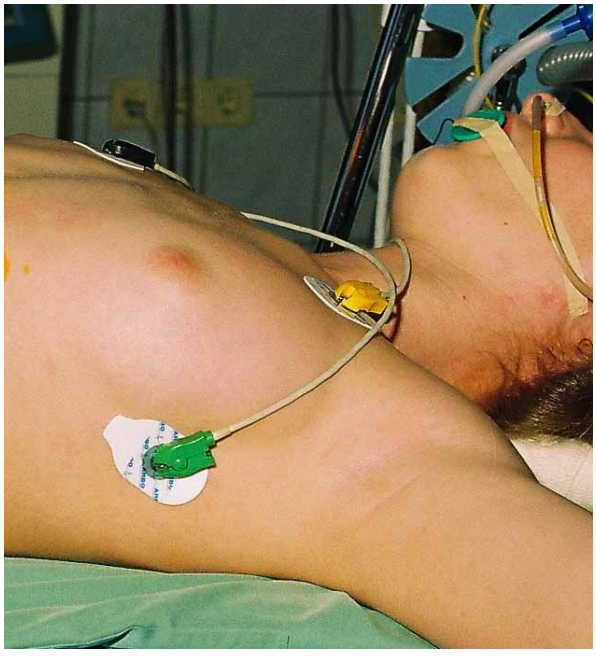

Figure 1. Well developed breast and absence of axillary hair.

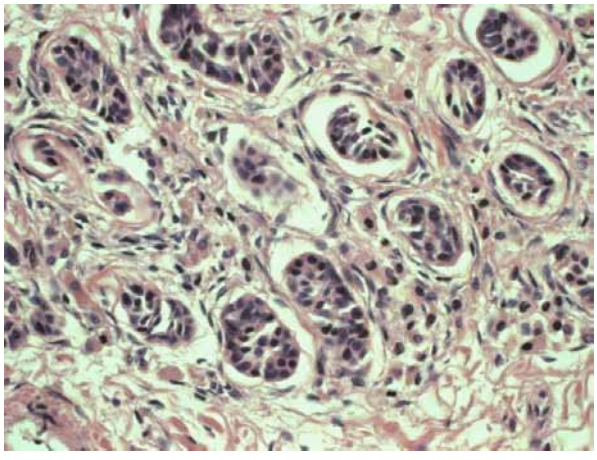

Figure 2. Immature testis with seminiferous tubules with Sertoli and spermatogonal cells. Grouped Laydig cells within ducts. Fibrous interstitial tissue with rough septi forming pseudotubules (Hex200).

finding showed immature testicular tissue on the both sides (Figure 2). The postoperative period was excellent and she started with substitutional hormonal therapy (ethinyl oestradiol according to protocol) two weeks later. Indication for vagina lengthening was also done but the patient refused it.

Case 4.

A 7-month-old baby girl was admitted for severe gastroenterocolitis problem. Pediatrician in charge noticed a moderately enlarged clitoris at the external genitalia. After the intestinal problem was solved investigation of

the peripheral blood specimen showed 46,XY karyotype, but the parents refused any further investigation. When the child was two years old they came back for inguinal hernia on both sides. The examination confirmed the diagnosis of CAIS and the patient underwent bilateral herniectomy and gonadectomy. Biopsy and pathohistological findings confirmed testicle tissue on both sides. Parents expressed readiness to cooperate with pediatric endocrinologist until the child is adult.

3. Discussion

Androgen Insensitivity Syndrome as described by J. Morris in 1953 was initially well-known as testicular feminization syndrome [1,5]. In the past the syndrome was usually diagnosed during bilateral herniorrhaphy in girls, or in primary amenorrheic women [6,7]. At present it is reported as a family-form of MPH inherited on X-linked recessive or sex limited autosomal dominant. This syndrome can result from the absence of the androgen receptor, or qualitative defect of androgen receptors, or due to a post-receptor defect affecting the nuclear binding of the steroid receptor complex, or it can result from a defect in transcription [7].

The most common form of MPH is MPH with Mullerian remnants and AIS. The reported incidences range from 1 in 20 000 to 1 in 62 400 live births [2,8]. Despite the reported literature data of familial inheritance [9], patient histories in our four cases were not significant.

Many authors suggest that one gonad has to be left until puberty to stimulate development of secondary sex characteristics by endogenous testosterone converted to estrogen by aromatase [1]. Others consider the expectancy of the tumor to be a sufficient reason for early removal of both gonads [9]. There is still some controversy in prophylactic gonadectomy, so we reached the decision in each case through the consultation with the multidisciplinary expert team. The main reason for prepubertal gonadectomy is the risk of malignancy in CAIS – which is considerable and occurs at later age. Although it is known that the patients over 30 are at the greatest risk for malignancy development [10-12] in recent literature malignant alteration of retained testicles has been reported in both prepubertal and in adult patients [13,14]. Today the laparoscopical method is a “gold standard” as a diagnostic and surgical approach [15].

Early detection of CAIS is a kind of prevention of testicular tumors diagnosed in adult age [1,2,8,10]. In our cases of CAIS detection no trace of tumor was found.

Recent diagnostics modalities offer detection of CAIS earlier than it was in the past: diagnostic is possible in utero for a female phenotype is visible at 16th weeks’ gestation by two-dimensional or four-dimensional sonography and can be compared with karyotype analysis [16,17].

It is also very important that psychosexual orientation of persons with CAIS is entirely female: medically, legally, and socially they are females. Clinical psychologist has to be involved in consultation so as to help parents to understand and to accept the status of their child. The challenges are far greater for adolescent girls, since it requires a lot of time and effort for them to accept specific limitations in their future lives.

4. Conclusion

Careful examination the gonads in girls with bilateral hernia during hernia repair is important, especially if the family history is significant. Pediatricians and specialist in school medicine have the responsibility to examine all the amenorrheic girls at the age of fifteen by using pelvic ultrasonography as a noninvasive method for confirming normal internal female genitalia. Cooperation between pediatric surgeons, pediatricians, clinical genetics and endocrinologists is essential for early and correct diagnosis of CAIS and can decrease the incidence of malignant tumors in adult amenorrheic patients.

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List of abbrevations:
AIS -Androgen Insensitivity Syndrome
MPH -Male Pseudohermaphroditism
CAIS–Complete Androgen Insensitivity Syndrome
MAIS -Mild Androgen Insensitivity Syndrome
PAIS–Partial Androgen Insensitivity Syndrome