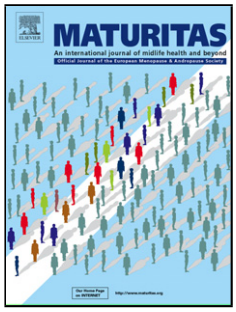

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Authors: Konstantia Kosti, Loukas Athanasiadis, Dimitrios G. Goulis

PII: S0378-5122(19)30542-0
DOI: https://doi.org/10.1016/j.maturitas.2019.06.004
Reference: MAT 7202

To appear in: *Maturitas*

Received date: 26 May 2019
Revised date: 2 June 2019
Accepted date: 4 June 2019

Please cite this article as: Kosti K, Athanasiadis L, Goulis DG, Long-term consequences of androgen insensitivity syndrome, *Maturitas* (2019), https://doi.org/10.1016/j.maturitas.2019.06.004

Long-term consequences of androgen insensitivity syndrome

Konstantia Kosti (1), Loukas Athanasiadis (2), Dimitrios G. Goulis (1)

(1) Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, Greece

(2) Third Department of Psychiatry, Medical School, Aristotle University of Thessaloniki, Greece

Corresponding author: Dr. Konstantia Kosti, Unit of Reproductive Endocrinology, 1st Department of Obstetrics and Gynaecology, Medical School, Aristotle University of Thessaloniki, "Papageorgiou" General Hospital, Ring Road, 56403 Nea Efkarpia, Greece, e-mail: kosti.endo@gmail.com.

Highlights

- Individuals with androgen insensitivity syndrome are subject to long-term complications.
- The increased risk of germ cell tumours implies the need for gonadectomy for the majority of patients.
- Osteoporosis has been observed even before gonadectomy.
- Surgical procedures may be indicated due to gynaecomastia, hypospadias or blind-ending vagina.
- Besides infertility, increased risks of cardiovascular disease, obesity, diabetes and psychiatric disorders have been demonstrated.

Abstract

Androgen insensitivity syndrome (AIS) is one of the most common sexual developmental disorders. According to the grade of the remaining androgen receptor (AR) function, AIS is classified as complete (CAIS), partial (PAIS) or mild (MAIS). In CAIS, the prevalence of germ cell tumours is increased compared with the general population. Although patients with CAIS used to undergo gonadectomy before puberty, nowadays a gonadectomy is recommended after spontaneous puberty, and up to 15% of patients can retain their gonads. Nevertheless, the risk of germ cell tumour increases gradually after puberty. Annual follow-up with ultrasound or magnetic resonance imaging (MRI) is recommended. Unfortunately, these imaging methods are not sensitive enough for the diagnosis of an *in situ* germ cell tumour. In PAIS, the risk of germ cell tumour is higher than in CAIS; therefore, an early gonadectomy or an orchidopexy is indicated. Optimal hormone replacement therapy (HRT) is necessary for long-term health. The risks of osteopenia and of osteoporosis are higher in patients with early gonadectomy or a suboptimal HRT regimen. Infertility is the rule in CAIS and PAIS. A few mutations do not affect fertility detrimentally, and these are responsible for MAIS. In PAIS leading to a predominantly male phenotype or ambiguous genitalia, multiple surgical procedures for gynaecomastia and/or hypospadias are required. Some small studies have found a higher risk of obesity, hyperlipidaemia and impaired insulin sensitivity. Psychological support is essential, as the prevalence of psychiatric disorders is increased. In conclusion, the diagnosis of AIS has long-term consequences for which shared decision-making (physicians, patients, parents) is appropriate.

Keywords: osteoporosis, germ cell tumour, infertility, hypospadias, gynaecomastia

1. Introduction

Androgen insensitivity syndrome (AIS) is a rare X-linked disorder characterized by mutations of the androgen receptor (AR) gene, causing variable degrees of androgen resistance in individuals with the XY karyotype. AIS is one of the most common XY disorders of sexual development (1, 2), with an estimated prevalence between 2 and 5 per 100.000 (3).

As the association between genotype and phenotype is not strong, great phenotypic heterogeneity has been described (4). The AIS phenotype mainly, but not completely, depends on the degree of the remaining activity of the AR. Over 600 AR mutations have been described in AIS; of them, 70% are inherited, and 30% are *de novo* (5). According to the phenotype, individuals with AIS are divided into three broad groups: complete (CAIS), partial (PAIS) and mild (MAIS).

Individuals with CAIS have a female phenotype with well-developed external genitalia and breasts, a short, blind-ending vagina and intra-abdominal, intra-inguinal or intra-labial testes. They lack internal female genitalia and are characterized by the absence or the elementary existence of Wolffian duct derivatives. There is absence or

scarcity of pubic and/or axillary hair. The diagnosis of CAIS frequently takes place in puberty due to primary amenorrhoea (2,3,6).

PAIS has a broad spectrum of phenotypes. According to the degree of androgen insensitivity, the patients are classified into three subgroups:

1. Predominantly female phenotype, with intra-inguinal or intra-labial testes, mild enlargement of the clitoris and/or posterior fusion of the labia.
2. Ambiguous external genitalia, with intermediate structures between penis and clitoris, descended or undescended testes and hypospadias or urogenital sinus. These patients frequently develop gynaecomastia in puberty.
3. Predominantly male phenotype, with perineal hypospadias and/or micropenis, cryptorchidism and/or bifid scrotum. They can also present gynaecomastia in puberty.

Finally, patients with MAIS are phenotypically men with normal external genitalia. Some of them undergo reduced virilization in puberty and may be diagnosed with infertility and/or pubertal gynaecomastia (3, 6, 7).

Due to androgen resistance, individuals with AIS have elevated levels of serum luteinizing hormone (LH) and testosterone. After puberty, oestrogen concentrations can be elevated compared with male subjects (8). In PAIS, assessment of testosterone precursors, testosterone and dihydrotestosterone before and after stimulation with human chorionic gonadotropin is necessary to establish the differential diagnosis between AIS, testosterone biosynthesis defect and 5α-reductase deficiency. Although

the clinical evaluation and the endocrine profile are suggestive of an AIS diagnosis, only genetic investigations can confirm it (9).

Although the diagnostic and therapeutic approach to AIS has been thoroughly investigated, this is not the case for its long-term consequences. These can include malignant disease, low bone mineral density and fractures, infertility, impaired metabolism, cardiovascular disease and mental disorders. This narrative review presents and critically appraises the current evidence on the long-term consequences of AIS.

2. Methods

For this narrative review, a search was performed using the PubMed, Scopus, Google Scholar and Central electronic databases. The search terms were: “androgen insensitivity syndrome”, “androgen resistance”, “androgen receptor deficiency”, “male pseudohermaphroditism”, “testicular feminization” and “Reifenstein's syndrome” combined with: malignant disease, cancer, germ cell tumours, osteopenia, osteoporosis, fractures, infertility, subfertility, gynaecomastia, hypospadias, cardiovascular risk, arterial hypertension, diabetes mellitus, dyslipidaemia and mental disease. Articles in English were selected.

3. Long-term health in AIS

3.1. Malignant disease

AIS belongs to the disorders of sexual development that involve the Y chromosome; in these conditions, an increased rate of type II germ cell tumours has been observed (10). The risk of germ cell tumour in CAIS is low but increases gradually after

puberty (1). There is only one reported case of germ cell tumour before puberty: a metastatic yolk-sac tumour of an abdominal testis in a 17-month-old girl with CAIS (11).

In a study of 133 individuals with CAIS (12), only 2 (1.5%) were diagnosed with germ cell tumour. In two review articles, a prevalence of germ cell tumour under 1% (13) and 2% (14) has been estimated. The low rate of germ cell tumour in CAIS could be attributed to the rapid reduction of the germ cell population after the first year of life (15). The majority of individuals diagnosed with CAIS used to undergo prophylactic gonadectomy in childhood or early puberty; thus, there is little long-term information about intra-abdominal gonads in adults (14). Nowadays, many centres postpone the gonadectomy in CAIS at least till late adolescence, when spontaneous pubertal development is complete (16), and up to 15% of women with CAIS maintain their gonads (17). Females who maintain their gonads in puberty can achieve a higher and even normal bone mineral density and spontaneous breast development (18) through the peripheral aromatization of androgens to oestrogens. In addition, the decision to undergo gonadectomy can be taken by the patient and does not have to be made early on by the parents (19).

The follow-up of patients who have retained gonads can be achieved with ultrasound (inguinal or labio-scrotal testes) or magnetic resonance imaging (MRI) (intra-abdominal, inguinal or labio-scrotal testes). Unfortunately, none of these imaging methods is specific enough for the diagnosis of an *in situ* germ cell tumour (10). The classic markers for germ cell tumour, beta-chorionic gonadotropin and alpha-fetoprotein, are typically elevated in non-seminomas and not in seminomas, which

constitute the most common germ cell tumour type in CAIS; therefore, they cannot be used as reliable tumour markers in patients with retained gonads (20). Screening based on new biomarkers, such as specific micro-RNA and single-nucleotide polymorphisms (SNPs), are being investigated (10).

In PAIS, the risk of germ cell tumour has been shown to be higher than with CAIS, at approximately 15% (13, 21). In patients with untreated, undescended gonads this risk can reach 50%, whereas the risk for those with scrotal testes remains unclear (22). Consequently, PAIS patients with a male phenotype should undergo orchidopexy and their counterparts with a female phenotype should have their intra-abdominal gonads removed (23).

3.2. Low bone mineral density and fractures

In the majority of studies, a reduced bone mineral density and bone mineral apparent density (i.e. bone mineral density adjusted for differences in bone size), mainly at lumbar spine, have been reported. On average, the final height of patients with CAIS and PAIS is greater than the mean female height and lower than the mean male height (24).

A reduced lumbar bone mineral density and a normal femoral neck bone mineral density were found in women with CAIS who had not undergone gonadectomy (24, 25, 26, 27, 28, 29). There was considerable heterogeneity among these studies, possibly due to different reference ranges of dual-energy X-ray absorptiometry, unknown vitamin D concentrations, and even lack of molecular confirmation of the AR gene mutation. In a cohort of women with CAIS who had undergone

gonadectomy, both lumbar and femoral neck bone mineral density were significantly reduced compared with their counterparts with intact testes (28, 30). On the other hand, in a recent study of 113 subjects with CAIS (31), no association was found between the bone mineral density and age at gonadectomy. In addition, in this study, there was no evidence of a further reduction in bone mineral density after gonadectomy.

Very few studies have looked at bone mineral density and bone mineral apparent density in subjects with PAIS. Two of three subjects with PAIS and intact testes showed normal bone mineral apparent density (24) and two patients with the same characteristics presented bone mineral density and a weight-matched Z-score within the normal range (32). In a case series of six patients with PAIS who had undergone gonadectomy, the Z-scores of all participants did not differ from the population reference range (33).

There are limited data on the fracture rate of patients with AIS who maintain their gonads (29). A wide range of fracture rates, from 2% (1/43) (28) to 27% (6/22) (33), has been reported for women with CAIS who had undergone gonadectomy.

To improve the bone mineral density in patients with AIS, good compliance with hormone replacement treatment (HRT) has to be ensured following gonadectomy, in conjunction with optimization of lifestyle, regular physical exercise and adequate intake of vitamin D and calcium. The maintenance of gonads, at least till puberty is completed, is being discussed (29, 30). An annual follow-up of the gonads with ultrasound or MRI is recommended (17). Young women with CAIS who undergo

gonadectomy appear to need higher doses of oestrogens to improve their bone mineral density (34, 35). Use of transdermal 17β-oestradiol is recommended. Progestins are not necessary, as there is no uterus; they are even contraindicated, especially medroxyprogesterone acetate, because of their adverse effects on bone (36).

New options for the therapy of women with CAIS and reduced bone mineral density are still a matter of debate. These include treatment with testosterone (29), a supplementation with sex steroids even before gonadectomy (30) and additional treatment with testicular hormones, such as testis-specific protein hormone from the Leydig cells (INSL3) (29).

3.3. Infertility

Sterility is the rule in CAIS and PAIS (8). CAIS is characterized by the absence of a uterus and normally functioning gonads; nevertheless, the population of testicular germ cells decreases rapidly after the first year of life. In PAIS, the remaining AR function is very frequently inadequate for the preservation of fertility (15). A recent case report showed fertility by intra-cytoplasmatic sperm injection (ICSI) in an individual with PAIS after prolonged treatment with high-dose testosterone (37). This treatment, as well as those with clomiphene citrate and aromatase inhibitors, should be further examined in appropriately designed studies (1). In some cases of MAIS, especially in patients with more favourable AR mutations, fertility can be preserved (38).

3.4. Gynaecomastia, hypospadias and short vagina

In a study of 52 male subjects with suspected PAIS, a mutation of the AR gene was confirmed in 29 of them (39). All individuals with an AR mutation developed gynaecomastia; five of them underwent a mastectomy. In addition, patients with hypospadias and confirmed AR mutations were more likely to require more surgical procedures than their counterparts with hypospadias without an AR mutation (39).

Women with CAIS and phenotypically female individuals with PAIS have a short, blind-ending vagina. If the patient is not able to have adequate intercourse, vaginal elongation is indicated. The majority of these patients achieve vaginal dilation through vaginal dilators and sexual activity (40). In the rare cases where vaginoplasty is required, a vaginal dilation is necessary after the surgical procedure (4).

3.5. Impaired metabolism and cardiovascular disease

Low androgen concentrations in men present an independent risk factor for the development of obesity and impaired insulin sensitivity (41). In a study of 18 women with CAIS (14 after gonadectomy and 4 with intact testes), body mass index was not increased compared with controls, although the prevalence of obesity was higher (16.7% vs 3.6%) compared with the reference female population of the same age. Fasting glucose, glycosylated haemoglobin and high-density lipoprotein-cholesterol were normal in all patients. Total cholesterol was elevated in 56% of the patients, low-density lipoprotein-cholesterol in 33%, triglycerides in 16% and HOMA-Index in 47%. According to these results, optimization of the metabolic status and the cardiovascular profile are recommended (42). Further studies are necessary to highlight the metabolic aspects and cardiovascular risk in patients with CAIS.

3.6 Mental disorder

Compared with controls, women with CAIS have a 5-fold higher risk of a psychiatric disorder, a 3-fold greater risk of mood disorders, a 4-fold greater risk of an anxiety disorder and a 20-fold greater risk of an obsessive-compulsive disorder (43). Confrontation with the diagnosis of an XY-karyotype, intra-abdominal testes and/or ambiguous or undervirilized genitalia contributes to impaired mental health (44). Male patients with PAIS are often dissatisfied due to the clinical signs of undervirilization (45). Sexual quality of life is reduced in both PAIS and CAIS patients (46).

4. Conclusion

The diagnosis of AIS is followed by a series of decisions which have to be shared among the physicians (paediatricians, endocrinologists, gynaecologists, urologists, psychiatrists, psychologists), the patients themselves and their parents. The patients may present to the clinicians with a wide spectrum of complaints depending on their age and type of AIS. Primary amenorrhoea (CAIS, PAIS) is the most prevalent complaint at a younger age, whereas germ cell tumours (CAIS, PAIS), impaired metabolism, cardiovascular disease, osteoporosis or infertility may occur in adult life. Gynaecomastia (PAIS, MAIS), short vagina (PAIS, CAIS) and mental disorders can be complaints at any age.

A key decision in CAIS is whether the patient should undergo gonadectomy or not, and if so, at what age. Patients who decide to retain their gonads have to be well informed about the risk of germ cell tumours and the need for regular follow-up. Due to the high risk of germ cell tumours, annual or biannual screening by ultrasound or

MRI is recommended in those individuals who retain their gonads. As the risk of osteoporosis is high, HRT optimization after gonadectomy, favourable lifestyle modifications, adequate physical exercise and vitamin D / calcium supplementation have to be applied to prevent a decrease in bone mineral density. HRT follows the same principles as for hysterectomized women of similar age diagnosed as having ovarian insufficiency (e.g. 2 mg oestradiol valerate daily or 50 μg transdermal oestradiol twice weekly). The dosage of HRT is optimized according to the clinical picture. The follow-up aims to detect impaired metabolism, cardiovascular disease or mental disorder early on.

More studies investigating new biomarkers that could be used as diagnostic tools are needed. In PAIS, the approach to sex-of-rearing decisions presents a clinical challenge. The families of these individuals should consult a multi-disciplinary team in a referral centre for disorders of sexual development. As the long-term health issues, in particular the disorders of sexual development, differ, the confirmation of an AR mutation is essential for optimal management. Future research should evaluate the risks of obesity, cardiovascular disease, diabetes and psychiatric disorders. Concerning fertility, new methods, such as preservation of testicular tissue in early childhood or treatment with high-dose testosterone, are yet to be investigated.

Contributors

All authors made a substantial intellectual contribution to this review and provided critical revision of the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was obtained for the preparation of this review.

Provenance and peer review

This article has undergone peer review.

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