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ANDROGEN INSENSITIVITY SYNDROME

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ABSTRACT

Androgen insensitivity syndrome (AIS) is the most frequency cause of 46 XY disorder in sex development (DSD). The pathogenesis of AIS is characterized by resistance to androgens due to dysfunction of the androgen receptor (AR). The degree of insensitivity to androgens underlies the mode of clinical presentation. Thus, the complete form [complete androgen insensitivity syndrome (CAIS)] is characterized by a female phenotype with an XY karyotype and normal-functioning testes with respect to androgen production. The partial form [partial androgen insensitivity syndrome (PAIS)] presents a wider phenotype, ranging from severe undermasculinization manifest mainly as female appearing external genitalia to a male with severe hypospadias and perhaps micropenis. A mild form [mild androgen insensitivity syndrome (MAIS)] is also recognized phenotypically as a male with normal development but presenting later with gynaecomastia and infertility. Management of DSD, in general, requires a multidisciplinary approach from diagnosis in infancy to adulthood. The key members of the team include specialists in endocrinology, urology, gynecology and clinical psychology. The diagnosis is confirmed by determining the exact mutation in the AR gene. The treatment of AIS is based on reinforcement sexual identity, gonadectomy planning, and hormone replacement therapy. The prognosis for CAIS is good if the testicular tissue is removed at the appropriate time. For PAIS, the prognosis depends on the ambiguity of the genitalia and physical and psychosocial adjustment to the assigned sex.

KEYWORDS: Androgen insensitivity syndrome, CAIS, PAIS, MAIS.

INTRODUCTION

Androgen Insensitivity Syndrome (AIS; testicular feminization; OMIM# 300068) is an X-linked disease characterized by variable defects in virilization of 46, XY individuals. This is due to loss-of -function mutations in the androgen receptor gene (AR; OMIM# 313700), which results in peripheral androgen resistance.[3] It is characterized by XY sex reversal and a female phenotype despite serum concentrations of testosterone often exceeding the normal adult male range. The X-linked AR gene appears to be universally resistant to activation by androgen ligand in CAIS as illustrated by normal female gender identity in women with CAIS.[4] It is a disorder resulting from complete or partial resistance to the biological actions of androgens in an XY man or boy with normal testis determination and production of age-appropriate androgen concentrations.[1] In 1953, Morris described the clinical phenotype of ‘‘testicular feminization’’ after reviewing 82 cases. Morris’ phenotype included a female body habitus with normal breast development and minimal pubic and axillary hair. Although the external genitalia were within normal limits, the vagina was typically absent or rudimentary and the uterus absent. Gonads, found in the labia majora, inguinal ring, or intra-abdominally, were variably noted on physical exam. The change in nomenclature from testicular feminization to androgen insensitivity syndrome (AIS) was prompted by the finding of normal urinary 17-ketosteroid levels, an androgen metabolite, as well as by absence of a treatment effect when 46, XY women were treated with methyl testosterone, suggesting androgen resistance rather than a deficiency.[1,2] Partial androgen insensitivity syndrome refers to a phenotype of varying degrees of masculinisation of the external genitalia due to partial androgen responsiveness. Mild androgen insensitivity syndrome is reported in healthy men and boys who can present with adolescent gynaecomastia or infertility in later life.

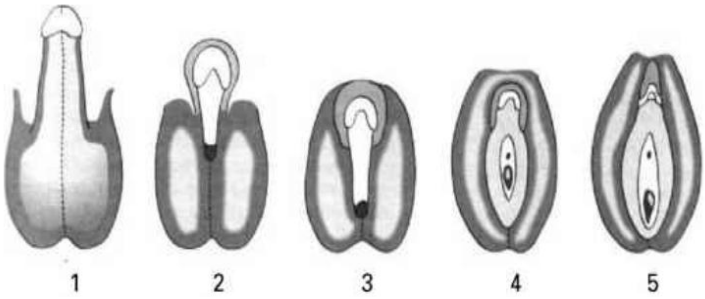

Figure 1: Clinical grades of ambiguous genitalia.

Figure 1 represents the virilization is dimished from grade 1 towards grade

classification

Androgen insensitivity syndrome (AIS) is typically characterized by evidence of feminization (i.e., undermasculinization) of the external genitalia at birth, abnormal secondary sexual development in puberty, and infertility in individuals with a 46, XY karyotype. AIS represents a spectrum of defects in androgen action and can be subdivided into three broad phenotypes.

- Complete androgen insensitivity syndrome (CAIS), with typical female external genitalia
- Partial androgen insensitivity syndrome (PAIS) with predominantly female, predominantly male, or ambiguous external genitalia
- Mild androgen insensitivity syndrome (MAIS) with typical male external genitalia(7)

Table 1: Classification of AIS Phenotypes.

Type	External Genitalia (Synonyms)	Findings
CAIS	Female ("testicular feminization")	• Absent OR rudimentary wolffian duct derivatives • Absence or presence of epididymides&/or vas deferens • Inguinal, labial, or abdominal testes • Short blind-ending vagina • Scant OR absent pubic &/OR axillary hair
PAIS	Predominantly female ("incomplete AIS")	• Inguinal OR labial testes • Clitoromegaly & labial fusion • Distinct urethral & vaginal openings OR aurogenital sinus
	Ambiguous	• Microphallus (<1 cm) with clitoris-like underdeveloped glans; labia majora-like bifid scrotum • Descended OR undescended testes • Perineoscrotal hypospadias OR urogenital sinus • Gynecomastia (development of breasts) in puberty
	Predominantly male	• Simple (glandular or penile) OR severe (perineal) "isolated" hypospadias w/normal-sized penis & descended testes OR severe hypospadias w/micropenis, bifid scrotum, & either descended or undescended testes • Gynecomastia in puberty
MAIS	Male ("undervirilized male syndrome")	• Impaired spermatogenesis &/OR impaired pubertal virilization • Gynecomastia in puberty

CAIS

CAIS individuals are raised as females because they have female external genitalia due to the inability of their cells to respond to androgens. However, CAIS-affected individuals have testes that can be located in variable places but are often found in the inguinal canals. AIS is frequently diagnosed by primary amenorrhea and sometimes, but less frequently, due to infertility. Amenorrhea is characterized by the absence of a uterus and is accompanied by a

lack of pubic and axillary hair. Amenorrhea has been described in women with normal or increased breast development, extreme height, and female hair without baldness..

PAIS

PAIS is less frequent than CAIS and has variable clinical presentations that range from almost complete feminization to almost normal masculinization to individuals with overt sexual ambiguity. This variability reflects the different AR gene mutations. The most ambiguous forms are diagnosed at birth or during infancy. During puberty, individuals with PAIS are eunuch-like and have gynecomastia. Individuals with PAIS that are characterized as women have been observed to have clitoromegaly and a fused labia during puberty.

MAIS

MAIS is manifested in males by normal or decreased virilization,some gynecomastia, and some spermatogenesis. Individuals with MAIS often develop normally throughout childhood and puberty. Furthermore, some plan to have a family, and others have children.[8]

CLINICAL FEATURES

CAIS – COMPLETE ANDROGEN INSENSITIVITY SYNDROME

Patients with AIS developed breasts with estradiol levels in normal male range suggesting that the lack of androgen action is the main driver of breast development in these patients, rather than an increased estrogen secretion. Menstrual cycles do not appear since normal production of antimullerian hormone (AMH) by the testis impeded uterus, cervix and proximal vagina to development.[6]

The typical presentation in CAIS is either as primary amenorrhea in an adolescent girl or, less frequently, with inguinal herniae in infancy. Sex of rearing is female in CAIS and gender identity is maintained. The uterus is absent, the gonads are testes and so menarche does not occur. Pubic and axillary hair growth is sparse or absent. However, breast development occurs spontaneously at the expected age of puberty because of increased production of estrogens from aromatization of excessive androgen substrate.[5]

PAIS – PARTIAL ANDROGEN INSENSITIVITY SYNDROME

Typically, there are severe hypospadias, micropenis and a bifid scrotum which may contain descended testes.[5]

The PAIS clinical phenotype varies according to the degree of AR residual function and ranges from proximal hypospadias to micropenis. Gynecomastia observed at puberty time in patients with atypical genitalia can be indicative of PAIS. Differential diagnosis of PAIS includes all causes resulting in a undervirilized male external genitalia such as chromosomal defects (Klinefelter syndrome), genetic diseases (Smith-LemliOpitz syndrome, Denys-Drash syndrome, Frasier syndrome), partial gonadal dysgenesis, LH receptor defects, biosynthetic enzyme deficiencies (17,20-lyase deficiency, P450 oxidoreductase deficiency, 17β-hydroxysteroid dehydrogenase deficiency type 3, 5α-reductase 2 deficiency and hypospadias in small for gestation age boys.[6]

MAIS – MILD ANDROGEN INSENSITIVITY SYNDROME

MAIS is associated with AR mutations but without external genitalia abnormalities. This diagnosis could be suspected in the investigation of male infertility or in pubertal gynecomastia. MAIS can also manifest in a patient with neurological disorder characterized by bulbar and muscular atrophy (Kennedy's disease). This condition is due to the hyperexpansion of the CAG repeats (> 38), present in AR exon 1. These patients present with normal male external genitalia, but testosterone resistance will develop with disease progression. For MAIS, the differential diagnosis includes other causes of male infertility.[6]

ENDOCRINE FEATURES

The hormonal profiles of patients with CAIS and PAIS are identical. Serum testosterone (T) and luteinizing hormone (LH) are at or above the upper normal limit during the first 3 months of life, while prepubertal patients generally have T and LH concentrations in the normal range for their age. In CAIS, testosterone levels are elevated at the time of puberty. Elevated luteinizing hormone (LH) levels are found, indicating androgen resistance at the hypothalamic-pituitary level. The high levels of testosterone, a substrate for aromatase activity, result in substantial amounts of estrogens, which are responsible for very good breast development at puberty in CAIS individuals. Adults with in situ testes usually have increased levels of LH, normal (sometimes elevated) concentration of T and follicle-stimulated hormone (FSH) as compared to normal males, and estradiol at the upper normal limits. In PAIS, hCG testing is necessary to demonstrate normal T and DHT production so as to exclude defects in testosterone biosynthesis and 5alpha-reductase 2 deficiency. High levels of LH result from a reduced sensitivity of the hypothalamus and hypophysis to the negative feedback regulation of gonadotropin secretion by sex steroids, probably due to impaired

androgen sensitivity. The increased LH secretion stimulates Leydig cell steroid production and results in increased production of testosterone and estradiol. In patients with AIS, Anti-Müllerian Hormone (AMH) concentration is normal as the secretion and function of sertoli cells is not impaired.[1, 3]

STRUCTURE OF THE HUMAN AR AND THE MECHANISM OF ANDROGEN ACTION

The AR belongs to a subfamily of steroid hormone receptors within a larger family of nuclear proteins that are likely to have evolved from a common ancestral gene.[10] The AR gene is located at chromosome Xq11-12, is encoded by eight exons and codifies a 919 amino acids protein. The primary structure of the human AR (hAR) has been determined from molecular cloning and characterization of the cDNA encoding the hAR.This sequence reveals an open reading frame of 2730 nucleotides encoding a protein of 910 amino acid residues with a calculated molecular mass of 99kDa. The gene is estimated to be,-~ 90 kb and is composed of 8 exons.[10]

The actions of androgens on target cells occur via the classical steroid receptor pathway. The process of AR transformation to a tight nuclear binding form has been studied extensively. Most Investigations have focused on in vitro transformation of AR and have shown that the untransformed, i.e. non DNA-binding, receptor is associated with several heat-shock proteins. The transformation of the receptor to the tight nuclear-binding form is a multistep process that involves the dissociation of the heat-shock proteins from the receptor. The complex androgen-activated AR is thus able to migrate in the nucleus and interact with the androgen response elements (ARE). The mechanism by which the receptor causes gene activation involves N-terminal sequences of the protein, but the molecular details of this activation process remain to be elucidated. Protein/protein interactions likely occur with other transcription factors. Both promoter and host cell specificity appear to influence the requirement for the N-terminal domain in transcriptional activation, suggesting that this region interacts with cell-specific transcription factors.[10]

MOLECULAR DEFECTS IN AIS

AIS is associated with a wide variety of molecular defects that may or may not affect androgen binding. These include: (a) single point mutations resulting in amino acid substitution or premature stop codon; (b) nucleotide insertions or deletions most often leading to a frameshift and premature termination; (c) complete or partial gene deletions (>10

nucleotides); and (d) intronic mutations in either splice donor or acceptor sites, which affect the splicing of AR RNA.[3]

PHENOTYPE-GENOTYPE CORRELATIONS OF AR MUTATIONS

Boehmer et al analysed the genotype-phenotype relationship in AIS and the possible causes of phenotypic variations in families with many affected individuals. Intrafamilial phenotypic variation was observed for mutations R846H and M771I. Patients with a functionally defective AR have some pubic hair, Tanner stage P2 and vestigial Wolffian duct derivatives despite absence of AR expression. He concluded that, while phenotypic variation was absent in families with CAIS, distinct phenotypic variation was frequently observed in families with PAIS. Mutations that affect splicing are found in CAIS as well as in PAIS patients.

Different factors have been suggested as influencing the expression of AR mutations. The traditional explanation is that the level of competence of coregulatory proteins acts as a genetic "background" factor in determining the overall clinical outcome Co-regulators are molecules that interact with nuclear receptors either to increase (co-activators) or to decrease (co-repressors) gene transcription in a ligand-dependent manner by forming a multiprotein complex which involves the basic transcription machinery. Furthermore, Holterhus et al have recently investigated a patient with PAIS phenotype and defective AR transcription and translation, despite the absence of a molecular abnormality in the entire AR gene. The authors attributed the reduced activity of the AR protein found in this case to the possible existence of a defective AR promoter caused by a mutation or by reduced cellular availability or dysfunction of an AR-promoter-interacting factor critical for the initiation of the AR transcription. Another probably important mechanism which may account for some variable expressivity is the presence of somatic mosaicism of mutant and wild-type alleles of AR, due to a de novo postzygotic somatic mutation.72,85 According to Hiort et al, the proportion of somatic mosaicism in a group of 30 families with AIS patients was relatively high (3 of the 8 patients had de novo mutations). Somatic mosaicism should always be considered in AIS individuals with unexpected normal virilization, which could be the result of the expression of the wild-type androgen receptor in some cell lines. In a recent report, Werner et al documented experimentally the contradictory effect of the combination of a short polyglycine (PolyG) repeat with the rare mutation of the hinge region A645D, resulting in seriously reduced AR activity when paired with a long polyglutamine (PolyQ) repeat and in almost wild-type AR activity when paired with a short PolyQ repeat.[3]

AIS AND ANDROGEN RECEPTOR GENE DEFECTS

Mutations can be identified in 95% of CAIS patients, whereas the detection rate is much less in PAIS. An abnormality in the AR gene is currently the only established cause for AIS, although there are numerous protein cofactors that interplay with the AR to elicit activation of androgen-responsive genes. Transcriptional activity of the mutant AR is generally absent or impaired when tested in vitro using physiological levels of androgens. The majority is single-base pair, about a third are nonsense mutations and less than 10% are small deletion or insertions which lead to premature stop codon or intron splice site mutations.[5]

About 30% of AR mutations in AIS are de novo and sequencing of the entire AR gene is recommended for all 46, XY DSD newborns, regardless of a familial history of DSD or AIS. In the absence of allelic variants in AR a multiplex ligation-dependent probe amplification (MLPA) can be helpful in order to detect deletions, insertions and duplications in the AR gene. Mutations are found along the AR gene, being more frequent in exon 1 (the largest AR exon, which encodes the NTD).Defects in the NTD domain are more frequent in CAIS's patients and variants in exons 5 and 6 (that encode LBD) are more frequent in PAIS's patients. Almost all AR mutations in MAIS were found in the NTD, but there is a low number of AR mutations related to this phenotype. The most common AR allelic variants in all AIS phenotypes are non-synonymous point mutations. Insertions and deletions causing a frameshift leading to a premature stop codon downstream are more frequently reported in CAIS's patients. Allelic variants affecting mRNA splicing are reported in CAIS and PAIS phenotypes. Rarely, synonymous allelic variants affecting splicing sites has been described in PAIS and in CAIS individuals. Large structural mutations (exon 1 deletion, exon 2 duplication, exon 3 deletion, exon 4-8 (LBD domain) deletion and deletion of entire AR gene) have been described but are very rare in AIS. Interesting, a deletion of an entire exon (exon 4) was described in a phenotypic male with azoospermia. Postzygotic AR allelic variants resulting in somatic mosaicism are rarely described in AIS. In this situation the variant appears in heterozygote instead of hemizygote state. AR allelic variants in heterozygosis was also identified in some individuals with 47, XXY karyotype causing AIS. There is not a perfect correlation between genotype and phenotype in AIS. In the AR mutation database, there are some AR allelic variants that can cause different phenotypes. The explanation for this is not completely understood. It is hypothesized that AR co-regulators (activators and repressors) are implicated with this phenomenon. Other

possibilities are variations in the level of 5α-reductase type 2 activity resulting in different DHT availability, and the presence.[6]

PAIS WITHOUT AN ANDROGEN RECEPTOR MUTATION

The frequency of finding an AR mutation in a patient with a PAIS-like phenotype may be influenced by a clinical evaluation, whether there is a positive family history and the method used to screen for mutations. The phenotype in the mutation-negative group is caused by other factor(s) which may also be associated with growth restriction. Furthermore, the severity of genital anomalies did not predict the likelihood of finding an AR gene mutation. Thus, the majority of infants with a phenotype similar to PAIS do not have a mutation in the AR gene as the cause. The acronym, PAIS, should be applied only when a pathogenic AR gene mutation has been identified.[5]

DIAGNOSIS

CAIS is diagnosed by clinical and laboratory findings and confirmed by the detection of a defect in the AR gene. CAIS is suspected in women who have amenorrhea, normal breast development, and an absence of pubic and axillary hair.[8] To establish the diagnosis of AIS, a 46, XY karyotype is essential, as well as determination (baseline or after HCG stimulation) of testosterone, testosterone precursors and DHT levels, in order to exclude defects in testosterone biosynthesis or 5alpha-reductase 2 deficiency.[3] Imaging studies, including the gold standard MRI, should be obtained in the CAIS patient to document internal anatomy.[2] If MRI is not available, trans abdominal pelvic ultrasound may be useful. In the adolescent patient, presenting with primary amenorrhea, a full physical exam should be performed in the office, with special attention to breast development and to pubic and axillary hair. A detailed exam of the external genitalia with documentation of hymenal anatomy should be performed. If the hymen is not easily identified, the provider should attempt to locate a patent's vagina by passing a sterile Q-tip.[2] In addition, to rule out a lower vaginal obstruction, a rectal exam should be performed. Imaging studies, such as ultrasound and MRI, are warranted to help delineate internal anatomy, localize testes, and rule out testicular tumors.[2] Imaging tests may show a short vagina, an absence of the uterus, or the presence of Müllerian or Wolffian duct remnants. Hormonal analysis will confirm if the gonads are testicle. A semen analysis should be performed for adult males.[8]

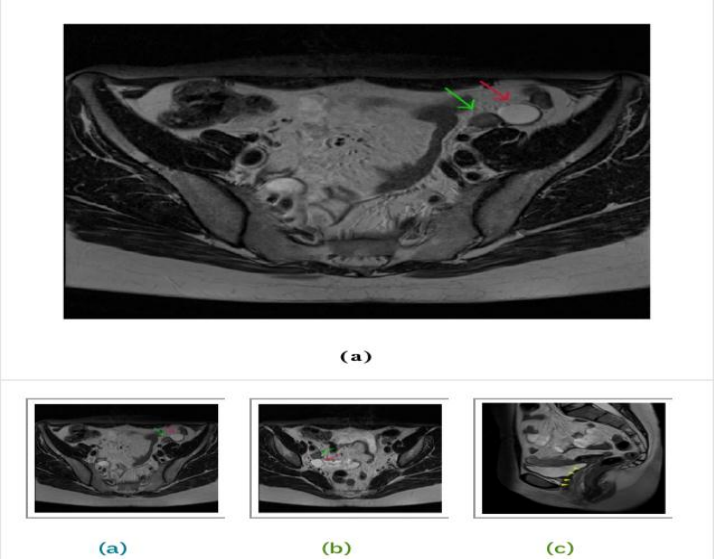

Figure 2: MRI scan exam of female with CAIS.

A survey of the Androgen Receptor Gene Mutations Database suggests that AIS may be attributable to factors other than the presence of *AR* variants. Findings that suggest the presence of other identifiable diagnoses in 46, XY individuals with predominantly female, ambiguous, or predominantly male genitalia include the following.[7]

- Elevated levels of testosterone precursors caused by a partial testosterone biosynthetic defect in which compensatory serum LH concentrations stimulate a normal plasma testosterone concentration
- The presence of müllerian duct derivatives as a result of a testicular organogenesis defect with impaired Sertoli cell production of anti-müllerian hormone
- The presence of wolffian duct-derived internal male reproductive structures that differentiate in response to testosterone, suggesting 5-α-reductase deficiency, a partial testosterone biosynthetic defect, or PAIS. 5-α-reductase deficiency (OMIM 264600) is the result of biallelic pathogenic variants in *SRD5A2*. The enzyme converts testosterone to dihydrotestosterone (DHT), which is primarily responsible for the development of the external genitalia before birth.

DIFFERENTIAL DIAGNOSIS

- Mayer-Rokitansky-Kuster-Hauser(MRKH)syndrome
- Hypospadias
- MAIS
- Undermasculinization of the external genitalia and pubertal undervirilization

- 46,XY infants born small for gestational age
- Deficiency of the 5α-reductase enzyme
- Kallmann syndrome
- Leydig cell agenesis due to LH receptor anomalies.[7]

PRENATAL DIAGNOSIS

The absence of male genitalia in the ultrasound of a fetus previously diagnosed with a 46, XY karyotype from a heterozygous mother indicates that the fetus may have AIS.[30] Diagnosis can be performed by sequencing the AR gene from the amniotic fluid cells, chorionic fluid, or fetal blood obtained by amniocentesis, chorionic villus biopsy, or cordocentesis, respectively.[8]

MANAGEMENT

The surgical goal of management in DSD aims for an outcome that has a good cosmetic appearance to the genitalia and functionality that provides satisfactory sexual sensitivity and responsiveness. Hormone replacement therapy should ensure normal breast development for patients with CAIS who have had their gonads removed. Some women may prefer additional androgen replacement. Patients with PAIS raised female normally undergo gonadectomy to avoid virilization at puberty; they also require estrogen replacement. Those raised male may need multiple surgical procedures to correct severe hypospadias, scrotal displacement and cryptorchidism. Androgen supplementation is often required to achieve puberty. Psychological management and support is fundamental from the outset, especially when transitioning to young adulthood.[5]

CLINICAL MANAGEMENT OF CAIS

Kohler et al suggest a testosterone treatment trial in all patients with PAIS in order to evaluate the virilizing capacity of the newborn external genitalia before sex assignment. However, in the case of an AR somatic mosaicism identified at birth, a testosterone treatment trial could be warranted because a certain type of the wild-type receptor is present and likely functionally active. In the same study, Kohler et al presented two PAIS patients with somatic mosaicism, who showed sufficient virilization at puberty due to the functional wild-type AR. XY individuals with complete androgen insensitivity syndrome in whom the external genitalia are those of a normal female pose no dilemma of sex assignment. Affected individuals are raised as females. A common practice is to remove the testes after puberty

when feminization of the affected individual is complete, since feminization occurs partly by testicular estrogen and partly by peripheral conversion of androgen to estrogen. Goulis et al reported a case of bilateral testicular hamartomata in an 18-year-old individual with CAIS, who carried the R831X mutation of the AR gene. Prepubertal gonadectomy is indicated if inguinal testes are physically or esthetically uncomfortable and if inguinal herniorrhaphy is necessary. In this case, estrogen replacement therapy is necessary to initiate puberty, maintain feminization and avoid osteoporosis. Vaginal length may be short and require dilatation in an effort to avoid dyspareunia.[3]

HORMONAL REPLACEMENT IN AIS

Androgens are necessary for skeletal development because they are converted to estrogens. Therefore, AIS patients only achieve normal bone mass at the end of puberty in the presence of testicular hormones if they have not been orchidectomized. AIS individuals who have been orchidectomized have hypoestrogenism, which justifies pharmacological estrogen replacement.[8] It has been proposed that in the absence of or for poorly developed secondary sexual characteristics, estrogen administration should be gradually increased until reaching the desired breast and genital development.[8] Adequate estrogen replacement during late adolescence and in the twenties will help build bone, but these patients need to be maintained on calcium and vitamin D as well as to institute regular weight bearing exercise. DEXA scanning should be instituted early with the addition of bisphosphonate therapy when indicated.[2] Estrogen can be introduced in low doses (one quarter of the adult dose), at 9 – 11 years of age, with titration of this dosage every 6 months. The time for complete feminization is expected to be about 2 years. Oral or transdermic estrogen are alternative ways for estrogen replacement. The initial dose is 0.25 mg/day of 17β-estradiol increasing the dose each 6 months considering the progression of breast development. After complete breast development, a regular dose can be introduced (1-2 mg/day of 17β-estradiol continuously). In male individuals, the testes are able to produce testosterone. In male AIS, at pubertal age, high testosterone doses (200–500 mg twice a week) can be used, in order to increase the penile size and to promote virilization. Maximum penile length is obtained after six months of treatment with high testosterone doses. After this period, the dose of testosterone when necessary should return to the maintenance dose. The use of DHT in male PAIS has been tested (0.3 mg/kg of androstanolone gel 2.5% for 4 months) and mixed results were obtained following DHT therapy.[6]

GONADECTOMY

Ethinylestradiol is frequently used at a starting dose of 2 μg daily from roughly 11 years of age. This dose is increased in increments of 2–4 μg over about 2 years to reach a daily dose of 30 μg (unpublished). Thereafter, and in women who have a gonadectomy after puberty, several preparations are available, including the natural oestrogen estradiol, which can be given orally or transdermally. Synthetic oestrogens can be given in the form of the combined oral contraceptive pill. Some evidence supports the use of natural oestrogens as transdermal hormone replacement therapy because this administration method might be more physiological than oral delivery. Since women with complete androgen insensitivity syndrome do not have a uterus, they can be treated with continuous, unopposed oestrogen. Some women also take supplementary testosterone because they think that it improves wellbeing (including libido).[1] Serum gonadotropin levels increase further after gonadectomy, but are only partially suppressed with estrogen substitution. This observation suggests resistance to the negative-feedback effect of androgens on hypothalamic-pituitary control of gonadotropin secretion in CAIS, but maintenance of a partial negative feedback by estrogens.[4] Laparoscopy is the surgical technique preferred for gonadectomy because it is associated with reduced morbidity and length of hospital stay compared to open techniques.[8] Vaginal surgery is rarely indicated for the creation of a functional vagina. Vaginal dilators are an effective first line treatment.[1]

RISK OF GONADAL NEOPLASIA

Tumours associated with androgen insensitivity syndrome are in the type 2 category of seminoma, non-seminoma, and dysgerminoma. These tumours arise from a premalignant precursor called carcinoma in situ or intra-tubular germcell neoplasia, unclassified. Carcinoma in situ arises from gonocytes or primordial germ cells and is thought to be the result of a developmental arrest of fetal germ cells. It is characterised by an abundance of germ cells concentrated in the seminiferous tubules that stain positively for tumour markers—eg, placental-like alkaline phosphatase, octamer-binding transcription factors 3 and 4, and stem-cell factor.Carcinoma in situ leads to the development of a gonadoblastoma in more than 50% of cases.[1] MRI is a sensitive tool for monitoring the presence of benign changes in a retained gonad such as paratesticular cysts and Sertoli cell adenoma, but it clearly fails to detect histological changes of premalignancy. An alternative monitoring approach is laparoscopic biopsy and gonadopexy to site the gonad on the anterior abdominal wall.[5]

FERTILITY IN AIS

A women diagnosed with PAIS could choose oocyte donation or pre-implantation after determination of the sex of the embryo and after ensuring that the embryo does not have the genetic mutation.[6] In the case of sterile males, who have PAIS, the only option is semen donation.[8] For it, MAIS individuals can present only infertility.[6]

PSYCHOSOCIAL MANAGEMENT

Psychosocial support is central to the multidisciplinary approach to management of complete androgen insensitivity syndrome. Mothers of girls with complete androgen insensitivity syndrome might feel a sense of guilt for having passed on the disorder and fear rejection after the facts are disclosed (unpublished). A heuristic approach to the ideas and components of sex development is a useful principle to adopt to understand physical and psychological sex-related development. Long-term psychosexual outcome in complete androgen insensitivity syndrome suggests a trajectory of female-typical development, with the assimilation of a female identity and female-typical behaviour, and psychological wellbeing similar to that of other women.[1]

PARTIAL ANDROGEN INSENSITIVITY SYNDROME

Maximum virilization effect is observed after 6 months of high androgen usage treatment, subsequently; androgen therapy can be withdrawn in the patients with normal testes and preserved testosterone secretion. For individuals raised as females, bilateral gonadectomy is recommended in childhood to avoid virilization and to eliminate the risk of testicular tumors. Genitoplasty is usually necessary in PAIS females and estrogen replacement is mandatory at pubertal time.[6] Micropenis with undeveloped corpora is a particular challenging procedure for penis enlarging surgery in later life. Androgen supplementation, either to induce puberty or to enhance virilisation post-puberty, is commonly required. Oral and parenteral testosterone preparations (25 mg intramuscularly monthly for 3 months) can be tried and often in high doses, reflecting the degree of androgen resistance. Gynecomastia is invariably a feature of PAIS. It may respond to aromatase inhibitors, such as anastrozole or the anti-estrogen, tamoxifen, but eventually the adolescent male will choose definitive treatment with a mammoplasty.[4] Surgery is done during the second to third year of life to repair hypospadias and bring undescended testes into the scrotum. Breast cancer can occur rarely in men with PAIS. An infant with PAIS who is assigned female will need a genitoplasty

procedure and gonadectomy before puberty to avoid the risk of virilisation. Oestrogen replacement is needed to induce female puberty.[1]

MILD ANDROGEN INSENSITIVITY SYNDROME

Promotion of spermatogenesis would be the main goal, and sperm retrieval would not be necessary in the context of an intact sperm-delivery system. Apart from one successful experience with mesterolone(1a-methylandrostan-17β-ol-3-one) in promoting spermatogenesis and fertility twice in a man with MAIS, experience with long-term natural androgen pharmacotherapy is meager and its value unclear.[3] Individuals having MAIS need reduction mammoplasty for gynaecomastia and supplemental androgens to treat oligospermia.[1] Gynecomastia and infertility are the usual clinical presentation of this phenotype and mastectomy is recommended for gynecomastia correction.[6]

CONCLUSION

Androgen insensitivity syndrome is the most common molecular diagnosis in newborns with 46, XY DSD and results of an AR defect. AR defects are found along AR gene in all AIS phenotypes. Non-synonymous point mutations are the commonest AR defects reported in AIS. Molecular diagnosis is achieved in almost all patients with CAIS and in a lower frequency in PAIS individuals. Management of androgen insensitivity syndrome should be undertaken through gonadectomy to avoid gonad tumours in later life and appropriate sex-hormone replacement at puberty. Identification of AR mutations and their functional consequences can be useful for genotype-phenotype correlations and serve to a better management of CAIS patients.

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