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**The XY Female: Exploring care for adolescent girls with Complete Androgen Insensitivity Syndrome**

Kate Davies

Children’s Advanced Nurse Practitioner

Senior Lecturer in Non Medical Prescribing, London South Bank University

Honorary Research Fellow in Paediatric Endocrinology, Queen Mary University of London / Barts and the London School of Medicine

[Kate.davies@lsbu.ac.uk](mailto:Kate.davies@lsbu.ac.uk)

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**Abstract**

Differences in Sex Development – DSD – encompasses many diagnoses, where the development of chromosomal make-up, gonadal development or anatomical development is atypical. XY, DSD is a classification under the recent international consensus statement, and XY females commonly encapsulate disorders of androgen synthesis and androgen action. Complete Androgen Insensitivity Syndrome (CAIS) is the most common XY, DSD diagnosis, which results in an individual having XY chromosomes, but the person is phenotypically female. This article explores the care and management of children and young people with a DSD, and focuses on the diagnosis of CAIS in adolescence. Medical and surgical management is discussed, alongside sexual function, gender identity and the psychological impact of the diagnosis. The involvement of the multidisciplinary team is stressed, together with emphasis on the investment that is needed in psychological and nursing support for girls with CAIS, and their families.

**Key words and Key terms**

Androgen

CAIS

DSD

Gender Identity

Sexual function

**Abbreviations**

AIS – Androgen Insensitivity Syndrome

AMH – Anti-Mullerian Hormone

CAIS – Complete Androgen Insensitivity Syndrome

DSD – Disorder / Differences in Sex Development

LH – Luteinising hormone

MDT – Multidisciplinary team

MIS – Mullerian Inhibiting Substance

MURCS – Mullerian, renal, cervicothoracic somite abnormalities

PAIS – Partial Androgen Insensitivity Syndrome

**Disclosure statement**

*The author is a Trustee of the UK based charity and patient advocacy group* ***dsdfamilies***

**What is a DSD?**

DSD – Disorders, or Differences of Sex Development, is an umbrella term used to describe particular complex congenital conditions, where the development of the chromosomes, gonads or anatomy is atypical, or different to what is ‘expected’ (White and Sinclair 2012). Terms such as ‘intersex’ or ‘hermaphrodite’ may have once been used, but are confusing and controversial, and patient advocacy groups and ethical issues surrounding care necessitated a revision of the terminology (Lee, Houk et al. 2006)

Historically, ‘intersex’ was used to describe the clinical picture of an infant or child with ambiguous genitalia, whereas ‘hermaphrodite’ was used to describe a person with both ovarian *and* testicular tissue (Davies 2019). Advances in molecular genetics and the causes of sex differentiation therefore has led to the new revised nomenclature, which is seen in Table 1.

**Table 1: DSD Classification table**

|  |  |  |
| --- | --- | --- |
| **XY, DSD** | **XX, DSD** | **Mixed Sex Chromosome DSD** |
| 1 – Disorders of testicular development   * Ovotesticular DSD * Swyer syndrome * Gonadal regression * Partial gonadal dysgenesis   2 – Androgen synthesis or action disorders   * 5-α -eductase deficiency * CAIS * PAIS * LH receptor defects * AMH receptor disorders | 1 – Disorders of ovarian development   * Ovotesticular DSD * Testicular DSD * Gonadal dysgenesis   2 – Androgen Excess   * Congenital adrenal hyperplasia (21-hydroxylase deficiency) * Aromatase deficiency  1. - Other syndromes eg MURCS | 1 – Turner syndrome (and variants – 45, X)  2 – Klinefelter syndrome ( and variants – 47, XXY)  3 – Mixed gonadal dysgenesis, ovotesticular DSD (45, X / 46, XY)  4 – Chimeric, ovotesticular DSD (46, XX / 46, XY) |

Adapted from (Davies 2019)

Here, it can be clearly seen how DSDs are now categorised by utilising a chromosomal focus: 46, XY DSD – disorders of testicular development or androgen synthesis / action; 46, XY DSD – disorders of ovarian development or adrenal androgen excess, and finally sex chromosome DSD, where other variants are possible.

Investigations into DSD and the subsequent management must be undertaken by specialised multidisciplinary teams, including endocrinologists, psychologists, urologists, and gynaecologists (Brain, Creighton et al. 2010). The involvement of the specialist nurse is paramount, (Davies 2019), who is best placed to provide ongoing support and continuity outside of the clinical environment (Sanders, Edwards et al. 2017), alongside specialist support groups.

Diagnostic pathways (Ahmed, Achermann et al. 2015) can advise on the investigations and examinations that should be undertaken when a team is presented with an infant, child or adolescent with a DSD. Specific care pathways are suggested and implemented for the management of infants with ambiguous genitalia (Davies 2019), including exploring the clinical status of the baby, their history, maternal and family history, and family knowledge and expectations, followed by detailed assessment, resulting in an ultimate diagnosis and plan of care. Conversely, however, a small group of DSD can present in adolescence, encompassing girls presenting with primary amenorrhoea (where menses have not yet commenced), girls with virilzation, such as hirsutism or clitoromegaly, or boys with delayed puberty.

**46, XY DSD**

The 46, XY classification is complex, and usually encompasses diagnoses and presentations of ambiguous or female external genitalia, and either the absence or presence of Mullerian structures (Mendonca, Costa et al. 2010). Mullerian structures involve the fallopian tubes, uterus, the cervix and part of the vagina, whereas the Wolffian structures will develop into the epididymis, the two vas deferens, and the seminal vesicles in the male reproductive system. However, abnormalities of karyotype, formation of gonads, androgen synthesis and androgen action are the principle causes that result in under-virilisation – that is, under masculinisation of ‘biological’ XY individuals (Massanyi, Dicarlo et al. 2013). Sometimes, the Wolffian ducts may not form properly in early stages of embryological development, resulting in a non-endocrine related picture, and also gonadal dysfunction and hypogonadism can be the result of insufficient testosterone. Disorders of androgen synthesis, such as 5-α-reductase deficiency are found in individuals with female or ambiguous genitalia at birth who later virilize at puberty, which can sometimes lead to a personal decision to change gender (Michala and Creighton 2010). However, Complete Androgen Insensitivity Syndrome results from androgen *receptor* dysfunction (Mongan, Tadokoro-Cuccaro et al. 2015), and is the most common condition leading to the presentation of an XY female, with an estimated incidence of 1 in every 40,000 – 60,000 births (Michala and Creighton 2010).

**Androgen Insensitivity Syndrome**

The clinical presentation is dependent on the degree of the insensitivity to the androgens: that is, a partial or a complete inability for cells to respond to the androgens. Therefore, Partial Androgen Insensitivity Syndrome – PAIS – has a much wider phenotype, ranging from the appearance of female external genitalia, to a male appearance but with a severe hypospadias or micropenis (Tadokoro-Cuccaro and Hughes 2014). However, Complete Androgen Insensitivity Syndrome – CAIS – is characterised by a female external phenotype (ie looks like a ‘typical’ female on the outside), but has a male XY karyotype with testes which produce age appropriate normal concentrations of androgens (Hughes, Davies et al. 2012)

**Anatomy and Physiology**

AIS is a genetic condition, with the AR gene responsible found on the long arm of the X chromosome at Xq11-12 (Oakes, Eyvazzadeh et al. 2008). There is no activity at all at the androgen receptors in CAIS, which is how the female phenotype occurs, and the testes in-situ will produce ‘normal’ physiological levels of testosterone and DHT – dihydrotestosterone. AMH (anti-mullerian hormone) or MIS (Mullerian inhibiting substance) is usually released by the Sertoli cells in foetal testes which have an ‘anti-mullerian’ role - that is, the release inhibits the development of the Mullerian structures, such as the uterus, fallopian tubes and upper portion of the vagina. This is therefore the picture in CAIS, which results in the individuals not having these structures in place.

**Clinical Presentation of CAIS**

CAIS can present in infancy, where the baby will present with an inguinal hernia or labial swelling which contains a testis: this is rare, in about 1-2% of CAIS cases are diagnosed at this time (Hughes, Davies et al. 2012), although 80-90% of older girls with CAIS can eventually develop an inguinal hernia (Oakes, Eyvazzadeh et al. 2008). However, CAIS primarily presents in adolescence, where an adolescent girl presents with primary amenorrhoea, but will have normal breast development, little or no pubic and axillary hair, and may be taller than the ‘average’ female (Michala and Creighton 2010). Externally, the genitalia will look undoubtedly female, although the vagina will have a ‘blind’ ending and be shorter, but can vary in length, and there is no uterus. This was highlighted in a recent UK television series ‘Call the Midwife’, a semi-fictional period drama set in 1960s London (BBC1, 2019). The focus in one episode was on a young unmarried woman who was concerned she had not yet started her periods and wanted to know if she would be able to have intercourse and conceive and carry a baby after she was married. She was eventually diagnosed with ‘Testicular Feminization Syndrome’ as it was once called, and the story centred on her diagnosis and the psychological impact it had. The model Hanne Gaby Odiele also recently detailed her condition to the Sunday Times Newspaper, and what made her ‘go public’, although according to the article, she identifies as ‘intersex’, although this is not always the case for all individuals (Pavia 2017).

**The diagnosis of CAIS and its impact**

The diagnosis and management of CAIS is complex, resulting in specialised investigations and genetic testing to identify the particular genetic complication. Family members may be offered screening in order to identify possible affected siblings, or asymptomatic carriers (Minto, Crouch et al. 2005), although this screening is not currently routine in the UK. Ultrasound will be performed to identify the position of the testes, which could be abdominal, inguinal or labial. A strong emotional reaction to the diagnosis of CAIS should be expected, and feelings of shock, grief, anger and shame have been reported (Slijper, Frets et al. 2000). Girls presenting with primary amenorrhoea particularly worry about how their female body is going to function; adolescence is a time when the individuals want to be the same as their peers: the girls with this new diagnosis of CAIS can suddenly feel very different, leading to immense disappointment, grief and shame (Slijper, Frets et al. 2000).

It is therefore imperative that the revelation of such a diagnosis from healthcare professionals is dealt with in a sensitive manner. It is believed that from around 12 years of age, girls of average intelligence and maturity can take in and understand the diagnosis (Hutson and Warne 2012). Factors that also need to be considered include *where* the diagnosis is disclosed, and *who* is present – ideally both parents. The healthcare professional needs to gain an understanding of what the girl and her family already know, and must use the same terminology as them. They need to explain the concepts of genetics and sex development, hormones and hormonal differences, and the implications for all of this for the girl and her family. It is imperative that they have space to ask questions, and that the discussion is not rushed, allowing time for the information to be absorbed (Warne and Hewitt 2012).

**Treatment Options**

**Gonadectomy**

There is, unfortunately, an increased risk for the development of germ cell tumours in individuals with AIS, which are tumours which form from reproductive cells that produce eggs or sperm (Patel, Casey et al. 2016). Prophylactic gonadectomy commenced in the 1950s, and historically the procedure was undertaken prior to puberty. The recent consensus statement (Hughes, Houk et al. 2006) does state that gonads should be removed in order to prevent malignancy, but it does not detail at what age this should occur. It does, however highlight that parental concerns can allow for the surgery to be delayed until during adolescence. Once a gonadectomy has been performed, hormone replacement therapy (HRT) (Hewitt and Zacharin 2015) is required, in order to maintain the secondary sexual characteristics – predominantly the breasts – alongside bone and cardiovascular health, general wellbeing and sexual function (Ko, King et al. 2017). The HRT is usually an oestrogen based preparation such as oral tablets, transdermal patches or vaginal preparations, or some testosterone gel preparations or injections.

However, an increasing number of women and adolescent girls are not wanting to opt for a gonadectomy, despite counselling on the risk of malignancy. Reasons for this can include clashes with academic studies (so an interference with daily activities), the need for HRT, and also a desire in an attempt to preserve fertility (Deans, Creighton et al. 2012). The treatment for infertility in CAIS, and indeed, some DSD overall, is limited, although there may potentially one day be an option for post-pubertal sperm collection, or pre-pubertal cryopreservation of non-malignant tissue (Johnson and Finlayson 2016) with the assistance of advanced reproductive technologies, although the long-standing ethics of this have yet to be explored, and are only more commonplace in pubertal boys prior to cancer treatment (Gan and Spoudeas 2013). Women who do not wish to undergo gonadectomy will need to be under regular surveillance by their medical team.

**Sexual Function**

A shortened vagina is common in girls with CAIS, and penetration difficulties are likely to occur when they become sexually active. This can be managed with vaginal dilation techniques, alongside nursing and psychological support, and can be successful in around 80% of cases (Michala and Creighton 2010). Surgery is also an option, such as vaginoplasty. If these avenues are not explored, then it has been shown that women can be unhappy with the length of their vagina, resulting in a lack of sexual confidence and sexual satisfaction (Fliegner, Krupp et al. 2014), although reports of orgasm satisfaction are reassuring (Sandberg 2018), and the role of testosterone therapy in female sexuality has yet to be explored fully. Therefore, the balance between endocrinological and psychological interventions needs to be addressed in order to optimise physical and mental wellbeing; regular vaginal dilation should be encouraged, which can result in a depth sufficient for penetrative intercourse (Wilson, Arnhym et al. 2011)

**Gender Identity and Psychosexual Function**

Gender identity intensifies during adolescence, and can highlight an increased pressure to perform to culturally sanctioned gender roles (Steensma, Kreukels et al. 2013), although this is becoming increasingly less so in light of the recent burgeoning transgender movement (Connolly, Zervos et al. 2016), although it is stressed that gender identity and gender dysphoria issues are entirely separate amongst individuals with a DSD and a transgender individual. Nevertheless, hormones clearly influence gender development (Berenbaum and Beltz 2016), and early androgens can also play a part: there are reports where a male gender identity is conformed to after a CAIS diagnosis had been given, following a female sex of rearing up till then (T'Sjoen, De Cuypere et al. 2011). Certainly, individuals with PAIS can be assigned either a male or female sex of rearing, depending on the degree of virilisation (Michala and Creighton 2010). However, most girls with an XY karyotype and complete hypoandrogenisation, such as in girls with CAIS, show girl typical behaviours and interests (Jurgensen, Hiort et al. 2007), and girls and women have a female gender identity, with the vast majority having heterosexual relationships. It has also been shown that exposure to androgens prenatally can actually affect sexual orientation: a moderate exposure could therefore lead to the sexual attraction to females (Callens, Van Kuyk et al. 2016), so it is clear that there is no evidence for this in XY females with CAIS, leading to a female gender identity and heterosexual orientations. Yet, as seen in Table 1, CAIS is not the only diagnosis under the XY, DSD classification: 5-α-reductase deficiency and 17-β-hydroxysteroid dehydrogenase deficiency diagnosed individuals, however, are often reared as girls, and change to a male gender identity at puberty, due to the testosterone effects (Yang, Baskin et al. 2010), although these conditions do present more rarely.

However, some sexual problems in women with CAIS have been reported, such as low sexual desire or an inability to become aroused, despite the female gender identity (Cohen-Kettenis 2010), although on the whole, women with CAIS do overall report to function psychologically well in the long term (de Neve-Enthoven, Callens et al. 2016). Nevertheless, adolescents with a CAIS diagnosis should be offered the opportunity to raise their concerns repeatedly yet privately, with psychological and / or gynaecological services.

**Quality of Life and Long Term Prospects**

The diagnosis of CAIS can be distressing for the girl and her family (Chikkanayakanahally 2014) and they must be given support on any perceived shame or stigmatization, which should be raised by the health care professional: it is unlikely that the adolescent themselves would spontaneously raise concerning issues (Kleinemeier, Jurgensen et al. 2010). Most women, in hindsight, find this approach and support invaluable, and do continue to seek support in adult life, whether through psychological services, or patients associations and support groups, depending on their specific needs (D'Alberton, Assante et al. 2015). The strength of support groups cannot be underestimated, as they can contribute to a sense of empowerment by sharing experiences, provide advice and enhance overall social wellbeing (van Uden-Kraan, Drossaert et al. 2009). Long term psychological counselling may also be beneficial, since the emotional reaction to the diagnosis is strong and can be long-lasting (Slijper, Frets et al. 2000).

In the long term, medically and surgically, girls with CAIS may face the prospects of vaginoplasty and / or dilation, and gonadectomy, alongside HRT. Reports have also demonstrated low bone mineral density in some women with CAIS, so higher oestrogen doses may be needed (Berra, Liao et al. 2010). Coupled with the need for long term psychological and medical interventions, it is clear that adolescents newly diagnosed with CAIS need well rounded support and care continuing into adulthood (Wisniewski, Migeon et al. 2000). Sensitive transition processes from paediatric to adult care can impact a girl’s future physical and psychological wellbeing, and can encourage autonomy and empowerment (Crouch and Creighton 2014).

**Conclusion**

Typical female psychosexual development is well documented in phenotypically female individuals with an XY,DSD (Palmer, Wisniewski et al. 2012). As a CAIS diagnosis is usually made in adolescence, the involvement of a full multidisciplinary team, including psychologists and nurse specialists, is mandatory in order to fully support the girl and her family. This support is vital, as questions regarding gender identity and potential medical and surgical management will need exploring. Adolescence is a time of challenges and risks, and also accepting physical changes and clarifications of sexual identity and orientation (Kleinemeier, Jurgensen et al. 2010), and diagnosis of CAIS at this time may provoke feelings of isolation, low self-esteem and social insecurity (Cohen-Kettenis and Pfaefflin 2003). It is imperative that these young women and their families receive the support and care in order for them to live successfully. Understanding DSD issues and the psychological impact is needed amongst the wider community.

**Useful Websites**

[www.dsdfamilies.org](http://www.dsdfamilies.org)

[www.dsdteens.org](http://www.dsdteens.org)

[www.aissg.org](http://www.aissg.org)

[www.isna.org](http://www.isna.org)

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