Swyer Syndrome

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Abstract

Purpose of review:

This review focuses on the pathogenesis, diagnosis, management and long term outcomes of disorders of sex development (DSD), specifically women with Swyer syndrome (46,XY complete gonadal dysgenesis).

Recent findings:

Recent discoveries have broadened our understanding of the complex pathways involved in normal and abnormal sex development. In 46,XY gonadal dysgenesis, lack of testis development may be triggered by *SRY*, *NR5A1*, *DHH*, or testis-determining gene loss of function mutations, *DAX1* or *WNT4* duplication, or *MAP3K1* gain of function mutations. The diagnosis and management of patients with Swyer syndrome is complex and optimal care requires an experienced multidisciplinary team. Early diagnosis is vital, firstly because of the significant risk of germ cell tumour, and bilateral gonadectomy should be performed. Secondly, early sex hormone treatment is necessary to induce and maintain typical pubertal development and to achieve optimal bone mineral accumulation. Pregnancy is possible via ova donation, and outcomes are similar to women with 46,XX ovarian failure.

Summary:

Further pathogenic gene mutations are likely to be identified, and the function, interaction and phenotypic effects of new and existing mutations will be further defined. Patients require long term follow up in specialist centres.

Keywords:

Swyer syndrome, Gonadal dysgenesis, Disorders of sex development, Gonadoblastoma,

Fertility

Introduction

Disorders of sex development (DSD) are congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical. They occur in approximately 1 in 4,500 births (1). In 1955, Swyer reported two cases of sex reversal that differed from the known forms of what was then referred to as 'male pseudohermaphroditism' (2). The two women had presented with primary amenorrhoea, they were tall with eunuchoid proportions, had little or no breast development but normal axillary and pubic hair. They had female external genitalia (although one had an enlarged clitoris) and normal – albeit hypoestrogenised – vagina and cervix, with small uterus and no palpable adnexa. Adrenal hyperplasia was excluded by normal urine 17-ketosteroids. Chromosomal analysis demonstrated 46,XY karyotype, using the newly evolving technique of analysing peripheral leucocytes. The condition named after Swyer was later linked to dysgenetic gonads and is also known as pure or complete gonadal dysgenesis, and is estimated to have an incidence of 1 in 80,000 births (3).

Following the 2006 consensus group, DSD are broadly classified into three groups based upon cytogenetic, hormonal, gonadal histology, and clinical findings: 46,XY DSD, 46,XX DSD, and sex chromosome DSD (1). This classification supersedes the previous terms pseudohermaphrodite, intersex and sex reversal, which are no longer used. The 46,XY DSD group can be further classified into disorders of gonadal (testicular) development, which shall be reviewed here, or disorders in androgen synthesis or action, which are reviewed in

another section of this journal. Gonadal development disorders comprise of complete dysgenesis (Swyer syndrome), partial dysgenesis, gonadal regression and ovotesticular DSD.

Pathogenesis of DSD

The development of a testis or an ovary from common gonadal primordial is governed by complex male-specific and female-specific molecular networks of gene expression, dosing and interaction. Most of our current understanding of the genetic control of normal sex development has arisen from the mutational and functional analyses of patients with DSD (4). Definitive diagnosis of DSD relies on clinical findings, hormonal analysis, gonadal histology, chromosome analysis and genetic testing (5). Currently, a specific molecular diagnosis is only made in approximately 20% of patients with DSD, however reducing costs of next generation sequencing, exome and complete genome sequencing offer much richer possibilities for understanding disease in the future (6).

In normal development, expression of the *SRY* gene on the Y chromosome initiates a genetic cascade that causes the undifferentiated gonad to develop as a testis. In the developing testis, secretion of anti-mullerian hormone (AMH) from Sertoli cells causes regression of the Mullerian ducts. Testosterone secreted from Leydig cells promotes the differentiation of the Wolffian ducts and into seminal vesicles, vas deferens, and epididymis (4). In the absence of a Y chromosome, the testes do not develop and the Mullerian ducts persist to form fallopian tubes, uterus, and upper third of the vagina. If the genetic pathway of gonadal development is faulty, so that gene functions are lost or overridden, DSD result (5).

Associated Genetic Syndromes

Sometimes the gonadal DSD may be a feature of a genetic syndrome, such as campomelic dysplasia, Denys-Drash syndrome, Frasier syndrome, or adrenal hypoplasia congenita (5). Recent results from the large international DSD (I-DSD) registry showed that 112 of 460 (24%) cases of 46,XY DSD had an associated anomaly (7). These included small for gestational age in 23%, cardiac anomalies in 20%, and central nervous system disorders in 20%. Even after exclusion of known syndromes associated with DSD, the rates of associated anomalies were significantly higher than expected in the background population, suggesting that new associations and pathogenic mechanisms are yet to be discovered.

Causative Genes

To date, several causative genes have been identified in 46,XY DSD gonadal dysgenesis, including *ARX, ATRX, CBX2, DHH, DMRT1, GATA4, MAMLD1, MAP3K1, NR0B1, NR5A1, SOX9, SRY, WNT4, WT1* and *WWOX* (4). Here we review the major genetic mutations:

***SRY* gene**

In 1990, a *de novo* mutation in a candidate gene for testis determining factor on the Y chromosome, termed *SRY*, was identified in a woman with 46,XY DSD (8). Subsequent analysis has shown that 10 to 20% of women with Swyer syndrome have a deletion in the DNA-binding region of the *SRY* gene. In the remaining 80 to 90% of cases, the *SRY* gene is normal and mutations in other testis determining factors are probably implicated (3).

Steroidogenic Factor-1 (SF-1)

The orphan nuclear receptor SF-1 is encoded by the gene *NR5A1* and regulates the transcription of multiple genes involved in steroidogenesis, reproduction, and male sexual differentiation (9). In 1999, a heterozygous *de novo* loss-of-function SF-1 mutation was described in a patient with primary adrenal failure and complete 46,XY gonadal dysgenesis, indicating that haploinsufficiency of this factor is sufficient to cause a severe clinical phenotype (10). A recent large series discovered novel SF-1/*NR5A1* mutations in 9% of 46,XY DSD patients, with a broad clinical phenotype and no apparent genotype-structure-function-phenotype correlation (11).

Failure of SOX9 regulation

The *SOX9* gene has become known as a pivotal sex-determining gene across all vertebrate species, regardless of the switch mechanism controlling sex determination (5). In humans, mutations in *SOX9* cause campomelic dysplasia, a condition characterised by skeletal malformation and 46,XY DSD (12). Regulation of *SOX9* expression in the gonad is tightly controlled, and the earliest developmental step in sex determination is activation of *SOX9* transcription by *SRY*. *SRY* and SF-1 co-operate to activate the human homologous *SOX9* testis-specific enhancer (*hTES*), a process dependent on phosphorylated SF-1. *SOX9* also activates *hTES*, augmented by SF1, suggesting a mechanism for maintenance of *SOX9* expression by auto-regulation. Mutations in *SRY*, *NR5A1*, and *SOX9* observed in patients with 46,XY partial or complete gonadal dysgenesis have a reduced ability to activate *hTES*. Hence these three human sex-determining factors are likely to function during gonadal development around *SOX9* as a hub gene, with different genetic causes of 46,XY DSD due to a common failure to upregulate *SOX9* transcription (13).

Role of the MAPK Pathway

Specific mutations in the signal transduction gene, *MAP3K1*, tilt the balance from the male to female sex-determining pathway, and mutations have been found in 13-18% of cases of both sporadic and familial 46,XY DSD (5, 14). These MAP3K1 mutations mediate this balance by enhancing *WNT*/β-catenin/*FOXL2* expression and β-catenin activity and by reducing *SOX9*/*FGF9*/*FGFR2*/*SRY* expression. These effects are mediated at multiple levels involving *MAP3K1* interaction with protein co-factors and phosphorylation of downstream targets. Although *MAP3K1* is not usually required for testis determination, normal development can be disrupted through these gain of function mutations (15).

Future Developments

These recent developments provide a more complete view of the complex genetic control of normal and abnormal sex determination. With expanding technology, more genes are likely to be identified, and the function, interaction and phenotypic effects of new and existing mutations will be defined. With increasing volumes of genetic information available, involvement of the clinical geneticist in the multidisciplinary team is going to be ever more important. There is also a need to collect data in a standardised manner and to share information across databases in order to expand our knowledge and to improve management of these rare conditions (6).

Diagnosis of Swyer Syndrome

Individuals with Swyer syndrome are phenotypically female with unambiguously female genital appearance at birth and normal Mullerian structures (3). As the gonads have no hormonal potential, the condition typically presents during adolescence with primary amenorrhoea and delayed puberty. Given the normal pre-pubertal phenotype, earlier diagnosis is only possible if a karyotype is performed for other reasons such as prenatal screening for aneuploidy or as part of familial screening following the diagnosis of a sibling with the condition. The vast majority of subjects however have no family history with only 4% having an affected sibling in our clinic population.

As per current recommendations, specialist referral should be considered in girls with primary amenorrhoea where there has been no pubertal development by age 14. It should be noted that physical examination and medical photography can be embarrassing and stressful for adolescent patients. The potential psychological impact should be considered and examination could be deferred to a specialist adolescent gynaecologist so that an assessment need take place only once. A more detailed examination of genitalia may only be appropriate under an anaesthetic, particularly if it is clear that surgery will be required (16).

Height

A characteristic and often differentiating feature of women with Swyer syndrome is their increased adult height, and in our series, the median height was 173 cm compared to the average height for English women of 161cm. Increased stature may be caused by the influence of the Y chromosome (17) or delayed epiphyseal closure from low sex steroid

levels, however we found no correlation between age at induction of puberty and final adult height (3).

Laboratory

Initial investigations are shown in Figure 1, and should include measurements of serum electrolytes, luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin, thyroid stimulating hormone (TSH), free thyroid hormone (FT4), sex hormone binding globulin (SHBG), androstenedione, oestradiol (E2), testosterone (T). Anti-mullerian hormone (AMH) and inhibin measurements are optional additions if there is a query about gonadal status but generally do not add further information if the serum FSH is raised.

Routine peripheral blood karyotype should be requested in all individuals presenting with delayed puberty and raised gonadotrophins. There is rarely an overlap between non-mosaic Swyer syndrome (46,XY) with the very rare 46,XX/46,XY mosaicism who usually retain more gonadal function and are virilised. Similarly, 45,X/46,XY mosaicism span a spectrum with clear features of Turner Syndrome or notable virilisation.

Urinary steroid profile analysis performed by gas chromatography mass spectrometry (GC-MS) is only important if an enzyme deficiency of testosterone or cortisol biosynthesis is considered. Urinary steroid profile is particularly useful for the differential diagnosis of 5 alpha reductase deficiency but this rarely causes clinical confusion.

Tumour markers should be considered when the diagnosis of gonadal dysgenesis is confirmed; these include alpha fetoprotein, beta human chorionic gonadotrophin, lactate

dehydrogenase and placental alkaline phosphatise. Although these tests are often postponed until a gonadal mass is identified there is a place for confirming tumour marker status before all surgery (18, 19).

Sequencing of specific causative genes is not widely available and so far the benefit of identifying specific causative genes is unproven. One exception is *NR5A1* in those with an unusual family history as the pattern of inheritance is unpredictable and therefore it is useful for genetic counselling. *NR5A1* mutations however, are probably rare in complete gonadal dysgenesis with no family history so the value of routine screening of this phenotype is uncertain (20).

The overall pattern seen in patients with Swyer syndrome is that of low androgens and androgen precursors, elevated gonadotrophins, low or undetectable AMH and cytogenetic analysis will reveal a non-mosaic 46,XY karyotype. Adrenal function is usually normal unless the underlying defect is in steroidogenic factor-1 (SF-1) or related adrenal or gonadal factors (21).

Imaging

First line imaging is transabdominal pelvic ultrasound by a sonographer who has experience of adolescent appearances. Magnetic resonance imaging (MRI) should be reserved for cases where ultrasonography has failed to delineate the relationship of the Mullerian structures and where there are abnormalities of the urinary tract (21). The usual picture in Swyer syndrome is one of intra abdominal streak gonads with present mullerian structures because of impaired AMH secretion in early fetal development.

Confusion often arises with the over diagnosis of the very rare phenotype of streak gonads and absent uterus. With streak gonads, the lack of AMH usually results in normal uterine development. The problem arises because it is difficult to confirm the presence of a prepubertal uterus by ultrasonography, MRI or even laparoscopy until the organ has been adequately exposed to oestrogen. Repeat imaging after a 6-month course of oestrogen may therefore be required if this combination is found before concluding on uterine status (21-23).

Delayed Diagnosis

As with all causes of primary amenorrhoea, many women with Swyer syndrome experience delay in reaching an accurate diagnosis, which is often only reached several years after first presenting to their primary care physician (3). In our series 90% of the women presented in adolescence because of delayed puberty and the median time from presentation to diagnosis was 1.5 years (range 0.16-18 years). Given the change in modern practice, we divided women into those who had presented before and after 1990. In the younger group the median age at diagnosis was 16 years (range 0-29 years) with a delay in diagnosis of 6 months (range 0.17-14 years), versus the older group that had a median age at diagnosis of 23 years (range 13-55 years) with a delay in diagnosis of 7 years (range 0.5-18 years).

Management

The diagnosis and management of DSD is complex and optimal care for children and adolescents requires an experienced multidisciplinary team that should be accessible through regional centres (21). Early diagnosis is important because of the risk of gonadal malignancy, and to allow for early sex hormone treatment to induce and maintain typical pubertal development, psychosexual development and to achieve adequate peak bone mass.

Germ Cell Neoplasia

There is a significant risk of germ cell neoplasia and current practice is to perform bilateral gonadectomy as soon as the diagnosis of 46,XY DSD is made. Gonadoblastomas are benign germ cell neoplasias that arise almost exclusively from persisting undifferentiated gonadal tissue within dysgenetic gonads. They can be unilateral or bilateral and are typically discovered at the time of diagnosis during adolescence, however they can occur at any age and have been reported in infancy (24, 25). The histology is similar to that found in the embryonic gonad prior to expression of the SRY gene and contains germ cells scattered in stroma and presertoli-granulosa cells (26). Gonadoblastomas are linked to the presence of Y-chromosome material and development of tumour is associated with expression of the testis specific protein, Y-linked (*TSPY*) gene, and with the presence of *SRY*, *SOX9* and *WT1* mutations (25, 27, 28).

Gonadoblastomas are benign tumours but they can be precursors to germ cell malignancy such as dysgerminoma, teratoma, embryonal carcinoma and endodermal sinus tumours. Dysgerminoma is the most common of these, accounting for 22-66% of gonadal malignancies, and the youngest patient with dysgerminoma in our series was 10 years old at

diagnosis (3, 19). Two of our cases presented with dysgerminoma and were only diagnosed with Swyer syndrome several years later when they were investigated for delayed puberty.

Previous studies have estimated the risk of germ cell neoplasm to be between 15 and 35% (1). We reported an incidence of 45% in our series of 29 patients, and more recent international series from China (n=33) and Indonesia (n=7) have shown an incidences of 9% and 43% respectively (3, 29, 30). A recent review of 50 patients with malignant ovarian germ cell tumours found that the clinical outcome, including stage distribution and recurrence rate was similar in women with XX and XY karyotype (31). Given the incidence of gonadoblastoma and high risk of progression to malignancy, gonadal biopsy has no role and patients should proceed straight to bilateral gonadectomy at the time of diagnosis of Swyer syndrome.

Hormonal Treatment

The hormonal management of Swyer syndrome is in line with other causes of female oestrogen deficiency and involves induction of puberty with oestrogen to develop secondary sexual characteristics. This is followed by cyclical oestrogen and progesterone replacement therapy which is continued throughout life until the age of 50 when treatment can usually cease. In those with delayed presentation breast hypoplasia continues to be a problem despite adequate oestrogen dosing. In our cohort, 5 women (17%) had documented concerns about deficient breast development and three underwent breast augmentation surgery (3).

Bone Mineral Density (BMD)

Early institution of oestrogen therapy is vital to allow for adequate accrual of bone mass during adolescence, and delay in treatment may cause reduced BMD. In our cohort, the median T-score in the lumbar spine was -1.5 (range -1.4 to -2.5) and 60% of women had osteopenia (T-score less than -1.0) on dual-energy x-ray absorptiometry (DXA) (3). It is our policy to use higher than average doses of oestrogen in young women with low bone density in preference to formal anti-resorptive treatment for bone in order to maximise 'catch up' increase in normal bone.

Psychosocial Management

Psychosocial management is important for the patients and their families to promote positive adaptation to their condition, and care should be provided by counsellors or psychologists with expertise in DSD. Healthcare professionals should allow adolescent patients the opportunity to talk with or without their parents and should also encourage participation in support groups, which can enhance their ability to discuss concerns comfortably (1). A rational and empathic approach that relies on the skills and knowledge of the experts within the multidisciplinary team is essential for optimal care (21).
Compared to virilised forms of DSD who are often considered to have greater psychological difficulties, the burden for women with Swyer syndrome adjusting to infertility with the presence of a Y chromosome may often be overlooked but should be explored in every case as the impact is unpredictable, especially in those with a late diagnosis.

Fertility

In our cohort, we found that uterine size (measured by ultrasound at least 2 years after induction of puberty) was significantly smaller than in controls (cross sectional area 15.3 vs. 25.1 cm^2) (3). Despite this difference, the outcome of pregnancy via ova donation appears to be no different from women with 46,XX ovarian failure, based on anecdotal reports. Since the first reported successful pregnancy in a patient with pure gonadal dysgenesis in 1988, several further cases have been described worldwide, and these have been carried to term with normal birth weight (32, 33). Twin pregnancies have also recently been reported (34, 35). Initial reports suggested a high rate of caesarean section, possibly due to hypoplastic uteri (34). Three women in our cohort had successful pregnancies, with 2 vaginal deliveries and one caesarean section at 36 weeks for pre-eclampsia. Two other women were contemplating or awaiting ova donation and two women had adopted a child (3).

Conclusion

Swyer syndrome is a rare condition that should be considered in females presenting with delayed puberty, primary amenorrhoea and high gonadotrophins. The diagnosis and management is complex and optimal care requires a specialist centre with an experienced multidisciplinary team. Early diagnosis is important because of the risk of gonadal malignancy, and to allow for early sex hormone treatment to induce and maintain typical pubertal development, and to achieve optimal bone mineral accumulation. Pregnancy is possible via ova donation, and outcomes are similar to women with 46,XX ovarian failure. Recent discoveries have broadened our understanding of the pathways involved in normal and abnormal sex development, and more complex genetic pathways are likely to be discovered in the future.

Key Points

1. Early diagnosis is important to allow for early sex hormone treatment to induce and maintain typical pubertal development, and to achieve optimal bone mineral accumulation.
2. There is a significant risk of gonadoblastoma and dysgerminoma and bilateral gonadectomy should be performed as soon as the diagnosis is made.
3. The outcome of pregnancy via ova donation appears to be no different from women with 46,XX ovarian failure.
4. More pathogenic gene mutations are likely to be identified, and the function, interaction and phenotypic effects of new and existing mutations will be further defined.

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