

XY females: revisiting the diagnosis

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Objectives To investigate the accuracy of assigned diagnosis in XY female intersex conditions.

Design Cross sectional hospital case notes review.

Setting Tertiary hospital multidisciplinary intersex clinic.

Sample Forty-six adult intersex women with a complete or mosaic XY karyotype.

Methods All clinical features and investigation results were reviewed and a diagnosis was assigned. This was compared to the original diagnosis assigned.

Main outcome measures Data collected included presentation, all investigations, subsequent clinical course and all treatments (medical and surgical). These data were employed to assign an up-to-date intersex diagnosis, which was compared with the recorded diagnosis in the hospital case notes. Diagnoses were then rated according to level of accuracy.

Results The 47.8% patients had an accurate diagnosis, 32.6% of diagnoses were inaccurate and currently under review, 13% had a wrong diagnosis and 6.5% remain with an unknown aetiology for their XY intersex condition.

Conclusions Diagnostic accuracy is assumed to be high when evaluating published work on these conditions; however, this study shows 52.1% of patients have unknown, inaccurate or wrong diagnoses. Assigning the wrong diagnosis may be harmful, for example, if it leads to irreversible virilising changes or development of a gonadal malignancy, and for all cases excludes accurate condition management and genetic counselling for both the patient and their immediate family.

INTRODUCTION

Females are born with XY chromosomes when there is disruption to the normal cascade of events in fetal sex determination leading to an intersex condition. Alternatively babies may be assigned to a female-sex-of-rearing (despite a 46XY karyotype) when born with a condition such as micropenis or aphallia. These conditions that result in XY females are rare and complex, and diagnoses can be difficult to make. However, an accurate diagnosis is essential to enable appropriate management decisions to be made, provide genetic counselling and to allow patients to have a complete explanation of the condition. Diagnostic accuracy is also important when evaluating published research estimating malignancy risk and other condition-related issues such as bone mineral density, gender identity and other long term outcomes.

Certain conditions such as 5-alpha-reductase deficiency (5ARD) will lead to irreversible virilising changes at puberty and in females these may be prevented with appropriate treatment. Other conditions, such as Swyer's syndrome, carry an increased risk of malignancy in dysgenetic gonads

necessitating early gonadectomy. With a greater understanding of the genetic alterations causing some of these conditions, genetic counselling may benefit other family members by identifying affected individuals and unaffected carriers. An inaccurate diagnosis can preclude individuals and families from appropriate management options.

Previously diagnoses have been largely based on clinical signs, with some basic endocrinology and histology tests in support. However, both biochemistry and molecular genetics have advanced enormously in the past 10 years, and now genetic investigations can sometimes provide a more precise definition of the aetiology. In this study we reviewed the diagnosis of all patients seen at our adult female intersex clinics over a two-year period. Our aim was to appraise the accuracy of diagnoses in XY female patients by evaluating the intersex diagnosis in the light of current knowledge.

METHODS

This study was a cross sectional review of notes from a clinic specialising in adult female intersex conditions in a tertiary referral centre. The study was registered with the Research and Development Unit at the hospital, and ethics committee approval was not required. Hospital case notes were obtained for all women with a complete or mosaic XY karyotype that had attended the monthly clinic over a consecutive two-year period. Data were extracted on original mode of presentation, all investigations, subsequent

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Table 1. List of intersex conditions showing number of subjects with the condition as their original diagnosis and/or reviewed diagnosis.

Intersex condition	Original diagnosis	Notes on original diagnosis	Reviewed diagnosis ^a
5ARD	2	1 changed to 17 β HSD	1
17 β HSD	3	1 changed to Swyer's	7 ^b
CAIS	15	1 changed to unknown 1 changed to PAIS 1 changed to LCH	12 ^c
Leydig cell hypoplasia (LCH)	0		1
Mixed gonadal dysgenesis (MGD)	1		3 ^d
Partial androgen insensitivity syndrome (PAIS)	3	1 changed to unknown 1 changed to 17 β HSD	4 ^d
Rudimentary testes	1	Changed to PAIS	0
Swyer's syndrome	9	1 changed to TH	10
Testicular agenesis	3	3 changed to 17 β HSD	1 ^b
Testicular dysgenesis	2	1 changed to testicular agenesis 1 changed to MGD	0
True hermaphrodite (TH)	2		3 ^c
Turner's mosaic	2	1 changed to MGD	1 ^b
Unknown XY female	3	1 changed to PAIS 1 changed to MGD	3

^a Subjects with an assigned diagnostic category as inaccurate have been listed by their most likely diagnosis as assessed by the authors. This led to a change in listed diagnosis in 9/15 (60%) of those assigned as inaccurate.

^b Includes one subject with reviewed diagnosis assigned as inaccurate.

^c Includes four subjects with reviewed diagnosis assigned as inaccurate.

^d Includes three subjects with reviewed diagnosis assigned as inaccurate.

^e Includes two subjects with reviewed diagnosis assigned as inaccurate.

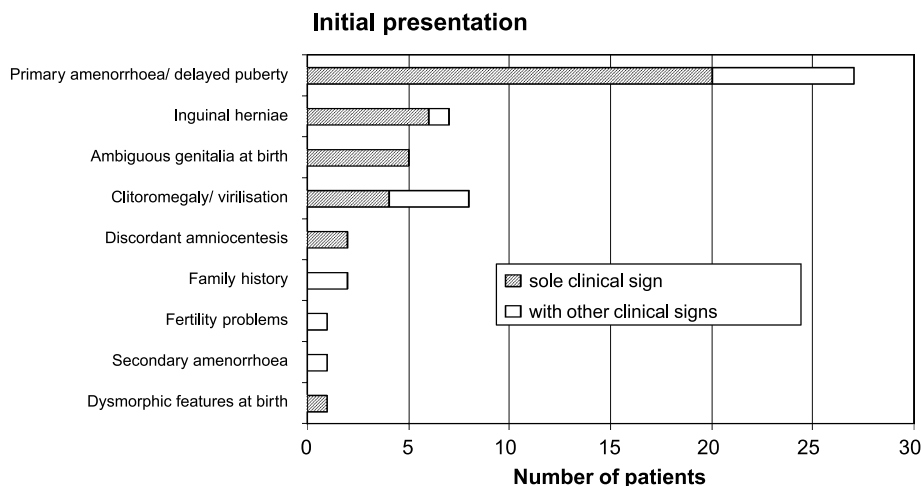
clinical course and all treatments (medical and surgical). These data included details of endocrine, cytogenetic, molecular genetic and biochemical tests, imaging of the pelvis and assessment of mullerian or wolffian structures if present, surgical findings and histopathology assessments. Clinical examination details were also recorded, including

presence of hirsutism, acne, stage of breast development, Tanner grade of pubic hair and genital configuration including vaginal length. Patients were excluded if they were new referrals from general practitioners and had not completed diagnostic investigations.

The extracted data were then analysed by the authors and the most accurate intersex diagnosis assigned in view of current knowledge (reviewed diagnosis). The reviewed diagnosis was compared with the listed diagnosis in the current case notes (original diagnosis). Patients were then placed into one of the following categories reflecting diagnostic accuracy (see Table 1): accurate (review of the extracted data strongly reinforce the original diagnosis), inaccurate (review of the extracted data suggest an alternative diagnosis should be considered along with the original diagnosis), wrong (review of the extracted data strongly suggest an alternative diagnosis) and inconclusive (review of the extracted data was insufficient to allow a diagnosis to be assigned). For example complete androgen insensitivity syndrome (CAIS) would be considered an inaccurate or wrong diagnosis and other conditions considered if one or more of the following features were present; pubic hair tanner stage 3 or more, presence of normal axillary hair, clitoromegaly, evidence of a uterus or gonadal histology not consistent with normal testes.

RESULTS

Forty-six female patients with a complete or mosaic XY karyotype were identified. Hospital case notes were available for all and data were extracted. Age range was from 15 to 53 years (mean 27.0 [10.4]). Information on initial presentation was available for all patients (Fig. 1). Age at diagnosis was not recorded in 18 case notes. In the remaining 28 subjects age at diagnosis varied from birth to 28 years (mean 10.1 [8.2]).

**Fig. 1.** Mode of initial presentation.

Gonadectomy had been performed in 42 patients, age range at time of gonadectomy was 0.2–33 years with a mean of 12.7 and a median of 1–2 years. Histology results were noted for 32 patients, in four patients gonadectomy had not been undertaken and in 10 patients no details on gonadectomy findings were recorded. Of the four patients who had not undergone gonadectomy, one had testicular agenesis, two had original diagnoses of testicular agenesis and reviewed diagnoses of 17- β -HSD-3 deficiency (aged 15 and 17) and one was a 41-year-old patient with an inconclusive reviewed diagnosis.

Table 1 shows a breakdown of the original and reviewed diagnoses. Twenty-two patients (47.8%) were considered to have an accurate diagnosis, three having confirmed genetic mutations. Fifteen (32.6%) were considered inaccurate and are currently under review. Six diagnoses (13%) were categorised as wrong, and have been changed, and three patients (6.5%) remain with an unknown intersex diagnosis due to pre-gonadectomy endocrine investigations either not undertaken ($n = 1$) or not available in the case notes ($n = 2$).

In four of the six patients with a wrong diagnosis there were important management implications and potential adverse outcomes due to the diagnostic inaccuracy. Three sisters with an original diagnosis five years previously of testicular agenesis were given a reviewed diagnosis of 17-beta-hydroxysteroid-dehydrogenase-3 (17 β HSD) deficiency. All three had developed signs of virilisation including acne and clitoromegaly since originally diagnosed. All three chose gonadectomy and after counselling one sister also elected to undergo clitoral reduction surgery. One patient with a referred diagnosis of 17 β HSD deficiency was given a reviewed diagnosis of Swyer's syndrome. In this patient's case a uterus was confirmed on ultrasound and the patient now has the option of fertility with donated ova. In the other two patients the changes in diagnoses (from CAIS to Leydig cell hypoplasia and from 5ARD to 17-beta-hydroxysteroid-3 deficiency due to molecular genetic testing) did not cause any clinical concerns but may have implications for the patients and their families.

DISCUSSION

Inaccurate and wrong diagnoses were surprisingly high in this study, with only 47.8% of patients considered to have an accurate diagnosis. Of more immediate concern were the 13% of patients with a wrong diagnosis, in some cases leading to irreversible virilising changes or high risk of gonadal malignancy. Diagnostic accuracy is assumed to be high when evaluating published work on these conditions; however, this may not be the case. This study has a small sample size ($n = 46$) although is a large study when considered in the context of intersex conditions. The clinic consists of gynaecological, endocrinological and psychological expertise and this may lead to a bias, with a larger

proportion of the sample consisting of intersex conditions that present with primary amenorrhoea or delayed puberty. However, many patients were referred on from paediatric services for adolescent and adult care and therefore the sample may be considered representative.

Intersex conditions present at a variety of ages from birth to adult life and in a variety of ways. Prevalence is thought to be low with the average UK clinician seeing only a few patients in their clinical lifetime. Diagnosis is not simple and a variety of specialist investigations, not generally available, may be required. Once a detailed diagnosis has been made, genetic tests may identify a specific mutation, and in this situation family members may undergo screening to identify affected siblings or asymptomatic carriers. In CAIS, androgen receptor mutations can be identified in up to two-thirds of cases. Currently such screening tests are often not available as part of the national health service and are generally performed by research groups in the UK and abroad. A careful clinical diagnosis is therefore essential in order to select the appropriate genetic test, if available, and reduce costs and avoid unnecessary investigations. Many patients will have had their intersex condition diagnosed decades ago—in our study the mean age at diagnosis was 10 years of age, and most subjects had been diagnosed 17 or more years ago. Both the knowledge and techniques available in molecular genetics have advanced enormously in that time,^{1–9} and this may explain the surprisingly high degree of diagnostic inaccuracy found.

Different intersex conditions may present in similar ways but often carry significant differences in management and clinical progression. The timing of gonadectomy is often controversial but is reliant on the correct diagnosis having been made. Women with CAIS may choose to have a gonadectomy performed after they have gone through puberty in order to allow a more natural puberty to take place due to their endogenous hormone production. Others will have had a gonadectomy before puberty and will therefore require hormone replacement therapy. Malignancy risk is believed to be lower than previously reported in CAIS, and some patients may even choose to retain their gonads. However, such an option is only appropriate to consider if the diagnosis of CAIS is accurate. It is also important to appreciate that these undescended testes are normal in structure and may have healthy germ cells, and the option of preserving reproductive tissue should be considered. With potential future advances in fertility techniques these germ cells may be used to create offspring although the ethical issues surrounding this are complex. Pure gonadal dysgenesis (Swyer's syndrome) presents in a similar manner to CAIS with primary amenorrhoea; however, it has a much higher risk of early gonadal neoplastic change (up to 30%) and removal of dysgenetic gonadal tissue should be undertaken urgently. For the same reason early gonadectomy is recommended in Denys–Drash syndrome and Frasier syndrome; in addition both of these conditions lead to renal failure and the need for eventual

transplant, so the involvement of nephrology services is mandatory. In contrast to CAIS, in conditions with gonadal dysgenesis where the gonads are non-functioning there is no endogenous hormone production and therefore there is no advantage in delaying gonadectomy to await a 'natural' puberty. However, patients with gonadal dysgenesis should be counselled that they have a uterus and may successfully conceive with ovum donation, give birth and breastfeed.¹⁰ The 14 women in this sample with gonadal dysgenesis were aged 16–42, and such information is of relevance to all of them, especially as many of the age-related pregnancy risks to the fetus are determined by the age of the ovum donor and not the ovum recipient.

Virilisation will occur at puberty for certain conditions, such as 5ARD or 17βHSD deficiency. Some of these changes, such as deepening of the voice, can be permanent and potentially irreversible despite subsequent gonadectomy and hormonal replacement. Surgery is available for clitoromegaly but sexual function may be compromised in favour of a better cosmetic appearance.^{11,12} Gonadectomy is therefore recommended prior to puberty for those individuals who have been raised and wish to remain female. Vaginal surgery or dilator therapy may be required for some women with vaginal hypoplasia, which can occur in some intersex conditions such as CAIS, in order to have comfortable penetrative intercourse. These treatments require a great deal of motivation, and support, and can be a difficult aspect of the condition for women to cope with. However, women with gonadal dysgenesis, such as Swyer's syndrome, will have a normal vagina and cervix. They should not need any treatment to the vagina and in addition will need to be included in the local cervical screening programme.

Intersex conditions are complex, and too often in the past clinicians have been tempted to manage isolated patients who were regarded as 'interesting cases'. This clearly is inappropriate and tertiary referral to appropriate regional centres is crucial. In this study 13% of patients were assigned an inconclusive diagnosis due to inadequate investigation prior to gonadectomy. The vital information from hormonal assays must be performed with the gonads *in situ*. It is much more difficult, if not impossible, to make an accurate diagnosis after gonadectomy.

In view of the rapidly changing scientific advances, intersex patients should be managed by a dedicated and expert multi-disciplinary intersex team. These clinicians should be familiar with recent advances in the field and revisit the diagnosis for patients not recently seen in clinic. Patients should be re-evaluated in the light of improvements in

diagnostic tests. Our surprisingly poor results highlight the need for continuing vigilance in assigning a diagnosis to this complex group.

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